Chapter 10
The Impact of Environmental Stressors on DNA Methylation, Neurobehavioral Development, and Chronic Physical Aggression: Prospects for Early Protective Interventions

Richard E. Tremblay, Linda Booij, Nadine Provençal, and Moshe Szyf

Abstract There is now convincing evidence from prospective and retrospective epidemiological studies that prenatal and early post-natal stressors have long term impacts on life span health and well-being. Unraveling the mechanisms by which early environmental stressors have an impact on DNA methylation and neurobehavioral development should provide the foundation for creating effective early protective interventions. We review the recent convergence of four research domains to explain the mechanisms leading to chronic physical aggression (behavior development, epigenetics, serotonin neurotransmission and immunology) and we discuss the next generation of studies that are needed to identify effective pre and post natal preventive interventions.

Keywords Environmental stressors • Aggression • Neurodevelopment • Epigenetics • Prevention

R.E. Tremblay, Ph.D. (✉)
School of Public Health, University College Dublin, Belfield, Dublin, Ireland

Université de Montréal, 3050, Édouard-Montpetit Blvd, Montréal, QC H3T 1J7, Canada
e-mail: richard.tremblay@ucd.ie; richard.ernest.tremblay@umontreal.ca

L. Booij, Ph.D.
Department of Psychology, Concordia University,
7141 Sherbrooke St. West, Montreal, QC H4B 1R6, Canada

CHU Sainte-Justine, 3175 Chemin de la Côte Sainte-Catherine, Montréal, QC, Canada
e-mail: linda.booij@concordia.ca; linda.booij@umontreal.ca

N. Provençal, Ph.D.
Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, 80804 Munich, Germany
e-mail: nadine_provencal@psych.mpg.de

M. Szyf, Ph.D.
Department of Pharmacology and Therapeutics, McGill Faculty of Medicine,
McIntyre Medical Building, 3655 Prom. Sir-William-Osler, Room 1309/1310,
Montreal, QC H3G 1Y6, Canada
e-mail: moshe.szyf@mcgill.ca

C.L. Hughes, M.D. Waters (eds.), *Translational Toxicology*, Molecular and Integrative Toxicology, DOI 10.1007/978-3-319-27449-2_10

10.1 The Developmental Origins of Chronic Physical Aggression

The development of physical aggression throughout early childhood has only very recently been studied with large population samples. This lack of attention to the developmental origins of physical aggression during early childhood appears to be the result of a long-held belief that humans start to use physical aggression after early childhood as a result of exposure to violent behavior (e.g., Bandura 1977; Lefkowitz et al. 1977; Zimbardo 2007). Indeed the 2002 World Health Organization report on violence concluded: "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 et al. 2002). The putative developmental mechanisms leading to this phenomenon had been described a decade earlier 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 and Roth 1993).

However, from an evolutionary perspective there are good reasons to doubt that humans have to learn to aggress. Physical aggression is a crucial component of human's behavioural heritage. Our ancestors needed to be skilled in the art of physical aggression to eat, to defend themselves against predators, to compete for mating, to protect their brood, and to acquire resources. However, like all other social animals, humans need to learn to use aggression sparingly because physically aggressive encounters can be fatal, and lack of self-control among social animals leads to social exclusion (Boivin et al. 2005; Suomi 2005). The relative absence of fear from being murdered is recent. Historical analyses of homicide rates indicate that physical violence has systematically and substantially decreased among European citizens over the past 500 years (Eisner 2003). Homicides in European cities decreased from 40 to 1 per 100,000 citizens per year. Looking further back from an evolutionary perspective, the estimated rate of "homicide" among our closest non-human relatives, chimpanzees, is 261 per 100,000 (Wrangham et al. 2006).

10.2 Development of Physical Aggression During Early Childhood

Studies of physical aggression during infancy have clearly shown 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. (Alink et al. 2006; Hay et al. 2011; Naerde et al. 2014; Tremblay et al. 1999). For example, analyses of

physical aggression developmental trajectorie from 17 to 60 months with a population birth cohort (Côté et al. 2007) showed that all children increased the frequency of their physical aggression from 17 to 42 months of age and then decresed their frequency until 60 months. thatA third of the children were on a low trajectory of physical aggression, half were on a middle trajectory, while 17 % were on a high trajectory.

These analyses are based on prospective repeated assessments of physical aggressions reported by mothers over 4 years. The prospective studies of physical aggression during early childhood indicate that the peak frequency in use of physical aggression for most humans is somewhere between 2 and 4 years of age (Tremblay and Côté 2009; NICHD Early Child Care Research Network 2004)

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 CPA trajectory (Broidy et al. 2003; Campbell et al. 2010; Nagin and Tremblay 1999). That percentage tends to be higher for preschool children (Côté et al. 2007; Tremblay et al. 2004) and lower for adolescents (Brame et al. 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.

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 and 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 and Laub 2003; see also Sweeten et al. 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 et al. 2009).

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 and 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 dropout. 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).

10.3 Early Risk Factors of Chronic Physical Aggression and Putative 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., Baillargeon et al. 2007; 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 et al. 2003), furthermore, a large part of the variance in frequency of aggression change over time was attributed to genetic factors (Lacourse et al. 2014).

Although these results suggest a substantial contribution to frequency of physical aggression by genetic factors from infancy to school entry, this development does not happen in a vacuum, 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 et al. 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 et al. 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).

10.4 Physical Aggression, Brain Development, and the Role of Serotonin

Although the neurobiological substrates of physical aggression are many, one of the most consistent biological correlates of physical aggression is altered serotonin (5-HT) neurotransmission (Siever 2008). Following the early observation that low levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) is associated with impulsive aggression (Brown et al. 1979), a number of studies have further confirmed this association, using other indices of 5-HT neurotransmission, such as neuro-endocrine challenge methods (e.g., Coccaro et al. 1989) and tryptophan depletion procedures (Cleare and Bond 1995; Moeller et al. 1996).

Neuro-imaging studies provided evidence that aggression problems might result from top-down suppression deficits in (cortical regions (Orbitofrontal (OBFC), anterior cingulate) in combination with excessive *bottom up* signalling by the amygdala (Booij et al. 2010; Davidson et al. 2000; Siever 2008). All of these brain regions are densily innervated with 5-HT neurons and 5-HT receptors (Azmitia and Gannon 1986; O'Rourke and Fudge 2006; Steinbusch 1981). As 5-HT in the Prefrontal

cortex (PFC) facilitates inhibition of the amygdala, impaired 5-HT function in these regions could result in an increased amygdala response to social threat, which could trigger an aggressive response (Davidson et al. 2000; Siever 2008). Consistent with this, neuro-imaging studies in individuals with high levels of aggression found reduced metabolic response in the frontal-limbic regions in response to administration of 5-HT agonists (New et al. 2002; Siever et al. 1999). In addition, Positron Emission Tomography (PET) studies in combination with 5-HT radioligands showed that individuals with high levels of impulsive aggressive behaviors indicated lower 5-HT transporter (SLC6A4) density (Frankle et al. 2005) and lower 5-HT synthesis capacity, in the same regions (Leyton et al. 2001; Leyton et al. 2006), relative to controls. Taken these findings together suggests that altered 5-HT function in the frontal-limbic circuits are associated with aggression problems.

Of relevance is our study, investigating 5-HT synthesis in a community sample of healthy 27 year adult males who were rated regularly between age 6 and 15 by their teachers on measures of physical aggression as well as on a variety of psychosocial and psychological factors. Subjective measures of aggression confirmed that individuals in the high physical aggression developmental trajectory exhibited more aggressive behaviors during childhood and adolescence, but not in adulthood. However, males with high physical aggression in childhood compared to those with low physical aggression during childhood and adolescence had lower brain 5-HT synthesis bilaterally and specifically in the OBFC (Booij et al. 2010). Though 5-HT function was not measured in childhood and adolescence in this sample, the results are in line with studies in nonhuman primates, showing that 5-HT metabolism remains stable for at least a decade (Howell et al. 2007). Hence, diminished 5-HT neurotransmission in the frontal-limbic circuitry may be a persisting trait rather than state characteristic. Notably, our cohort members did not differ in terms of current aggression levels, impulsivity, mood, working memory or psychosocial functioning; Although other biological factors cannot be ruled out, taken these findings together suggest that 5-HT alterations may be an important etiological predisposing biological factor in aggression. However, whether actual aggressive behaviors are expressed, is likely to depend on other biological factors, experiences and environmental support during development. In line with this so-called "diathesis-stress" model are studies of gene-environment interactions, showing associations between specific genotypes of 5-HT genes (i.e., monoamine oxidase A enzyme (MAOA) gene, SLC6A4 gene) and aggression, but only in the context of early life adversity (Aslund et al. 2011; Caspi et al. 2002; Reif et al. 2007; Suomi 2006).

