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

Laura Fusan-Poli, Thanaveadee Prachason, Gamze Erzin, Lotta-Katrin Pries, Natascia Brondino, Pierluigi Politi, Philippe Delespaul, Gunter Kenis, Jurjen J Luykx, Bochao D Lin, Alexander L Richards, Berna Akdede, Tolga Binbay, Vesile Altunyazar, Beren Yalncetin, Guven Gumus-Akay, Burcin Cihan, Haldun Soygur, Halis Ulas, Eylem Sahin Cankurtaran, Semra Ulusoy Kaymak, Marina M Mihaljevic, Sanja Andric-Petrovic, Tijana Mirjanić, Miguel Bernardo, Gisela Mezquida, Silvia Amoretti, Julio Bobes, Pilar A Saiz, Maria Paz Garcia-Portilla, Julio Sanjuan, Maria Jose Escarti, Jose Luis Santos, Estela Jimenez-Lopez, Manuel Arrojo, Angel Carracedo, Gonzalo Lopez, Javier Gonzalez-Penas, Mara Parelada, Nadja P Maric, Cem Atbasoglu, Alp Ucok, Koksal Alptekin, Meram Can Saka, Celso Arango, Michael O’Donovan, Jim van Os, Bart PF Rutten, Sinan Guloksu

* Corresponding author at: Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Vijverdalseweg 1, P.O.Box 616 6200, Maastricht, MD, The Netherlands.
E-mail address: sinan.guloksu@maastrichtuniversity.nl (S. Guloksu).

https://doi.org/10.1016/j.psychres.2023.115184

Accepted 26 March 2023

Available online 28 March 2023
0165-1781/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
condition, with the strongest evidence for processing speed, verbal
( Mohn-Haugen et al., 2022 ). According to the literature, trajectories of
learning and memory, executive function, and social cognition
domains involved ( Green et al., 2019 ). Longitudinal studies have shown
et al., 2020 ; Pries et al., 2020 ; Zwicker et al., 2018 ) are involved in
effects 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 neurocognitive
functioning compared with non-users ( Yücel et al., 2012 ). More recently, Sánchez-Gutiérrez et al. found that cannabis use is not
necessarily 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 compli-
cations ( Amoretti et al., 2022 ). The association between other envi-
ronmental 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 ( Gulok-
suz et al., 2018a, 2018b; Pries et al., 2021a ). By taking into account the
interdependency of environmental exposures, ES-SCZ prevents over-
estimation of each exposure’s effect size for schizophrenia risk (Pries et al., 2019, 2021a). ES-SCZ may be useful in the context of risk strati-
fication 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
EUGENI 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 (van Os et al., 2014) 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. Fusar-Poli et al., 2023) 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; Schaffer 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) (Byler 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 (Veithorst 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...
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 (7.72)       | 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)         | 523 (30.65)                 |
| 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 -0.04, 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 -0.03, 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...
Additionally, certain types of medications - 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 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 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 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 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 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 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.
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.

Role of funding source

The EUGEI project was supported by the grant agreement HEALTH-F2-2010-241909 from the European Community’s Seventh Framework Programme. The authors are grateful to the patients and their families for participating in the project. L. Pries is supported by the Kootstra Programme. The authors are grateful to the patients and their families for participating in the project. L. Pries is supported by the Kootstra Programme. The authors are grateful to the patients and their families for participating in the project. L. Pries is supported by the Kootstra Programme.

Declaration of Competing Interest

Celso Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda.

Julio Bobes has received research grants and served as a consultant, advisor, or speaker within the last 5 years for AB-Biotics, Acadia Pharmaceuticals, Alkermes, Allergan, Ambrosetti-Angelini, Biogen, Casen Recordati, D&A Pharma, Exelixis, Gilead, Indivior, GW Pharmaceuticals, Janssen-Cilag, Jazz Pharmaceuticals, Lundbeck, Mundipharma, Newron, Otsuka, Pfizer, Roche, Sage Therapeutics, Servier, Schwabe Farma Ibérica, Shire, and Takeda and has received research funding from the Spanish Ministry of Economy and Competitiveness – Centro de Investigación Biomédica en Red area de Salud Mental (CIBERSAM) and Instituto de Salud Carlos III – and the Spanish Ministry of Health.

Maria Paz García-Portilla has been a consultant to and/or has received honoraria/grants from Angelini, Otsuka-Lundbeck Alliance, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and Sage Therapeutics.

Pilar A. Sáiz has been a consultant to and/or has received honoraria/research grants from Adamed, Alter Medica, Angelini Pharma, CIBER-SAM, Ethlypharm Digital Therapy, European Commission, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas, and Servier.

Miguel Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda.

Acknowledgments

The authors are grateful to the patients and their families for their participation in this study.
participating in the project. They also thank all research personnel involved in the GROUP project, in particular J. van Baaren, E. Veerman, G. Driessen, T. Driesen, E. van’t Hag and J. de Nijs.

