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Examining the association between exposome score for schizophrenia and cognition in schizophrenia, siblings, and healthy controls: Results from the EUGEI study

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ABSTRACT

Background: People with schizophrenia spectrum disorders (SSD) frequently present cognitive impairments. Here, we investigated whether the exposome score for schizophrenia (ES-SCZ) - a cumulative environmental exposure score - was associated with impairments of neurocognition, social cognition, and perception in patients with SSD, their unaffected siblings, and healthy controls.

Methods: This cross-sectional sample consisted of 1200 patients, 1371 siblings, and 1564 healthy controls. Neurocognition, social cognition, and perception were assessed using a short version of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), the Degraded Facial Affect Recognition Task (DFAR), and the Benton Facial Recognition Test (BFR), respectively. Regression models were used to analyze the association between ES-SCZ and cognitive domains in each group.

Results: There were no statistically significant associations between ES-SCZ and cognitive domains in SSD. ES-SCZ was negatively associated with T-score of cognition in siblings ($B = -0.40$, 95% CI -0.76 to -0.03) and healthy controls ($B = -0.63$, 95% CI -1.06 to -0.21). Additionally, ES-SCZ was positively associated with DFAR-total in siblings ($B = 0.83$, 95% CI 0.26 to 1.40). Sensitivity analyses excluding cannabis use history from ES-SCZ largely confirmed the main findings.

Conclusions: Longitudinal cohorts may elucidate how environmental exposures influence the onset and course of cognitive impairments in trans-syndromic psychosis spectrum.

1. Introduction

Schizophrenia spectrum disorders (SSD) are associated with impairments across neurocognition, social cognition, and perception domains (Green et al., 2019). Cognitive dysfunctions are largely heterogeneous across the psychotic spectrum in terms of severity and domains involved (Green et al., 2019). Longitudinal studies have shown that cognitive deficits are frequently present prior to the onset of the condition, with the strongest evidence for processing speed, verbal learning and memory, executive function, and social cognition (Mohn-Haugen et al., 2022). According to the literature, trajectories of cognition in SSD are sparse, with no consistent evidence for a cognitive decline over the lifespan (Habtewold et al., 2020; McCutcheon et al., 2023). Importantly, cognitive impairments appear associated with poorer functional outcomes in people with SSD (Halverson et al., 2019; Mucci et al., 2021).

A large number of environmental (Arango et al., 2021; Lin et al., 2022; Radua et al., 2018) and genetic (Singh et al., 2022; Trubetsky et al., 2022) factors, as well as their interactions (Guloksuz et al., 2019; Mas et al., 2020; Pries et al., 2020; Zwicker et al., 2018) are involved in the etiopathogenesis of SSD. It is known that approximately half of the variance in general cognition in SSD can be attributed to genetic factors (Haworth et al., 2010), which are partially independent from those that predispose to SSD *per se* (Richards et al., 2020). However, genetics cannot fully explain the cognitive impairments frequently seen in people with SSD, and environment may play a substantial role.

Several studies have investigated the impact of environmental

exposures on cognitive outcomes in SSD individually (Lipner et al., 2023). Recent meta-analytic evidence suggested that overall cognition and working memory were negatively associated with childhood trauma in individuals with SSD. However, this association was less strong in SSD than the healthy population (Vargas et al., 2019). These findings were in line with a systematic review reporting that patients with psychosis and a history of childhood trauma displayed more deficits in general cognitive ability in psychotic patients with a history of childhood trauma than those without. Associations with other cognitive functions were mixed, with more inconsistency in chronic schizophrenia than ultra-high-risk individuals, first-episode patients, and healthy controls (Dauvermann and Donohoe, 2018).

Findings on the impact of cannabis use on cognitive functioning in patients with SSD are sparse. A meta-analysis of ten studies reported that patients with SSD and a history of cannabis use have superior neuropsychological functioning compared with non-users (Yücel et al., 2012). More recently, Sánchez-Gutiérrez et al. found that cannabis use is not generally associated with neurocognitive functioning in patients with first-episode psychosis (Sánchez-Gutiérrez et al., 2020).

Recently, it has been shown that people with SSD and obstetric complications show poorer performance in verbal and working memory compared to those with SSD but without a history of obstetric complications (Amoretti et al., 2022). The association between other environmental factors, such as winter birth or hearing impairment, and cognition in SSD has yet to be explored.

