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Review

Probabilistic epigenesis: An alternative causal model for conduct disorders in children and adolescents[☆]

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ABSTRACT

Most models of conduct disorders are based on a biopsychosocial perspective. In such models, genetic and/or neuropsychological determinants are assumed to have a core hierarchical role by conferring vulnerabilities during a child's development. Based on a review of recent literature, I will show that other views are attempting to integrate the diversity and complexity of factors that influence these behavioural manifestations. The model that best integrates the complexity of these different factors is a developmental model of probabilistic epigenesis. In this paper, I summarise several lines of study that support this model. In addition to the categorical approach of psychiatric nosography, I will adopt a dimensional approach of phenomenology that will help to follow and focus on specific pertinent dimensions such as clinical signs, psychological characteristics, environmental and/or genetic factors in order to study their interactions and their possible developmental outcomes. This model also permits a specific temporal focus on early interactions that many authors consider crucial in terms of developmental cues.

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1. Introduction

Conduct disorders (CD) are the most common psychiatric diagnoses in the general population for both children and adolescents. They are also one of the most common reasons for

clinical referral (Kazdin, 2000). In international classifications, conduct disorders are part of larger group of externalizing disorders that include attention deficit hyperactivity disorder, or ADHD, and oppositional defiant disorder, or ODD (Table 1). The position of genetic or neuropsychological determinants have recently dominated the debates that concern the aetiopathological understanding of externalizing disorders, the archetypal model being the vulnerability model (e.g., Gorwood et al., 2007; Jans et al., 2007; Bakermans-Kranenburg and Van Ijzendoorn, 2007). The human genome project, however, has revealed that there are ~22,000 genes, as opposed to ~100,000 as previously thought. Even 100,000 genes, however, is insufficient to contain enough

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Table 1
DSM-IV-TR criteria for externalizing disorder in children and adolescents.

ADHD	Oppositional defiant disorder	Conduct disorder
<p>Six or more of the following symptoms of <i>inattention</i> have been present for <i>at least 6 months</i> to a point that is disruptive and inappropriate for developmental level: (1) Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities; (2) Often has trouble keeping attention on tasks or play activities; (3) Often does not seem to listen when spoken to directly; (4) Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace; (5) Often has trouble organizing activities; (6) Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time; (7) Often loses things needed for tasks and activities; (8) Is often easily distracted; (9) Is often forgetful in daily activities.</p> <p>OR</p> <p>Six or more of the following symptoms of <i>hyperactivity-impulsivity</i> have been present for <i>at least 6 months</i> to an extent that is disruptive and inappropriate for developmental level:</p> <p><i>Hyperactivity</i>: (1) Often fidgets with hands or feet or squirms in seat; (2) Often gets up from seat when remaining in seat is expected; (3) Often runs about or climbs when and where it is not appropriate; (4) Often has trouble playing or enjoying leisure activities quietly; (5) Is often "on the go" or often acts as if "driven by a motor"; (6) Often talks excessively.</p> <p><i>Impulsivity</i>: (1) Often blurts out answers before questions have been finished; (2) Often has trouble waiting one's turn; (3) Often interrupts or intrudes on others.</p> <p>Some symptoms were present <i>before age 7 years</i>. Some impairment is present in two or more settings with clear evidence of significant impairment.</p>	<p>A pattern of <i>negativistic, hostile, and defiant behaviour</i> lasting <i>at least 6 months</i>, during which four (or more) of the following are present: (1) often loses temper; (2) often argues with adults (3) often actively defies or refuses to comply with adults' requests or rules; (4) often deliberately annoys people; (5) often blames others for his or her mistakes or misbehaviour; (6) is often touchy or easily annoyed by others; (7) is often angry and resentful; (8) is often spiteful or vindictive.</p> <p>The disturbance in behaviour causes clinically significant impairment in social, academic, or occupational functioning.</p>	<p>A repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of three (or more) of the following criteria in <i>the past 12 months</i>, with at least one criterion present in the past 6 months: <i>Aggression to people and animals</i>: (1) often bullies people, threatens, or intimidates others; (2) often initiates physical fights; (3) has used a weapon that can cause serious physical harm to others; (4) has been physically cruel to people; (5) has been physically cruel to animals; (6) has stolen while confronting a victim; (7) has forced someone into sexual activity.</p> <p><i>Destruction of property</i>: (8) has deliberately engaged in fire setting with the intention of causing serious damage; (9) has deliberately destroyed others' property.</p> <p><i>Deceitfulness or theft</i>: (10) has broken into someone else's house, building, or car; (11) often lies to obtain goods or favours or to avoid obligations; (12) has stolen items of non-trivial value without confronting a victim.</p> <p><i>Serious violations of rules</i>: (13) often stays out at night despite parental prohibitions, beginning before age 13 years; (14) has run away from home overnight at least twice while living in parental or parental surrogate home (15) is often truant from school, beginning before age 13 years.</p>

information to organise a fully developed social mind (Panksepp, 2007). Externalizing behaviours, such as disturbances of social abilities, have indeed been associated with a great variety of risk factors (see below) that include non-neurobiological factors (Loeber et al., 2000; Farrington and Loeber, 2000). Furthermore, genetics is not the exclusive mode of inheritance in humans, as at least three other modes – epigenetic, behavioural and symbol-based – have been described (for a recent detailed review, see Jablonka and Lamb, 2007).

In an effort to present an integrated view, I will show that another model, one that attempts to integrate the diversity and complexity of factors that influence these behavioural manifestations, indeed exists. These factors include genetic, neuropsychological and hormonal factors, as well as environmental and developmental determinants. The developmental and environmental determinants vary greatly, as they include exposure to drugs and toxins as well as social and cultural factors. Moreover, they include traumatic life experiences, such as physical abuse (Cohen, 2008).

The model that best encompasses the complexity of these different factors is a developmental model of probabilistic epigenesis, which is a model of biological development that integrates bidirectional interactions between the different structures and determinants (Gottlieb, 2007). In short, this model assumes that neural structures (or other structures) start to operate before they are completely mature, and that this operation is derived either from intrinsic activity or from extrinsic interactions. The pre-activation of neural structures will play a significant role in the developmental process. The coordination of

functional influences and formative structures at the source of a factor and between several factors is not perfect, and a probabilistic element is therefore necessary for all developing human systems and their results (Gottlieb, 2007). When the result happens to be an externalizing disorder, this model allows us to involve every factor and the different determinants that are known, and to integrate how their bidirectional interactions lead to strengthening and/or cumulative effects (Breton, 1999).

