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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 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 II. Focus on adversities in paediatric depression: the moderating role of serotonin transporter

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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 moderating role of serotonin transporter on the effect of environmental adversities over time, particularly during childhood and adolescence, which is when level of internalizing symptoms and prevalence of mood disorders change substantially. Environmental adversities will not include abuse and maltreatment that have been reviewed before (see Bellani *et al.* 2012) and child's broader social ecology that will be reviewed in the next section.

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A clear empirical link exists between stress and depression in children and adolescents (Vitiello, 2011), where 'stress' refers to environmental adversities that pose challenge for children's development. Stress may occur either as an acute event or a chronic adversity, and as a major life event or as minor accumulated events. Stressful events may be normative (e.g. school transition) or pathological (e.g. being bullied), and may be dependent on, or independent of, an individual's attitude. Nevertheless, individuals vary in their response to stress, and how they respond can affect their future adjusting and emotional well-being. Such response heterogeneity is associated with pre-existing individual differences in temperament, personality, cognition and autonomic physiology, all of which are known to be under genetic influences (Plomin, 2001). In recent years, G × E interaction involving specific gene polymorphisms has been identified both in animals and humans. In these studies, particular focus has been placed on the interaction of a deletion/insertion polymorphism in serotonin transporter gene-linked polymorphic region (5-HTTLPR). The short ("*S*") allele in the 5-HTTLPR is associated with lower transcriptional efficiency of the promoter compared with the long ("*L*") allele *in vitro* (Lesch *et al.* 1996) and *in vivo*, both in adults and in children and adolescents (Nobile *et al.* 1999). In 2003, Caspi *et al.* (Table 1), using a prospective

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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.* (2003)	847 population-based sample	3–26	Longitudinal study (23 years)	5-HTTLPR	• LHC • DIS • Questionnaire on symptoms of depression	5-HTTLPR gene interacts with life events to predict increase in depression symptoms, depression diagnoses, new-onset diagnoses, suicidality, and informant's report of depressed behaviour.
Chipman *et al.* (2007)	PATH20 sample: 2.095 population-based sample ATP sample: 584 population-based sample	PATH20: 20–24 ATP sample: 15–18	PATH20: community survey ATP: Longitudinal study (2 years)	5-HTTLPR	• GADS • BIS/BAS • EPQ • List of stressful life events experienced over the 6 months preceding interview • List of childhood adversity up to the age of 16 years • SMFQ • Index of family adversity	Significant G × E interaction between 5-HTTLPR and persistently high levels of family adversity over a 6-year period in predicting emotional problems. Non-significant findings for G × E interactions between the 5-HTTLPR genotype and recent stressful life events on depression.
Laucht *et al.* (2009)	309 subjects	0–19	Epidemiological cohort study Longitudinal study (19 years)	5-HTTLPR L_AL_G 5-HTTLPR	• SCID • BDI • TCI • Parent interview on family adversity • MEL	Individuals with the LL genotype of 5-HTTLPR who were exposed to high family adversity displayed higher rates of depressive or anxiety disorders and had more depressive symptoms than those without either condition. No evidence for G × E with regard to current stressful life events and trait anxiety.
Gibb *et al.* (2009*a*)	74 mother–child pairs 40 depressed mother 34 non-depressed mother	8–12 9.96 mean age	Longitudinal (6 months)	5-HTTLPR L_AL_G	• SADS-L • K-SADS-PL • BDI-II • CDI • Modified dot-probe task	Evidence for a three-way interaction predicting children's depressive symptoms: the relation between mother and child depressive symptom levels over time was strongest among children carrying the 5-HTTLR S or L_G allele who also exhibited attentional avoidance of sad faces.

Gibb *et al.* (2009*b*)	100 mother–child pairs 52 depressed mother 48 non-depressed mother	8–12 9.97 mean age	Longitudinal (6 months)	5-HTTLPR L_AL_G	• SADS-L • K-SADS-PL • BDI-II • CDI • FMSS • CASQ • CCSQ	Among children with negative inferential styles, 5-HTTLPR genotype moderates the relation between maternal criticism and children's depressive symptoms, with the highest depressive symptoms among children carrying two copies of the 5-HTTLPR lower expressing alleles (S or L_G) who also exhibited negative inferential styles and experienced high levels of criticism.
Hammen *et al.* (2010)	346 population-based sample	15–25 23.7 mean age	Longitudinal (10 years)	5-HTTLPR 5-HTTLPR L_AL_G	• SCID • BDI-II • Semi-structured life stress interview • Interview on quality of marital and parental functioning • UCLA-CSI • DAS • MCTS • CRPBI	Chronic family stress (family discord) at age 15 interacts with 5-HTTLPR genotype to predict higher depression scores at 20 only for females. Gene–environment interactions with acute stress were non-significant.
Kumsta *et al.* (2010)	125 adopted subjects 51 institutional deprivation 74 controls	0–15	Longitudinal (15 years)	5-HTTLPR 5-HTTLPR L_AL_G	• RRS • SDQ • CAPA • LES	Significant G × E interaction between 5-HTTLPR and severe institutional deprivation in predicting emotional problems. Furthermore, s/s carriers in the severe ID group who experienced a high number of stressful life events between 11 and 15 years had the largest increases in emotional problem scores. In supplementary analyses with 5-HTTLPR L_AL_G genotype interactions were not significant.

