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Sviluppo e prevenzione dell'aggressività fisica cronica

Development and prevention of chronic physical aggression

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Abstract
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. 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: physical aggression, early prevention, epigenetics.

Riassunto
Questo lavoro si propone di illustrare come gli studi sulla psicopatologia dello sviluppo, l'epigenetica e gli esperimenti di prevenzione comincino ad essere integrati al fine di comprendere le cause dell'aggressività fisica cronica e di aiutare a prevenire tale tipo di aggressività ed i problemi fisici, mentali e sociali ad essa associati. Programmi di prevenzione realizzati durante la gravidanza e la prima infanzia, con uno specifico focus sui meccanismi epigenetici, e rigorosamente controllati mediante randomizzazione, costituiscono lo strumento più adatto per far avanzare le nostre conoscenze sui meccanismi bio-psico-sociali che conducono all'aggressività cronica e l'unico modello di ricerca che può identificare gli intervento efficaci per prevenirla.

Parole chiave: aggressività fisica, prevenzione precoce, epigenetica.

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1. Development and prevention of chronic physical aggression

Until recently there were surprisingly few longitudinal studies with population samples that tried to chart the development of physical aggression before the elementary school years. This lack of attention to physical aggression during early in life seems to be the result of a long-held belief that physical aggression appears during late childhood and early adolescence as a result of bad peer influences, television violence and increased levels of male hormones. This view of antisocial development was very clearly described more than 200 years ago by Jean-Jacques Rousseau. The first phrase of his book on child development and education (Rousseau, 1762/1979), makes the point very clearly: "*Everything is good as it leaves the hands of the Author of things; everything degenerates in the hands of man.*" A few pages later he is still more explicit and appears to be writing the agenda for 20th-century research on the development of antisocial behaviour: "*There is no original sin in the human heart, the how and why of the entrance of every vice can be traced." Rousseau's strong stance was meant to be a clear opposition to Thomas Hobbes, who, a century earlier, had described infants as selfish machines striving for pleasure and power, and concluded: "It is evident therefore that all men (since all men are born as infants) are born unfit for society; and very many (perhaps the majority) remain so throughout their lives, because of mental illness or lack of discipline… Therefore man is made fit for Society not by nature, but by training.*" (Hobbes, 1647/1998).

A good summary of the modern version of Rousseau's social learning perspective can be found in the 1993 report of the US Academy of Science Panel on Understanding Violent Behavior: "*Modern Psychological perspectives emphasize that aggressive and violent behaviors are learned responses to frustration, that they can also be learned as instruments for achieving goals, and that the learning occurs by observing models of such behavior. Such models may be observed in the family, among peers, elsewhere in the neighborhood, through the mass media ...*" (Reiss & Roth, 1993). The 2002 World Health Organization report on violence was still more explicit on the timing of physical aggression onset: "*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.*" (Krug, Dahlberg, Mercy, Zwi, & Lozano, 2002).

In 1984 we initiated a longitudinal study of 1037 boys from low socioeconomic environments in Montreal to test this social learning hypothesis for chronic physical aggression. Results were very surprising (Nagin & Tremblay, 1999). The physically aggressive behaviour of the boys was assessed regularly from kindergarten to high school (Figure 1): 17 percent of the boys appeared never to have been physically aggressive; four percent showed a high frequency of physical aggression from six to 15 years of age; 28 percent started with a high level of physical aggression at age six and became less and less physically aggressive with time; while the majority (52%) had a low level of physical aggression at age six and also became less and less aggressive with time. In contrast to the social learning hypothesis and to the late onset hypothesis for antisocial behaviour (Moffitt, 1993) we did not find any group of boys in which there appeared to be an "onset" and maintenance of moderate or high levels of physical aggression for a significant number of years after age six. We also observed that for every group of boys the peak level of physical aggression frequency was during the first year of the study when they were in kindergarten.