I will present recent studies that support this model and will help in the understanding of the diversity of aetiopathogenic determinants of externalizing disorders. In addition to the categorical approach of psychiatric nosography, I will adopt a dimensional approach of phenomenology for this purpose. This will help to follow and focus on specific pertinent dimensions such as clinical signs, psychological characteristics, environmental and/or genetic factors in order to study their interactions and their possible developmental outcomes (Cohen, 2008). In particular, aggressiveness will be detailed as an example. I will also briefly review how genetic factors can influence human behaviours or phenotypes (Caspi and Moffitt, 2006), and how environmental factors contribute to externalizing disorders, including CD (Mealey, 1995). In addition, I will summarise animal models that focus on early life adversities, which will help in the understanding of how stress can impact development and behaviour (Denenberg, 2000). In contrast to what has been hypothesised in some theoretical models of genetic by environmental interactions focusing on genotype influence of the environment (e.g., Scarr and McCartney, 1983), these animal experimental models have shown that the environment can shape neural structure as well. I

will also recall some mathematical models of cellular network development that refer to this probabilistic or statistical dimension (Milgram and Atlan, 1983), focusing on the integrative view they offer to development and psychopathology and the recent confirmation of this mathematical model in the field of language learning (Saffran et al., 1996).

Finally, I will propose integration of all the aforementioned factors in a non-hierarchical developmental model of probabilistic epigenesis. Again, a key issue regarding probabilistic epigenesis (as opposed to the deterministic/vulnerability model) relies on the possibility to accept bidirectional interactions between all biopsychosocial levels (Gottlieb, 2007). This model also permits a specific temporal focus on early interactions that many authors consider crucial in terms of developmental cues (Cohen, 2008).

2. Clinical and developmental cues regarding externalizing disorders

Externalizing disorders in children include behavioural problems such as agitation, impulsiveness, aggressiveness and lack of obedience. International nosography places these symptoms into three different diagnoses. According to the DSM-IV-TR (Table 1), ADHD (or hyperkinetic disorder in the ICD-10) consists of lack of attentiveness coupled with hyperactivity and impulsiveness. ODD is a collection of negative and provocative behaviours, including being disobedient and hostile towards those in a position of authority. Conduct disorders consist of repetitive and persistent behaviours that go against the fundamental rights of others and the societal norms and rules (Marcelli and Cohen, 2009). Although anti-social personality is a diagnosis reserved for adults, it is considered to belong to the same spectrum of externalizing disorders.

Beyond their descriptive aspects, externalizing disorders require a developmental perspective in the expression and development of their diagnosis (Loeber et al., 2000). Certain disorders have age-dependent diagnostic criteria. Disorders such as ADHD and ODD occur in childhood, while CD usually occurs in pre-adolescence or adolescence (Loeber et al., 2000; Guile and Cohen, 2008). Studies have shown that, contrary to popular belief, ADHD does not evolve into a conduct disorder unless the ADHD has already been associated with ODD and includes a dimension of hyperactivity and impulsiveness (Loeber et al., 2000; Nagin and Tremblay, 1999; Satterfield et al., 2007). Several clinical dimensions, including hyperactivity, physical aggressiveness, impulsiveness, opposition, verbal aggressiveness, an anti-social dimension, anxiety, emotional dysregulation and especially depression and manic defence, are pertinent when diagnosing an externalizing disorder (Cohen, 2008; Mealey, 1995; Guilé and Cohen, 2008). Today, most authors admit an important heterogeneity both between and within the different externalizing disorder constructs (Marcelli and Cohen, 2009). There is a clear difference between early onset and life-course-persistent CD and adolescent and limited CD (Farrington and Loeber, 2000; Nagin and Tremblay, 1999).

Psychologically speaking, there are other significant dimensions to consider as well, such as attention and executive functions (in particular the failure to use inhibitory skills), self esteem and narcissistic personality traits, disorganised and insecure attachment styles, attribution disorders, callous-unemotional traits and the absence of moral and sentimental development or access to guilt (Mealey, 1995; Carrasco et al., 2006; Panksepp, 2007; Guilé, 2007). Furthermore, the child develops while interacting with a specific environment, which implies that we should consider developmental interactions over time. Panksepp (2007) questioned whether the practice of play could diminish ADHD by facilitating executive function maturation and the construction of

the social brain. Parallel to a child's development is the idea that parents must be equally engaged in a parental role, a role that also has developmental needs. Galinski (1981) has described five principal steps for parental roles: representation and parental cognition (prenatal), early interactions and attachments (0–2 years old), educational structuring (2–5 years old), opening (5–12 years old) and the interdependence stage (12–18 years old) (Roskam et al., 2007). Several treatment programs regarding youths with CD have focused on parental needs with some success (Kazdin, 2000; Perisse et al., 2006).

3. Biopsychosocial bases of aggressiveness

It is not within the scope of this paper to extensively review all psychological dimensions associated with externalizing disorders or to propose a synthesis of all etiological hypotheses. I will only briefly consider the dimension of aggressiveness and the failure to inhibit it (Panksepp, 2007). Numerous models have been proposed to articulate externalizing disorders in children with aggressiveness. These models often run in parallel to each other and tend to favour one perspective or another. When an integrative proposition becomes public, we often hear about the biopsychosocial bases (Marcelli and Cohen, 2009). On one hand, these models can be the work of physiologists, either pursuing the idea of a pharmacological perspective and testosterone's role (Mealey, 1995), favouring a neuropsychological position and the role of the amygdala and frontal lobes (Pincus, 2000) or supporting a more genetic position in regard to the controversy surrounding XYY (Mealey, 1995). On the other hand, ethologists have also proposed an interesting perspective that takes into consideration the universal nature of intentional aggressive behaviour. For example, Hubert Montagner described a sequence of behaviours specific to human babies that fits into a combat behavioural continuum (e.g., crying, biting, pushing, clawing and hitting) (Marcelli and Cohen, 2009). Sociologists have proposed several interesting factors to take into account in aggressive behaviours, such as poverty, discouragement of social groups, family disorganization and brutality and violence among social groups (Mealey, 1995; Currie, 2000). Psychoanalysts refer to Melanie Klein's work regarding the idea of the divide between good and bad objects with a rigid superego or refer to Bowlby's work regarding the theory of attachment (Guilé and Cohen, 2008).