Continued

Table 1. *Continued*

Study	Sample	Age range (years)	Type of study	Genetic variant	Assessment and diagnostic	Findings
Fergusson *et al.* (2011)	893 population-based sample	0–30	Longitudinal (30 years)	5-HTTLPR	• Retrospective reports on childhood sexual abuse, childhood physical abuse and inter-parental violence • Prospectively data on changes of family situation • Avoidance of Restriction and punishment subscale of the HOME Inventory • Life-event checklist • Reports on prolonged unemployment • Questioning on welfare dependence • ELSI • CTS • Report on abortion/unwanted pregnancy • CIDI	No evidence to support the hypothesis that 's' alleles of 5-HTTLPR are associated with increased responsivity to life stressors.
Hankin *et al.* (2011)	220 population-based sample	9–15 11.4 mean age	Longitudinal (1 year)	5-HTTLPR 5-HTTLPR L_AL_G	• CDI • MASC • ALEQ	Significant G × E interaction between 5-HTTLPR and idiographic stressors (but not nomothetic stressor) in predicting prospective elevations in depressive, but not anxious, symptoms.
Jenness *et al.* (2011)	200 population-based sample	7–16 12.09 mean age	Longitudinal (6 months)	5-HTTLPR 5-HTTLPR L_AL_G	• CDI • CSI • LSI • PDS	Chronic family stress, but not recent episodic stressors, predicted prospective elevations in depressive symptoms among youth who possessed the 's' allele of 5-HTTPLPR gene.

Petersen *et al.* (2012)	574 subjects population-based sample	12–17	Longitudinal (5 years)	5-HTTLPR L_AL_G 5-HTTLPR	• CBCL • YSR • DIS • CAQ	Adolescents with lower serotonin transcriptional efficiency (TE) genotypes and more stressful life events show more anxious/depressed symptoms and a greater increase in the development of symptoms of anxiety and depression than were higher TE adolescents, particularly at ages 16 and 17.
Nobile *et al.* (submitted for publication)	287 population-based sample	15–19 17.7 mean age	Longitudinal (5 years)	5-HTTLPR 5-HTTLPR L_AL_G	• CBCL • Socio-economic status • Family structure	A moderating role of 5-HTTLPR on the effect of family status in determining the presence of internalizing problems was found only during early adolescence. Early-adolescence internalizing problems strongly predict internalizing problems in late-adolescence, especially in S-allele carriers.

ALEQ, Adolescent Life Events Questionnaire; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BIS/BAS, Behavioral Inhibition System/Behavioral Activation System Scales; CAPA, Child and Adolescent Psychiatric Assessment Interview; CAQ, Changes and Adjustments Questionnaire; CASQ, Children's Attributional Style Questionnaire; CBCL, Child Behavior Checklist; CCSQ, Children's Cognitive Style Questionnaire; CDI, Children's Depression Inventory; CIDI, Composite International Diagnostic Interview; CRPBI, Children's Report of Parental Behavior Inventory; CSI, Chronic Stress Interview; CTS, Conflict Tactics Scale; DAS, Dyadic Adjustment Scale; DIS, Diagnostic Interview Schedule; ELSI, Economic Living Standards Index; EPQ, Eysenck Personality Questionnaire Revised; FMSS, Five Minute Speech Sample; GADS, Goldberg Depression and Anxiety Scales; HOME Inventory, Home Observation for Measurement of the Environment Inventory; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; LES, Life Event Scale; LHC, Life History Calendar; LSI, Life Stress Interview; MASC, Multidimensional Anxiety Scale for Children; MCTS, Modified Conflict Tactics Scale; MEL, Munich Events List; PDS, Pubertal Development Scale; RRS, Revised Rutter Scale; SADS-L, Schedule for Affective Disorders and Schizophrenia–Lifetime Version; SCID, Structured Clinical Interview for DSM-IV; SDQ, Strengths and Difficulties Questionnaire; SMFQ, Short Mood and Feelings Questionnaire; TCI, Temperament and Character Inventory; UCLA-CSI, UCLA Chronic Stress Interview; YSR, Youth Self-Report.

longitudinal design, reported that carriers of the S allele exhibit elevated depressive symptoms, diagnosable depression and suicidality after experiencing stressful life events and childhood maltreatment (Caspi *et al.* 2003). This generated evidence for validity of the construct of genetically driven individual differences in stress sensitivity. More recently, a new single nucleotide polymorphism (SNP) called rs25531 has been identified within the repeats of 5-HTTLPR: the L_G variant has a level of serotonin transporter expression comparable to the S allele, and both have lower levels than L_A variant (Hu *et al.* 2006). Even if the functional interpretation of the L_G allele has been questioned, some more recent studies used this classification.

