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BRIEF REPORT

The relationship between genetic liability, childhood maltreatment, and IQ: findings from the EU-GEI multicentric case–control study

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Abstract
This study investigated if the association between childhood maltreatment and cognition among psychosis patients and community controls was partially accounted for by genetic liability for psychosis. Patients with first-episode psychosis ($N=755$) and unaffected controls ($N=1219$) from the EU-GEI study were assessed for childhood maltreatment, intelligence quotient (IQ), family history of psychosis (FH), and polygenic risk score for schizophrenia (SZ-PRS). Controlling for FH and SZ-PRS did not attenuate the association between childhood maltreatment and IQ in cases or controls. Findings suggest that these expressions of genetic liability cannot account for the lower levels of cognition found among adults maltreated in childhood.

Keywords Childhood adversity · Cognition · Family history of psychosis · First episode · Polygenic risk score · Psychosis

Introduction

Literature suggests that the association between childhood maltreatment (i.e., abuse and neglect) and later cognitive functioning might be weaker among people with psychosis compared with unaffected controls [1]. Indeed, in a previous study on the EU-GEI sample of patients with first-episode psychosis (FEP) and community controls, we found that the association between reported exposure to maltreatment in childhood and a lower Intelligence Quotient (IQ) in adulthood was weaker among patients than controls [2]. This difference might be due to the confounding effect of other risk factors associated with both childhood maltreatment and cognition that are more prevalent among people with psychosis than unaffected controls, such as genetic liability to psychotic disorders [3–7]. Moreover, among individuals with psychosis, the impact of environmental risk factors (such as maltreatment) on cognition might be reduced by a floor effect related to genetic liability and neurodevelopmental alterations [8, 9].

Only a few studies have explored the relationship between genetic liability, childhood maltreatment, and cognition among people experiencing psychosis. For instance, the NAPLS-3 study found that among youth at clinically high risk for psychosis, family history of psychosis (FH) was associated with both greater trauma exposure and lower IQ compared with no-FH [10]. Polygenic risk scores for schizophrenia (SZ-PRS) [11, 12] have been associated with lower IQ in the general population [9, 13–15], but the findings have not consistently been replicated among people with schizophrenia [16–18]. Although SZ-PRS has also shown a modest association with childhood maltreatment [19], to our knowledge no study has investigated the role of genetic liability for psychosis in the association between childhood maltreatment and cognition.

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Therefore, in this study, we aimed to investigate whether the association between childhood maltreatment (overall maltreatment, and abuse and neglect separately) and IQ could be partially accounted for by genetic liability (defined as either having FH or based on SZ-PRS). We hypothesised that genetic liability to psychosis would contribute to attenuating the association between reported exposure to maltreatment in childhood and lower IQ in adulthood among FEP patients but not among controls.

Methods

Participants and procedure

The EU-GEI study is a multi-centre case–control study carried out between May 2010 and April 2015 in five European countries and Brazil [20, 21]. The study was approved by the Internal Review Boards of the study centres and conducted according to International ethical standards.

People with FEP were individuals aged 18–64, living in the study catchment areas, who approached mental health services for the first time for a primary diagnosis of a psychotic disorder (ICD-10 diagnoses: F20–F33) during the study period. Community controls were individuals who were representative of the same population as the cases, and who had never been referred or treated for psychotic disorders. Information about inclusion and exclusion criteria, sampling methods, and diagnostic procedures, have been detailed elsewhere [21, 22] and are described in the Supplementary Materials.

Measures

Cognitive functioning was estimated from IQ, assessed using an abbreviated, psychometrically robust version of the Wechsler Adult Intelligence Scales (WAIS-III) [23–25].

Genetic liability was defined as: (a) family history of psychosis (FH) and (b) polygenic risk scores for schizophrenia (SZ-PRS). FH was defined as having a first-degree relative affected by a psychotic disorder and assessed using the Family Interview for Genetic Studies (FIGS) [26]. SZ-PRSs were calculated only on the sub-sample of European ancestry participants, using the genotype procedure, population stratification, and SZ-PRS calculation as described previously [27–29] and in the Supplementary Materials.

Self-reported exposure to childhood maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ) [30]. Mean ratings for physical, sexual, and emotional abuse items were used to create a childhood abuse score, mean ratings for physical and emotional neglect items were used to create a childhood neglect score, and the mean of all items was used to create an overall childhood maltreatment score. Consistent with previous studies [2, 8], these variables were dichotomised using the 80th percentile of the control group's score as the cut-off value. These cut-offs were identical to those used in the original study [2]. In the subset with SZ-PRS data, the empirically derived cut-off used to calculate dichotomic measures of childhood abuse (present/absent) was slightly lower than that used in the original study (1.33 vs. 1.40, respectively).