From a developmental point of view, these ideas have helped to formulate conditions and components of development for a child's mental health and well-being. This development requires prior existence of unwavering personal tools with the answer to the child's fundamental needs. These tools include the capability to love (i.e., recognizing the child as a person with feelings), the gaining of confidence and the ability to affirm their aggression but taking care to not compromise the rights of others or their integrity (Hayez and Lazartigues, 2003). Two periods have been isolated as particularly crucial to the child's psychological growth: (1) early childhood and the first interactions with caregivers, and (2) adolescence and the resulting upheaval (Breton, 1999). Several recent studies have continued to investigate the different dimensions listed above and their correlations. Through a longitudinal study of 868 youths, Carrasco et al. (2006) showed that the dimensional variables associated with aggressive behaviour and vandalism in teens are impulsiveness, anxiety, hyper-energy and a lack of empathy. van Honk et al. (2005) showed in a placebo-controlled crossover experiment that a dose of testosterone could reduce the effect of unconscious fearful faces in a Stroop style task, but had no effect on the conscious feeling of anxiety. Finally, Marsh et al. (2008) and Jones et al. (2008) found a reduced amygdala response to fearful expressions in youths with callous-unemotional traits

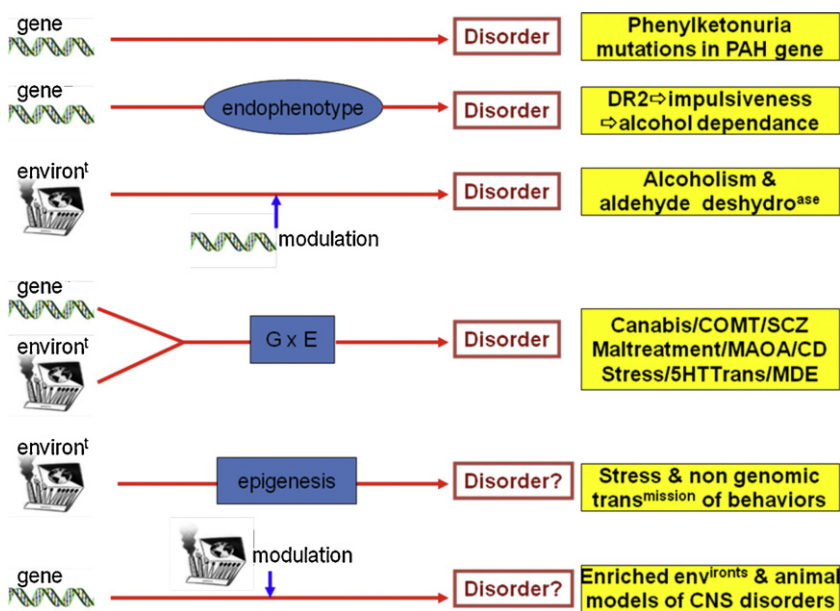


Fig. 1. Genetic and epigenetic influences (mainly DNA centered) on human behaviors and psychiatric diseases (modified from Caspi and Moffitt, 2006). PHA: Phenylalanine hydroxylase; DR2: Dopamine receptor 2; COMT: Catecholamine O methyl transferase; SCZ: schizophrenia; MAOA: Mono-amine oxydase A; CD: Conduct disorder; 5HTTrans: Serotonin transporter; MDE: Major depressive episode; CNS: Central nervous system. In yellow: specific examples to illustrate each possibility are shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

and disruptive behaviours compared to healthy or adolescents with ADHD.

4. Does a genetic determinism that contributes to externalizing disorders exist?

The idea of genetic determinism has met with some complex developments in recent years (Karmiloff-Smith, 1998). To simplify this, several types of genetic determinisms can be distinguished (Fig. 1). The first is a relatively direct form of determinism. It is found in the psychiatric field in certain aetiologies of autism and mental retardation (Cohen et al., 2005), although most of the literature is prevalent with examples of patients with atypical phenotypes (meaning that the genetic abnormality usually associated with autistic disorders or mental retardation is not) (e.g., Cohen et al., 2007). One should keep in mind, however, that animal models of degenerative diseases or mental retardation have shown that environmental conditions could dramatically influence the adult phenotype (Fig. 1, bottom line) (Coppedé et al., 2005; Nithianantharajah and Hannan, 2006). Despite the significant amount of research, the literature in the field of externalizing disorders and especially in CD is extremely limited. Targeting a Dutch family with a mild form of mental retardation and severe CD (including aggression, impulsive behaviour, rapes), Brunner and colleagues found that these disorders were associated with a truncating mutation in monoamine oxydase A (MAOA), which is encoded by a gene situated on the X chromosome (Brunner et al., 1993a,b). The idea of direct determinism, however, is somewhat limited in these pathologies.

The second type of determinism is based on the concept of endophenotypes. In this case, genetic determinism is carried through a variable known as an endophenotype, which is directly linked to externalizing disorders. A classic example in the mental health field is the link between alcohol and impulsiveness. Numerous studies have shown that a polymorphism of the dopamine D2 receptor was linked to impulsiveness in subjects; if they were exposed to alcohol consumption once, they could become dependent on it. Impulsiveness plays the role of the intermediary between alcohol consumption and genetic determin-

ism (Limosin et al., 2003). In the field of externalizing disorders, this variable could be described as a valuable endophenotype candidate, or characteristic intermediary. Another example of this is the empathy variable that is linked to callous-unemotional traits (Guilé, 2007). Besides the Carrasco study cited earlier, studies on clinical samples have noted an association between weak empathy and the severity of a child's anti-social behaviour in a difficult family context (Enebrink et al., 2005). They have also noted significant differences between the empathy levels of anti-social adolescents and controlled witnesses. The importance of genetic influence on anti-social behaviour was well described in a study that tested 3600 pairs of twins (Viding et al., 2005). In this developmental study, the authors investigated genetic heritability by comparing the absence of empathy and the presence or absence of anti-social behaviour in both monozygotic and dizygotic twins. They found the heritability level of a lack of empathy to be high (67%). What was even more remarkable, however, was the separation between anti-social subjects with low empathy (a heritability score of 81%) compared to anti-social subjects with no empathy disorders (their heritability score fell to 30%). It is evident that when weak empathy development is associated with anti-social disorders, genetic influences are much stronger than environmental effects. In contrast, when an anti-social trait is present without an impairment in empathy, the genetic influence is weaker even though the shared environment is strong (Viding et al., 2005).

