

*Review*

# Understanding development and prevention of chronic physical aggression: towards experimental epigenetic studies

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The aim of this paper was to highlight how developmental psychopathology, epigenetics and prevention experiments are starting to blend together to explain the developmental causes of chronic physical aggression (CPA) and, more importantly, to help prevent CPA and its associated physical, mental and social problems. After defining the keywords (prevention, chronic and physical aggression), a selected review of published studies is used to answer the following four questions: when should we attempt to prevent onset of CPA? What are the risk factors for CPA? Have early childhood interventions been shown to prevent CPA? Can early preventive interventions benefit from epigenetic studies? The last section of this paper gives two examples of experimental prevention designs that integrate present knowledge of CPA development, risk factors, early childhood preventive interventions and epigenetic programming of brain development during pregnancy and early childhood. I conclude that randomized control trials of preventive interventions during pregnancy and early childhood with a specific focus on epigenetic effects are the research design most likely to advance our understanding of the biopsychosocial mechanisms that lead to CPA, and the only research design that can identify effective interventions for preventing the development of CPA.

**Keywords:** aggression; development; epigenetic

... (both) the lack of regularity in the succession of living beings, (and) the variation in species which produces monsters with reference to the typical being, must come from either the germ or an external cause. The first doctrine was still tenable at a time when we could believe in the pre-existence of germs; but nowadays I admit, with everybody, the doctrine of epigenesis. Every normal egg which gives birth to an abnormal individual is influenced by external agents whatever they are; this is what I call action of the milieu. (Quatrefages 1863, p. 381)<sup>1</sup>

## 1. INTRODUCTION

The above citation from Armand de Quatrefages comes from a heated debate with one of his colleagues at the Anthropological Society in Paris after Quatrefages read a letter he had solicited from Charles Darwin in July 1863. The nature-nurture debate has always been a central issue not only among naturalists but also moral philosophers. The first phrase of Rousseau's

(1762, see [http://www.ilt.columbia.edu/pedagogies/rousseau/em\\_eng\\_bk1.html](http://www.ilt.columbia.edu/pedagogies/rousseau/em_eng_bk1.html)) masterpiece on children's education is a good example: 'Everything is good as it leaves the hands of the author of things, everything degenerates in the hands of man'. A century later, Charles Darwin took a diametrically opposite view. In his autobiography, he writes:

I can say in my own favour that I was as a boy humane, but I owed this entirely to the instruction and example of my sisters. I doubt indeed whether humanity is a natural or innate quality.

(Darwin 1876, p. 11)

The social learning theorists who dominated research on the development of aggression during the last half of the twentieth century were clearly siding with Rousseau rather than Darwin. The main thrust of their argument was that children learned to aggress from their environment, that is, the family, peers, neighbourhoods and the media (e.g. Bandura 1973; Reiss & Roth 1993; Human Capital Initiative Coordinating Committee 1997; Anderson *et al.* 2003; NIH 2004).

The learning of aggression hypothesis led to the idea that some children learn to aggress early in life while others learn later. In its report 'Violence and Health', the World Health Organization (2002, p. 31) concluded

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that 'The majority of young people who become violent are adolescent-limited offenders who, in fact, show little or no evidence of high levels of aggression or other problem behaviours during their childhood'. The citation of that phrase suggests that the WHO experts came to the conclusion that violent behaviour is learned *de novo* during adolescence based on a 2001 report from the US Surgeon General (DHHS 2001) written by a committee of USA experts on the development of aggression.

Determining when violent individuals learn to aggress is critical for finding means of preventing chronic physical aggression (CPA). Before summarizing the state of knowledge on this issue, a definition is needed for the term 'prevention'. The traditional classification of disease prevention efforts is useful here (Mrazek & Haggerty 1994): (i) primary prevention attempts to prevent the onset of the disease, (ii) secondary prevention attempts to prevent the progression of the disease, and (iii) tertiary prevention attempts to prevent the negative consequences of the disease.