Three meta-analyses (Munafo *et al.* 2009; Risch *et al.* 2009; Karg *et al.* 2011) and two consecutive reviews of Uher & McGuffin (2008, 2010), which include multiple age-ranges, assessing the moderating role of 5-HTTLPR on the relationship between depression and environmental adversities, have shown mixed results. Nevertheless, they were able to identify important study characteristics that influence study outcome, i.e., the stress assessment method and stressor type. The evidence of genetic moderation was stronger among studies that used objective measures (e.g. 'family structure') or interpersonal interviews, while it was attenuated by inaccuracies of retrospective self-report questionnaires. The actual duration of the stressor was another critical point: evidence of moderating effect was greater for chronic stressors. Furthermore, in most of these studies, although data have been collected longitudinally, the association between environmental exposure and outcome has been analyzed cross-sectionally. Therefore, even if time is a crucial factor, both in terms of window vulnerability, and in the cascade of maturational events that lead to the unfolding of depression, little is known about the impact of genetic risk factors and environmental exposure over time.

Only few G × E studies have been conducted with youths using rigorous methods, particularly a prospective design and contextual interview to assess both chronic and episodic stress and their prediction on longitudinal change in depressive symptoms, and only recently data have been analysed using time-sensitive techniques. Overall, most of these studies found some evidence supporting a G × E effects (see Table 1). Most studies confirmed the prominent role of chronic adversities (e.g. chronic family stress) *v.* episodic stressors (Gibb *et al.* 2009*a*, 2009*b*; Hammen *et al.* 2010; Jenness *et al.* 2011, Table 1), and also the possible interaction between early life chronic trauma and recent stressful life events (Kumsta *et al.* 2010), even if mixed results concerning the risk allele were found: two studies (Chipman *et al.* 2007; Laucht *et al.* 2009) reported that the S allele was associated with reduced risk. Only one study (Fergusson *et al.* 2011) did not find any evidence of G × E.

The recent use of time-sensitive analytic technique focused attention on other important issues according to developmental perspective. The first issue was the conceptualization and analysis of environmental stress in idiographic stressors (i.e., increases relative to the child's own average level over time) *v.* nomothetic stressors (i.e., higher stress exposure relative to the sample). In a community sample of youth aged 9–15 years assessed prospectively every 3 months over 1 year (5 waves of data), lagged hierarchical linear modelling analyses showed that 5-HTTLPR interacted with idiographic stressors, but not nomothetic stressors, to predict prospective elevations in depressive symptoms (Hankin *et al.* 2011). This study's findings suggest that 5-HTTLPR allelic variation may underlie individuals' stress reactivity to increases in one's typical exposure to stressors.

The second issue concerned the possibilities of different developmental trajectories of symptoms and of different time sensitivity to different environmental adversities. In the same way, also genes could encounter attenuation or potentiation of their effects during adolescence.

Petersen *et al.* (2012) (Table 1) tested the interaction between 5-HTTLPR and stressful life events on adolescents' trajectories of anxious/depressed symptoms in 574 adolescents followed from ages 12–17 years. They found an effect of G × E in predicting acceleration of anxious/depressed symptoms only at ages 16 and 17, not at the initial level age 12, growth at age 13, or acceleration at age 14 and 15, thus suggesting that vulnerability to acute life events may be stronger in late than early adolescents. In a 5-year follow-up study in general adolescent population sample Nobile *et al.* (submitted for publication) found a moderating role of 5-HTTLPR on the effect of family status in determining the presence of internalizing problems, but only during early adolescence, while during late-adolescence socioeconomic status seems to play a pivotal role, probably influencing the social conditions surrounding youth. Furthermore, 5-HTTLPR polymorphism was found to play an important role in determining the stability of this psychopathological trait: early-adolescence internalizing problems were revealed to be stronger predictors of internalizing problems in late-adolescence, especially in youths who carry the S-allele, thus confirming theory, that *5-HTTLPR* S-carriers are characterized by the stable trait of negative affectivity that is converted to psychopathology only under conditions of stress.

In conclusion, a life-course approach seems ideal for understanding determinants of developmental depression: causation in depression appears to be multifactorial, including interaction between genes and stressful life events, or between early life trauma and

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later stress in life; timing of onset and remission vary widely, indicating different trajectories of symptoms over time. A more 'dynamic' G × E perspective could be useful in study regarding transition period, including the use of different measures to assess stressful events in adolescence and the use of time-sensitive modelling techniques that are able to incorporate multiple interacting factors across time.

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