An important question in this context is *how* 5-HT alterations develop, and how these alterations could lead to physical aggression. In addition to being a neurotransmitter, animal and human studies have shown that 5-HT is important for the development and maturation of the human brain (see Booij et al. 2014, review). For instance, in humans, the first 5-HT neurons in the raphe neurons appear already by 5 weeks of gestation (Booij et al. 2014; Whitaker-Azmitia 2001, review). Many aspects of 5-HT system development, including innervation, fiber density and synthesis appear to be largely matured in early childhood. However, 5-HT receptors, enzymes and proteins appear to have a unique developmental pattern, with some

them fluctuating up to adulthood, while other 5-HT proteins and enzymes stabilizing already early in life (Booij et al. 2014). The expression of specific receptors, enzymes and generally relevant proteins appears in turn to modulate specific brain developmental processes (Gaspar et al. 2003).

Of particular interest in the context of physical aggression is the gene coding MAOA; an enzyme responsible for breaking down monoamines, and thus an important regulator of the levels of monoamines throughout the brain, including 5-HT. A deficiency of this enzyme has been associated with aggression in animal models (Cases et al. 1995) and humans (Brunner et al. 1993). In terms of development, research has shown that activity of the MAOA enzyme in the human frontal cortex increases up to birth, then diminishes during the first year of life, and stabilizes around age 2 (Kornhuber et al. 1989); a pattern quite consistent with what has been observed in rodents (see Booij et al. 2014). Notably, this developmental pattern (early peak, stabilization in early life) seems to precede, and is quite similar to the developmental pattern of physical aggression (see above).

Although the specific role of SLC6A4 in aggression is less clear, with studies both positive and negative associations, it has now widely been demonstrated that SLC6A4 in particular plays a major role in brain development (Booij et al. 2013, 2014; Gaspar et al. 2003; Lesch and Mössner 2006). Studies have shown that SLC6A4 is one of the first 5-HT molecules to develop during pregnancy (Booij et al. 2014, review). When it is stabilized in development depends on brain region. For instance, studies in rodents have shown that SLC6A4 density in the forebrain increases up to adulthood, while densities remain steady after P25 (late adolescence) in the striatum, midbrain and brain stem (Booij et al. 2014).

Hence, both MAOA and SLC6A4 are important regulators of 5-HT neurotransmission, and also have been implicated in physical aggression. Although it is clear that no specific 5-HT molecule is unequivocally associated with any specific behaviour, it would be of interest for longitudinal studies to further examine developmental changes in 5-HT expression levels over time, and how these changes in 5-HT molecules are associated with developmental changes in aggression. Given the observed sex differences in chronic aggression (see above), as well as the observed sex differences in (adult) serotonin functioning (Nishizawa et al. 1997), it would further be of interest to study how sex differences in physical aggression would relate to sex differences in 5-HT development.

Given the role of 5-HT in brain development and in aggression, it is reasonable to assume that a disruption in the very early stage in the system could interfere with normal brain development, with consequences for risk of physical aggression. Most clear evidence supporting this notion comes from genetic knockout studies. For example, SLC6A4 KO mice show functional and structural cortical brain alterations (e.g., Ansorge et al. 2004). In addition, in a sample of transgenetic mice, deletion in the gene encoding MAOA led to increased levels of aggressive behaviors and several changes in brain structure, some of them persisting in adulthood (Cases et al. 1995; Shih et al. 1999). The increased aggression levels in MAOA KO mice can be reversed by SSRIs, suggesting that the behavioural effects possibly underlie devel-

opmental alterations of the SLC6A4 (Godar et al. 2014), thereby further supporting the important role of SLC6A4 in brain development.

In humans, the role of 5-HT in brain development is supported by molecular imaging studies (see Booij et al. 2014, review). For instance, a number of studies now have shown that carriers of so called "risk" alleles (i.e., the s allele of the serotonin transporter, the low expression variant of the MAOA gene), show increased amygdala activity in response to emotional stimuli and diminished activation in the PFC, including the OFBC and the cingulate; limbic volume reductions; and altered connectivity between the prefrontal cortex and amygdala (e.g., Buckholtz et al. 2008; Canli et al. 2006; Heinz et al. 2005; Meyer-Lindenberg et al. 2006; Munafo et al. 2008).

Psychosocial stressors in early life can also alter 5-HT function. For instance, early maternal separation in rodents alters 5-HT neurotransmission in the frontal cortex (Jezierski et al. 2006; Matthews et al. 2001). In primates, rhesus macaques that have previously experienced high rates of rejection from their mothers after birth have lower levels of the 5-HT metabolite 5-HIAA in adulthood (Higley et al. 1996). The influence of early psychosocial adversity on the development of the 5-HT system is further supported by in vivo PET studies of the SLC6A4, showing that adolescent monkeys who were raised by their peers had, relative to mother-raised monkeys, decreased SLC6A4 and 5-HT_{1A} binding in the raphe and frontal-limbic regions (Ichise et al. 2006; Stevens et al. 2009). In vivo measures of reduced SLC6A4 density have also been associated with higher levels of impulsive aggression in humans (Frankle et al. 2005). Evidence for 5-HT alterations as a result of adversity also exists in humans. For instance, adults in low socioeconomic environments or who reported high rates of parental neglect in childhood showed blunted prolactin response to fenfluramine challenge (Manuck et al. 2005), as an indicator of impaired 5-HT function, and lower 5-HT metabolite levels in the cerebrospinal fluid (Roy et al. 2002). In a study of males followed since childhood, we observed that lower 5-HT synthesis in the frontal-limbic circuitry (OBFC and hippocampus) was associated with maternal smoking in pregnancy, lower birth weight and birth complications. All of these three in utero and early postnatal adversities have previously been shown to be predictive of physical aggression (Arseneault et al. 2002; Huijbregts et al. 2008). Hence it is tempting to speculate that 5-HT alterations in these regions may be an underlying mechanism of how such early adversities can translate into risk for chronic physical aggression.

10.5 Epigenetic Effects of Early Stressors and Pathways to Chronic Physical Aggression

10.5.1 The Serotonergic System

An emerging number of studies provide evidence for the role of epigenetic processes as physiological mechanism through which genetic and environmental factors may interact, and consequently brain and behavioural alterations may develop (Booij

et al. 2014). Following the initial observation of how early stress affect methylation in rodents and in the post-mortem human brain (McGowan et al. 2009; Weaver et al. 2004), a number of studies have shown that early stress was associated with altered levels of methylation in 5-HT genes like MAOA and SLC6A4 in the living human brain, using peripheral cells (see Booij et al. 2013, review). For example, Beach et al. (2011) identified an association between women victims of child sexual abuse and overall hypermethylation of the SLC6A4 (5HTT) promoter region (Beach et al. 2011). In addition, they observed a significant association between DNA methylation in SLC6A4 promoter with symptoms of ASPD in women that was also partly mediated by 5-HTTLPR polymorphism (Beach et al. 2011). Thus, child sexual abuse may create long-lasting epigenetic changes in the SLC6A4 gene promoter and lead to female antisocial behavior. With regard to physical aggression, we observed that SLC6A4 promoter methylation in white blood cells of adults was associated with higher childhood physical aggression and with lower in vivo measures of brain 5-HT synthesis in adult males (Wang et al. 2012). Although causality cannot be established in any of these studies, it can be hypothesized that early stress may lead to altered methylation levels of the SLC6A4 promoter, with consequences here for brain chemistry and behaviour. This was further supported by a very recent report that greater SLC6A4 methylation assessed in whole blood DNA, was associated with lower hippocampal volume, a brain region with rich 5-HT innervation and important for stress regulation (Booij et al. 2015). Similarly, we recently observed greater methylation in the MAOA promoter in individuals with Antisocial Personality disorders relative to controls (Checknita et al. 2015); while another research group reported a correlation between MAOA methylation levels and in vivo PET measures of MAOA (Shumay et al. 2012).

Hence, taken together these findings suggest that, in addition to genetic factors, the in utero or early postnatal environment influence 5-HT homeostasis. A disruption in 5-HT homeostasis, could alter the trophic properties of 5-HT at play during the critical periods of brain development, in many different ways, affecting the brain at various levels, through various mechanisms. It may alter 5-HT innervation, expression levels of certain proteins, enzymes, receptor functioning, synthesis, all of which may interact. This may in turn predispose the individual to structural and functional alterations in brain circuits such as the frontal cortex and the amygdala, previously identified as key regions in the modulation of aggression; and increase vulnerability to enduring patterns of aggressive behaviors, in the context of further adversity.

It is clear that 5-HT neurotransmission and associated proteins are also influenced by multiple factors other than the trophic factors considered here; those include, among others, age and sex, other 5-HT molecules, and, importantly, the impact of other biological systems. The specific consequences on behaviour on disrupting 5-HT neurotransmission, if any, ultimately depend on the complex interplay between these various factors.