My focus in this paper is primary prevention of CPA, hence prevention of its onset. Two other terms need to be defined to clear any misunderstanding: 'physical aggression' and 'chronic'. Physical aggression is the use of behaviours, such as the following, in antagonistic interactions with other humans: hitting; slapping; kicking; biting; pushing; grabbing; pulling; shoving; throwing objects; beating; twisting; and choking. CPA is defined as the use of physical aggressions at a significantly higher rate than ones' birth cohort members over an extended period of time. The time period needs to be defined according to the study objectives.

I stress the importance of definitions because research on aggression has long been handicapped by misunderstandings concerning the behaviour being studied (Hartup & Dewit 1974; Tremblay *et al.* 1991; Tremblay 2000, 2003). A recent example comes from an exhaustive meta-analysis of prevention experiments. In an article titled 'School-based interventions for aggressive and disruptive behavior', Wilson & Lipsey (2007) compiled results of 249 experimental and quasi-experimental prevention studies in schools (pre-kindergarten to 12th grade) published in English. The authors reported that 'Positive overall intervention effects were found on aggressive and disruptive behavior and other relevant outcomes' and concluded that 'Schools seeking prevention programs may choose from a range of effective programs with some confidence that whatever they pick will be effective'. This meta-analysis published in one of the leading prevention journals appears to be extremely good news for the prevention of physical violence among our youth and for society in general. Unfortunately, a footnote in Methodology tempers our enthusiasm. The authors write:

Ideally, we would have liked to examine program effects only on aggressive behavior. However, almost none of the measures that call themselves aggressive behavior measures focus solely on physically aggressive interpersonal behaviour. Many include disruptiveness, acting out and other forms of behavior problems that are negative, but not necessarily aggressive

(Wilson & Lipsey 2007, p. 134)

This Wilson & Lipsey article is extremely important because it leads us to the conclusion after 249 preventive experiments, over more than half a century, we have little evidence of the extent to which we can prevent CPA by interventions with school-age children. In fact, it is unclear what we can prevent when investigators use total scores of deviant behaviours that have different developmental trajectories and different causal mechanisms. For example, Barker *et al.* (2007) recently showed that physical aggression and theft during adolescence have different developmental trajectories and are inversely correlated with neurocognitive performance.

Do we need to start the last 50 years of research all over again with a slight modification to our evaluation design, that is, insuring that we do assess CPA after preventive interventions with school-age children?

If CPA onset is during adolescence, as claimed by the US Surgeon General and the WHO, one would expect that the best time to implement preventive interventions would be during the elementary and early secondary school years. This clearly appears to be what prevention researchers have been thinking over the past 50 years if we rely on Wilson & Lipsey's meta-analysis. They reported that 49% of the interventions targeted youths who were older than 10 years of age, 43% targeted children who were between 6 and 10 years of age, while only 8% targeted 4- to 5-year-old children. Interestingly, when a random sample of the Canadian population was asked the best age for preventing physical aggression, their opinion matched almost perfectly what the researchers have been doing over the past half-century (Tremblay *et al.* 2003). However, recent longitudinal studies of physical aggression from infancy to adulthood suggest that we need to revisit the traditional beliefs of the general public and the prevention researchers.

## 2. WHEN SHOULD WE ATTEMPT TO PREVENT THE ONSET OF CHRONIC PHYSICAL AGGRESSION?

The public's focus on violence during adolescence and its prevention during the school years is easy to understand since physical dangerousness, defined as the potential physical harm to a victim, increases with age in young humans and reaches its peak in late adolescence. The most obvious reason for this increase in dangerousness with age is that physical growth from birth to late adolescence increases height, weight and the power of muscles needed for physical aggression. With the advent of puberty, and a spectacular increase in testosterone levels, the change of magnitude in muscle power is especially noteworthy for adolescent males. In other words, it is less dangerous for a teacher or a neighbour to gain control of a physically aggressive 6-year-old boy than a 17-year-old adolescent.