Recently, we have estimated the exposome score for schizophrenia (ES-SCZ), a cumulative environmental exposure score for SSD (Guloksuz et al., 2018a, 2018b; Pries et al., 2021a). By taking into account the interdependency of environmental exposures, ES-SCZ prevents overestimation of each exposure's effect size for schizophrenia risk (Pries et al., 2019, 2021a). ES-SCZ may be useful in the context of risk stratification and outcome prediction in SSD, as well as in the general

¹ (Discharged by statutory decree No:701 at 8th July of 2018 because of signing "Peace Petition").

² The Genetic Risk and Outcome of Psychosis (GROUP) investigators in EUGEI are listed in the Appendix.

population (Guloksuz et al., 2020; Pries et al., 2019, 2021b). Higher ES-SCZ is associated with poorer mental and physical outcomes in the general population (Pries et al., 2020), with greater associations for older age and female sex (Paquin et al., 2022). It is also negatively associated with global functioning in people with SSD, their unaffected siblings, and healthy controls (Erzin et al., 2021b), and represents a stable severity indicator of poor functioning in first-episode psychosis (Erzin et al., 2021a).

In the present study, we aimed to investigate for the first time whether ES-SCZ was associated with cognitive functioning domains (i.e., neurocognition, social cognition, perception) in people with SSD, their unaffected siblings, and healthy controls.

2. Methods

2.1. Study participants

Data of patients diagnosed with SSD, their unaffected siblings, and healthy controls were derived from the “vulnerability and severity” work-package 6 (WP6) of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EUGEI) study (van Os et al., 2014) collected in Turkey, Spain and Serbia, and the baseline wave of the Genetic Risk and Outcome of Psychosis (GROUP) study (Korver et al., 2012), collected in the Netherlands. Both projects (EUGEI and GROUP) were approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent, and such a consent was also obtained from parents or legal guardians in the case of minors.

Patients were diagnosed with SSD according to the DSM-IV-TR, which was further validated using the Operational Criteria Checklist for Psychotic and Affective Illness (McGuffin et al., 1991) in EUGEI-WP6, and the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) or the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) in GROUP. Healthy controls who had no lifetime psychotic disorder history were collected from the same population as the patients. For all participants, a diagnosis of psychotic disorder due to another medical condition, a history of head injury with loss of consciousness, and an intelligence quotient <70 were exclusion criteria. No specific diagnostic interview was conducted to exclude the presence of non-psychotic mental disorders in siblings and healthy controls.

The sample of this study consisted of 1200 patients with SSD, 1371 siblings, and 1564 healthy controls.

2.2. Exposome Score for Schizophrenia

To estimate the cumulative environmental load, we calculated the ES-SCZ based on our formerly validated estimates. Conforming to our previous studies, we constituted the ES-SCZ by summing log-odds weighted environmental exposures (each exposure defined as absent = “0” and present = “1”) including cannabis use, hearing impairment, winter-birth, and childhood adversity domains (emotional and physical neglect, emotional, physical and sexual abuse, and bullying). For ease of interpretation, a constant of 2 is added to ES-SCZ. The assessments and definitions of environmental exposures conforming to previous analyses (Guloksuz et al., 2019; Pries et al., 2020, 2019) are provided below.

Childhood adversity was assessed using the Childhood Trauma Questionnaire Short Form (CTQ) (Bernstein et al., 2003). This form consists of 28 items, rated on a 5-point Likert scale, measuring five domains of maltreatment (emotional and physical neglect; emotional, physical and sexual abuse). The psychometric characteristics of the translated versions (Spanish, Turkish, Dutch and Serbian) of the CTQ have been comprehensively studied (Hernandez et al., 2013; Sar et al., 2004; Thombs et al., 2009). To dichotomize each childhood adversity domain (0 = “absent” and 1 = “present”), consistent with previous work

in the EUGEI (Guloksuz et al., 2019; Kraan et al., 2018; Pries et al., 2020), we used the following cut-off scores for each domain: ≥ 9 for emotional abuse; ≥ 8 for physical abuse; ≥ 6 for sexual abuse; ≥ 10 for emotional neglect; and ≥ 8 for physical neglect.

Cannabis use was assessed using the Cannabis Experiences Questionnaire (modified version) (Barkus et al., 2006) in EUGEI-WP6 and the Composite International Diagnostic Interview (CIDI) (L section) (Robins et al., 1988) in GROUP. The Cannabis Experiences Questionnaire (0 = “none”; 1 = “only once or twice”; 2 = “a few times a year”; 3 = “a few times a month”; 4 = “once or more a week”; 5 = “everyday”) and CIDI (0 = “none”; 1 = “less than weekly”; 2 = “weekly”; 3 = “daily”) are Likert type scales. Following previous work (Guloksuz et al., 2019; Pries et al., 2020, 2018; Radhakrishnan et al., 2019; van Winkel, 2011) a binary regular cannabis use variable was constructed by using the cut-off value of one or more per week during the lifetime period most frequent use.