10.5.2 The Immune System

Using peripheral blood cells DNA from monocytes and T cells, we recently reported an association between childhood CPA in men and differential DNA methylation in regulatory regions of cytokine and transcription factor genes (Provencal et al. 2013b). Moreover, these cytokines were also shown to be repressed in men with CPA compared to men on normative developmental trajectory of aggressive behaviour (Provençal et al. 2013a). Interestingly, one of these downregulated cytokine in men with CPA, Interleukin-6 (IL-6), was previously shown to be involved in aggressive behaviour in mice since it's knockout (IL-6 (–/–)) resulted in increased aggressive behaviour phenotype in these mice (Alleva et al. 1998). In humans, a growing body of research also suggests that inflammatory cytokines might have systemic effects in addition to their traditional roles in the immune response. Indeed, recent studies have shown that cytokines are associated with various behavioural disorders such as anxiety, depression, suicide, childhood mood disorder and PTSD (Dowlati et al. 2010; Groer and Morgan 2007; Hoge et al. 2009; Janelidze et al. 2010; Koo and Duman 2008; Smith et al. 2011; von Kanel et al. 2007) as well as aggression (Marsland et al. 2008; Suarez et al. 2002). Moreover, early life stress such as social isolation and prenatal anxiety has been found to alter the immune system (Barreau et al. 2004; Danese et al. 2007; Powell et al. 2013; Sloan et al. 2007). Previous studies from our group and others that have examined associations of genome-wide DNA methylation profiles with adverse exposures have pointed to immune pathways, both in the brain and in the periphery. Maternal deprivation in rhesus macaques (Provençal et al. 2012), early life socioeconomic position (Borgho l et al. 2012; Kieseppa et al. 2004), child abuse (Suderman et al. 2014) and PTSD (Mehta et al. 2013; Smith et al. 2011; Uddin et al. 2010), all found DNA methylation associations in promoters regulating genes in the immune response pathways. Together these results suggest that immunoregulators are responsive to early life stress and might be involved in aggression where DNA methylation could be one of the mechanisms that mediate this association. These immonuregulators could influence brain circuitry and behaviour through a wide variety of other biological systems, including serotonin and the HPA-axis. For instance, with regard to 5-HT, cytokines have been shown to influence 5-HT synthesis and transporter expression (Capuron and Miller 2011). The interaction between cytokine and 5-HT has been hypothesized as a mechanism for the etiology of depression (Myint and Kim 2003). It could be speculated that it may also hold for chronic aggression.

Importantly, effects of immuneregulators also occur through their action on the hypothalamic-pituitary-adrenal (HPA) axis previously shown to play a role in aggression.

The HPA axis is considered to be the most important system in stress regulation. Upon its activation corticotrophin releasing hormone (CRH) and vasopressin (AVP) are released from the hypothalamus and stimulate adrenocorticotropic hormone (ACTH) release from the pituitary into the blood. This results in cortisol secretion from the adrenal cortex. The cellular actions of the cortisol are mediated by its bind-

ing to the glucocorticoid receptor (GR) and the mineralocorticoid receptor that act as transcription factors and are expressed in most tissues. Once activated, GR and MR translocate into the nucleus where they can exert their function as transcription factors regulating adaptive responses to stress, including metabolism, immune activation and cell proliferation and differentiation. At multiple levels of the HPA axis, the activation of the GR will initiate a negative feedback loop that is responsible for terminating the stress response and therefore the secretion of cortisol. A decrease in GR expression/activation is generally associated with an increase in the response to stress due to an impaired negative feedback. In addition, there is strong evidence of a crosstalk between the immune system and the brain through the HPA axis. It is well known that increases in glucocorticoid levels in response to activation of the HPA axis results in a profound silencing of gene expression of pro-inflammatory proteins and cytokines. Also, it was shown that early life social class can affect the expression of genes bearing response elements to transcription factors regulating immune genes such as CREB/ATF, NFKB and GR. Thus, the effects observed on the immune system in relation to aggression could be due to a dysregulated HPA axis and therefore alterations in the cortisol release and actions.

In general, correlations have been found between reduced cortisol levels and increased aggression levels in adolescents and young men (Loney et al. 2006; Popma et al. 2007; Shirtcliff et al. 2005). In contrast, boys with conduct disorder (CD) from the same cohort as the one studied here had elevated salivary cortisol levels compared to those without CD. Moreover, boys with an aggressive form of CD had even higher cortisol levels. A strong correlation was also observed between reactive aggression and elevated cortisol (van Bokhoven et al. 2005). It is important to note that maltreatment in childhood also leads to low basal cortisol in association with conduct and aggressive disorders (Tarullo and Gunnar 2006). Together, these results indicate that both hyper- and hypoactive HPA axis might explain children's aggression, where hyperactivity may be involved in reactive aggression and hypoactivity may be involved in proactive aggression.

Prenatal stress exposure to high levels of glucocorticoids, were also shown to promote aggressive behaviour (Glover 2011). In chicken, *in ovo* injection of high dose of cortisol during embryonic development was shown to increase aggressive behaviours through alteration of the HPA axis and serotonin system (Ahmed et al. 2014). Reduced hypothalamic levels of GR protein and CRH mRNA levels accompanied by increase in DNA methylation in the GR and CRH gene promoters were observed in the chicks. Here, prenatal cortisol exposure caused epigenetic reprogramming of critical genes that in turn, altered the HPA axis and enhanced aggressive behaviour.

In rats, exposure to early adverse life experiences was shown to induce high and sustained rates of increased aggressive behaviour in adulthood. In their model, Marquez et al. found that peripubertal exposure to stress (fear-induction experiences) induces pathological aggression in male rats (Marquez et al. 2013). These peripubertal stressed rat also exhibited hyperactivity in the amygdala and hypoactivity in the medial orbitofrontal cortex after exposure to social challenge. Interestingly, these neuroimaging brain activity data were accompanied by a

sustained increase in *MAOA* expression in the PFC of stressed animals that is likely to be explained by epigenetic modulation. Indeed, they found an increase in histone 3, but not histone 4, acetylation levels in the promoter of the *MAOA* gene. Histones acetylation are known to promote gene transcription by increasing the accessibility to active transcription regulators binding (Kuo and Allis 1998) and especially histone 3 acetylation have been shown to play a role in regulating long-term changes in gene expression (Tsankova et al. 2007). Together these finding with the previous work on *MAOA* gene support the hypothesis that either MAOA hypo- or hyperactivity contribute to pathological aggression (Nelson and Trainor 2007) possibly through epigenetic programming.

The epigenetic association studies presented above mainly focused on candidate genes that either were suspected or previously shown to be involved in aggression. Another approach that was successfully used in the past to find significant association with diseases and behaviour is an unbiased genome-wide approach (Mehta et al. 2013). Using this approach to analyze men T cell epigenomes, we previously identified significant associations of DNA methylation levels with childhood CPA in distinct gene promoters (n = 448) involved in biological pathways related to behaviour and immune function, and their colocalisation in genomic clusters (Provençal et al. 2014). Interestingly, some of these differentially methylated genes, such as the *AVP receptor* 1A (*AVPR1A*), *SLC6A3* (dopamine transporter) and *serotonin receptor 1D* (*HTR1D*), were previously associated with aggressive phenotype in humans (Guo et al. 2007; Vage et al. 2010; Vaughn et al. 2009) and animals (Ferris et al. 2006; Hammock et al. 2005). As anticipated from our previous study in cytokine genes (Provencal et al. 2013b), the inflammatory and immune biological function with specific signalling pathway such as cytokines signalling between immune cells, IL-6 and IL-10 signalling were found enriched with genes differentially methylated in men with CPA. Specific cytokines and receptors involved in these pathways were previously shown to be involved in aggression and human mood disorders such as IL1R1 and IL1RN (Pesce et al. 2011). Together, these findings suggest a well-defined, genome-wide epigenetic pattern associated with chronic physical aggression in men.

Not only aggressive behaviour in men but also in women were studied for DNA methylation associations. Indeed, in another study performed by our group, we observed similar DNA methylation signatures associated with childhood CPA in women (N = 430 promoters) as seen in men where 31 gene promoters were significantly associated in both sexes (Guillemin et al. 2014). Interestingly, a significant portion of this overlap is due to identical genomic sites being differentially methylated in a sex-independent fashion. The almost perfect overlap between functional categories represented by both men and women signatures provides further evidence for these signatures to be, at least in part, associated with aggression rather than confounding factors. Here also, specific genes involved in serotonin metabolism and HPA axis regulation, previously shown to be involved in aggression, were found differentially methylated in women with childhood CPA. These HPA regulating genes (*NR3C1* and *CRHBP*) were only found differentially methylated in women with CPA. This may be explained in part by the fact that the HPA axis nega-

tive feedback control have been shown to be more sensitive in females than in males (Keck et al. 2002). These sex-specific and sex-independent components of the epigenetic signature are consistent with the existence of sex differences and similarities observed in human physical aggression.

10.6 Prenatal and Early Postnatal Prevention of CPA

The observation of the long-term influence of adverse factors occurring during the prenatal or early postnatal period on development of biological systems (brain, immune, HPA-axis), is consistent with the notion that early interventions in at risk populations should start as close as possible to conception, and continue supporting the family and the child as long as needed (Petitclerc and Tremblay 2009; Tremblay 2010). Preventive interventions during pregnancy for at risk pregnant women and family members are in fact corrective interventions for women who have a long history of social and mental adjustment problems. Many of them started to have children during adolescence and choose mates that also have a long history of behavior problems, thus increasing the likelihood of numerous forms of adversity during and after pregnancy. Interestingly, this was one of the main conclusions of the Swiss child psychiatrist Lucien Bovet in the first report the World Health Organization commissioned after its creation (Bovet 1951).