Research on antisocial behaviour has also focused on the school years because schools are a convenient place to recruit samples of youth, interview them and experiment with interventions. Furthermore, pre-adolescents and adolescents are more likely to understand written questionnaires than younger children. Thus, most longitudinal studies on the development of behaviour

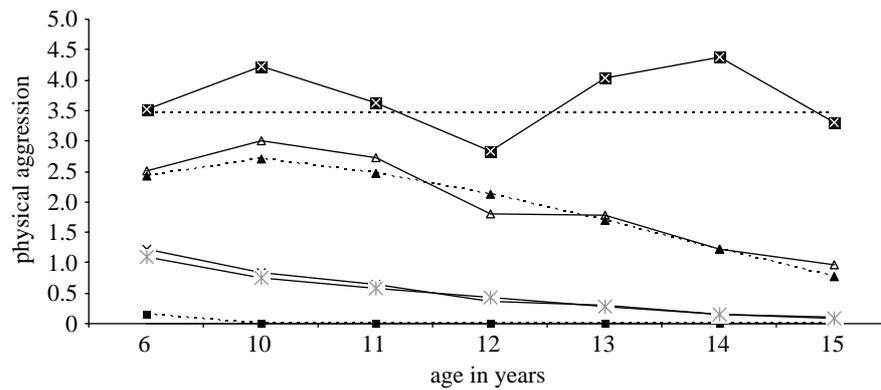


Figure 1. Trajectories of physical aggression between 6 and 15 years of age ( $n = 1037$  males; adapted from Nagin & Tremblay 1999). Black squares, low 17%; stars, moderate desisters 52%; triangles, high desisters 28%; cross in square, chronic 4%.

problems over the past half-century focused on pre-adolescents and adolescents. Our understanding of the origin and development of physical aggression was further handicapped by 'aggression' studies that focused on disruptive or antisocial behaviours in general rather than on physical aggression (Tremblay *et al.* 1991; Tremblay 2000; Wilson & Lipsey 2007).

The first long-term prospective annual assessment of children's physical aggression development was published at the end of the 1980s by Cairns *et al.* (1989). Results were far from confirming that children learn to physically aggress during adolescence. The mean frequency of physical aggressions by boys and girls from poor areas in North Carolina was shown to decrease substantially from 10 to 18 years of age. This was true whether teacher reports or self reports were used to monitor the development of physical aggression.

The main argument offered to explain the discrepancy between the observed developmental data and the popular developmental theories was that although the mean level of physical aggression decreases with age, there is a group of children who eventually start to physically aggress chronically during adolescence without having used physical aggression during childhood. Although some were suggesting that this would be a small group of individuals (Loeber & Stouthamer-Loeber 1998), most reviews of the literature still conclude that physical aggression is learned from one's environment, especially peers and the media, during adolescence (DHHS 2001; World Health Organization 2002; Anderson *et al.* 2003; NIH 2004; Tremblay 2006). Declining mean levels of physical aggression from 10 to 18 years of age were not sufficient to convince aggression specialists that physical aggression is not learned during adolescence. Analyses of the variability in developmental trajectories of physical aggression with long-term prospective repeated assessments were needed to challenge the traditional learning hypothesis. The first analysis of physical aggression trajectories from 6 to 15 years of age used a sample of males from low socio-economic areas in a large North American city (figure 1; Nagin & Tremblay 1999). Results led to three important conclusions: (i) frequency of physical aggressions reported by the teachers peaked at the start of the study when the boys were in kindergarten, (ii) the frequency of physical aggressions reported by the teachers was decreasing from 6 to 15 years of age

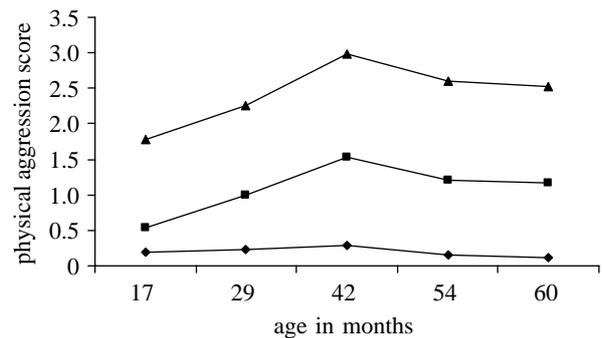


Figure 2. Trajectories of physical aggression between 17 and 60 months of age ( $n = 1758$  females and males; adapted from Côté *et al.* (2007) AGP). Diamonds, low 32.5%; squares, moderate 50.5% and triangles, high 17%.

for 96% of the boys, and (iii) the boys on the high-frequency physical aggression trajectory (4%) were most likely to report high frequency of physical violence at 17 years of age. Similar results were obtained with other large samples of males in New Zealand and the USA (Broidy *et al.* 2003).