Conforming to previous studies exploring the association between the season of birth and SSD in the Northern hemisphere sites (Davies and Greenwood, 2020), the high-risk birth period was the winter solstice (December-March).

Hearing impairment in the last 12 months was assessed using a self-report evaluation (0 = “absent” and 1 = “present”) (Guloksuz et al., 2019).

The short version of Retrospective Bullying Questionnaire (RBQ) was used to evaluate the history of exposure to childhood bullying (emotional, psychological, or physical violence) before the age of 17 (Hunter et al., 2004; Schäfer et al., 2004). The RBQ measures the severity of the bullying experience as 0 = “none”; 1 = “some” (no physical injuries); 2 = “moderate” (minor injuries or transient emotional reactions); 3 = “marked” (severe and frequent physical or psychological harm). By using the cut-off point ≥ 1 , childhood bullying was dichotomized as 0 = “absent” and ≥ 1 = “present”, conforming to previous studies (Guloksuz et al., 2019; Pries et al., 2020, 2019).

2.3. Outcomes

2.3.1. Neurocognition: Wechsler Adult Intelligence Scale

An abbreviated Wechsler Adult Intelligence Scale (WAIS-III) (Blyler et al., 2000), comprising the digit symbol coding, arithmetic, block design, and information subtests, was used to measure performance in the domains of processing speed, working memory, visuospatial processing, and verbal knowledge, respectively. In the EUGEI, simplified versions of the subtests were administered. Specifically, the digit symbol coding was administered for the standard time, along with every second item of the block design and arithmetic subtests, and every third item of the information subtest. This abbreviated WAIS-III version was developed for EUGEI and provides a reliable approximation of intelligence quotient (IQ) and the four subtests (Velthorst et al., 2013). In the GROUP, all items of each subtest were administered. In line with our previous work (van Os et al., 2020), for each test, the Z-score was calculated separately for each country and sex. Total cognition was estimated calculating the mean of the Z-scores of the different tests, expressed as a T-score (total cognition scores shifted and scaled to have a mean of 50 and a standard deviation of 10). T-score was regarded as the main outcome for the domain of neurocognition.

2.3.2. Social cognition: Degraded Facial Affect Recognition Task

The Degraded Facial Affect Recognition Task (DFAR) (van't Wout et al., 2004) a measure of facial emotion recognition, was used as a domain of social cognition, in line with previous studies (Fusar-Poli et al., 2022a, 2022b; Menghini-Müller et al., 2020). This task measures emotional face recognition in degraded photographs and was administered in both the EUGEI and GROUP. Subjects were presented with photographs of four individuals (two males and two females), depicting emotional facial expression. Subjects were asked to indicate the expression of each face and to respond as accurately as possible. The photographs of the faces were passed through a filter resulting in a reduced visual contrast by 30%. This method was adopted to increase

the difficulty and enhance the contribution of perceptual expectancies and interpretation. Subjects were presented with 64 trials (16 for each condition: angry, happy, fearful and neutral) (van't Wout et al., 2004). Higher scores indicate a better ability to recognize facial expressions of a particular emotion. DFAR-total was regarded as the main outcome for the domain of social cognition.

2.3.3. Perception: Benton Facial Recognition Test

The Benton Facial Recognition Test (BFR) (Benton et al., 1994) is an accurate measure of the ability to match non-emotional unfamiliar faces. It is traditionally used to assess face perception skills in neurological, clinical and psychiatric conditions. The short version of the BFR was administered in both the EUGEI and GROUP. Participants were simultaneously presented with one target face and six other black and white photos of unfamiliar male or female faces with their hair and clothing shaded out. Afterwards, they were asked to: (1) match a frontal view of the target with an identical photo, (2) match a frontal view of the target face with 3 photos taken from different angles, and (3) match a frontal view of the target face with three photos of that person taken under different lighting conditions. The number of correct responses was used as the outcome measure. In the short version of the BFR, the total score can range between 0 and 27.

2.4. Statistical analyses

Linear regressions were applied to evaluate the association between ES-SCZ and cognitive variables. Analyses were stratified by the subgroups: patients, unaffected siblings, and healthy controls. All analyses were a priori adjusted for age, sex, and country. We reported unstandardized regression coefficients (B). Since our previous work has shown a significant association between a history of regular cannabis use and social cognition (Fusar-Poli et al., 2022b), we conducted sensitivity analyses after removing a history of regular cannabis use (as per above definition) from the ES-SCZ calculation. Stata software version 16.0 was used for the analysis (StataCorp, 2019). The nominal statistical significance threshold was set to $p=0.05$. In accordance with the proposition of Rothman (Rothman, 1990) for obtaining fewer errors of interpretation in observational studies, no statistical significance correction for multiple comparisons was applied for explorative analyses of subdomains of cognition.