Preventive interventions with at risk women during and after pregnancy will not modify the genetic code, but they are likely to impact DNA expression. Epigenetic studies are giving tools to assess the epigenetic effects of preventive interventions during pregnancy and infancy. Because short term effects of adversity during pregnancy on DNA expression may be good markers of long term effects, they should be used to compare the effectiveness of different forms of interventions. These experimental preventive interventions can also be used to test environmental effects on the cascade of biological effects that follow gene expression and lead to the behavior problems which we described above. For example, we can test the effects of smoking cessation experimental interventions during pregnancy on DNA expression at birth and eventually on CPA (Caporaso et al. 2009; Markunas et al. 2014; Nielsen et al. 2014).

However, interventions that only target specific risk factors such as smoking during pregnancy are unlikely to have long term impacts on children's development since most of the at risk women have a large array of risk factors besides smoking during pregnancy (ex. stressful marital relations, inadequate nutrition, depression, impulsive and antisocial behaviour). Preventive interventions need to target all the risk factors. To our knowledge no experimental prenatal or early postnatal interventions have specifically targeted the reduction of CPA in the offspring. However, good models of preventive interventions targeting women with many risk factors during the prenatal and the early post natal period were implemented three decades ago and have shown long term impacts on numerous aspects of children's development that are related to CPA. For example, in the Elmira Home Visitation prevention

experiment (Donelan-McCall et al. 2009; Olds et al. 1997, 1998) participants were mostly low-income, unmarried, pregnant adolescents. Other pregnant women were included in the study to prevent stigmatization. Three experimental groups were created by random allocation. Women in the first group were visited weekly by a nurse for the first month after enrolment in the study, twice a month until birth, weekly for the first 6 weeks after birth, twice a month until the baby reached 21 months, and monthly until the child reached the end of the second year. Women in the second group received home visits only during pregnancy, while women in the third group had a screening interview after birth and free transport to the health clinic between the child's birth and the end of the second year. Mothers and children have been followed up to the children's early adulthood and significant positive impacts were observed from early childhood (Olds et al. 1986) to early adulthood (Eckenrode et al. 2010). We do not know to what extent the intervention had an impact of CPA because this range of behavior was not systematically assessed, but the population they targeted includes those that are at high risk of having children with CPA, while the content and intensity of the intervention would be expected to impact the cascade of biological processes described above. Interestingly, the assessment 19 years after the children's birth indicated that the female children had benefited more from the intervention than the males. The girls from the intervention group had been significantly less involved in deviant behavior. Also the girls born to unmarried mothers and low-income mothers had significantly fewer children and less Medicaid use (Eckenrode et al. 2010). These results suggest that intensive support to at risk pregnant mothers has significant impacts, not only on their female offspring, but also on the third generation. Much progress has been made in the past decade in terms of refinements in techniques to study DNA methylation, as well as immune system and 5-HT system development. Such techniques allow the evaluation of the impact of preventive experiments on a large spectrum of putative mechanisms.

10.7 Summary and Conclusion

The present chapter reviewed recent research on the mechanisms leading to chronic physical aggression during childhood and adolescence, with an emphasis on familial characteristics, epigenetics, immunology and the serotonin system. While most of the studies on the biological mechanisms leading to chronic physical aggression investigated solely associations between one biological variable (e.g., neurotransmitters, neuro-immunoregulators, hormones) and behavioral outcome (i.e., chronic aggression), an emerging number of studies now have provided support for a more refined hypothesis on mechanisms of chronic physical aggression, taking into account the importance of the developmental role of these factors on brain developmental processes; and how early environmental factors could alter the functioning of these biological systems, with consequences for risk for chronic physical aggression. Specifically, there is now emerging evidence that early social-familial adversity

leads to long lasting epigenetic alterations. These alterations may influence brain development, and, consequently, the ability to learn to regulate and control aggressive behaviour. In the context of early adversity and chronic physical aggression, epigenetic alterations in genes regulating the serotonin system, the immune system and the HPA axis, are especially of interest. These systems may also interact with other biological factors, thereby further complicating neurobiological theories.

In addition, the finding that many of these biological factors involved in chronic physical aggression develop very early (i.e., before birth), highlights the need to not only study the impact of the early postnatal environment on physical aggression, but also to take into account what is happening between conception and birth.

Indeed, a number of studies have now identified perinatal risk factors for a wide variety of behavioral problems (e.g., hyperactivity, opposition, rule breaking) that are highly related to maternal characteristics and maternal behavior during pregnancy. The effects of the perinatal environment on gene expression is presently the most interesting hypothesis. However, the reader needs to realize that we are only starting to explore this avenue. It is tempting, in a leap of faith, to jump on a band wagon, but many recent cases of unbridled enthusiasm should lead to restrained optimism (Risch et al. 2009).

The benefits of prevention starting as close as possible to conception seems obvious. If the earlier the risks the more wide spread the negative effects, then the corollary is the earlier the preventive intervention the more wide spread the benefits. The later we intervene, the less chance we have to impact the basic weaknesses of the organism. Preventive interventions should help at risk pregnant women live a life style that will facilitate "normal" gene expression. If we wait 3 or 4 years after birth (still worse if we wait until adolescence) we are dealing with a disruptive child who, as a figure of speech, may have only half of his gene expression potential to gain control over himself, and we are dealing with a mother who has a life long experience of failure now facing the probability of the same life-course for her child.

Although the focus of this chapter was on early risk factors for chronic aggression, early prevention and their underlying biological mechanisms related to serotonin, the immune system and the HPA-axis, since they have been most widely studied in the context of aggression, it is important to take into account the role of *protective* factors that may mitigate the impact of an adverse environment. One factor of particular interest is breastfeeding. Breastfeeding has been shown to be associated with many positive behaviors, including increased maternal sensitivity and increased attachment security (e.g., Tharner et al. 2012). One possible mechanism underlying these associations is the stimulating effect of breastfeeding on the production of the hormone oxytocin (see e.g., Febo et al. 2005). Oxytocin has also been shown to have a positive influence on child development, (Carter 2003; Insel 2010) and experimental placebo controlled studies using intranasal oxytocin has shown a positive effect of oxytocin on prosocial behaviors (MacDonald and MacDonald 2010). Two important research questions can be formulated from this perspective: (a) is to what extent can breastfeeding enhance the efficacy of preventive interventions for aggression problems in at risk populations? (b) what would be the consequences for the serotonin system, immune regulation and HPA-axis functioning?

The focus of this review was chronic physical aggression, but the basic principles of the epigenetic process suggest that intensive prenatal interventions will have an impact on numerous aspects of physical and mental health as well as social adjustment, including the major modern health problems: low birth weight, obesity, cardiovascular problems, cancer, hyperactivity, mood disorders and substance abuse.

Finally, one of the major conclusions we can draw from five decades of longitudinal studies on chronic physical aggression is that the time is ripe for investments in large collaborative early experimental preventive interventions. Randomized control trials are the best tools to test causal hypotheses while testing effective interventions (Schwartz et al. 1981; Tremblay 2003). It is hard to believethat there have been so few bio-psycho-social experimental interventions with pregnant women at risk of intergenerational transmission of the psychiatric problems that start during early childhood. Good models were implemented two decades ago (Donelan-McCall et al. 2009; Olds et al. 1998). We need to use these interventions that are well tested and study carefully the development of their potential bio-psycho-social effects from the prenatal period to at least the third generations' prenatal period.

This chapter is an adaptation of the following papers:

- Booij, L., Tremblay, R. E., Szyf, M., Benkelfat, C. (2014). Genetic and early environmental influences on the serotonin system: Consequences for brain development and risk for psychopathology. *Journal of Psychiatry and Neuroscience*. Oct 7. doi: 10.1503/jpn.140099. [Epub ahead of print]
- Booij, L., Wang, D., Lévesque, M. L., Tremblay, R. E, & Szyf, M. (2013). Looking beyond the DNA Sequence: the relevance of DNA methylation processes for the stress-diathesis model of depression. *Philosophical Transactions of the Royal Society B-Biological Sciences, 368*(1615), 1–16. doi: 10.1098/rstb.2012.0251
- Provençal, N., Booij, L., & Tremblay, R. E. (2015). The developmental origins of chronic physical aggression: Early life adversity, epigenetics and impact on other biological systems. *Journal of Experimental Biology*
- Tremblay, R. E. (2010). Developmental origins of disruptive behaviour problems: The 'original sin' hypothesis, epigenetics and their consequences for prevention. *Journal of Child Psychology and Psychiatry, 51*(4), 341–367. doi: 10.1111/j.1469-7610.2010.02211.x

References

Ahmed AA, Ma WQ, Ni YD, Zhou Q, Zhao RQ (2014) Embryonic exposure to corticosterone modifies aggressive behavior through alterations of the hypothalamic pituitary adrenal axis and the serotonergic system in the chicken. Horm Behav 65(2):97–105. doi:10.1016/j.yhbeh.2013.12.002