The results of these developmental trajectory analyses were clearly showing that the postulated 'learning' of physical aggression by males as well as the onset of CPA was either occurring during the kindergarten year or before kindergarten, not during the elementary school years, and certainly not during adolescence.

It became very clear that we needed to describe the development of physical aggression during the pre-school years to understand the onset of physical aggression as well as of CPA. However, none of the longitudinal birth cohorts that were initiated between the 1940s and the 1980s had made repeated assessments of physical aggression during the pre-school years. New longitudinal studies of birth cohorts were needed. The results from four of these studies in Canada (Tremblay *et al.* 1999, 2004; Côté *et al.* 2006, 2007), The Netherlands (Alink *et al.* 2006) and the USA (NICHD & Network 2004) led to the same observations (see figures 1 and 2; Côté *et al.* 2007): (i) physical aggression starts between the end of the first and second years after birth, (ii) the frequency peaks between the end of the third and fourth years, (iii) females desist earlier than males, and (iv) CPA onsets with onset of physical aggression in infancy.

These observations lead to three conclusions that are at odds with the traditional view that humans learn to use physical aggression and that they do so by imitation, especially of the media (Reiss & Roth 1993; Human Capital Initiative Coordinating Committee 1997; Anderson *et al.* 2003): (i) children spontaneously use physical aggression, (ii) rather than learn to physically aggress they learn not to physically aggress, and (iii) children learn not to physically aggress mainly during the pre-school years.

These three conclusions have important consequences for the prevention of physical aggression. First, there is probably no good reason to prevent the onset of physical aggression if it is a normal behaviour that is eventually replaced by more 'civilized' forms of anger expression, resource acquisition and assertiveness. Second, efforts to prevent CPA should probably target high-risk individuals before or during the developmental period when they are normally learning alternatives to physical aggression. Third, preventive interventions should target factors that increase the risk of frequent physical aggressions as well as factors that increase the probability of learning alternatives to physical aggressions.

### 3. WHAT ARE THE RISK FACTORS FOR CHRONIC PHYSICAL AGGRESSION?

Longitudinal studies tracing the developmental trajectories of physical aggression have also identified risk factors that could be used as targets for preventive interventions. For example, results from the Québec longitudinal study of children (Tremblay *et al.* 2004) showed that two of the classic family risks, parent separation before birth and low income, predicted high physical aggression during early childhood. Mother characteristics before birth were among the best predictors: frequent antisocial behaviour during adolescence; giving birth before 21 years of age; not having finished high school; and smoking during pregnancy. Smoking apparently affects the development of the foetus brain (Wakschlag *et al.* 1997; Brennan *et al.* 1999; Maughan *et al.* 2004; Button *et al.* 2007; Jacobsen *et al.* 2007; Huijbregts *et al.* in press). As expected, males were more at risk than females of being on the high physical aggression trajectory, even when the assessment started at 17 months of age. After controlling for prenatal assessments, the fifth month after birth assessments revealed two significant predictors: family dysfunction and coercive-hostile parenting by the mothers. Interestingly, a twin study also showed that at 17 months of age more than half of the variation in frequency of physical aggression was explained by genetic factors (Dionne *et al.* 2003). One would expect that many of the mother characteristics that were identified as risk factors are mediators of mother's genetic characteristics (Maughan *et al.* 2004) or interact with the child's genetic characteristics (Kim-Cohen *et al.* 2006).

In summary, the traditional predictors of adolescent antisocial behaviour are predicting CPA during the pre-school years. An important finding for planning the timing of preventive interventions is that all of the risk factors are present during pregnancy or soon after

birth. Hence, they could be the target of interventions starting during the prenatal and early post-natal periods.