The last genetic determinism resides in the possibility of a gene–environment interaction. This should be distinguished from genetic modulation of clear environmental effects on development, such as breast-feeding effects on IQ by genetic variation in fatty acid metabolism (Caspi et al., 2007). For the past twenty years, numerous studies have investigated the possibility of a gene–environment interaction in the field of mental health for pathologies as diverse as depression, schizophrenia and externalizing disorders. Among these many studies, the work of Cadoret et al. (1995) used an adoption design. They showed that behavioural disorders in adopted children depended not only on their biological parents, but also on the environmental conditions in their adoptive family. Another analysis by Jaffee et al. (2005)

offered the same results using a twin-study design. By ranking genetic risk between monozygotic and dizygotic twins, which corresponded to behavioural problems presented by the twins, the authors were able to show that a linear relation existed between genetic risks and the appearance of behavioural difficulties. Moreover, they found that the risk increased equally when the variable of abuse was introduced as an environmental variable. Once again, a gene–environment interaction model enabled the articulation of the vulnerability of behavioural difficulties. Caspi et al. (2002) studied a group of 440 young male New Zealanders who were followed from birth to the age of 26. Their violent behaviour, CD and anti-social personality disorders were associated with abusive situations that occurred before the age of 11. This effect could be modified by a functional polymorphism of MAOA. This modulation effect of early life adversities by MAOA polymorphism was confirmed by other groups using different designs—a twin-study (Foley et al., 2004) and a study using boy siblings (Haberstick et al., 2005).

In three out of four independent samples of ADHD patients, it was found that a functional polymorphism of the catecholamine-O-methyl transferase (COMT), a key enzyme in dopamine metabolism, was associated with more frequent aggressive symptoms and comorbid conduct disorders. From a developmental perspective, this finding may offer a demonstration of the genetic modulation of early clinical conditions and their consequences on later maturation (Caspi et al., 2008). Similarly, Mill et al. (2006) showed that a polymorphism in the dopamine D4 receptor and the dopamine transporter 1 genes were associated with a variation in IQ among children diagnosed with ADHD. They were able to predict the poorer prognoses in two independent birth cohorts. However, Sonuga-Barke et al. (2008) did not replicate the association between IQ and dopamine genes. In the field of childhood depression, Kaufman et al. (2004, 2006) showed that the occurrence of depression in maltreated children was moderated by polymorphisms of brain-derived neurotrophic factor and serotonin transporter genes as well as social support that tended to be protective.

5. Environmental variables contribution to externalizing disorders

It is not possible to consider all environmental factors. Their impact on a child's development is often not specific (Poulton et al., 2002; Danese et al., 2007). It seems clear, especially in the domain of externalizing disorders, that the factors are multiple and extremely varied (Mealey, 1995). Many longitudinal studies point to the cumulative effects of stressors and suggest that multi-problem families are a key target for prevention (Jaffee et al., 2007). Some, including toxic, micro- and macro-levels, have been listed in Table 2, according to their respective major impact level (Denenberg, 2000). Besides this classification proposal, other authors insist on distinguishing risk factors versus protective factors (Breton, 1999) and moderators versus mediators (Baron and Kenny, 1986), as it may help us better understand longitudinal psychosocial data and plan a prevention programme (definitions are given in Table 2).

For a first estimate, we can isolate the contribution of poisonous environments, especially for certain toxins that a child can be exposed to during pregnancy. The effects of alcohol or tobacco, as well as other drugs, can now be considered classic factors. Recent studies have shown that these environmental variables could be passed on through intermediary variables, for example, the correlation between cigarette consumption during a pregnancy and the birth weight (Wang et al., 2002) as well as through genetic modulations. Alcohol abuse during pregnancy has been suggested to introduce a higher risk of ADHD, and this risk is controlled by a

Table 2

Environmental factors associated with externalizing disorders classified by subject's distance.

<i>Toxic and perinatal factors</i> that impact brain development either during pregnancy and/or infancy
Alcohol and other abuse during pregnancy
Smoking during pregnancy
Malnutrition
Low birth weight
<i>Micro-environmental variables</i> that impact the child and his/her family in a proximal way
Low socioeconomic status
Early separation
Single/disrupted parent (father absence)
Large number of siblings
Individual handicap or poor social skills
Sexual and/or physical abuse
Family violence and/or alcoholism
Mentally ill parent (e.g., maternal depression; anti-social personality)
Parental use of punishment as opposed to reward
<i>Macro-environmental variables</i> that impact at a more general societal level
Urban residency and high population density
TV exposure
Minority in situation of social exclusion or discrimination
Rejection from school favouring poor education, social disadvantage, poor self-esteem
Inclusion in at-risk pro-social alternatives (peer grouping: e.g., ganging, drug abuse)
Competitive and violent culture

Risk factor (vs. protective factor): a variable that enhances (vs. decreases) the risk of occurrence of a dependent variable; Moderator: a variable that affects the direction and/or strength of the relation between an independent or predictor variable and the dependent variable; Mediator: a variable that accounts for the relation between the predictor variable and the dependant variable. In sum, moderators specify when certain effects will hold, mediators speak to how and why such effects occur (Baron and Kenny, 1986).

polymorphism in a dopamine transporter (Brookes et al., 2006). In another study, alcohol and cigarette consumption during pregnancy was found to correlate with the emergence of hyperactive and oppositional symptoms at six years old. Once again, these symptoms were linked to a polymorphism in a dopamine transporter (Kahn et al., 2003). It seems that some factors may be more strongly associated with one disruptive diagnosis than another, depending on the study (e.g., Nigg and Breslau, 2007; Hultman et al., 2007).