Analyses

General linear regression models stratified for cases and controls were conducted to explore whether the association between overall childhood maltreatment (and separately childhood abuse and childhood neglect) and IQ (model 1), was attenuated by the inclusion in the model of FH or SZ-PRS (model 2). The analyses were then additionally controlled for sex, age, ethnicity, education, study country, and lifetime cannabis use (model 3); and then also for current use of antipsychotics (model 4) only in the FEP group. Measurement of covariates is described in the Supplementary Materials. Results are reported as regression coefficients (B) and standardized regression coefficients (β). Analyses were run using the Statistical Package for the Social Sciences (SPSS) program version 27.0.

Results

Association between childhood maltreatment, FH, and IQ

Information about FH was available for 91.1% of the FEP cases ($n = 755$) and 95% of controls ($n = 1219$) from the original sample (see Supplementary Table 1 for sample demographics). Associations between case status and (i) childhood maltreatment and (ii) lower IQ are reported in Supplementary Table 2 and were similar to those detected in the full sample [2].

In the crude models, IQs were on average substantially lower among community controls exposed to childhood maltreatment ($B = -5.29$ [−7.86, −2.72], $p < 0.001$), childhood abuse ($B = -6.27$ [−8.89, −3.65], $p < 0.001$), and childhood neglect ($B = -5.16$ [−7.69, −2.63], $p < 0.001$), compared with unexposed controls. Among people with FEP, only childhood neglect was associated with lower IQ ($B = -2.90$ [−5.50, −0.29], $p = 0.029$) (see Table 1 & Supplementary Table 3)—and to a more modest extent than among controls.

FH was more prevalent among FEP cases than among controls (OR = 3.10 [2.23, 4.31], $p < 0.001$). FH was associated with childhood abuse in the control group (OR = 1.94 [1.09, 3.47], $p = 0.025$) and with childhood neglect in both groups (controls: OR = 1.88 [1.06, 3.32], $p = 0.030$; FEP:

Table 1 Association between childhood maltreatment and IQ controlled for family history of psychosis and social and clinical confounders

Unstandardized models	Model 1			Model 2			Model 3			Model 4		
	B	95% CI	*p*	B^{a}	95% CI	*p*	B^{a+b}	95% CI	*p*	B^{a+b+c}	95% CI	*p*
Controls	*N* = 1219			*N* = 1219			*N* = 1216					
Overall maltreatment*	**−5.29**	**−7.86, −2.72**	**< 0.001**	**−5.25**	**−7.82; −2.68**	**< 0.001**	**−2.30**	**−4.55; −0.54**	**0.045**			
Abuse	**−6.27**	**−8.89, −3.65**	**< 0.001**	**−6.22**	**−8.85; −3.60**	**< 0.001**	**−3.08**	**−5.36; −0.79**	**0.008**			
Neglect	**−5.16**	**−7.69, −2.63**	**< 0.001**	**−5.11**	**−7.65; −2.57**	**< 0.001**	**−2.67**	**−4.91; −0.44**	**0.019**			
FEP patients	*N* = 755			*N* = 755			*N* = 754			*N* = 705		
Overall maltreatment*	−2.17	−4.78, −0.45	0.104	−2.09	−4.71; 0.53	0.118	−0.41	−2.75; 1.92	0.729	−0.07	−2.50; 2.35	0.954
Abuse	−0.42	−2.70; 2.61	0.975	0.01	−2.65; 2.66	0.996	1.57	−0.78; 3.92	0.191	2.25	−0.20; 4.70	0.071
Neglect	**−2.90**	**−5.50, −0.29**	**0.029**	**−2.80**	**−5.42; −0.19**	**0.036**	−0.96	−3.28; 1.38	0.422	−0.63	−3.06; 1.80	0.613
Standardized models	Model 1			Model 2			Model 3			Model 4		
	Beta	95% CI	*p*	$Beta^{a}$	95% CI	*p*	$Beta^{a+b}$	95% CI	*p*	$Beta^{a+b+c}$	95% CI	*p*
Controls	*N* = 1219			*N* = 1219			*N* = 1216					
Overall maltreatment*	**−0.30**	**−0.44; −0.15**	**< 0.001**	**−0.30**	**−0.44; −0.15**	**< 0.001**	**−0.13**	**−0.26; −0.00**	**0.045**			
Abuse	**−0.35**	**−0.50; −0.21**	**< 0.001**	**−0.35**	**−0.50; −0.20**	**< 0.001**	**−0.17**	**−0.30; −0.04**	**0.008**			
Neglect	**−0.29**	**−0.43; −0.15**	**< 0.001**	**−0.29**	**−0.43; −0.15**	**< 0.001**	**−0.15**	**−0.28; −0.03**	**0.019**			
FEP patients	*N* = 755			*N* = 755			*N* = 754			*N* = 705		
Overall maltreatment*	−0.12	−0.26; 0.03	0.104	−0.12	−0.26; 0.03	0.118	−0.02	−0.15; 0.11	0.729	−0.00	−0.14; 0.13	0.954
Abuse	−0.00	−0.15; 0.15	0.975	−0.00	−0.15; 0.15	0.996	0.09	−0.04; 0.22	0.191	0.13	−0.01; 0.26	0.071
Neglect	**−0.16**	**−0.30; −0.02**	**0.029**	**−0.16**	**−0.30; −0.01**	**0.036**	−0.05	−0.18; 08	0.422	−0.04	−0.17; 0.10	0.613