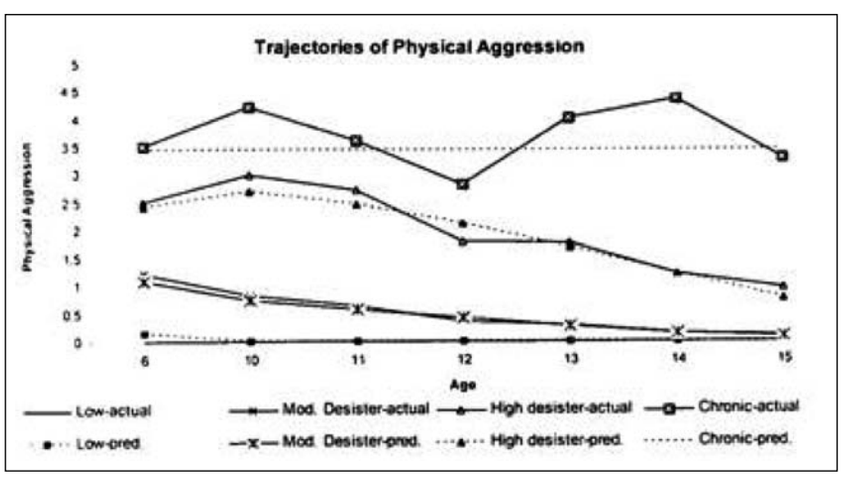

Grafico 1. Trajectories of Physical Aggression from 6 to 15 years of age (Nagin & Tremblay, 1999)

These results clearly challenge the idea that the frequency of physical aggression increases with age. They also challenge the notion that there is a significant group of children who show chronic physical aggression during late childhood or adolescence after having successfully inhibited physical aggression throughout childhood, as concluded by the WHO report on violence (Krug et al., 2002). This leaves us with the following question: If, between kindergarten and high school, children are at their peak level of physical aggression during their kindergarten year, when do they actually start to aggress physically?

2. Development of physical aggression during early childhood

To understand when children start to use physical aggression we initiated a longitudinal study of a random sample of births with annual assessments of physical aggression from 17 months of age. Results from this study and others afterwards (Alink et al., 2006; Hay et al., 2011; Tremblay et al., 1999) clearly showed that humans start to use physical aggression towards the end of the first year after birth when they have acquired the motor coordination to push, pull, hit, kick, etc. Figure 2 illustrates the results of the physical aggression developmental trajectory analyses from 17 to 60 months with the population birth cohort (Côté et al., 2007). We can see that half of the children are in the middle trajectory of physical aggression frequency, a third are on a low trajectory, while 17% are on a high trajectory.

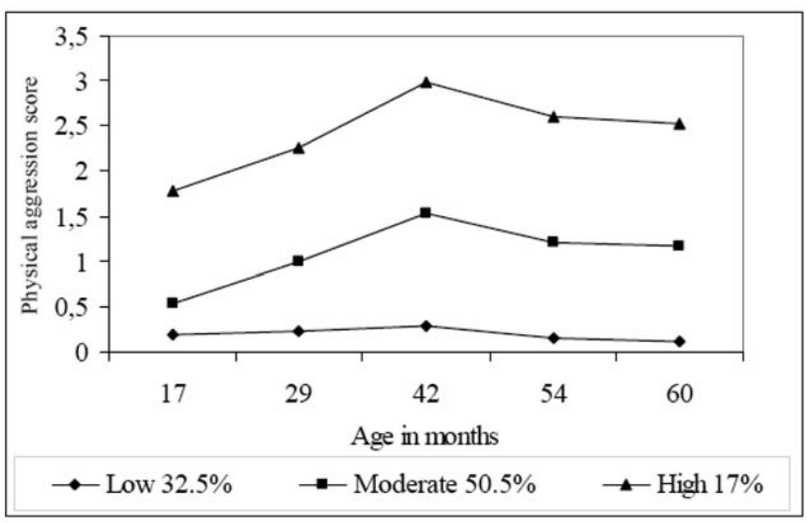

Grafico 2. Developmental trajectories of physical aggression from 17 to 60 months (Côté et al., 2007)

These analyses are based on prospective repeated assessments of physical aggressions reported by mothers over four years. From this perspective developmental trajectories should be a better estimate of a chronic behaviour problem than an assessment at a given point in time, even if that assessment attempts to reconstruct past behaviour. Longitudinal data has shown that within a year mothers do not recall the age of onset of their children's physical aggressions (Tremblay, 2000). In a clinical study of boys between 7 and 12 years of age the mean age of physical aggression onset reported by parents was 6.75 years (Frick et al., 1993). Retrospective information collected in the Pittsburgh Youth Study (Loeber & Hay, 1997; Loeber & Stouthamer-Loeber, 1998) compared to prospective data is a good example of the problem with retrospective dating of physical aggression onset. The subjects (N = 503) represented the Pittsburgh public schools' male 8th graders and were close to 14 years old (*mean age* = 13.8; *SD* = .80) at the first data collection. The cumulative age of onset of physical aggressions reported by the mothers and the boys at that first data collection indicated that by age 5 years less than 5% of the boys had initiated use of physical aggression and almost no one had initiated fighting. In sharp contrast, the prospective data represented in Figure 2 on physical aggression from 17 months after birth indicate that children who do not initiate physical aggression before 3 years of age are extremely rare. These prospective studies suggest that the peak frequency in use of physical aggression for most humans is somewhere between 2 and 4 years of age (see Figure 2 and NICHD Early Child Care Research Network, 2004). The recall problem suggests that retrospective assessments of children or adolescents cannot identify the age of onset and developmental trajectories of physical aggression use or of chronic physical aggression. Hence the conclusion reached by the World Health Organisation report on Violence (Krug et al., 2002) cited above needs to be seriously amended.