The second type of environmental factors is individual and familial factors, which are known as micro-environments. Most studies refer to different micro-environments called precursory, maintenance and prognostic factors (Burke et al., 2002). These environmental factors are physical abuse, sexual abuse, family lack of discipline, family use of extreme punishments, poverty, minorities, the urban environment, a previous psychiatric history in the family, failure in school and isolated parents (Mealey, 1995; Burke et al., 2002; Roskam et al., 2007). A major study contributing to the understanding the role of these variables is the E-RISK study, which studied the development of almost 1200 pairs of same-sex twins. In this study, the precursory factor of physical abuse showed a strong relationship between the severity of the physical abuse and the appearance of anti-social behavioural disorders in children between 5 and 7 years old (Jaffee et al., 2004). Furthermore, early maternal depression has been shown to have a close relationship with anti-social behaviours, the number of post-partum depression episodes having a cumulative effect (Kim-Cohen et al., 2005). Other recent studies involving environment factors should be cited. The intergenerational transmission of childhood conduct problems largely mediated by environmental variables was again recently shown, especially in males, in a large twin study ($N = 889$) conducted in an Australian high-risk sample (D'Onofrio et al., 2007). Moreover, Costello et al. (2003) showed, in a representative

sample of 1420 rural children, where 25% were American Indians that poverty contributed specifically to CD and ODD. These data support a social causation explanation as opposed to a social selection explanation of childhood externalizing disorders.

A third group of environmental factors is constituted by cultural factors, referred to as macro-environments. The distinction between these micro- and macro-factors has been discussed for many years by sociologists and economists, but their differences have been reinforced by recent studies with data coming from experimental and evolutionary psychology (Denenberg, 2000). Nance and Kearsy (2004) showed how different cultural factors could influence the frequency of a certain deafness gene. The gene DNF1, which is one of the most frequent genetic origins for deafness, occurs more frequently in the USA, whereas the incidence has been steadily decreasing in Mongolia. This variation could be explained by the fact that a thriving deaf culture, specific schools and the teaching of sign language has existed for more than 200 years in the USA, which may influence marriages between deaf people. A similar phenomenon has been described on the Island of Benkala in Bali for the DN1FB3 gene (Nance and Kearsy, 2004). In experimental psychology, experiments on the learning techniques of chimpanzees demonstrated that techniques were transmittable and that the constraint of social conformity was participating in the learning and the choice of the techniques used (Whiten et al., 2005).

Several studies have shown that externalizing disorders in children are encouraged by competitive societies that advocate short-term efficiency (Mealey, 1995). They have also shown that higher population density was associated with higher incidence of CD, especially when there are a variety of cultures linked to immigration (Mealey, 1995). In a prospective study from Quebec, Lacourse et al. (2006) showed that the association with an anti-social group during adolescence was characterised by (1) a temporal dynamic with two trajectories when it came to group affiliation, one in the beginning of adolescence and another in the middle; and (2) the increase in the aggravation of behavioural disorders when a youth entered the group and a decrease when one leaves the group. In another paper that used the same longitudinal study of 1037 boys from Montreal's poor neighbourhoods, the authors were able to show that hyperactive/fearless youths who came from a difficult family fell into anti-social groups at a higher rate. The family variable was insufficient in explaining all of the risks (Lacourse et al., 2006).

6. Contribution of animal models to the understanding of the effect of stress on development

The involvement of both the physiological system of regulation, especially at the hypothalamic–pituitary–adrenal–cortical (HPA) axis, and stress factors has been well established in affecting general physical and mental health (Poulton et al., 2002). Numerous pathologies have been associated with stress factors, and the list of environmental factors involved in externalizing disorders in children is no different (Cohen, 2008). Despite the pioneering efforts of Victor Denenberg in the 1960s and 70s, who first showed the non-genomic transmission of behavioural traits in animals (Denenberg and Whimby, 1963; Denenberg and Rosenberg, 1967), the swing towards genetic studies in the 1980s made it difficult to understand the importance of stress factors until recently with work done by Michael Meaney and colleagues (Fig. 1, 2nd line from the bottom). Using animal studies (rats or mice), these authors were able to show that early stress, maternal care and stress during the gestation period impacted the development of future generations through the HPA axis and epigenetic modifications. It was found that these modifications could be

transferred from generation to generation, and were independent of an animal's genetic inheritance.

Briefly, the following important points learned from these experiments are: (1) early experiences have a long-term effect on behaviour and biological systems, especially when the mother and baby are separated or when the quality of maternal care varies dramatically (Denenberg and Rosenberg, 1967; Liu et al., 1997). (2) Certain early experiences could affect future generations, providing a non-genomic mechanism for the transmission of behavioural traits (Denenberg and Whimby, 1963; Francis et al., 1999). And (3) the uterine environment affects development through environmental factors rather than genetic ones (Denenberg et al., 1998; Francis et al., 2003).

Meaney and others completed these general principles by describing how maternal care impacted development through a behavioural programme and through the future adult's pathological responses to stress. The quality of maternal care influenced the response to stress in the HPA axes of children (Liu et al., 1997), cytochrome and hippocampal synaptic development as well as memory and spatial development (Liu et al., 2000; Mirescu et al., 2004). Moreover, the quality of maternal care greatly influenced the epigenesis of the following generation's children. This effect was reversed by improving the quality of maternal care by entrusting these infants to more affectionate mothers or by blocking histone acetylation shortly after birth, as this treatment stops the epigenomic marking of the DNA (Weaver et al., 2004). Furthermore, naturally occurring variations in maternal behaviour (increase pup licking/grooming and arched back nursing) are associated with differences in estrogen-inducible central oxytocin receptors, which are known to be involved in pro-social behaviours (Champagne et al., 2001). Variation in maternal care also alters GABA_A receptor subunit expression in brain regions associated with fear (amygdala, hippocampus, medial prefrontal cortex) (Caldgi et al., 2003, 2004).