Alink LR, Mesman J, van Zeijl J, Stolk MN, Juffer F, Koot HM, Bakersman-Kranenburg MJ, van Ijzendoorn MH (2006) The early childhood aggression curve: development of physical aggression in 10- to 50-months-old children. Child Dev 77(4):954–966

Alleva E, Cirulli F, Bianchi M, Bondiolotti GP, Chiarotti F, De Acetis L, Panerai AE (1998) Behavioural characterization of interleukin-6 overexpressing or deficient mice during agonistic encounters. Eur J Neurosci 10(12):3664–3672. doi:10.1046/j.1460-9568.1998.00377.x

Ansorge MS, Zhou MM, Lira A, Hen R, Gingrich JA (2004) Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 306(5697):879–881. doi:10.1126/science.1101678

Arseneault L, Tremblay RE, Boulerice B, Saucier J-F (2002) Obstetrical complications and violent delinquency: testing two developmental pathways. Child Dev 73(2):496–508

Aslund C, Nordquist N, Comasco E, Leppert J, Oreland L, Nilsson K (2011) Maltreatment, MAOA, and delinquency: sex differences in gene-environment interaction in a large population-based cohort of adolescents. Behav Genet 41(2):262–272. doi:10.1007/s10519-010-9356-y

Azmitia EC, Gannon PJ (1986) The primate serotonergic system: a review of human and animal studies and a report on Macaca fascicularis. Adv Neurol 43:407–468

Baillargeon RH, Zoccolillo M, Keenan K, Côté S, Pérusse D, Wu H-X, Boivin M, Tremblay RE (2007) Gender differences in physical aggression: a prospective population-based survey of children before and after 2 years of age. Dev Psychol 43(1):13–26

Bandura A (1977) Social learning theory. Prentice Hall Inc., Englewood Cliffs

Barker ED, Séguin JR, White HR, Bates ME, Lacourse E, Carbonneau R, Tremblay RE (2007) Developmental trajectories of male physical violence and theft: relations to neurocognitive performance. Arch Gen Psychiatry 64(5):592–599. doi:10.1001/archpsyc.64.5.592

Barreau F, Cartier C, Ferrier L, Fioramonti J, Bueno L (2004) Nerve growth factor mediates alterations of colonic sensitivity and mucosal barrier induced by neonatal stress in rats. Gastroenterology 127(2):524–534. doi:10.1053/s0016-5085(04)00865-0

Beach SRH, Brody GH, Todorov AA, Gunter TD, Philibert RA (2011) Methylation at 5HTT mediates the impact of child sex abuse on women's antisocial behavior: an examination of the Iowa adoptee sample. Psychosom Med 73(1):83–87. doi:10.1097/PSY.0b013e3181fdd074

Boivin M, Vitaro F, Poulin F (2005) Peer relationships and the development of aggressive behavior in early childhood. In: Tremblay RE, Hartup WW, Archer J (eds) Developmental origins of aggression. Guilford Press, New York, pp 376–397

Booij L, Szyf M, Carballedo A, Frey NN, Morris D, Ly V, Fahey C, Meaney J, Gill M, Frodi T (submitted) The role of SLC6A4 DNA methylation in stress-related changes in hippocampal volume: a study in depressed patients and healthy controls

Booij L, Tremblay RE, Leyton M, Seguin JR, Vitaro F, Gravel P, Perreau-Linck E, Levesque ML, Durand F, Diksic M, Turecki G, Benkelfat C (2010) Brain serotonin synthesis in adult males characterized by physical aggression during childhood: a 21-year longitudinal study. PloS One 5(6). doi:10.1371/journal.pone.0011255

Booij L, Wang DS, Levesque ML, Tremblay RE, Szyf M (2013) Looking beyond the DNA sequence: the relevance of DNA methylation processes for the stress-diathesis model of depression. Philos Trans R Soc B Biol Sci 368(1615):1–16. doi:10.1098/rstb.2012.0251

Booij L, Tremblay RE, Szyf M, Benkelfat C (2014) Genetic and early environmental influences on the serotonin system: consequences for brain development and risk for psychopathology. J Psychiatry Neurosci 39(5):1400–1499. doi:10.1503/jpn.140099

Booij L, Szyf M, Carballedo A, Frey M, Morris D, Dymov S, Vaisheva F, Ly V, Fahey C, Meaney J, Gill M, Frodl T (2015) DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls. PLoS One 10(3), e0119061

Borghol N, Suderman M, McArdle W, Racine A, Hallett M, Pembrey M, Hertzman C, Power C, Szyf M (2012) Associations with early-life socio-economic position in adult DNA methylation. Int J Epidemiol 41(1):62–74. doi:10.1093/ije/dyr147

Bovet L (1951) Psychiatric aspects of juvenile delinquency. World Health Organization, Geneva

Brame B, Nagin DS, Tremblay RE (2001) Developmental trajectories of physical aggression from school entry to late adolescence. J Child Psychol Psychiatry 42(4):503–512

Broidy LM, Nagin DS, Tremblay RE, Bates JE, Brame B, Dodge KA, Fergusson D, Horwood JL, Loeber R, Laird R, Lynam DR, Moffitt TE, Pettit GS, Vitaro F (2003) Developmental trajecto-

ries of childhood disruptive behaviors and adolescent delinquency: a six site, cross national study. Dev Psychol 39(2):222–245

Brown GL, Goodwin FK, Ballenger JC, Gover PF, Major LF (1979) Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatr Res 1(2):131–139

Brunner HG, Nelen MR, Van Zandvoort P, Abeling NG, Van Gennip AH, Wolters EC, Kuiper MA, Ropers HH, Van Oost BA (1993) X-linked borderline mental retardation with prominent behavioral disturbance: phenotype, genetic localization, and evidence for disturbed monoamine metabolism. Am J Hum Genet 52(6):1032–1039

Buckholtz JW, Callicott JH, Kolachana B, Hariri AR, Goldberg TE, Genderson M, Egan MF, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008) Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. Mol Psychiatry 13(3):313–324. doi:10.1038/sj.mp.4002020

Campbell SB, Spieker S, Vandergrift N, Belsky J, Burchinal M, NICHD Early Child Care Research Network (2010) Predictors and sequelae of trajectories of physical aggression in school-age boys and girls. Dev Psychopathol 22(1):133–150. doi:10.1017/s0954579409990319

Canli T, Qiu M, Omura K, Congdon E, Haas BW, Amin Z, Herrmann MJ, Constable RT, Lesch KP (2006) Neural correlates of epigenesis. Proc Natl Acad Sci U S A 103(43):16033–16038. doi:10.1073/pnas.0601674103

Caporaso N, Gu F, Chatterjee N, Sheng-Chih J, Yu K, Yeager M, Chen C, Jacobs K, Wheeler W, Landi MT, Ziegler RG, Hunter DJ, Chanock S, Hankinson S, Kraft P, Bergen AW (2009) Genome-wide and candidate gene association study of cigarette smoking behaviors. PLoS One 4(2):e4653

Capuron L, Miller AH (2011) Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther 130(2):226–238. doi:10.1016/j.pharmthera.2011.01.014

Carter CS (2003) Developmental consequences of oxytocin. Physiol Behav 79(3):383–397

Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, Muller U, Aguet M, Babinet C, Shih JC, Demaeyer E (1995) Aggressive-behavior and altered amounts of brain-serotonin and norepinephrine in mice lacking MAOA. Science 268(5218):1763–1766. doi:10.1126/science.7792602

Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002) Role of genotype in the cycle of violence in maltreated children. Science 297(5582):851–854. doi:10.1126/science.1072290

Checknita D, Maussion G, Labonté B, Comai S, Tremblay RE, Vitaro F, Turecki N, Bertazzo A, Gobbi G, Côté G, Turecki G (2015) Monoamine oxidase A gene promoter methylation and transcriptional downregulation in an offender population with antisocial personality disorder. Br J Psychiatr 206(3):216–222

Cleare AJ, Bond AJ (1995) The effect of tryptophan depletion and enhancement on subjective and behavioral aggression in normal-male subjects. Psychopharmacology (Berl) 118(1):72–81. doi:10.1007/bf02245252

Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL (1989) Serotonergic studies in patients with affective and personality-disorders: correlates with suicidal and impulsive aggressive-behavior. Arch Gen Psychiatry 46(7):587–599

Côté SM (2007) Sex differences in physical and indirect aggression: a developmental perspective. Eur J Crim Policy Res 13(3–4):183–200

Côté SM, Vaillancourt T, LeBlanc JC, Nagin DS, Tremblay RE (2006) The development of physical aggression from toddlerhood to pre-adolescence: a nation wide longitudinal study of Canadian children. J Abnorm Child Psychol 34(1):71–85

Côté SM, Boivin M, Nagin DS, Japel C, Xu Q, Zoccolillo M, Tremblay RE (2007) The role of maternal education and non-maternal care services in the prevention of children's physical aggression. Arch Gen Psychiatry 64(11):1305–1312

Danese A, Pariante CM, Caspi A, Taylor A, Poulton R (2007) Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A 104(4):1319–1324. doi:10.1073/pnas.0610362104