3. Results

3.1. Characteristics of participants

Characteristics of participants are presented in Table 1. Performances in cognitive tasks are displayed in Table 2.

Table 1
Characteristics of participants.

| | Patients (n = 1200) | Siblings (n = 1371) | Healthy controls (n = 1564) |
|---------------------|------------------------|------------------------|--------------------------------|
| Age, M (SD) | 31.52 (8.72) | 31.21 (9.23) | 33.49 (10.71) |
| Sex, male n (%) | 849 (70.75) | 633 (46.17) | 744 (47.57) |
| Country, n (%) | | | |
| Turkey | 430 (35.83) | 482 (35.16) | 951 (60.81) |
| Spain | 273 (22.75) | 291 (21.23) | 253 (16.18) |
| Serbia | 44 (3.67) | 46 (3.36) | 37 (2.37) |
| Netherlands | 453 (37.75) | 552 (40.26) | 323 (20.65) |
| Education, n (%) | | | |
| No qualifications | 77 (6.54) | 53 (3.93) | 34 (2.20) |
| With qualifications | 271 (23.01) | 219 (16.25) | 306 (19.77) |
| Tertiary | 318 (26.99) | 256 (18.99) | 303 (19.57) |
| Vocational | 344 (29.20) | 449 (33.31) | 480 (31.01) |
| University | 168 (14.26) | 371 (27.52) | 425 (27.45) |
| ES-SCZ, M (SD) | 4.01 (1.34) | 3.29 (1.17) | 2.83 (0.93) |

Legend: ES-SCZ: Exposome Score for Schizophrenia.

3.2. Associations between ES-SCZ and cognitive domains

Results of the associations between ES-SCZ and cognitive domains are reported in Table 3. Main analyses showed no significant association between ES-SCZ and cognitive domains in patients with SSD. A significant negative association between ES-SCZ and T-score in siblings ($B=-0.40$, 95% CI -0.76 to -0.03 , $p=0.03$) and healthy controls ($B=-0.63$, 95% CI -1.06 to -0.21 , $p=0.004$). Additionally, ES-SCZ was positively associated with DFAR-total in siblings ($B=0.83$, 95% CI 0.26 to 1.40 , $p=0.004$).

As for the subdomains of neurocognition, secondary exploratory analyses showed that ES-SCZ was positively associated with information subtest ($B=0.09$, 95% CI 0.04 to 0.14 , $p=0.001$) in patients with SSD. Moreover, ES-SCZ was negatively associated with digit symbol in unaffected siblings ($B=-0.05$, 95% CI -0.10 to -0.004 , $p=0.03$) and healthy controls ($B=-0.08$, 95% CI -0.14 to -0.02 , $p=0.005$). Similarly, a negative association between ES-SCZ and arithmetic was found in siblings ($B=-0.08$, 95% CI -0.13 to -0.02 , $p=0.004$) and healthy controls ($B=-0.11$, 95% CI -0.17 to -0.05 , $p<0.001$). As for social cognition, ES-SCZ was positively associated with DFAR-fearful in patients with SSD ($B=1.66$, 95% CI 0.68 to 2.64 , $p=0.001$), and with DFAR-neutral in siblings ($B=1.14$, 95% CI 0.23 to 2.05 , $p=0.01$), respectively.

3.3. Sensitivity analyses excluding history of regular cannabis use from ES-SCZ

Results of the sensitivity analyses are reported in Table 4. As for main outcomes, a significant negative association was found between T-score and ES-SCZ in healthy controls ($B=-0.60$, 95% CI -1.08 to -0.13 , $p=0.01$), in line with the main analyses. There was a trend towards significant association between T-score and ES-SCZ in siblings ($B=-0.38$, 95% CI -0.78 to 0.03 , $p=0.07$). DFAR-total was positively and significantly associated with ES-SCZ only in siblings ($B=0.90$, 95% CI 0.26 to 1.53 , $p=0.006$). BFR was negatively associated with ES-SCZ in controls ($B=-0.16$, 95% CI -0.31 to -0.003 , $p=0.04$).