On the one hand, these animal models offer a truly revolutionary paradigm to the perspective of genetic pre-determinism or genotype shaping of one's environment, which is often a product of theoretical models (Scarr and McCartney, 1983; Karmiloff-Smith, 1998). In effect, by showing a transgenerational transmission that is independent of genetic heritage, paradigms must be completely modified to consider not only unidirectional interactions, but bidirectional interactions as well. On the other hand, these models, which imply a certain number of early stress factors, help to shed light on early childhood treatment and the importance of the temporality of the aforementioned environmental factors. In these animal models, environmental enrichment during the peripubertal period indeed leads to a functional reversal of the effects of maternal separation (HPA and behavioural response) through compensation rather than reversal of the neural effects of early life adversity (Francis et al., 2002). These studies therefore demonstrate the need to consider not only gene by environment interactions, but also gene by environment by developmental time interactions, as it is hypothesised in pleiotropic effects of neurotransmission during development (Thompson and Stanwood, 2009).

The effect of severe early deprivation of human contact is also well known in human infants, and the reversibility depends on the age when restoring normal family rearing (Rutter & O'Connor, 2004). Interestingly, attempts have been made to understand how genetic by environment interactions contribute to child attachment during development. They favour a differential susceptibility model rather than the one of classic vulnerability (Bakermans-Kranenburg and Van Ijzendoorn, 2007). In the case of attachment, genetic factors appear to moderately contribute. Certain clinical studies have examined the evolution of children placed under a milder, very early stress. For example, O'Connor et al. (2002, 2005)

followed the evolution of 74 parents and children in the AVON longitudinal study. They showed that prenatal maternal anxiety predicted behavioural and emotional problems by the age of 4 years old, problems that were linked to individual differences in the cortisol levels in pre-adolescents. In another study, Van den Bergh and Marcoen (2004) demonstrated that prenatal maternal anxiety was linked to symptoms of hyperactivity, externalizing problems and a higher level of anxiety in children between 8 and 9 years old. Furthermore, Caspi et al. (2004) were able to demonstrate that among pairs of monozygotic twins, the child that received the most negative maternal attention and the least amount of warmth began to more frequently show anti-social behaviour by the age of seven. The other twin was viewed as subjectively more positive by the mother. The maternal view was measured through a subjective questionnaire that mothers responded to before their children were 5 years old. In the same twin sample, Jaffee et al. (2003) investigated the father's role by evaluating the effect of their behavioural disorders on the child's development. In the end, the results depended on the father's behaviour. When fathers who displayed less anti-social behaviours spent more time with their children, their child exhibited fewer externalizing disorders. Conversely, if the fathers displayed anti-social behavioural disorders, the more time spent with their children, the greater chance the children presented with externalizing disorders. In summary, the effect of the father's presence in the child's life depended directly on the father's behaviour. Also, in a study that compared depressed mothers with non-depressed mothers, it was shown that maternal depression could significantly impact the development of empathy in children, focusing again on early life adversities (Jones et al., 2000). Finally, Belsky et al. (2007) longitudinally investigated the interactions of parenting and a child's attention on later externalizing problems. They showed that greater maternal sensitivity predicted better attentional scores, resulting in fewer externalizing problems at later ages. They also found that attentional control partially mediated the effect of parenting on externalizing problems.

7. Probabilistic automata as a model for the epigenesis of cellular networks

The pertinence of this model to brain development has been suggested since the 1970s. The theory of adaptive self-organization was suggested by Atlan, and was based on the reduction of initial redundancy by partially random, noise producing, environmental factors (Atlan, 1979). This theory helps to understand the logic of a positive, "organizing" effect of randomness as a source of biological organization in addition to the deterministic genetic programme. Using mathematical models of growing networks made of dividing, interconnected cells, Milgram and Atlan (1983) compared probabilistic automata to deterministic automata. They showed that the number of necessary states in the initial generating cell automaton was dramatically reduced when the automaton was probabilistic rather than deterministic. An automaton was defined by (1) the set of its internal states, (2) the set of its inputs, and (3) a set of transition matrices representing the various possibilities of the automaton to go from one state to another upon receiving a given input. Within *deterministic automaton*, transitions are produced in a unique and unambiguous way for each input. Matrices only have one element "1" in each line. Within *probabilistic automaton*, transitions are produced by probabilities ϵ , the values being anything between 0 and 1.

Fig. 2 summarises the respective strengths and weaknesses of each type of automaton in terms of accuracy and complexity. It appears that (1) probabilistic programming is more efficient than deterministic programming in accounting for the generation of complex networks (high number of cells, diversity of interactions), (2) probabilistic automata have self-organizing properties that make them adequate to account for non-directed learning at cellular and multi-cellular levels, and (3) in particular, changes in the structure of a network can come about in the results of its functioning. In this theoretical work, Milgram and Atlan (1983) showed that probabilistic automata could generate networks with some specificity despite the loss of accuracy compared to

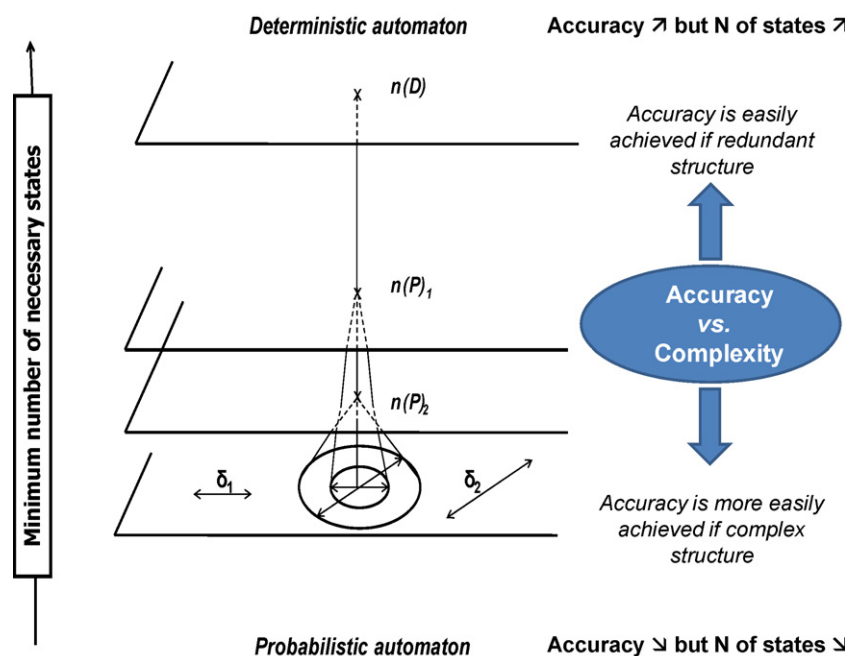


Fig. 2. Strengths and weaknesses of deterministic and probabilistic automata (modified from Milgram and Atlan, 1983). To each deterministic automaton capable of generating a network N with infinite accuracy (zero dispersion δ) and a minimum number of states $n(D)$ is a corresponding probabilistic automaton able to realize the same network with a lower minimum number of states $n(P)_i$. The minimum number of states $n(P)_i$ necessary for the same task is a measure of the complexity of the target network. The lower the number of states $n(P)_i$ in the probabilistic automaton, the wider the dispersion of the resulting network. e.g., see comparison of probabilistic automata P_1 and P_2 : $n(P)_1 > n(P)_2$ but $\delta_1 < \delta_2$.