Davidson RJ, Putnam KM, Larson CL (2000) Dysfunction in the neural circuitry of emotion regulation – a possible prelude to violence. Science 289(5479):591–594

Dionne G, Tremblay RE, Boivin M, Laplante D, Pérusse D (2003) Physical aggression and expressive vocabulary in 19 month-old twins. Dev Psychol 39(2):261–273

Donelan-McCall N, Eckenrode J, Olds DL (2009) Home visiting for the prevention of child maltreatment: lessons learned during the past 20 years. Pediatr Clin North Am 56(2):389–403. doi:10.1016/j.pcl.2009.01.002

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL (2010) A meta-analysis of cytokines in major depression. Biol Psychiatry 67(5):446–457. doi:10.1016/j.biopsych.2009.09.033

Eckenrode J, Campa M, Luckey DW, Henderson CR, Cole R, Kitzman H, Anson E, Sidora-Arcoleo K, Power J, Olds D (2010) Long-term effects of prenatal and infancy nurse home visitation on the life course of youths: 19-year follow-up of a randomized trial. Arch Pediatr Adolesc Med 164(1):9–15

Eisner M (2003) Long-term historical trends in violent crime. In: Tonry M (ed) Crime and justice: a review of research, vol 30. University of Chicago Press, Chicago, pp 83–142

Febo M, Numan M, Ferris CF (2005) Functional Magnetic Resonance Imaging shows oxytocin activates brain regions associated with mother–pup bonding during suckling. J Neurosci 25(50):11637–11644

Ferris CF, Lu SF, Messenger T, Guillon CD, Heindel N, Miller M, Koppel G, Bruns FR, Simon NG (2006) Orally active vasopressin V1a receptor antagonist, SRX251, selectively blocks aggressive behavior. Pharmacol Biochem Behav 83(2):169–174. doi:10.1016/j.pbb.2006.01.001

Fontaine N, Carbonneau R, Barker ED, Vitaro F, Hébert M, Côté SM, Nagin DS, Zoccolillo M, Tremblay RE (2008) Girls' hyperactivity and physical aggression during childhood and adjustment problems in early adulthood. Arch Gen Psychiatry 65(3):320–328

Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang YY, Hwang DR, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever LJ (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [11C]McN 5652. Am J Psychiatry 162(5):915–923. doi:10.1176/appi.ajp.162.5.915

Gaspar P, Cases O, Maroteaux L (2003) The developmental role of serotonin: news from mouse molecular genetics. Nat Rev Neurosci 4(12):1002–1012. doi:10.1038/nrn1256

Glover V (2011) Prenatal stress and the origins of psychopathology: an evolutionary perspective. J Child Psychol Psychiatry 52(4):356–367. doi:10.1111/j.1469-7610.2011.02371.x

Godar SC, Bortolato M, Castelli MP, Casti A, Casu A, Chen K, Ennas MG, Tambaro S, Shih JC (2014) The aggression and behavioral abnormalities associated with monoamine oxidase A deficiency are rescued by acute inhibition of serotonin reuptake. J Psychiatr Res 56:1–9. doi:10.1016/j.jpsychires.2014.04.014

Groer MW, Morgan K (2007) Immune, health and endocrine characteristics of depressed postpartum mothers. Psychoneuroendocrinology 32(2):133–139. doi:10.1016/j.psyneuen.2006.11.007

Guillemin C, Provençal N, Suderman M, Côté SM, Vitaro F, Hallett M, Tremblay RE, Szyf M (2014) DNA methylation signature of childhood chronic physical aggression in T cells of both men and women. PLoS One 9(1):1–16 (e86822). doi:10.1371/journal.pone.0086822

Guo G, Roettger ME, Shih JC (2007) Contributions of the DAT1 and DRD2 genes to serious and violent delinquency among adolescents and young adults. Hum Genet 121(1):125–136. doi:10.1007/s00439-006-0244-8

Hammock EAD, Lim MM, Nair HP, Young LJ (2005) Association of vasopressin 1a receptor levels with a regulatory microsatellite and behavior. Genes Brain Behav 4(5):289–301. doi:10.1111/j.1601-183X.2005.00119.x

Hay DF, Mundy L, Roberts S, Carta R, Waters CS, Perra O, Jones R, Jones I, Goodyer I, Harold G, Thapar A, van Goozen S (2011) Known risk factors for violence predict 12-month-old infants' aggressiveness with peers. Psychol Sci 22(9):1205–1211. doi:10.1177/0956797611419303

Heinz A, Braus DF, Smolka MN, Wrase J, Puls I, Hermann D, Klein S, Grusser SM, Flor H, Schumann G, Mann K, Buchel C (2005) Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. Nat Neurosci 8(1):20–21. doi:10.1038/nn1366

Higley JD, Mehlman PT, Higley SB, Fernald B, Vickers J, Lindell SG, Taub DM, Suomi SJ, Linnoila M (1996) Excessive mortality in young free-ranging male nonhuman primates with low cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations. Arch Gen Psychiatry 53(6):537–543

Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM (2009) Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depress Anxiety 26(5):447–455. doi:10.1002/da.20564

Howell S, Westergaard G, Hoos B, Chavanne TJ, Shoaf SE, Cleveland A, Snoy PJ, Suomi SJ, Higley JD (2007) Serotonergic influences on life-history outcomes in free-ranging male rhesus Macaques. Am J Primatol 69(8):851–865. doi:10.1002/ajp.20369

Huijbregts SCJ, Séguin JR, Zoccolillo M, Boivin M, Tremblay RE (2008) Maternal prenatal smoking, parental antisocial behavior, and early childhood physical aggression. Dev Psychopathol 20(2):437–453. doi:10.1017/S0954579408000217

Ichise M, Vines DC, Gura T, Anderson GM, Suomi SJ, Higley JD, Innis RB (2006) Effects of early life stress on C-11 DASB positron emission tomography imaging of serotonin transporters in adolescent peer- and mother-reared rhesus monkeys. J Neurosci 26(17):4638–4643. doi:10.1523/jneurosci.5199-05.2006

Insel TR (2010) The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behaviour. Neuron 65(6):383–397

Janelidze S, Mattei D, Westrin A, Träskman-Bendz L, Brundin L (2010) Cytokine levels in the blood may distinguish suicide attempters from depressed patients. Brain Behav Immun 25(2):335–339. doi:10.1016/j.bbi.2010.10.010

Jezierski G, Braun K, Gruss M (2006) Epigenetic modulation of the developing serotonergic neurotransmission in the semi-precocial rodent Octodon degus. Neurochem Int 48(5):350–357. doi:10.1016/j.nueint.2005.11.009

Keck ME, Wigger A, Welt T, Muller MB, Gesing A, Reul J, Holsboer F, Landgraf R, Neumann ID (2002) Vasopressin mediates the response of the combined dexamethasone/CRH test in hyperanxious rats: implications for pathogenesis of affective disorders. Neuropsychopharmacology 26(1):94–105. doi:10.1016/s0893-133x(01)00351-7

Kieseppa T, Partonen T, Haukka J, Kaprio J, Lonnqvist J (2004) High concordance of bipolar I disorder in a nationwide sample of twins. Am J Psychiatry 161(10):1814–1821. doi:10.1176/appi.ajp.161.10.1814

Koo JW, Duman RS (2008) IL-1 beta is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci U S A 105(2):751–756. doi:10.1073/pnas.0708092105

Kornhuber J, Konradi C, Mackburkhardt F, Riederer P, Heinsen H, Beckmann H (1989) Ontogenesis of monoamine oxidase-A and oxidase-B in the human-brain frontal-cortex. Brain Res 499(1):81–86. doi:10.1016/0006-8993(89)91136-0

Krug EG, Dahlberg LL, Mercy JA, Zwi AB, Lozano R (2002) World report on violence and health, 2002, from www.who.int/violence_injury_prevention/violence/world_report/wrvh1/en

Kuo MH, Allis CD (1998) Roles of histone acetyltransferases and deacetylases in gene regulation. Bioessays20(8):615–626.doi:10.1002/(sici)1521-1878(199808)20:8<615::aid-bies4>3.0.co;2-h

Lacourse E, Boivin M, Brendgen M, Petitclerc A, Girard A, Vitaro F, Paquin S, Ouellet-Morin I, Dionne G, Tremblay RE (2014) A longitudinal twin study of physical aggression in early childhood: evidence for a developmentally dynamic genome. Psychol Med 44(12):2617–2627. doi:10.1017/S0033291713003218

Lefkowitz MM, Eron LD, Walder LO, Huesmann LR (1977) Growing up to be violent. A longitudinal study of the development of aggression. Pergamon Press, New York

Lesch KP, Mössner R (2006) Inactivation of 5HT transport in mice: modeling altered 5HT homeostasis implicated in emotional dysfunction, affective disorders, and somatic syndromes. Handb Exp Pharmacol (175):417–456

Leyton M, Okazawa H, Diksic M, Paris J, Rosa P, Mzengeza S, Young SN, Blier P, Benkelfat C (2001) Brain regional alpha- C-11 Methyl-(L)-Tryptophan trapping in impulsive subjects with borderline personality disorder. Am J Psychiatry 158(5):775–782. doi:10.1176/appi.ajp.158.5.775