Secondary exploratory analyses on neurocognitive outcomes showed that information subtest was positively and significantly associated with ES-SCZ in patients with SSD ($B=0.11$, 95% CI 0.05 to 0.17 , $p<0.001$). Conversely, a negative significant association was found between ES-SCZ and digit symbol both in siblings ($B=-0.06$, 95% CI -0.11 to -0.01 , $p=0.03$) and healthy controls ($B=-0.08$, 95% CI -0.14 to -0.02 , $p=0.01$). Similarly, ES-SCZ was negatively associated with arithmetic in both siblings ($B=-0.07$, 95% CI -0.12 to -0.01 , $p=0.02$) and healthy controls ($B=-0.11$, 95% CI -0.17 to -0.04 , $p=0.001$). Secondary sensitivity analyses on subdomains of social cognition revealed a positive association between ES-SCZ and DFAR-fearful both in patients with SSD ($B=1.79$, 95% CI 0.67 to 2.91 , $p=0.002$) and siblings ($B=1.08$, 95% CI 0.03 to 2.12 , $p=0.04$).

4. Discussion

We tested the association between the ES-SCZ and cognitive domains in patients with SSD, their unaffected siblings, and healthy controls, respectively. Our results provide evidence for different patterns of association between ES-SCZ and cognition across the three groups.

In people with SSD, we did not detect any significant association between ES-SCZ and the three main cognitive outcomes. The lack of significant association in SSD might be related to a "floor effect", i.e. the impact of ES-SCZ is "trumped" by other sources that impact on cognitive alterations, such as altered motivation to engage in neuropsychological testing (Fervaha et al., 2014), medication-associated burden (Joshi et al., 2021), or genetics. In fact, it is known that cognitive abilities in SSD are substantially influenced by genes, with approximately half of the variance in general cognition attributed to genetic factors (Haworth et al., 2010). Although there is evidence of genetic overlap between SSD

Table 2
Performance in cognitive tasks.

| | Patients n | Mean (SD) | Siblings n | Mean (SD) | Healthy controls n | Mean (SD) |
|--|---------------|---------------|---------------|---------------|-----------------------|---------------|
| Neurocognition | | | | | | |
| T-score | 1141 | 44.72 (8.19) | 1332 | 49.79 (7.89) | 1495 | 50.02 (7.51) |
| Digit symbol, z-score (processing speed) | 1128 | -0.88 (1.00) | 1322 | 0.01 (1.03) | 1491 | -0.004 (1.00) |
| Arithmetic, z-score (working memory) | 1132 | -0.57 (1.12) | 1328 | -0.06 (1.11) | 1494 | 0.004 (0.99) |
| Block design, z-score (visuospatial processing) | 1123 | -0.34 (1.15) | 1325 | 0.12 (1.06) | 1494 | -0.008 (1.01) |
| Information, z-score (verbal knowledge) | 1131 | -0.33 (1.10) | 1323 | -0.16 (1.08) | 1490 | 0.01 (0.99) |
| Social cognition | | | | | | |
| DFAR-total | 1109 | 66.49 (14.13) | 1296 | 72.30 (12.29) | 1536 | 74.33 (16.55) |
| DFAR-neutral | 1109 | 71.59 (22.93) | 1296 | 77.45 (19.20) | 1536 | 79.40 (21.41) |
| DFAR-happy | 1109 | 85.39 (16.80) | 1296 | 88.07 (14.22) | 1536 | 87.41 (17.85) |
| DFAR-fearful | 1109 | 47.07 (21.67) | 1296 | 54.68 (20.11) | 1536 | 59.88 (22.48) |
| DFAR-angry | 1109 | 62.18 (22.33) | 1296 | 69.30 (21.13) | 1536 | 70.86 (24.06) |
| Perception | | | | | | |
| BFR | 1124 | 21.75 (3.06) | 1324 | 22.59 (2.30) | 1547 | 23.39 (2.53) |

Legend: BFR: Benton Facial Recognition task; DFAR: Degraded Facial Affect Recognition task.

Table 3
Associations between ES-SCZ and cognitive domains.