### 4. HAVE EARLY CHILDHOOD INTERVENTIONS BEEN SHOWN TO PREVENT CHRONIC PHYSICAL AGGRESSION?

As would be expected from the Wilson & Lipsey (2007) meta-analysis, to our knowledge, no pre-school preventive intervention assessed long-term impact on CPA. However, two preventive interventions during the pre-school years have shown long-term preventive effects on general antisocial behaviour. The Perry pre-school experiment with 3- and 4-year olds (Schweinhart *et al.* 2005) was focused on stimulating cognitive development and showed impressive reduction of adult criminal behaviour among males. A home visitation by nurses from pregnancy to 24 months after birth also reported long-term impact on adolescent delinquency. Investigators randomly allocated a nurse home visitation programme to young underprivileged pregnant women from New York State at high risk of child abuse and neglect. These children were obviously also at high risk of CPA. The long-term follow-up of the children from the intervention group showed that they were less frequently abused and neglected, and also less likely to exhibit delinquent behaviours during adolescence (Olds *et al.* 1986, 1998).

Finally, an adoption study is of interest here because it may indicate the maximum effect that can be expected from an early intensive intervention. Van Dusen *et al.* (1983) used Danish records to collect the criminal convictions of adopted females ( $n=6374$ ) and males ( $n=5649$ ) with reference to the biological and adoptive parents' socio-economic status (SES). Males with high SES biological parents were less likely to have a criminal conviction if they were adopted into a high SES family (9.3%) than if they were adopted into a low SES family (13.8%). Similarly, males with low SES biological parents were less likely to have a criminal record if they were adopted into a high SES family (12.98%) than if they were adopted into a family with the low SES of their biological parents (18.04%). Note that the former (low SES biological-high SES adoptive) were as likely to have a criminal record as the high SES biological-low SES adoptive (12.98% versus 13.8%). The largest difference between groups of males was between the high SES biological-high SES adoptive (9.3%) and the low SES biological-low SES adoptive (18.04%). The latter are close to two times more likely to have a criminal conviction. If we were successful in changing the behaviour of high-risk low SES parents, then it would be surprising that we would achieve better results than placing a high SES biological parent male into a high SES adoptive family.

To find which early preventive interventions will be most cost-effective for preventing CPA, we need to compare interventions with different targets (e.g. parent versus child), different intensities (e.g. pregnancy to 2 years versus pregnancy to 5 years) and different timings (e.g. pregnancy to 2 years versus 3-5 years). Such comparisons are also important for understanding the mechanisms that lead to or prevent CPA.

## 5. CAN EARLY PREVENTIVE INTERVENTIONS BENEFIT FROM EPIGENETIC STUDIES?

Children have the physical, cognitive and emotional means of being physically aggressive towards others by 12 months of age (Tremblay 2008). As described above, most children will 'onset' hitting, biting or kicking another child or even an adult before their second birthday. However, their environment will play an important role in the developmental trajectories of these newly acquired skills. If children are surrounded by adults and children who frequently physically aggress, they will probably learn that physical aggression is a useful strategy in everyday social interactions. On the other hand, if a child lives in an environment that does not tolerate physical aggression, it is probable that he/she will acquire the habit of using means other than physical aggression to obtain what he/she wants, or for expressing frustration.

Thus, physical aggression is not a behaviour children learn like reading or writing, nor an illness children 'catch' like poliomyelitis or smallpox. It is rather like crying, eating, grasping, throwing and running, which young humans do when the physiological structure is in place. The young human learns to regulate these 'natural' behaviours with age, experience and brain maturation. The learning to control process implies regulating your needs to adjust to those of others, and this process is generally labelled 'socialization'.

It is not hard to imagine why the evolutionary process would have given humans a genetic programme coding for all the basic mechanisms in order to react to hunger and to threat. Young children activate their muscles to run, push, kick, grab, hit, throw and yell with extreme force when hungry, when angry or when they are strongly attracted by something. However, stating that humans are genetically programmed to physically aggress when needed is different from stating that the frequency of the physical aggressions they use is genetically programmed.

From the available data, it seems clear that all 18-month olds who have developed normally use physical aggression out of fear, anger, disgust, curiosity and greed. However, not all do so at the same frequency and with the same vigour. To what extent are these individual differences due to the genetic programme they have inherited or to the environment in which they have been growing? The trajectories shown in figure 2 clearly indicate that these individual differences exist at any given point, starting in early childhood, but the most interesting phenotype is described by the developmental trajectories, that is, intra-individual change over time. Most children learn to reduce the frequency of physical aggression, a behaviour which they apparently did not need to learn. However, relatively stable differences remain among individuals.