Leyton M, Paquette V, Gravel P, Rosa-Neto P, Weston F, Diksic M, Benkelfat C (2006) alpha- C-11 Methyl-L-tryptophan trapping in the orbital and ventral medial prefrontal cortex of suicide attempters. Eur Neuropsychopharmacol 16(3):220–223. doi:10.1016/j.euroneuro.2005.09.006

Loney BR, Butler MA, Lima EN, Counts CA, Eckel LA (2006) The relation between salivary cortisol, callous-unemotional traits, and conduct problems in an adolescent non-referred sample. J Child Psychol Psychiatry 47(1):30–36. doi:10.1111/j.1469-7610.2005.01444.x

MacDonald K, MacDonald TM (2010) The peptide that binds: a systematic review of oxytocin and its prosocial effects. Harv Rev Psychiatry 18(1):18–21

Manuck SB, Bleil ME, Petersen KL, Flory JD, Mann JJ, Ferrell RE, Muldoon MF (2005) The socio-economic status of communities predicts variation in brain serotonergic responsivity. Psychol Med 35(4):519–528. doi:10.1017/s0033291704003757

Markunas CA, Xu ZL, Harlid S, Wade PA, Lie RT, Taylor JA, Wilcox AJ (2014) Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. Environ Health Perspect 122(10):1147–1153. doi:10.1289/ehp.1307892

Marquez C, Poirier GL, Cordero MI, Larsen MH, Groner A, Marquis J, Magistretti PJ, Trono D, Sandi C (2013) Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. Translat Psychiatry 3:e216. doi:10.1038/tp.2012.144

Marsland AL, Prather AA, Petersen KL, Cohen S, Manuck SB (2008) Antagonistic characteristics are positively associated with inflammatory markers independently of trait negative emotionality. Brain Behav Immun 22(5):753–761. doi:10.1016/j.bbi.2007.11.008

Matthews K, Dalley JW, Matthews C, Tsai TH, Robbins TW (2001) Periodic maternal separation of neonatal rats produces region- and gender-specific effects on biogenic amine content in postmortem adult brain. Synapse 40(1):1–10. doi:10.1002/1098-2396(200104)40:1<1::aid-syn1020>3.0.co;2-e

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 12(3):342–348. doi:10.1038/nn.2270

Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, Rex-Haffner M, Loeschner A, Gonik M, Mercer KB, Bradley B, Muller-Myhsok B, Ressler KJ, Binder EB (2013) Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. Proc Natl Acad Sci U S A 110(20):8302–8307. doi:10.1073/pnas.1217750110

Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri RA, Pezawas L, Blasi G, Wabnitz A, Honea R, Verchinski B, Callicott JH, Egan M, Mattay V, Weinberger DR (2006) Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc Natl Acad Sci U S A 103(16):6269–6274

Moeller FG, Dougherty DM, Swann AC, Collins D, Davis CM, Cherek DR (1996) Tryptophan depletion and aggressive responding in healthy males. Psychopharmacology (Berl) 126(2):97–103. doi:10.1007/bf02246343

Munafo MR, Brown SM, Hariri AR (2008) Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. Biol Psychiatry 63(9):852–857. doi:10.1016/j.biopsych.2007.08.016

Myint AM, Kim YK (2003) Cytokine-serotonin interaction through IDO: a neurodegeneration hypothesis of depression. Med Hypotheses 61(5–6):519–525. doi:10.1016/s0306-9877(03)00207-x

Naerde A, Ogden T, Janson H, Zachrisson HD (2014) Normative development of physical aggression from 8 to 26 months. Dev Psychol 50(6):1710–1720. doi:10.1037/a0036324

Nagin D, Tremblay RE (1999) Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. Child Dev 70(5):1181–1196

Nelson RJ, Trainor BC (2007) Neural mechanisms of aggression. Nat Rev Neurosci 8(7):536–546

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Reynolds D, Mitropoulou V, Sprung L, Shaw RB, Koenigsberg H, Platholi J, Silverman J, Siever LJ (2002) Blunted prefrontal cortical (18)

fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. Arch Gen Psychiatry 59(7):621–629. doi:10.1001/archpsyc.59.7.621
NICHD Early Child Care Research Network (2004) Trajectories of physical aggression from toddlerhood to middle school: predictors, correlates, and outcomes. SRCD Monogr 69(4, 278):1–146
Nielsen CH, Larsen A, Nielsen AL (2014) DNA methylation alterations in response to prenatal exposure of maternal cigarette smoking: a persistent epigenetic impact on health from maternal lifestyle? Arch Toxicol Dec 6. [Epub ahead of print]. doi:10.1007/s00204-014-1426-0
Nishizawa S, Benkelfat C, Young SN, Leyton M, Mzengeza S, de Montigny C, Blier P, Diksic M (1997) Differences between males and females in rates of serotonin synthesis in human brain. Proc Natl Acad Sci U S A 94(10):5308–5313
Olds D, Henderson CR, Chamberlin R, Talelbaum R (1986) Preventing child abuse and neglect: a randomized trial of nurse home visitation. Pediatrics 78:65–78
Olds DL, Eckenrode J, Henderson CR Jr, Kitzman H, Powers J, Cole R, Sidora K, Morris P, Pettitt LM, Luckey D (1997) Long-term effects of home visitation on maternal life course and child abuse and neglect: fifteen-year follow-up of a randomized trial. JAMA 278:637–643
Olds D, Henderson CR, Cole R, Eckenrode J, Kitzman H, Luckey D, Pettitt L, Sidora K, Morris P, Powers J (1998) Long-term effects of nurse home visitation on children's criminal and antisocial behavior: 15-year follow-up of a randomized controlled trial. JAMA 280(14):1238–1244
O'Rourke H, Fudge JL (2006) Distribution of serotonin transporter labeled fibers in amygdaloid subregions: implications for mood disorders. Biol Psychiatry 60(5):479–490. doi:10.1016/j.biopsych.2005.09.020
Pesce M, Speranza L, Franceschelli S, Ialenti V, Patruno A, Febo MA, De Lutiis MA, Felaco M, Grilli A (2011) Biological role of Interleukin-1 beta in defensive aggressive behavior. J Biol Regul Homeost Agents 25(3):323–329
Petitclerc A, Tremblay RE (2009) Childhood disruptive behaviour disorders: review of their origin, development, and prevention. Can J Psychiatry Revue Canadienne De Psychiatrie 54(4):222–231
Pingault J-B, Côté SM, Lacourse E, Galéra C, Vitaro F, Tremblay RE (2013) Childhood hyperactivity, physical aggression and criminality: a 19 year prospective population-based study. PLoS One 8(5):1–7
Plomin R (1994) Genetics and experience: the interplay between nature and nurture. Sage, Thousand Oaks
Popma A, Vermeiren R, Geluk C, Rinne T, van den Brink W, Knol DL, Jansen LMC, van Engeland H, Doreleijers TAH (2007) Cortisol moderates the relationship between testosterone and aggression in delinquent male adolescents. Biol Psychiatry 61(3):405–411. doi:10.1016/j.biopsych.2006.06.006
Powell ND, Sloan EK, Bailey MT, Arevalo JMG, Miller GE, Chen E, Kobor MS, Reader BF, Sheridan JF, Cole SW (2013) Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via beta-adrenergic induction of myelopoiesis. Proc Natl Acad Sci U S A 110(41):16574–16579. doi:10.1073/pnas.1310655110
Provençal N, Suderman MJ, Guillemin C, Massart R, Ruggiero A, Wang D, Bennett AJ, Pierre PJ, Friedman DP, Côté SM, Hallett M, Tremblay RE, Suomi SJ, Szyf M (2012) The signature of maternal rearing in the methylome in Rhesus Macaque prefrontal cortex and T cells. J Neurosci 32(44):15626–15642. doi:10.1523/JNEUROSCI.1470-12.2012
Provençal N, Suderman MJ, Caramaschi D, Wang DS, Hallett M, Vitaro F, Tremblay RE, Szyf M (2013a) Differential DNA methylation regions in cytokine and transcription factor genomic Loci associate with childhood physical aggression. PLoS One 8(8). doi:10.1371/journal.pone.0071691
Provencal N, Suderman MJ, Vitaro F, Szyf M, Tremblay RE (2013b) Childhood chronic physical aggression associates with adult cytokine levels in plasma. PLoS One 8(7):1–7 (e69481). doi:10.1371/journal.pone.0069481

Provençal N, Suderman MJ, Guillemin C, Vitaro F, Côté SM, Hallett M, Tremblay RE, Szyf M (2014) Association of childhood chronic physical aggression with a DNA methylation signature in adult human T cells. PLoS One 9(4):1–10 (e89839). doi:10.1371/journal.pone.0089839

Provençal N, Booij L, Tremblay RE (2015) The developmental origins of chronic physical aggression: biological pathways triggered by early life adversity. J Exp Biol 218(Pt 1): 123–133

Quetelet A (1984) Research on the propensity for crime at different ages (trans: Sylvester SF). Anderson, Cincinnati (Original work published in 1833)