3. Developmental trajectories of physical aggression after early childhood

The developmental trajectories of physical aggression after early childhood have now been studied in many different cultures. From these studies we can expect between 7% and

11% of elementary school children on a chronic physical aggression (CPA) trajectory (Broidy et al., 2003; Campbell et al., 2010; Nagin & Tremblay, 1999). That percentage tends to be higher for preschool children (Côté et al., 2007; Tremblay et al., 2004) and lower for adolescents (Brame, Nagin, & Tremblay, 2001). This decrease in CPA cases with age corresponds to the general decrease in frequency of physical aggression with age, after the peak in early childhood (see Figure 3 from Tremblay & Côté, 2009).

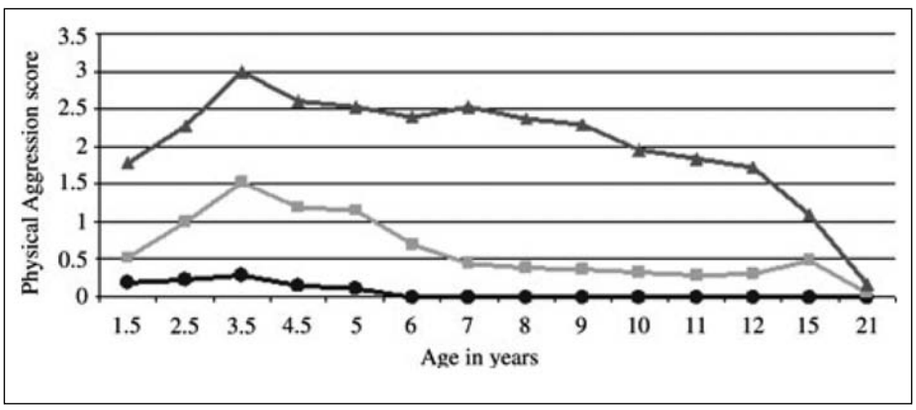

Grafico 3. Trajectories of physical aggression from infancy to adulthood (Tremblay & Côté, 2009)

Most children use physical aggression during the preschool years, but most children also learn to use alternatives to physical aggression with age, and this applies to a number of chronic cases during early childhood and preadolescence (Nagin & Tremblay, 1999). In fact there is good evidence that the learning process to gain control over physical aggression continues throughout adulthood. A longitudinal study of juvenile delinquents up to old age showed that the number of their violent offenses decreased with age (Sampson & Laub, 2003; see also Sweeten, Piquero, & Steinberg, 2013).

Crime records from the middle ages to modern times suggest that this phenomenon is not new. The likelihood of committing a homicide and most other crimes has always decreased from late adolescence and early adulthood to old age (Eisner, 2003; Quetelet, 1984). Trajectories of physical aggression covering different age periods (early childhood to childhood, childhood to adolescence, adolescence to adulthood) also indicate that CPA very rarely onsets after early childhood (Barker et al., 2007; NICHD Early Child Care Research Network, 2004; van Lier, Vitaro, Barker, Koot, & Tremblay, 2009).

4. Long term outcome of chronic physical aggression

Longitudinal studies of physical aggression trajectories during childhood have been used to study how well the trajectories predict future outcomes such as school performance, social adjustment, mental health and violent behavior. The first longitudinal study to describe developmental trajectories of physical aggression from school entry to adolescence (Nagin & Tremblay, 1999) reported that boys on a teacher-rated trajectory of frequent physical aggression from 6 to 15 years of age were at highest risk of self-reported violence as well as other forms of delinquency at 17 years of age, even after having controlled for hyperactivity and oppositional behavior. The chronically aggressive boys were also at highest risk of school drop-out. A study which used 6 longitudinal cohorts from Canada, New Zealand and the US (Broidy et al., 2003) reached the same conclusion for male adolescent violent delinquency, but not for female adolescent violent delinquency. The authors attributed the sex difference in prediction to the fact that the prevalence of female adolescent violent delinquency was too low. However, a later analysis of one of the female samples (Fontaine et al., 2008) reported that elementary school girls who were on a chronic physical aggression trajectory combined with a chronic hyperactivity trajectory were more likely than others to report physical and psychological aggression towards intimate partners by age 21 years. They were also more likely to report early pregnancy, welfare assistance, nicotine use problems and low educational attainment. A more recent analysis of a population sample of males and females (Pingault et al., 2013) reported that the 9.5% of children on a high physical aggression trajectory between 6 and 12 years, according to mother and teacher rating, represented 28.2% of all those who had a criminal record by age 24 years. In addition, they represented 45.9% of all recorded criminal charges and 57.4% of the violence charges. Therefore, children on a high trajectory of physical aggression during elementary school are not only more likely to have a criminal record but also to have more criminal charges. There is evidence that the criminal outcomes of childhood physical aggression during adolescence and adulthood are preceded by a large range of negative social and academic outcomes by the end of elementary school for boys and girls (Campbell et al., 2010).