To understand how we can prevent the development of CPA trajectories, we need to understand the gene-environment mechanisms that explain the change and stability. They are possibly very similar to the mechanisms that explain the developmental trajectories of growth in height. Genes code for the growth mechanisms, but there are individual differences in this coding, as well as environmental differences (e.g. access to food),

which lead to stable individual differences. Thus, the individual differences in the frequency of physical aggression at one point in time, and over time, can be due to a large number of 'causes', for example, to individual differences in the genetic coding for serotonin (e.g. Pihl & Benkelfat 2005) or testosterone (e.g. Van Goozen 2005), to language development (e.g. Dionne 2005) or cognitive development (e.g. Séguin & Zelazo 2005), or to environmental differences such as mother's tobacco use during pregnancy (e.g. Wakschlag *et al.* 2002), birth complications (e.g. Arseneault *et al.* 2002), parental care (e.g. Raine *et al.* 1997; Gatti & Tremblay 2005; Zoccolillo *et al.* 2005) and peer characteristics (e.g. Boivin *et al.* 2005). Thus, individual differences in frequency of physical aggression over time are very likely due to interactions between genetic and environmental mechanisms.

These gene-environment interactions have traditionally been studied from a statistical perspective with two types of samples: (i) twin studies by comparing differences among twins who share the same genes (monozygotes) and those who share only half of their genes (dizygotes; e.g. Dionne *et al.* 2003) and (ii) molecular genetic studies that compare differences between individuals who share the same or different polymorphic genes and the same or different environment (e.g. Caspi *et al.* 2002). However, gene-environment interactions are not simply an abstract mathematical concept. A third approach to understanding gene-environment interactions is epigenetic studies that attempt to understand the physiological mechanisms regulating gene expression. Genetic studies attempt to understand the genome that is identical in different cell types and throughout life. Epigenetic studies attempt to understand the epigenome that varies between cell type and during development. Numerous studies, especially cancer research, have shown that developmental, physiological and environmental signals lead to variation of the epigenome. Thus, genetic expression is a dynamic phenomenon dependent on developmental, physiological and environmental signals (Szyf 2003).

Unfortunately, our knowledge of gene-environment mechanisms that could explain and prevent the development of CPA is perilously close to zero. The first reason for this gap in our knowledge is that gene-environment interaction studies are recent. The second reason is that genetically informative longitudinal studies generally do not have repeated assessments of physical aggression from early childhood onwards (Rhee & Waldman 2002). The third reason is that these studies tend to concentrate on global antisocial behaviour phenotypes, often assessed at one point in time (Eley *et al.* 1999; Arseneault *et al.* 2003; Kim-Cohen *et al.* 2006). Genetic studies have simply followed the main trend that tends to rely on measurement scales constructed by lumping disruptive behaviour items that are shown to correlate at a given point in time.

Many molecular genetic studies have attempted to identify polymorphisms related to adult male aggressive behaviour in animals and antisocial behaviour in humans (Pihl & Benkelfat 2005). One of the rare studies to address the gene-environment interaction

issue with humans (Caspi *et al.* 2002) observed that males maltreated during their youth were at higher risk of being convicted of a violent crime before 27 years of age if they had the short version of the functional polymorphism in the gene coding for monoamine oxidase A (MAOA) activity. Replications of this study with other samples have found the same type of interaction (MAOA–maltreatment) but with different types of outcome. For example, one replication with adult males found the interaction for a composite measure of antisocial behaviour, and only for white subjects (Widom & Brzustowicz 2006); another replication found the same type of interaction for conduct disorder assessed during adolescence with a sample of male twins (Foley *et al.* 2004); and finally, a third replication with 7-year-old male twins (Kim-Cohen *et al.* 2006) found the significant gene–environment interaction for a composite mental health problem scale and attention deficit-hyperactivity disorder, but not for a total antisocial problem scale. Typically, physical aggression was not studied. Thus, we do not know if the MAOA–maltreatment statistical interaction found for physical violence assessed during adulthood is present during early childhood, childhood or adolescence. We also do not know if it is dependent on racial background and societal factors.