| Outcomes | Patients | | | | Siblings | | | | Healthy controls | | | |
|---|----------|--------------|-------------|--------|----------|--------------|---------------|--------|------------------|--------------|--------------|---------|
| | n | B (SE) | 95% CI | P | n | B (SE) | 95% CI | p | n | B (SE) | 95% CI | p |
| Neurocognition | | | | | | | | | | | | |
| T-score | 1141 | 0.21 (0.19) | -0.15, 0.58 | 0.25 | 1332 | -0.40 (0.19) | -0.76, -0.03 | 0.03* | 1495 | -0.63 (0.22) | -1.06, -0.21 | 0.004* |
| Digit symbol (processing speed) | 1128 | 0.01 (0.02) | -0.04, 0.05 | 0.80 | 1322 | -0.05 (0.02) | -0.10, -0.004 | 0.03* | 1491 | -0.08 (0.03) | -0.14, -0.02 | 0.005* |
| Arithmetic (working memory) | 1132 | -0.03 (0.03) | -0.08, 0.02 | 0.26 | 1328 | -0.08 (0.03) | -0.13, -0.02 | 0.004* | 1494 | -0.11 (0.03) | -0.17, -0.05 | <0.001* |
| Block design (visuospatial processing) | 1123 | 0.02 (0.03) | -0.03, 0.07 | 0.53 | 1325 | -0.03 (0.02) | -0.08, 0.02 | 0.21 | 1494 | -0.04 (0.03) | -0.10, 0.02 | 0.18 |
| Information (verbal knowledge) | 1131 | 0.09 (0.02) | 0.04, 0.14 | 0.001* | 1323 | 0.004 (0.02) | -0.04, 0.05 | 0.87 | 1490 | -0.02 (0.03) | -0.08, 0.03 | 0.39 |
| Social cognition | | | | | | | | | | | | |
| DFAR-total | 1109 | 0.35 (0.32) | -0.29, 0.99 | 0.28 | 1296 | 0.83 (0.29) | 0.26, 1.40 | 0.004* | 1536 | -0.17 (0.48) | -1.10, 0.77 | 0.72 |
| DFAR-neutral | 1109 | -0.33 (0.52) | -1.35, 0.69 | 0.53 | 1296 | 1.14 (0.46) | 0.23, 2.05 | 0.01* | 1536 | -0.36 (0.62) | -1.59, 0.86 | 0.56 |
| DFAR-happy | 1109 | -0.05 (0.39) | -0.82, 0.73 | 0.91 | 1296 | 0.58 (0.34) | -0.09, 1.26 | 0.09 | 1536 | -0.30 (0.52) | -1.32, 0.73 | 0.57 |
| DFAR-fearful | 1109 | 1.66 (0.50) | 0.68, 2.64 | 0.001* | 1296 | 0.78 (0.48) | -0.16, 1.72 | 0.10 | 1536 | -0.04 (0.63) | -1.28, 1.20 | 0.94 |
| DFAR-angry | 1109 | 0.14 (0.52) | -0.88, 1.16 | 0.79 | 1296 | 0.83 (0.50) | -0.15, 1.81 | 0.10 | 1536 | 0.04 (0.69) | -1.32, 1.40 | 0.95 |
| Perception | | | | | | | | | | | | |
| BFR | 1124 | -0.01 (0.07) | -0.14, 0.12 | 0.90 | 1324 | 0.05 (0.05) | -0.05, 0.16 | 0.31 | 1547 | -0.13 (0.07) | -0.27, 0.01 | 0.07 |

Legend: BFR = Benton Facial Recognition task; CI = Confidence Interval; DFAR = Degraded Facial Affect Recognition task; SE = standard error; *p<0.05. All models were adjusted for age, sex, and country (Turkey, Spain, the Netherlands, and Serbia).

and cognition (Hubbard et al., 2016; Ohi et al., 2018), cognitive variation within SSD might be partially independent from genetic mechanisms that predispose to schizophrenia (Richards et al., 2020). Previous research has reported that environmental risk factors for psychosis, such as childhood adversities, are not associated with IQ in people with SSD (Sideli et al., 2022; van Os et al., 2017). It is also possible that environmental factors not included in ES-SCZ may play a relevant role in cognitive variation within SSD. For instance, obstetric complications and immigration have been associated with both SSD and cognitive impairments (Radua et al., 2018; Wortinger et al., 2020). Of note, a recent meta-analysis has reported that obstetric complications are moderately associated with specific cognitive domains, such as working memory and verbal memory, in people with SSD (Amoretti et al., 2022). Additionally, certain types of medications – particularly anticholinergic

drugs - have been associated with cognitive impairments in SSD (Joshi et al., 2021). Future studies examining genetic and environmental risk factors not directly linked to the pathoetiology of SSD, as well as their interaction, may clarify the origins of cognitive heterogeneity in SSD.