5. Risk factors and causal mechanisms

Sex of the individual is one of the most important risk factor for chronic physical aggression. When children start using physical aggression at the end of the first year after birth there are no significant difference in frequency of physical aggressions between boys and girls (Hay et al.,

2011), however the differences appear soon after and increase until adolescence (e.g. Côté, 2007). Males between 10 and 15 years of age are close to 20 times (OR = 18.84) more at risk than females of being on a chronic physical aggression trajectory (van Lier et al., 2009).

Twin studies have become important tools to understand the contributions of environmental and genetic factors in the development of human characteristics, including aggression. However, to date there appears to be only one longitudinal study that used a large sample of twins from infancy onwards to study the contributions of genetic and environmental factors in the development of physical aggression. The study reported that 19 months after birth 58% of the variance in frequency of physical aggression rated by mothers could be attributed to genetic contributions and 42% to common environmental contributions (Dionne, Tremblay, Boivin, Laplante, & Pérusse, 2003). At 72 months after birth physical aggression was rated by kindergarten teachers. Genetic contribution to variance in frequency was then estimated to be 66% with 34% attributed to common environmental factors (van Lier et al., 2007).

Although these results suggest a substantial contribution to physical aggression by genetic factors to the use of physical aggression from infancy to school entry, environmental factors are also very important. The developmental trajectories of physical aggression described above indicate that the environmental conditions are essential to learn alternatives to physical aggression during early childhood. Studies of physical aggression trajectories during early childhood with singletons have identified the following types of environmental risk factors: a) Maternal characteristics, including life style and mental health, b) family characteristics, c) maternal parenting, d) child characteristics (Campbell et al., 2010; Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006; Hay et al., 2011; NICHD Early Child Care Research Network, 2004; Tremblay et al., 2004).

Maternal and family characteristics are key for planning preventive interventions because they can be used to identify pregnant women at risk of having children on a CPA trajectory (e.g. Olds et al., 1998). The maternal characteristics associated to chronic physical aggression include mothers' young age at birth of their child, mothers' smoking during pregnancy, mothers' antisocial behaviour during adolescence, mothers' depression, and mothers' low level of education. Family characteristics included low income, family dysfunction and the presence of siblings. High risk maternal parenting behaviour includes mother's hostile-coercive-harsh parenting and lack of sensitivity.

It is important to note that these studies of environmental risk factors were not done in the context of genetically informative designs (e.g. twin studies or sibling studies), hence we do not know to what extent the significant environmental risk factors are correlated or interact with genetic factors (Plomin, 1994; Szyf et al., 2009). Nonetheless, the environmental risk factors identified by these studies can be used to identify at risk groups for preventive experiments. Such experiments are useful to test the effectiveness of the interventions as well as test causal hypotheses (Schwartz, Flamant, & Lelouch, 1981; Tremblay, 2003). Maternal and family characteristics are especially key for early preventive interventions because they can be used to identify at risk pregnant women (e.g. Olds et al., 1998). The challenge for the future is to integrate preventive experiments within genetically informative longitudinal studies of risk factors.

The discovery of environmental effects on gene expression (epigenetics) is providing the tolls to meet this challenge (Tremblay, 2010; Tremblay & Szyf, 2010). The term "epigenetic" refers to the mechanisms which program genes and can change gene function without modifying gene sequence, mainly through changes in DNA methylation and chromatin structure. This programming is responsive to environmental effects, especially during foetal and early post natal development. Thus, environments can impact phenotypes through their chemical impact on programming of gene function (Mill & Petronis, 2008; Szyf et al., 2009).