CI confidence intervals, *FEP* first-episode psychosis, *IQ* intelligence quotient

[a]Adjusted for family history of psychosis

[b]Adjusted for sex, age, ethnicity, education, study country, and lifetime cannabis use

[c]Adjusted for antipsychotic treatment

*Exposure to overall childhood maltreatment, and separately childhood abuse, and childhood neglect were defined as mean CTQ > 80th percentile of the control group; significant associations ($p < 0.05$) are shown in bold type

OR = 1.54 [1.02, 2.33], $p = 0.039$). FH was not strongly associated with IQ in either group (controls: $B = -1.95$ [−6.52, 2.62], $p = 0.403$; FEP: B = −2.10 [−5.81, 1.62], $p = 0.269$) (see Supplementary Table 3). Multivariable analyses suggested that including FH in the model did not attenuate the association between childhood maltreatment and IQ in cases or in controls (see Table 1).

Association between childhood maltreatment, SZ-PRS, and IQ

Eight-hundred and fifty community controls and 488 FEP patients (i.e., 66.2% and 58.9% of the original sample, respectively) had complete measures of childhood maltreatment, IQ, and SZ-PRS (see Supplementary Table 4 for sample demographics).

In the control group, a 4–5-point decrease in IQ was associated with childhood maltreatment ($B = -5.11$ [−8.12, −2.10], $p < 0.001$), abuse ($B = -4.27$ [−7.12, −1.41], $p = 0.003$), and neglect ($B = -5.18$ [−8.09, −2.28], $p < 0.001$). In the FEP group, the association between childhood maltreatment ($B = -1.86$ [−5.10, 1.39], $p = 0.261$), abuse ($B = -0.51$ [−3.75, 2.73], $p = 0.757$), neglect ($B = -2.13$ [−5.34; 1.09], $p = 0.194$), and IQ were of a similar size to those detected in the analyses of the full sample, although failed to reach significance.

SZ-PRS were higher in FEP cases than in controls ($B = 0.54$ [0.43, 0.65], $p < 0.001$). In the case group, SZ-PRS was modestly associated with childhood maltreatment (OR = 1.32 [1.03, 1.68], $p = 0.027$) and with childhood neglect (OR = 1.26 [0.99, 1.60], $p = 0.060$). However, in the control group, no associations were found (SZ-PRS and childhood maltreatment OR = 1.00 [0.78, 1.27], $p = 0.970$; abuse OR = 1.00 [0.79, 1.26], $p = 0.974$; neglect OR = 0.98 [0.77, 1.25], $p = 0.890$).

In the control group, higher SZ-PRS was marginally associated with lower IQ ($B = -1.42$ [−2.93, 0.92], $p = 0.066$), as well as in the case group ($p = 0.180$). Multivariable analyses suggest that including SZ-PRS did not reduce the childhood maltreatment-IQ association in either the case or control group (see Supplementary Table 5).

Discussion

This study found that although FH and SZ-PRS were associated with a greater likelihood of reporting childhood maltreatment (indicating a potential gene-environment correlation), they were not so strongly associated with IQ, and did not attenuate the crude association between childhood maltreatment and IQ in either FEP cases or unaffected controls. These findings are consistent with previous studies suggesting that, although FH is three-to-seven times more common among patients compared to controls [31, 32], its effect on psychosis risk seems relatively independent from the effect of childhood maltreatment, and vice versa [33, 34].

In the subset of European ancestry participants with complete information about childhood maltreatment, IQ, and SZ-PRS, there was evidence of an association between childhood maltreatment and poor cognition, which failed to reach statistical significance among FEP cases. This is different from our previous analysis of this dataset [2] and might be due either to insufficient power, or to the exclusion of non-European ancestry FEP patients (i.e., potentially the relationship between childhood maltreatment and IQ might be more evident among non-European ancestry FEP patients), or to both. Among both cases and controls, SZ-PRS was weakly associated with IQ and did not attenuate the crude association between childhood maltreatment and IQ. This suggests that childhood maltreatment and genetic liability for schizophrenia may be independently associated with poor cognitive functioning.

In conclusion, our findings suggest that two measures of genetic liability for psychosis (FH and SZ-PRS) cannot account for the lower levels of cognition found among adults maltreated in childhood. Future research should use large longitudinal studies to prospectively investigate the impact of genetic liability and childhood maltreatment on different stages of cognitive development. Presently, the reason why the association between childhood adversity and cognition in patients with a psychotic disorder is weaker than in controls remains to be elucidated.

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Declarations

Conflict of interest Prof. Morgan is the Editor-in-Chief of this journal. Dr. Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Dr. 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. The other authors have declared that there are no conflicts of interest in relation to the subject of this study.

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