We found negative significant associations of ES-SCZ with neurocognition (T-score) in both siblings and healthy controls. Our results are consistent with previous research adopting a family design showing that childhood trauma was associated with lower IQ in siblings of people with SSD and in controls but not in patients (van Os et al., 2017). Given that siblings largely share genetics with patients, environment may represent a substantially important factor for determining cognitive functioning. Nevertheless, data from a longitudinal cohort (Kendler et al., 2016) have suggested that the environmental exposures that influence cognitive ability in relatives might be different from those that

Table 4

Sensitivity analyses of the association between ES-SCZ without cannabis use history and cognitive domains.

| Outcomes | Patients | | | | Siblings | | | | Healthy controls | | | |
|--|----------|--------------|-------------|---------|----------|---------------|--------------|--------|------------------|--------------|---------------|--------|
| | n | B (SE) | 95% CI | p | n | B (SE) | 95% CI | p | n | B (SE) | 95% CI | p |
| Neurocognition | | | | | | | | | | | | |
| T-score | 1141 | 0.29 (0.21) | -0.12, 0.71 | 0.16 | 1332 | -0.38 (0.21) | -0.78, 0.03 | 0.07 | 1495 | -0.60 (0.24) | -1.08, -0.13 | 0.01* |
| Digit symbol (processing speed) | 1128 | 0.005 (0.02) | -0.04, 0.05 | 0.85 | 1322 | -0.06 (0.03) | -0.11, -0.01 | 0.03* | 1491 | -0.08 (0.03) | -0.14, -0.02 | 0.01* |
| Arithmetic (working memory) | 1132 | -0.01 (0.03) | -0.07, 0.04 | 0.66 | 1328 | -0.07 (0.03) | -0.12, -0.01 | 0.02* | 1494 | -0.11 (0.03) | -0.17, -0.04 | 0.001* |
| Block design (visuospatial processing) | 1123 | 0.01 (0.03) | -0.05, 0.07 | 0.75 | 1325 | -0.03 (0.03) | -0.09, 0.02 | 0.29 | 1494 | -0.04 (0.03) | -0.10, 0.02 | 0.24 |
| Information (verbal knowledge) | 1131 | 0.11 (0.03) | 0.05, 0.17 | <0.001* | 1323 | 0.01 (0.03) | -0.04, 0.07 | 0.71 | 1490 | -0.02 (0.03) | -0.08, 0.04 | 0.58 |
| Social cognition | | | | | | | | | | | | |
| DFAR-total | 1109 | 0.33 (0.37) | -0.39, 1.06 | 0.37 | 1296 | 0.90 (0.32) | 0.26, 1.53 | 0.006* | 1536 | -0.49 (0.53) | -1.52, 0.55 | 0.36 |
| DFAR-neutral | 1109 | -0.30 (0.59) | -1.46, 0.86 | 0.61 | 1296 | 0.99 (0.52) | -0.03, 2.00 | 0.06 | 1536 | -0.88 (0.69) | -2.23, 0.48 | 0.20 |
| DFAR-happy | 1109 | -0.10 (0.45) | -0.97, 0.78 | 0.83 | 1296 | 0.58 (0.38) | -0.17, 1.33 | 0.13 | 1536 | -0.47 (0.58) | -1.60, 0.66 | 0.41 |
| DFAR-fearful | 1109 | 1.79 (0.57) | 0.67, 2.91 | 0.002* | 1296 | 1.08 (0.53) | 0.03, 2.12 | 0.04* | 1536 | -0.22 (0.70) | -1.60, 1.15 | 0.75 |
| DFAR-angry | 1109 | -0.04 (0.59) | -1.19, 1.12 | 0.95 | 1296 | 0.96 (0.56) | -0.14, 2.05 | 0.09 | 1536 | -0.34 (0.77) | -1.84, 1.17 | 0.66 |
| Perception | | | | | | | | | | | | |
| BFR | 1124 | -0.04 (0.08) | -0.20, 0.11 | 0.56 | 1324 | -0.003 (0.06) | -0.12, 0.11 | 0.96 | 1547 | -0.16 (0.08) | -0.31, -0.003 | 0.04* |

Legend: BFR = Benton Facial Recognition task; CI = Confidence Interval; DFAR = Degraded Facial Affect Recognition task; SE = standard error; * $p < 0.05$. All models were adjusted for age, sex, and country (Turkey, Spain, the Netherlands, and Serbia).

influence cognitive ability in people with SSD. So far, the relationship between environmental factors and cognition in first-degree relatives of people with SSD has been under-researched and deserves further clarification. The direction and strength of the association between ES-SCZ and neurocognition (T-score) in siblings after removing cannabis use from the ES-SCZ calculation remained consistent but was not nominally statistically significant ($P = 0.07$).