To grasp the potential contribution of epigenetics for understanding the mechanisms involved in the development of chronic physical aggression it is important to understand the difference between the traditional gene- environment interaction story and the epigenetic story. Key differences can be understood by comparing two studies which attempt to explain the effects of a maltreating environment on development. In the gene-environment statistical interaction approach (Caspi et al., 2002) males brought up in a "maltreating" environment were observed to be more at risk of violent behaviour if they had a short rather than a long allele on the promoter region of the MAOA gene. In this example, the maltreating environment does not physically interact with the MAOA gene. The interaction is statistical, i.e. obtained from a 2x2 table comparing four groups created from two variables: maltreating-not maltreating and short-long MAOA allele. It is presumed that individuals who inherited either short or long alleles react differently to the maltreating environment because their neural system functions differently and such differences are due to MAOA activity.

Epigenetic studies have a different approach; they focus specifically on the physical effects of the environment on gene expression at a given moment during development. The classic example for effects of neglectful environments comes from an experimental study of maternal behaviour in rats which showed that rat pups insufficiently licked by their mothers in the days following birth (i.e. neglected) have increased methylation of the gene encoding the Glucocorticoid receptor in the hippocampus, resulting in reduced expression (Weaver et al., 2004; Weaver, Meaney, & Szyf, 2006). The study further showed that this gene methylation effect had downstream effects on the hypothalamic–pituitary–adrenal axis which regulates stress responses in the body.

Epigenetic mechanisms are especially important because they provide a powerful explanation for early maternal and family effects on the development of physical and mental health problems, including chronic physical aggression. Furthermore, DNA methylation changes over time can be used as markers of environmental effects during development, including assessment of preventive and corrective intervention effects. The above discussion of early risk factors showed that trajectories of chronic physical aggression are specifically related to maternal characteristics: maternal age at first pregnancy, history of behaviour problems, education, smoking, depression, coercive parenting, etc. This can easily be understood from the traditional environmental perspective: a poor early environment has an impact on the developing foetus and infant. Mother characteristics turn out to be more important risk factors than father characteristics because the former carry

the child in their womb during foetal life and are more involved in care giving during early childhood. However, the exact bio-psycho-social mechanisms linking poor quality environment to disorganised behaviour remain unclear.

The epigenetic story provides a basic mechanism that has the advantage of being parsimonious, testable and promising for prevention. The most fascinating aspect of this mechanism is that it provides an environmentally based explanation of intergenerational transmission for physical and mental disorders which involves genes but is not genetically transmitted. These mechanisms are still far from being clearly understood, but they provide a challenging alternative perspective to the traditional gene vs. environment and gene-environment interaction hypotheses (McGowan, Meaney, & Szyf, 2008; McGowan et al., 2009; Rutten & Mill, 2009).

The first epigenetic study of children with chronic physical aggression (Wang et al., 2012) used subjects from the longitudinal study of boys living in low socio-economic environments described above (Nagin & Tremblay, 1999; Tremblay, Pihl, Vitaro, & Dobkin, 1994). Blood was collected from two groups of the boys when they were 27 years old to assess DNA methylation patterns (in monocytes and T cells) of the serotonin transporter (5-HT). The first group included boys who were on a high trajectory of physical aggression during childhood. The second group included boys who were on a normal trajectory of physical aggression. Brain imaging of serotonin synthesis was also obtained from the same boys around age 27 years. We found that chronic physical aggression during childhood was associated to increased DNA methylation in specific CpG sites in monocytes and T cells of the serotonin transporter gene. Interestingly, we also found associations between measures of serotonin synthesis in the brain and differential DNA methylation in T cells and monocytes in the same CpG sites that revealed association with chronic physical aggression during childhood. These findings are the first evidence of the association between environmentally related differences in DNA methylation in white blood cells and in vivo measures of 5-HT in the living human brain.

6. Conclusions: How to further advance knowledge on the prevention of chronic physical aggression

Experimental studies with rats and monkeys which started at birth (ex. Provençal et al., 2012; Weaver et al., 2004) are suggesting that the associations between DNA methylation and aggression observed in humans were caused by perinatal environmental effects. To confirm this hypothesis we will need two types of studies. The longitudinal studies approach would be to assess DNA methylation at birth and follow the children up to adulthood to confirm the differences observed in adults. However this would take a long time and would offer only correlational evidence. The shorter and more rigorous approach would be the use of experimental preventive interventions starting during the perinatal period. The maternal and family risk factors described above can be used to identify high risk pregnant women and randomly allocate them to preventive interventions that have been shown to have long term impacts on children's behaviour development (e.g. Eckenrode et al., 2010). By comparing the DNA methylation profiles at birth and throughout development of children in the experimental and control groups we will be able to confirm if inadequate prenatal environments impact methylation patterns and if these impacts can be reversed by pre and early postnatal preventive interventions (Tremblay, 2010).

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