Epidemiology and Psychiatric Sciences (2012), **21**, 347–351. © Cambridge University Press 2012
doi:10.1017/S2045796012000418

This Section of *Epidemiology and Psychiatric Sciences* regularly appears in each issue of the Journal to describe relevant studies investigating the relationship between neurobiology and psychosocial psychiatry in major psychoses. The aim of these Editorials is to provide a better understanding of the neural basis of psycho pathology and clinical features of these disorders, in order to raise new perspectives in every-day clinical practice.

Paolo Brambilla, *Section Editor* and Michele Tansella, *Editor* EPS

G × E interaction and neurodevelopment I. Focus on maltreatment

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In a short series of articles, we will review the evidence for genotype by environment interaction (G × E) in developmental psychopathology. We will focus specifically on the characteristics of types of exposure assessed with respect to both their methods and findings. This article aims to review the studies exploring the effects of child maltreatment on children, adolescents and young adults closer in time to maltreatment experience, in a G × E perspective.

Received 6 June 2012; Revised 8 June 2012; Accepted 9 June 2012; First published online 30 July 2012

Key words: Child abuse, genetics, maltreatment, psychopathology.

Child maltreatment consists of any acts of commission or omission by a parent or other caregiver that result in harm, potential for harm to a child (0–18 years of age) even if the harm is unintentional (Gilbert *et al.* 2009), and that can take the form of neglect, emotional maltreatment, physical abuse or sexual abuse (Barnett *et al.* 1993). Many studies underline a strong association between child maltreatment and its immediate and long-term psychopathological consequences (Wolfe *et al.* 2001; Bot *et al.* 2011); however, clinical evidence points out that not all subjects exposed to maltreatment will develop psychopathological symptoms; the variability in children's responses suggest that this heterogeneity may be within the sphere of genetic influence (Moffitt *et al.* 2006). Caspi *et al.* (2002) (Table 1) were the first to report on a G × E interaction in child maltreatment. They studied a large sample of male children from birth to adulthood and found that a functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) moderates the effect of maltreatment: individuals who were carriers of the low-activity allele, but not of the high-activity allele, were at an increased risk of antisocial behaviour disorders following maltreatment. After this work many researchers have adopted a multiple level of analysis over the course of the past few decades (Cicchetti & Blender, 2004). Recently, Fergusson *et al.* (2011) (Table 1) have replicated this result using a 30-year longitudinal study with a sample composed by male subjects, considering only physical and sexual abuse. Furthermore, Derringer *et al.* (2010) (Table 1) have extended the moderating role of MAOA to conduct disorder symptoms in a sample of same-sex twins for

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Table 1. *Summary of the studies described in this review*

Study	Sample	Age range (years)	Type of study	Genetic variant	Assessment and diagnostic	Findings
Caspi *et al.* (2002)	442 male subjects 154 maltreated 288 non-maltreated	3–26	Longitudinal (23 years), case-control	MAOA	• Psychological assessment • Interview about victimization and sexual abuse • Behavioural observations • Checklist on harsh discipline • Court records of violent convictions • MPQ – Aggression Scale • Report on antisocial personality by a knower	Maltreated children with high-activity MAOA were less likely to develop antisocial problems.
Kaufman *et al.* (2006)	196 subjects 109 maltreated 87 non-maltreated	5–15 9.3 mean age	Cross-sectional, case-control	BDNF	• Caseworkers, parents, children, and Department of Children and Family Services case records • Parent- and child-report questionnaires on depression • K-SADS-PL • CBCL • MFQ • ASSIS	Significant G × G × E interaction between BDNF, 5-HTTLPR and maltreatment history in predicting depression.
Cicchetti *et al.* (2007)	339 subjects 207 maltreated 132 non-maltreated	16.7 mean age	Cross-sectional, case-control	MAOA 5-HTTLPR	• MCS • DISC • YSR • A-COPE	Heightened depressive symptoms were found among extensively maltreated youth with low MAOA activity. Significant G × G × E interaction between MAOA, 5-HTTLPR and sexual abuse in predicting depression, anxiety and somatic symptoms.
Derringer *et al.* (2010)	841 subjects 158 maltreated 683 non-maltreated	11–25	Longitudinal (14 years), case-control	MAOA	• CIDI • DICA-R • Structured interview on antisocial behaviour and conduct disorder • Retrospective self-report on harsh discipline and childhood sexual assault	Childhood sexual assault interacts with MAOA genotype to predict antisocial behaviour and conduct disorder symptoms.
Li & Lee (2010)	2488 subjects 876 maltreated 1612 non-maltreated	12–20 15.6 mean age	Longitudinal (5 years), case-control	5-HTTLPR	• Interview on antisocial behaviour • Interview on maltreatment	5-HTTLPR moderates the relationship between maltreatment and antisocial behaviour in female subjects.