Social cognition (DFAR-total) was positively associated with ES-SCZ only in siblings. Although deficits in social cognition have been regarded as an intermediate phenotype for psychosis (Fusar-Poli et al., 2022a; Martin et al., 2020), a link between molecular genetic risk for schizophrenia (e.g. PRS for schizophrenia) and social cognition has yet to be established (Fusar-Poli et al., 2022a). It is likely that environment substantially contributes to the variation in social cognition, especially when the genetic load for schizophrenia is lower. Although this is the first study to test the link between a cumulative environmental exposure score for SSD and cognition, previous studies have already reported a positive association between social cognition and individual environmental risk factors for SSD in siblings. For instance, we recently reported that lifetime regular cannabis use – included in the ES-SCZ – was positively associated with facial emotion recognition in SSD, siblings, and controls (Fusar-Poli et al., 2022b). Given the cross-sectional design of our study, we cannot infer a cause-effect relationship. One possible explanation is that a better ability in emotion recognition might be adaptive in the context of increased environmental load, particularly social adversities (i.e., childhood trauma and bullying). Of note, findings from the analyses after removing lifetime regular cannabis use from the calculation of ES-SCZ were in line with our main results, therefore providing further support for the robustness of these findings.

Explorative analyses on subdomains revealed that WAIS-III Information subtest was positively associated with ES-SCZ in patients with SSD. Among neurocognitive domains, verbal comprehension has been regarded as the least genetically linked to schizophrenia, with negligible effects of shared environment, and substantial variation due to specific individual environmental factors (Toulopoulou et al., 2007). Arithmetic and digit symbol were instead negatively associated with ES-SCZ in

siblings and healthy controls. In accordance, a recent meta-analysis has shown that a history of childhood trauma was negatively associated with working memory, with a stronger association in the healthy population than in SSD (Vargas et al., 2019). Considering subdomains of social cognition, DFAR-fearful was positively and significantly associated with ES-SCZ in SSD. It has been shown that fear recognition is similarly impaired across different stages of SSD, suggesting its possible role as a vulnerability marker (Pena-Garijo et al., 2023). Therefore, variation in fear recognition could be better explained by environmental exposures rather than genetic mechanisms. Our result is in line with findings from a recent study reporting that psychotic patients with a history of childhood trauma other than sexual abuse were more capable of recognizing fear as a facial emotion (Brañas et al., 2022). Indeed, a history of childhood trauma in SSD is associated with increased stress reactivity later in life, suggesting an underlying process of behavioral sensitization (Lardinois et al., 2011). Ultimately, it is possible to hypothesize that patients with SSD have a better performance in fear recognition as an adaptation to social adversity. Moreover, DFAR-neutral, similar to DFAR-total, was negatively associated with ES-SCZ in siblings.

The family design, large sample size from a multinational cohort, and detailed analyses of different cognitive domains represent the main strengths of our study. Furthermore, we utilized ES-SCZ that was previously constructed, validated, and demonstrated to perform well in our study population (Pries et al., 2020, 2021b). However, it should be noted that this was a cross-sectional study; therefore, no conclusions about causality relationship could be drawn. Additionally, given the exploratory nature of our analyses, we did not adjust for multiple comparisons, which might increase the risk of false discovery. Finally, only one domain of social cognition, facial emotion recognition, was explored. In this regard, we cannot exclude that other domains, such as theory of mind, might be differently associated with ES-SCZ.

In conclusion, we found that ES-SCZ was negatively associated with neurocognition but positively with social cognition in non-psychotic samples. Longitudinal cohort studies may clarify whether the effect of additive and interactive environmental exposures may impact on the onset and course of cognitive heterogeneity in a trans-syndromal

psychosis spectrum (Barzilay et al., 2022).

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request under the condition of the approval of the EUGEI and GROUP steering committees.

Ethical standards

The projects were approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent and, in the case of minors, such consent was also obtained from parents or legal guardian.

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CRediT authorship contribution statement

Laura Fusar-Poli: Conceptualization, Formal analysis, Writing – original draft. **Thanavadee Prachason:** Writing – review & editing. **Gamze Erzin:** Writing – review & editing. **Lotta-Katrin Pries:** Data curation, Formal analysis. **Natascia Brondino:** Writing – review & editing. **Pierluigi Politi:** Writing – review & editing. **Philippe Dele-spaul:** Investigation, Project administration. **Gunter Kenis:** Investigation, Project administration. **Jurjen J Luykx:** Data curation, Formal analysis. **Bochao D Lin:** Data curation, Formal analysis. **Alexander I Richards:** . **Berna Akdede:** Investigation, Project administration. **Tolga Binbay:** Investigation, Project administration. **Vesile Altunazar:** Investigation, Project administration. **Berna Yalınçetin:** Investigation, Project administration. **Güvem Gümüş-Akay:** Investigation, Project

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Declaration of Competing Interest

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Appendix

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