These are important questions to answer for finding effective preventive interventions of CPA for specific groups of individuals. Useful answers should come from research on the mechanisms that underpin the statistical interactions (e.g. Kraemer *et al.* 2008). The MAOA activity is believed to be linked to antisocial behaviour because it plays a key role in regulating behaviour by selectively degrading serotonin, nor-epinephrine and dopamine following reuptake from the synaptic cleft. Based on the CPA trajectories presented above, one would expect that the interaction between MAOA and maltreatment would have its greatest biopsychosocial impact during early childhood when individuals are learning to regulate their behaviour, especially physical aggression.

Knowledge on the underlying mechanisms should help find the best timing for the preventive interventions. Can interventions soon after maltreatment prevent its long-term negative impact or do we need to prevent early maltreatment? Recent experimental evidence suggests that intensive nurse home visitations after maltreatment has been detected does not have a positive impact (MacMillan *et al.* 2005), while intensive nurse home visitation from pregnancy to age 2 for mothers at risk of maltreatment has been shown to reduce abuse (Olds *et al.* 1986). However, as mentioned above, the latter study did not assess the children's development of physical aggression. We do not know if the reduction of parental abuse and neglect prevented the development of CPA.

An alternative prevention strategy for males with low MAOA activity born in families at risk for abuse would be to give the child a chemical treatment that would correct or compensate for the low MAOA activity. Admittedly, this is a bold suggestion, but animal studies are pointing in that direction, suggesting that we need to go much beyond the simple demonstration

of gene–environment statistical interactions (Weaver *et al.* 2006).

Recent experimental manipulations of early post-natal maternal behaviour effects on brain functioning are indeed showing that the gene–environment mechanisms involved are likely to be at the level of the epigenome, that is, environmental programming of the genome. For example, Weaver *et al.* (2004) manipulated post-natal mothering behaviour with rat pups showing that frequency of licking has long-term effects on brain functioning because it regulates the expression of genes that influence the development of the hypothalamic–pituitary–adrenal axis. Thus, the environment affects long-established epigenetic programmes in the brain. Szyf *et al.* (2007) conclude that ‘Since epigenetic programming defines the state of expression of genes, epigenetic differences could have the same consequences as genetic polymorphisms’.

Following this work with rats, we postulated that the adverse early environmental characteristics that predict a CPA trajectory for human males should have an impact on gene expression. We used a sample of males from low socio-economic background, who were found to be on a high physical aggression trajectory between 6 and 12 years of age and compared them with boys from the same background, who followed a normal physical aggression trajectory (Broidy *et al.* 2003). Preliminary analyses indicate that males on the CPA trajectory have substantially more methylated alleles when we look at T cells and more specifically at the IL-1B cytokine. The developmental pattern of these immune system differences will be important to study. Are the differences in gene expression at the origin of the behaviour differences or are they the product of the behaviour differences? Our hypothesis from the rat-licking model is that early adverse environment negatively affects gene expression which in turn disturbs brain development and eventually prevents adequate control over aggressive responses. Experimental work with pregnant monkeys has indeed shown that stress and substance use during pregnancy have a negative impact on offspring cognitive and behavioural development as well as on the immune system (Schneider *et al.* 2002; Coe & Lubach 2005; Coe *et al.* 2007).

## 6. TOWARDS EXPERIMENTAL EPIGENETIC STUDIES OF CPA PREVENTION

Twin studies and molecular genetic studies can address the gene–environment interaction issue. However, they fail to address the causal mechanisms leading to CPA because they are limited to a statistical analysis of correlations. To test causal mechanisms, we need the type of true experiments that are being regularly done with rats and monkeys (Foley *et al.* 2005; Weaver *et al.* 2006; Kraemer *et al.* 2008). Such studies are ethically impossible if the manipulation involves stressing healthy pregnant women, however, attempts to prevent stress in high-risk pregnant women are ethical and necessary if we are to find effective preventive interventions. Thus, experimental preventive interventions can kill two birds with one stone: identify basic mechanisms leading to CPA and identify effective

preventive interventions. From both perspectives, they are more likely to rapidly provide useful knowledge than traditional longitudinal studies. Randomized preventive control trials that manipulate mother's behaviour pre- and post-natally are not new (e.g. Olds *et al.* 1986), however, they are extremely rare and have failed to monitor effects on the development of gene expression, physiological structures, neurocognitive functioning and behaviour.