Appendix

Genetic Risk and Outcome of Psychosis (GROUP) Investigators in EUGEI (GROUP-EUGEI) investigators are: Behrooz Z. Alizadeh1, Therese van Amelsvoort2, Richard Bruggeman3, Wiepke Cahn4, Lieuwde Haan5, Bart P. F. Rutten6, Jurjen J. Luykx7,8,9,10 and Ruud van Winkel1,2,11

1University of Groningen, University Medical Center Groningen, University Center for Psychiatry, Rob Giel Research Center, Groningen, The Netherlands

2Maastricht University Medical Center, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands

3University Medical Center Utrecht, Department of Psychiatry, UMC Utrecht Brain centre, Utrecht University, Utrecht, The Netherlands

4Altrecht, General Mental Health Care, Utrecht, The Netherlands

5Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands

6GGNet Mental Health, Apeldoorn, The Netherlands

Department of Translational Neuroscience, UMC Utrecht Brain Centre, UMC University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

King’s College London, King’s Health Partners, Department of Psychiatry Studies, Institute of Psychiatry, London, UK

KU Leuven, Department of Neuroscience, Research Group Psychiatry, Leuven, Belgium

References

Amoretti, S., Bobes, J., Parellada, M., Maric, N.P., Atbasoglu, C., Uçok, A., Alptekin, K., Saka, M. C., Arango, C., O’Donovan, M., Rutten, B.P.F., Guloksuz, S., 2022a. Examining facial emotion recognition as an intermediate phenotype for psychosis from the EUGEI study. Prog. Neuropsychopharmacol. Biol. Psychiatry 113, 110440.

Fusar-Poli, P., Pries, L.K., van Os, J., Radhakrishnan, R., Perez, A.Y., Erzin, G., Delepas, P., Kenis, G., Luykx, J.J., Lin, B.D., Richards, A.L., Akdede, B., Binbay, T., Alnyazur, V., Yalinicehtin, B., Gumus-Akay, G., Cihan, B., Soyurig, H., Ulug, H., Cankurtaran, E., Kaynak, S.U., Mihaljevic, M.M., Andric-Petrovic, S., Mirjancic, T., Bernardo, M., Mezquida, G., Amoretti, S., Bobes, J., Saiz, P.A., Garcia-Porilla, M.P., Sanjuan, J., Aguiru, E.J., Santos, J.L., Jimenez-Lopez, E., Arrojo, M., Carracedo, A., Lopez, G., Gonzalez-Pejas, A., Parellada, M., Maric, N.P., Atbasoglu, C., Uçok, A., Alptekin, K., Saka, M. C., Aguglia, E., Arango, C., O’Donovan, M., Rutten, B.P.F., Guloksuz, S., 2022b. The association between cannabis and facial emotion recognition in schizophrenia, siblings, and healthy controls results from the EUGEI study. Eur. Psychiatry 64, 225.

Fervaha, G., Zakzansk, K.K., Foussias, G., Graff-Guerrero, A., Agid, O., Remington, G., 2013. Motivational deficits and cognitive test performance in schizophrenia. JAMA Psychiatry 70, 1058–1064.

Fusar-Poli, P., Pries, L.K., van Os, J., Erzin, G., Delepas, P., Kenis, G., Luykx, J.J., Lin, B.D., Richards, A.L., Akdede, B., Binbay, T., Alnyazur, V., Yalinicehtin, B., Gumus-Akay, G., Cihan, B., Soyurig, H., Ulug, H., Cankurtaran, E., Kaynak, S.U., Mihaljevic, M.M., Andric-Petrovic, S., Mirjancic, T., Bernardo, M., Mezquida, G., Amoretti, S., Bobes, J., Saiz, P.A., Garcia-Porilla, M.P., Sanjuan, J., Aguiru, E.J., Santos, J.L., Jimenez-Lopez, E., Arrojo, M., Carracedo, A., Lopez, G., Gonzalez-Pejas, A., Parellada, M., Maric, N.P., Atbasoglu, C., Uçok, A., Alptekin, K., Saka, M. C., Aguglia, E., Arango, C., O’Donovan, M., Rutten, B.P.F., Guloksuz, S., 2022. Examining facial emotion recognition as an intermediate phenotype for psychosis from the EUGEI study. Prog. Neuropsychopharmacol. Biol. Psychiatry 113, 110440.

10. https://doi.org/10.1017/S0033291721004542.
Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr. Bull. 40, 729–736.

van Winkel, R. 2011. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. Arch. Gen. Psychiatry 68, 148–157.

Vargas, T., Lam, P.H., Azis, M., Osborne, K.J., Lieberman, A., Mittal, V.A., 2019. Childhood trauma and neurocognition in adults with psychotic disorders: a systematic review and meta-analysis. Schizophr. Bull. 45, 1195–1208.

Velthorst, E., Levine, S.Z., Henquet, C., de Haan, L., van Os, J., Myin-Germeys, I., Reichenberg, A., 2013. To cut a short test even shorter: reliability and validity of a brief assessment of intellectual ability in schizophrenia—a control-case family study. Cogn. Neuropsychiatry 18, 574–593.

Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN. Schedules for clinical assessment in neuropsychiatry. Arch. Gen. Psychiatry 47, 589–593.

Wortinger, L.A., Engen, K., Barth, C., Lonning, V., Jørgensen, K.N., Andreasen, O.A., Haukvik, U.K., Vaskinn, A., Ueland, T., Agartz, I., 2020. Obstetric complications and intelligence in patients on the schizophrenia-bipolar spectrum and healthy participants. Psychol. Med. 50, 1914–1922.

Yücel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M.J., Fornito, A., Wood, S.J., McGorry, P.D., Pantelis, C., 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr. Bull. 38, 316–330.

Zwicker, A., Denovan-Wright, E.M., Uher, R., 2018. Gene-environment interplay in the etiology of psychosis. Psychiat. Med. 48, 1925–1936.