deterministic procedures, in which the price for infinite accuracy would be paid by a much larger number of states. In sum, Milgram and Atlan were able to produce a probabilistic instrument that presented highly superior characteristics in comparison to the predetermined instruments for neural networks. They concluded that their model suggested that the controversial metaphor of genetic programming, in its most classic sense (meaning giving DNA a role in terms of specific genetic determinism), should be replaced by a more probabilistic instrument. Their mathematical solution permitted a spectacular reduction of the number of steps necessary to create the chains, rings and structures in trees from an initial cellular instrument generator. This proposal was particularly well adapted for neural network development and the immune system, given their high level of biological complexity (Atlan, 1979; Danchin, 1978).

After the seminal study by Saffran et al. (1996), empirical evidence for probabilistic or statistical learning has matured in the field of both auditory and visual inputs (Perruchet and Pacton, 2006). In the field of language acquisition, where cultural factors are determinants both in oral and written language, Atlan's intuition has been confirmed. It has been shown by Saffran et al. (1996), followed by Kuhl (2007), Kuhl (2004) and Kuhl et al. (1997), that (1) from birth, infants possess the ability to discriminate all languages at the phonetic level and to recognise their prosodic features; (2) they develop a strategy of learning based on input language signs and characteristics and explore language statistical properties, leading to so-called "statistical" or "probabilistic learning"; and (3) the language experience will commit the perceptual system at the neuronal level, increasing native-language speech perception and decreasing foreign-language speech perception with a "magnet effect" (Kuhl, 2000). Simple exposure, however, does not explain language learning. In both speech production and perception, the presence of a human being interacting with a child has a strong influence on learning (Goldstein et al., 2003; Kuhl, 2003).

Despite the fact that restrictive biological views are dominant in the field of reading (e.g., Meng et al., 2005), recent studies have shown that cultural factors can constrain neurobiological abnormalities associated with dyslexia (Siok et al., 2004). In addition, Dehaene et al. (2008) compared the Mundurucu, an Amazonian indigenous group with a reduced numerical lexicon and little or no formal education, to Western-educated participants. They showed that the mapping of numbers onto space is a universal intuition, and that this initial intuition of numbers is logarithmic. The concept of a linear number line that dominates in Western individuals appears to be a cultural invention that fails to develop in the absence of formal education. Integrating knowledge on both reading and arithmetic, Dehaene and Cohen (2007) proposed a model called "cultural recycling" of cortical maps. This is a mechanism by which a novel cultural object encroaches onto a pre-existing brain system as a result of brain plasticity and human evolution. They proposed this in order to explain the tremendous course of knowledge evolution in the last centuries. This proposal is of high interest for our purposes, as it supports the idea of bidirectional interactions at even the neuronal level (see below).

8. Working toward a probabilistic epigenetic developmental model for externalizing disorders

In keeping with the developmental perspective, it is clear that all of the determining factors of an externalizing disorder are almost impossible to thoroughly translate. This in turn implies factors in which the points of impact are situated at extremely different levels, namely genetic, cellular, neurological, behavioural, familial and cultural levels (Karmiloff-Smith, 1998). Models that favour a homogeneous point of view or the stratification of impact

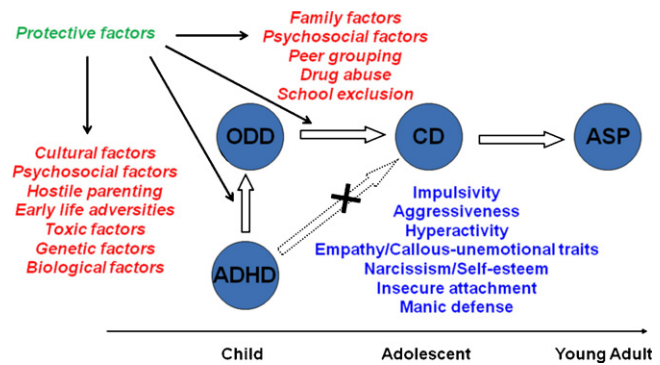


Fig. 3. A developmental view of externalized disorders (modified from Loeber et al., 2000). ADHD: Attention deficit-hyperactivity disorder; ODD: oppositional defiant disorder; CD: conduct disorder; ASP: anti-social personality. In red: factors influencing the occurrence of externalized disorders. In blue: psychological dimensions that have been associated with a risk of externalized disorder. In green: possible influence of protective factors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

levels based on a unidirectional and predetermined model cannot be supported, mainly because of the complexity of the studies that put several different levels into play (Atlan, 1979; Gottlieb, 2007). Fig. 3 groups together the factors, in red, that contribute to the principal diagnostics of externalizing disorders, which are arranged according to a developmental perspective from birth to adolescence. Certain clinical and psychopathological dimensions are similarly listed, in blue, according to their pertinence as a dimensional variable in the studies. Protective factors appear in green (Loeber et al., 2000).