I will end this paper with two examples of research designs that could relatively rapidly provide experimental evidence on prenatal and early post-natal environmental impacts on CPA through gene expression and brain development.

The first research design involves randomly allocating primiparous pregnant women who smoke to a preventive intervention. There is good evidence from human and animal studies that prenatal exposure to nicotine affects not only birth weight but also brain development and behaviour (Vaglenova *et al.* 2004; Hsu *et al.* 2007; Huang *et al.* 2007). On the other hand, we have good evidence from methylation studies in cancer research that smoking has important epigenetic effects (Feinberg 2007; Haussmann 2007). From this evidence, we can hypothesize that smoking during pregnancy has negative epigenetic effects on brain development that eventually lead to problems with regulation of emotions and learning alternatives to physical aggression. A randomized control trial of smoking cessation during pregnancy could be followed by an assessment of differences between experimental and control groups in offspring's gene expression at birth, cognitive development and regulation of physical aggression, taking into account genetic characteristics such as MAOA activity.

The second research design builds on the first to understand timing of intervention (environmental) effects. The evidence that enriched post-natal environment can prevent pre-school CPA (Côté *et al.* 2007) and adult criminality (Schweinhart *et al.* 2005) suggests that the adverse effects of the prenatal environment can be substantially attenuated by a cognitively stimulating environment during the pre-school years. Using the first research design, we could randomly allocate half of the control group to an enriched environment such as a high-quality day care environment. By comparing the differences in gene expression at birth to the differences after the post-natal intervention would reveal to what extent a post-natal intervention can have an impact on gene expression which eventually accompanies changes in cognitive and behavioural development.

## 7. CONCLUSIONS

The aim of this paper was to highlight how developmental psychopathology, developmental epigenetics, and prevention experiments are starting to blend together to explain the developmental causes of chronic violent behaviour and, more importantly, to help prevent the serious physical, mental and social problems associated with chronic violence.

Traditional research on the development and prevention of antisocial behaviour often referred to physical

aggression and violence to justify its importance, but rarely reported results on these specific behaviours. Most of the research concentrated on adult and adolescent general antisocial behaviour while arguing that physical violence is learned during adolescence.

By monitoring the development of physical aggression from infancy onwards, recent longitudinal studies show that human infants spontaneously use physical aggression and that humans learn not to physically aggress rather than learn to aggress.

These studies underscore the importance of the prenatal and early post-natal development for learning to regulate physical aggression. Meanwhile, epigenetic studies of animal behaviour started to show that the quality of the early environment impacts brain development and behaviour through its impact on gene expression.

All together, these studies suggest that preventive interventions for violent behaviour need to start as closely as possible to conception. Unfortunately, to our knowledge, no randomized control trial has yet been implemented to specifically prevent early CPA, and none of the general preventive interventions during early childhood monitored the early development of physical aggression.

I conclude that randomized preventive control trials during pregnancy and early childhood with a specific focus on epigenetic effects are the research designs most likely to advance our understanding of the biopsychosocial mechanisms that lead to CPA, and the only research design that can lead to the identification of interventions that will effectively prevent the development of CPA and thus prevent the serious physical, mental and social problems associated with chronic violence.

## ENDNOTE

<sup>1</sup>pour que la succession des êtres ne soit pas régulière, pour que l'espèce varie et produise des êtres qui par rapport au type sont des monstres, il faut que cela provienne ou du germe ou d'une cause extérieure. La première doctrine était encore soutenable à l'époque où l'on pouvait croire à la préexistence des germes; mais de nos jours j'admets, avec tout le monde, la doctrine de l'épigénèse. Tout œuf normal qui donne naissance à un individu anormal est influencé par les agents extérieurs quels qu'ils soient; c'est là ce que j'appelle actions de milieu.

(Quatrefages 1863, p. 381)

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