Alemany *et al.* (2011)	533 subjects 308 maltreated 225 non-maltreated	22.9 mean age	Cross-sectional, case-control	BDNF	• CAPE • CTQ • SPQ-B • STAI-T	The association between child abuse and positive dimension of psychotic-like experiences is moderated by the BDNF.
Aslund *et al.* (2011)	1825 subjects 402 maltreated 1423 non-maltreated	17–18	Cross-sectional, case-control	MAOA	• Questionnaire on maltreatment/ abuse • Questionnaire on delinquency	Boys with a short variant and girls with one or two long variants of the MAOA showed a higher risk for delinquency when exposed to maltreatment.
Cicchetti *et al.* (2011)	493 subjects 238 maltreated 255 non-maltreated	7–13 10.08 mean age	Cross-sectional, case-control	5-HTTLPR CRHR1	• CDI • TRF • MCS	Significant G × G × E interaction between CRHR1, 5-HTTLPR and child maltreatment in internalizing symptoms.
De Young *et al.* (2011)	614 subjects 339 maltreated 275 non-maltreated	8–13 11.3 mean age	Cross-sectional, case-control	CRHR1	• Department of Human Services records • MMCI • MCS • CCQ • TDA	The effects of specific types of maltreatment on neuroticism are differentially moderated by CRHR1 genotype, as are the effects of experiencing more or fewer types of maltreatment.
Fergusson *et al.* (2011)	398 male subjects 89 maltreated 309 non-maltreated	16–30	Longitudinal (25–30 years), case-control	MAOA	• Retrospective reports in child sexual and physical abuse • CTS	Stable G × E interaction involving MAOA, sexual/physical abuse exposure and antisocial behaviour across the life course.
Nilsson *et al.* (2011)	1586 subjects 246 maltreated 1340 non-maltreated	17–18	Cross-sectional, case-control	MAOA	• Questionnaire on family relationship • Questionnaire on sexual abuse • AUDIT-C	MAOA moderates the relationship between sexual abuse and alcohol consumption with sex difference in this G × E interaction.

A-COPE, Adolescent Coping Orientation for Problem Experiences; ASSIS, Arizona Social Support Interview Schedule; AUDIT-C, Alcohol consumption alcohol use disorder identification test; CAPE, Community Assessment of Psychic Experiences; CBCL, Child Behaviour Checklist; CCQ, California Child Q-sort; CDI, Children's Depression Inventory; CTQ, Child Trauma Questionnaire; CTS, Conflict Tactics Scale; DISC, Diagnostic Interview Schedule for Children; CIDI, Composite International Diagnostic Interview; DICA-R, Diagnostic Interview for Children and Adolescents-Revised; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School Aged Children; MCS, Maltreatment Classification System; MFQ, Mood and Feelings Questionnaire; MMCI, Maternal Maltreatment Classification Interview; MPQ, Multidimensional Personality Questionnaire; SPQ-B, Schizotypy Personality Questionnaire-Brief; STAI-T, State–Trait Anxiety Inventory; TDA, trait descriptive adjectives; TRF, Teacher Report Form; YSR, Youth Self Report.

sexually abused subjects. Similar results were found by Aslund *et al.* (2011) and Nilsson *et al.* (2011) (Table 1) examining, respectively, delinquent behaviour and high alcohol consumption. MAOA polymorphism was also found to enhance depressive symptoms but only among extensively maltreated youth (i.e. three or four maltreatment subtypes) (Cicchetti *et al.* 2007). Subsequent studies on G × E interaction in child maltreatment have focused their attention on several other genetic factors, such as serotonin-transporter-linked polymorphic region (5-HTTLPR), corticotropin releasing hormone receptor 1 (CRHR1) and brain-derived neurotrophic factor (BDNF). 5-HTTLPR polymorphisms were found to moderate the effect of maltreatment both on externalizing and internalizing symptoms. In a longitudinal study, an interaction between maltreatment and 5-HTTLPR on antisocial behaviour was found but only in girls (Li & Lee, 2010). A moderating role of 5-HTTLPR polymorphism in predicting higher depression, anxiety and somatic symptoms was also confirmed (Cicchetti *et al.* 2007, 2011), but only in interaction with sexual abuse. This relation was further moderated by MAOA activity level suggesting a three-way interaction [G × G × E].

An effect of the interaction between CRHR1 and maltreatment and early abuse on diurnal cortisol regulation was reported by Cicchetti *et al.* (2011): CRHR1 variations were related to cortisol dysregulation only among maltreated children, thus suggesting an allostatic load perspective on the effects of the chronic stress associated with child maltreatment on cortisol regulation and internalizing symptomatology as moderated by genetic variation.

The role of the hypothalamic–pituitary–adrenal (HPA) axis, the major biological system for stress response, was also investigated by De Young *et al.* (2011) (Table 1), which demonstrated that CRHR1 haplotype moderated the effects of maltreatment on neuroticism, during childhood. The effect of this haplotype on neuroticism was dependent not only on the presence of maltreatment but also on the most severe type of maltreatment and number of types of maltreatment.

The BDNF was found to significantly predict youth depression in a three-way interaction with 5-HTTLPR and maltreatment history (Kaufman *et al.* 2006), and to significantly moderate the association between childhood abuse and positive dimension of psychotic-like experiences (Alemany *et al.* 2011).

In conclusion, reported researches suggest that child maltreatment (especially physical and sexual abuse and extensive maltreatment) is a useful environmental candidate to investigate the effect of G × E interaction on the development of both developmental psychopathology and resilience. Nevertheless, considering the high variability of reported results we point out the need for future research to give greater attention to measurement and operationalization of child maltreatment, including frequency and duration, period of occurrence (developmental stage and distance from outcome) and, particularly, association with other risk or protective factors such as social context or gender. Future research should also broaden the emerging evidence that child maltreatment in interaction with specific genetic haplotypes induce significant biological changes in children (biological embedding), modifying the maturation and the operating balance of allostatic system, i.e. the biological systems responsible for maintaining physiological stability through environmental changes (Cicchetti *et al.* 2011).

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