Reif A, Rosler M, Freitag CM, Schneider M, Eujen A, Kissling C, Wenzler D, Jacob CP, Retz-Junginger P, Thome J, Lesch KP, Retz W (2007) Nature and nurture predispose to violent behavior: serotonergic genes and adverse childhood environment. Neuropsychopharmacology 32(11):2375–2383. doi:10.1038/sj.npp.1301359

Reiss AJ, Roth JA (eds) (1993) Understanding and preventing violence. National Academy Press, Washington, DC

Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR (2009) Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression a meta-analysis. JAMA 301(23):2462–2471

Roy A, Berman J, Williams R, Kuhn C, Gonzalez B (2002) Higher levels of CSF homovanillic acid in recently abstinent cocaine-dependent patients. Am J Psychiatry 159(6):1053–1055. doi:10.1176/appi.ajp.159.6.1053

Sampson RJ, Laub JH (2003) Life-course desisters? Trajectories of crime among delinquent boys followed to age 70. Criminology 41(3):555–592

Schwartz D, Flamant R, Lelouch J (1981) Clinical trials. Academic, London

Shih JC, Chen K, Ridd MJ (1999) Monoamine oxidase: from genes to behavior. Annu Rev Neurosci 22:197–217. doi:10.1146/annurev.neuro.22.1.197

Shirtcliff EA, Granger DA, Booth A, Johnson D (2005) Low salivary cortisol levels and externalizing behavior problems in youth. Dev Psychopathol 17(1):167–184. doi:10.1017/s0954579405050091

Shumay E, Logan J, Volkow ND, Fowler JS (2012) Evidence that the methylation state of the monoamine oxidase A (MAOA) gene predicts brain activity of MAO A enzyme in healthy men. Epigenetics 7(10):1151–1160. doi:10.4161/epi.21976

Siever LJ (2008) Neurobiology of aggression and violence. Am J Psychiatry 165(4):429–442. doi:10.1176/appi.ajp.2008.07111774

Siever LJ, Buchsbaum MS, New AS, Spiegel-Cohen J, Wei T, Hazlett EA, Sevin E, Nunn M, Mitropoulou V (1999) d, l-fenfluramine response in impulsive personality disorder assessed with F-18 fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology 20(5):413–423. doi:10.1016/s0893-133x(98)00111-0

Sloan EK, Capitanio JP, Tarara RP, Mendoza SP, Mason WA, Cole SW (2007) Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. J Neurosci 27(33):8857–8865. doi:10.1523/jneurosci.1247-07.2007

Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley B, Tang YL, Gillespie CF, Cubells JF, Ressler KJ (2011) Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. Am J Med Genet Part B Neuropsychiatr Genet 156B(6):700–708. doi:10.1002/ajmg.b.31212

Steinbusch HWM (1981) Distribution of serotonin-immunoreactivity in the central nervous-system of the rat: cell-bodies and terminals. Neuroscience 6(4):557–618. doi:10.1016/0306-4522(81)90146-9

Stevens HE, Leckman JF, Coplan JMD, Suomi SJ (2009) Risk and resilience: early manipulation of Macaque social experience and persistent behavioral and neurophysiological outcomes. J Am Acad Child Adolesc Psychiatry 48(2):114–127. doi:10.1097/CHI.0b013e318193064c

Suarez EC, Lewis JG, Kuhn C (2002) The relation of aggression, hostility, and anger to lipopolysaccharide-stimulated tumor necrosis factor (TNF)-alpha by blood monocytes from normal men. Brain Behav Immun 16(6):675–684. doi:10.1016/s0889-1591(02)00019-3

Suderman M, Borghol N, Pappas JJ, Pereira SMP, Pembrey M, Hertzman C, Power C, Szyf M (2014) Childhood abuse is associated with methylation of multiple loci in adult DNA. BMC Med Genomics 7:1–12. doi:10.1186/1755-8794-7-13

Suomi SJ (2005) Genetic and environmental factors influencing the expression of impulsive aggression and serotonergic functioning in Rhesus monkeys. In: Tremblay RE, Hartup WW, Archer J (eds) Developmental origins of aggression. Guilford Press, New York, pp 63–82

Suomi SJ (2006) Risk, resilience, and gene x environment interactions in rhesus monkeys. In: Lester BM, Masten AS, McEwen B (eds) Resilience in children, vol 1094. Blackwell Publishing, Oxford, pp 52–62

Sweeten G, Piquero AR, Steinberg L (2013) Age and the explanation of crime. Revisited [Published online]. J Youth Adolesc 1–18. doi:10.1007/s10964-013-9926-4

Szyf M, Weaver ICG, Provençal N, McGowan P, Tremblay RE, Meaney MJ (2009) Epigenetics and behaviour. In: Tremblay RE, van Aken MAG, Koops W (eds) Development and prevention of behaviour problems: from genes to social policy. Psychology Press, Hove, pp 25–59

Tarullo AR, Gunnar MR (2006) Child maltreatment and the developing HPA axis. Horm Behav 50(4):632–639. doi:10.1016/j.yhbeh.2006.06.010

Tharner A, Luijk MP, Raat H, IJzendoorn MH, Bakermans-Kranenburg MJ, Moll HA, Jaddoe VW, Hofman A, Verhulst FC, Tiemeier H (2012) Breastfeeding and its relation to maternal sensitivity and infant attachment. J Dev Behav Pediatr 33(5):396–404

Tremblay RE (2003) Why socialization fails? The case of chronic physical aggression. In: Lahey BB, Moffitt TE, Caspi A (eds) Causes of conduct disorder and juvenile delinquency. Guilford Publications, New York, pp 182–224

Tremblay RE (2010) Developmental origins of disruptive behaviour problems: the 'original sin' hypothesis, epigenetics and their consequences for prevention. J Child Psychol Psychiatry 51(4):341–367. doi:10.1111/j.1469-7610.2010.02211.x

Tremblay RE, Côté SM (2009) Development of sex differences in physical aggression: the maternal link to epigenetic mechanisms [comment]. Behav Brain Sci 32(3–4):290–291. doi:10.1017/S0140525X09990951

Tremblay RE, Japel C, Pérusse D, McDuff P, Boivin M, Zoccolillo M, Montplaisir J (1999) The search for the age of "onset" of physical aggression: Rousseau and Bandura revisited. Crim Behav Mental Health 9(1):8–23

Tremblay RE, Nagin D, Séguin JR, Zoccolillo M, Zelazo PD, Boivin M, Pérusse D, Japel C (2004) Physical aggression during early childhood: trajectories and predictors. Pediatrics 114(1):e43–e50

Tsankova N, Renthal W, Kumar A, Nestler EJ (2007) Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci 8(5):355–367. doi:10.1038/nrn2132

Uddin M, Aiello AE, Wildman DE, Koenen KC, Pawelec G, de los Santos R, Goldmann E, Galea S (2010) Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proc Natl Acad Sci U S A 107(20):9470–9475. doi:10.1073/pnas.0910794107

Vage J, Wade C, Biagi T, Fatjo J, Amat M, Lindblad-Toh K, Lingaas F (2010) Association of dopamine- and serotonin-related genes with canine aggression. Genes Brain Behav 9(4):372–378. doi:10.1111/j.1601-183X.2010.00568.x

van Bokhoven I, Van Goozen SHM, van Engeland H, Schaal B, Arseneault L, Séguin JR, Nagin DS, Vitaro F, Tremblay RE (2005) Salivary cortisol and aggression in a population-based longitudinal study of adolescent males. J Neural Transm 112(8):1083–1096. doi:10.1007/s00702-004-0253-5

van Lier PAC, Vitaro F, Barker ED, Koot HM, Tremblay RE (2009) Developmental links between trajectories of physical violence, vandalism, theft, and alcohol-drug use from childhood to adolescence. J Abnorm Child Psychol 37(4):481–492. doi:10.1007/s10802-008-9289-6

Vaughn MG, Delisi M, Beaver KM, Wright JP (2009) DAT1 and 5HTT are associated with pathological criminal behavior in a nationally representative sample of youth. Crim Justice Behav 36(11):1113–1124. doi:10.1177/0093854809342839

von Kanel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, Schnyder U (2007) Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res 41(9):744–752. doi:10.1016/j.jpsychires.2006.06.009

Wang D, Szyf M, Benkelfat C, Provençal N, Caramaschi D, Côté SM, Vitaro F, Tremblay RE, Booij L (2012) Peripheral SLC6A4 DNA methylation is associated with in vivo measures of human brain serotonin synthesis and childhood physical aggression. PLoS One 7(6):1–8 (e39501). doi:10.1371/journal.pone.0039501

Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ (2004) Epigenetic programming by maternal behavior. Nat Neurosci 7(8):847–854. doi:10.1038/nn1276

Whitaker-Azmitia PM (2001) Serotonin and brain development: role in human developmental diseases. Brain Res Bull 56(5):479–485

Wrangham RW, Wilson ML, Muller MN (2006) Comparative rates of violence in chimpanzees and humans. Primates 47(1):14–26

Zimbardo PG (2007) The Lucifer effect: understanding how good people turn evil. Random House, New York