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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 psychopathology and clinical features of these disorders, in order to raise new perspectives in every-day clinical practice.

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Genotype by environment interaction and neurodevelopment III. Focus on the child's broader social ecology

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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 the child's broader social ecology on child and adolescent internalizing and externalizing psychopathology, based on a G × E perspective.

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Child social environment, according to social epidemiological studies, typically refers to shared features of child's social ecology, over and above individual-level exposure. Social environmental factors may include urbanicity, neighbourhood socio-economic status (e.g. income distribution, levels of unemployment), residential segregation, levels of crime, local building condition or the amount of public parks etc. in an urban context, but it may also include neighbourhood social cohesion, availability of a social support network or of mental health services (Gayer-Anderson & Morgan, 2013).

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Recently, genotype by environment interaction (G × E) studies have moved their focus towards those features of social environment that could moderate the effects of genetic factors on mental disorders both in youths and in adults (Table 1).

Twin studies have suggested that the heritability of many phenotypes is modified by social environmental characteristics. That is, genetic influences on a phenotype become attenuated whenever external factors limit personal choice (e.g. the social constraint which once limited the use of tobacco in women) or provide so much of a 'social push' encouraging problematic behaviour that the importance of genetic factors diminish (Raine, 2002). For example, in boys, the heritability of adolescent antisocial behaviour has been shown to vary by social context, being higher in a socio-economically advantaged environment where the social risk factors that push or predispose an adolescent to

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

Study	Sample	Age range (years)	Type of study	Genetic variant	Assessment and diagnostic	Findings
Button *et al.* (2007)	1111 twin pairs 553 MZ 558 DZ	11–18 15.24 mean age	Twin study		• DISC-IV • EDPM	Delinquent peer affiliation was influenced by genetic, shared environmental and non-shared environmental factors; genetic factors contributed to the correlation between delinquent peer affiliations and conduct problems.
Kaufman *et al.* (2004)	101 subjects 57 maltreated 44 non-maltreated	5–15 10 mean age	Case-control	5-HTTLPR	• Information on maltreatment • ASSIS • MFQ • Parent- and child-report questionnaire for psychiatric diagnoses • K-SADS-PL	The depression scores of maltreated children with the s/s genotype and low supports were two times higher than the depression scores of controls with the same genotype and social support profile.
Kaufman *et al.* (2006)	196 subjects 109 maltreated 87 non-maltreated	5–15 9.3 mean age	Case-control	BDNF 5-HTTLPR	• Information on maltreatment • ASSIS • MFQ • Parent- and child-report questionnaire for psychiatric diagnoses • K-SADS-PL	Significant four-way interaction. Having both the met alleles of the BDNF polymorphism and two 's' alleles of 5-HTTLPR was associated with the highest depression scores in maltreated children. The quality of the child relationship with primary social support moderated risk for depressive symptomatology in maltreated children with the most vulnerable genotype.
Latendresse *et al.* (2011)	378 subjects population-based sample	12–22	Longitudinal (17 years)	CHRM2	• YSR • YASR • CBCL • TFR • Peer group antisocial behaviour as referred by subjects	Relative to a normative 'lower risk' externalizing trajectory, likelihood of membership in two 'higher risk' trajectories increased with each additional copy of the minor allelic variant at CHRM2, and this association was exacerbated among those exposed to higher levels of peer group antisocial behaviour.
Legrand *et al.* (2008)	608 same-sex twin pairs	16.55–18.52 17.47 mean age	Twin study		• Urban–rural classification coded by US 2000 census Rural–Urban Commuting Area (RUCA) system • DICA-R • CIDI	In male sample, for externalizing behaviour, constraining the genetic and shared environmental variance to be equal across urban–rural residency resulted in a significant decrement of fit. Genetic influences were greater in urban environments while shared environmental influences were more pronounced in rural settings.

Sjöberg *et al.* (2006)	200 population-based sample 119 females 81 males	16–19	Cross-sectional	5-HTTLPR	• Index of psychosocial risk • DSRS	5-HTTLPR genotype interacted significantly with the psychosocial risk index in relation to depression in the total sample. The genotype significantly interacted with the type of residence (for boys) and with the psychosocial risk index (for girls) in relation to depression.
Tuvblad *et al.* (2006)	1133 twin pairs	16–17	Twin study		• Questionnaire on antisocial behaviour • SEI • Data on neighbourhood socio-economic conditions	Genetic influences on antisocial behaviour were more important in adolescents in socio-economically more advantaged environments, whereas the shared environment was higher in adolescents in socio-economically less advantaged environments.
Uddin *et al.* (2010)	1084 subjects population based sample 560 females 524 males	12–20	Longitudinal (8 years)	5-HTTLPR	• CES-D, 17-item version • Public assistance (PA) as a measure of county-level deprivation and assessed using US Census data from 1990 • Questions on subjects' perceived value and support from family members, friends and teachers	Males with the *sl* genotype living in counties with high PA were protected against higher depressive symptom scores. No significant interaction effects were observed among females.
Uddin *et al.* (2011)	795 subjects population-based sample	12–20	Longitudinal (8 years)	5-HTTLPR	• CESD, 17-item version • Questions on subjects' perceived value and support from family members, friends and teachers • Questions on building upkeep as a measure of social environment	No significant gene–social environment interactions were detected for either gender, considering both the respondent-level building conditions and the neighbourhood-level building conditions.