A probabilistic, epigenetic theoretical model is the best way to take into consideration the complexity and diversity of all the different factors. This model takes into account the diversity of determinant factors (e.g., Mealey, 1995), recent developments in longitudinal studies (e.g., Caspi et al., 2004), studies on environmental effects (e.g., Jaffee et al., 2004), animal models that study early stress factors (e.g., Liu et al., 1997) and how the quality of maternal care affects the development of the baby (e.g., Rutter & O'Connor, 2004). In this model, the neural structures (or other structures) begin functioning before they have become completely mature. This activity, be it intrinsically derived or influenced from the outside, plays a significant role in the developmental process (Cohen, 2008). This also presupposes that all different participatory levels (i.e., the genetic level, the level of biological, cerebral and neurological functioning, the conduct and behavioural level and the environmental level including the physical, social and cultural environments) work and interact with each other, not only via unidirectional interactions but constant bidirectional interactions as well. Because the coordination of the formal influences between and within all of these different levels of analysis are not perfect, a probabilistic element is introduced into the systems of development and their evolution, regardless of whether the influences are structural or functional (Gottlieb, 2007). When the result is an externalizing disorder, this model permits the implication of the different known determinants at each level of analysis and integrates how their interactions often lead to potentiate the effects due to their bidirectional nature (Fig. 4).

Developmental studies have demonstrated that the first years of early childhood and adolescence are extremely sensitive time periods, leading to the concept of sensitive dependence on initial conditions (Breton, 1999). Each time a potential tension (or a critical moment) at a particular level occurs, there are subsequent down turns that appear on the trajectory. These potential tensions include the consequences of certain genetic polymorphisms (e.g., MAOA, Caspi et al., 2002), primary or secondary cerebral lesions

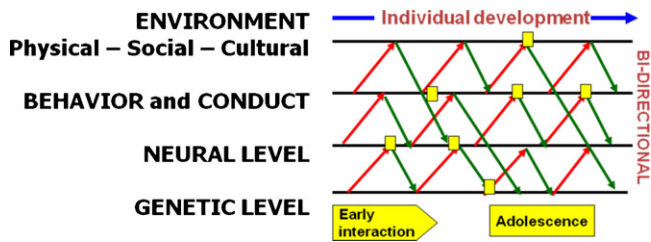


Fig. 4. Meta-theoretical model of probabilistic epigenesis as a model for externalized disorders (modified from [Gottlieb, 2007](#)). In this view, neural (and other) structures begin to function before they are fully mature. This activity, whether intrinsically derived or extrinsically stimulated plays a significant role in the developmental process. Since the coordination of formative functional and structural influences within and between all levels of analysis is not perfect, a probabilistic element is introduced in all developing systems and their outcome. Some tension may occur (e.g., in the case of externalized disorders: early life adversities, cultural influences, callous-unemotional traits, genetic factors). In the figure, four levels of functioning are described from the cellular/genetic (low/micro) to the environmental (high/macro) level. Red arrows refer to influences from a lower to a higher level, and vice versa for the green arrows. Yellow boxes refer to individual commitments that may occur during development and that will influence the course of later maturation (e.g., maternal language exposure, sexual abuse). Yellow signs refer to the two key periods of life in terms of both environmental and biological influences that is infancy and adolescence. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

(e.g., frontal dysfunction, [Pincus, 2000](#)), extremely diverse environmental problems (e.g., child's maltreatment, [Jaffee et al., 2004](#)) or behaviours, conducts and intermediary phenotypes (e.g., hyperactivity, [Loeber et al., 2000](#)) that could reflect psychopathological difficulties. The categorical logic of the nosographical classifications that distinguish ADHD, ODD and CD have had to be replaced by a more multidimensional perspective. This perspective permits easier monitoring of clinical, psychological, social and genetic aspects, and takes into consideration their interactions and possible developmental results ([Cohen, 2008](#)). This integrative view may be helpful for the development of prevention and promotion programs in the mental health of children and adolescents (for a detailed review see [Breton, 1999](#)).

9. Future research

To test whether this model has some validity, one needs to manipulate in experimental studies, or to test in longitudinal studies, carefully chosen candidate variables belonging to each level. Although there is no experimental model in the field of externalizing disorders that is able to manipulate all of these levels, [Barr et al. \(2004a,b\)](#) recently published two separate articles on an experiment with monkeys that showed these four levels of experimental manipulation to help explain alcoholism. The authors showed that when monkeys were raised separately from their mothers and placed into a situation of emotional depravity, it created a stress factor that was demonstrated by their adrenocorticotrophic (ACTH) levels. This effect was modulated by a functional genetic polymorphism that occurs in the serotonin transporter. As adults, only the monkeys that were emotionally deprived and had the serotonin transporter allele (s/l) developed an alcohol addiction when alcoholic drinks were included in their diet ([Barr et al., 2004a,b](#)). In another set of experiments, the same group showed that prenatal alcohol exposure to carriers of the s allele resulted in an increase in neonatal irritability and increased ACTH and cortisol compared to monkeys that were homozygous for the l allele raised under the same conditions and monkeys that were not exposed regardless of genotype ([Kraemer et al., 2008](#)). Interestingly, there are numerous arguments regarding corticosteroid/serotonin interactions in the neurobiological mechanisms of stress-related disorders ([Lanfumeu et al., 2008](#)).

In the field of human behaviour, [McGowan et al. study \(2009\)](#) on suicide is also remarkable. They were able to show, as predicted by animal models of stress, that markers of epigenetic regulation of the glucocorticoid receptor were present in brains obtained from suicide victims with a history of childhood abuse as opposed to both suicide victims with no childhood abuse and controls. Since childhood abuse alters HPA response to stress and increases the risk of suicide in humans, this report suggests a common effect of parental care on the epigenetic regulation of brain glucocorticoid receptor expression that contributes to individual differences in the risk of psychopathology. In the field of externalizing disorders, studies testing variables from all four different levels are still lacking.

10. Conclusion

Using different paradigms, such as the mathematical modelling of neural networks ([Milgram and Atlan, 1983](#)), development of biological organisms ([Gottlieb, 2007](#)), evolutionary theory ([Denenberg, 2000](#)) and infant development ([Kuhl, 2004](#)), several researchers have reached the conclusion that development and learning driven by cultural/environmental dependence on humans requires a probabilistic factor in order to be accurately predicted. Externalizing disorders in children present a major problem in clinical practice today, not only because of their frequency, but also because their study implies a change in the foundation of clinical practice. I argue that all classical viewpoints appear to be contradicted by studies in the social, psychological, biological and genetic perspectives. A multidisciplinary approach that integrates all of these viewpoints and places them in a probabilistic model appears to yield the most accurate representation of the diversity and complexity of externalizing disorders.

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