ASSIS, Arizona Social Support Interview Schedule; CBCL, Child Behavior Checklist; CESD, Center for Epidemiological Studies Depression Scale; CIDI, Composite International Diagnostic Interview; DICA-R, Diagnostic Interview for Children and Adolescents – Revised; DISC-IV, Diagnostic Interview Schedule for Children-IV; DSRS, Depression Self-Rating Scale; EDPM, Exposure to Delinquent Peers Measure; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School Aged Children; MFQ, Mood and Feelings Questionnaire; SEI, Socio Economic Index; TRF, Teacher Report Form; YASR, Young Adult Self-Report; YSR, Youth Self-Report.

behave antisocially are lacking (Tuvblad *et al.* 2006). Similarly, the heritability of adolescent substance use and rule-breaking behaviour turned out to be higher in urban environments than in rural environments (Legrand *et al.* 2008). Contrarily, according to the stress-diathesis model, genetic vulnerabilities should increase in the presence of adversities, e.g. affiliation with delinquent peers has been shown to moderate genetic influences on adolescent conduct problems, with genetic effects accounting for more of the variance in problem behaviour when individuals were exposed to higher levels of peer antisocial behaviour (Button *et al.* 2007).

Even though it is not currently clear how broader social environment and genes interact to produce complex behaviour (constraining/eliciting *v.* diathesis/stress) on the basis of this evidence, measured genotype–phenotype association studies recently moved their attention towards the effect of the broader social environment in children and adolescents too.

In 2004, Kaufman and co-workers, for the first time, examined social support indices together with genetic factors in predicting depression in maltreated children. This study demonstrated that risk for depression associated with the short (S) allele of the serotonin transporter polymorphism (5-HTTLPR) and stressful life events was moderated by social support quality and availability. These results were confirmed in a later study (Kaufman *et al.* 2006) that revealed a gene by gene interaction between brain-derived neurotrophic factor (BDNF) and 5-HTTLPR, and a moderating role of positive social environmental factors. These data suggested that the negative sequelae associated with early stress are not inevitable. Risk for negative outcomes may be modified by both genetic and environmental factors, with the quality and availability of social supports among the most important environmental factors in promoting resilience, even in the presence of genotypes otherwise expected to predispose to mental illness.

Subsequently, Sjöberg *et al.* (2006) reported a gender-modulation on the interaction between psychosocial background variables and 5-HTTLPR. Males and females carrying the S allele of the 5-HTTLPR responded to different environmental factors. Whereas males were negatively affected by living in public housing rather than in their own owned homes and by living with separated parents, females were affected by traumatic conflicts within the family. Furthermore, the responses of males and females carrying the short 5-HTTLPR allele to environmental stress factors went in opposite directions; whereas females tended to develop depressive symptoms, males seemed to be protected from depression.

Further evidence, that G × E interactions between 5-HTTLPR and broader social environment could influence risk for depressive symptoms and that this effect is modified by gender, was reported by Uddin *et al.* (2010). In males, county-level environments modified the association between 5-HTTLPR genotype and depressive symptoms across a one-year period, even when controlling for potential family-level confounders. No G × E associations were detected in adolescent females. County-level deprivation, assessed as the proportion of households receiving public assistance, turned out to be a reliable and specific environmental risk factor as in a further study on the same sample, using building maintenance level as a measure of exposure to poor social environment, no evidence of G × E effect was found (Uddin *et al.* 2011).

It is worth noting that the G × E effect involving broader social environment was mainly detected among males in contrast to previous reports (for a review see Bellani *et al.* 2013), which suggested a preponderance of G × E interactions among adolescent females when the environmental risk is measured as stressful life events. More generally, these results suggest that among adolescents, macro-social context may have differential effects by gender, such that adolescent males are more susceptible to contextual effects than their female counterparts.

One possible explanation is that the variables that affect males are associated with social status, while those affecting females are more associated with human relationships. However, the results could reflect a true difference between the sexes, which in turn might reflect a difference in the interaction between the 5-HTTLPR polymorphism and, for example, gonadal and/or adrenocortical hormones.

Finally, moderation by the broader social environment, assessed as exposure to antisocial behaviour within adolescents' peer groups, was evaluated for the association between CHRM2, a gene encoding the muscarinic acethylcoline receptor M2 and implicated in neurocognitive process such as disinhibition on the one hand, and externalizing trajectories on the other in a population-based follow-up study (Latendresse *et al.* 2011). Findings suggested that CHRM2 was associated with altered developmental patterns of externalizing behaviour from early adolescence through to young adulthood, and that this association was exacerbated among those exposed to higher levels of peer group antisocial behaviour.

In conclusion, the data emerging from this novel field of G × E investigation suggest the importance of including macro-social environmental features in future research in population-based representative samples. Even though the relative risk of disease conferred by the social environment is lower than that conferred by individual-level risk factors, the pervasiveness of exposure to broader social variables suggests that their role in determining the risk of

externalizing or internalizing behaviour at population level will be considerable. Furthermore, macro-social variables could play the role of potential confounders in G × E studies which limit environmental measures to individual-level features. Much more work is needed to replicate or refute the findings reported here and to understand the mechanisms underlying these observations (Sündermann *et al.* 2013).

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