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REVIEW

The developmental origins of chronic physical aggression: biological pathways triggered by early life adversity

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ABSTRACT

Longitudinal epidemiological studies with birth cohorts have shown that physical aggression in humans does not appear suddenly in adolescence as commonly thought. In fact, physically aggressive behaviour is observed as early as 12 months after birth, its frequency peaks around 2–4 years of age and decreases in frequency until early adulthood. However, a minority of children (3–7%) maintain a high frequency of physical aggression from childhood to adolescence and develop serious social adjustment problems during adulthood. Genetic factors and early social experiences, as well as their interaction, have been shown to play an important role in the development of chronic aggressive behaviour. However, the biological mechanisms underlying these associations are just beginning to be uncovered. Recent evidence suggests that epigenetic mechanisms are responsive to adverse environments and could be involved in the development of chronic aggression. Using both gene candidate and genomic approaches, recent studies have identified epigenetic marks, such as DNA methylation alterations in genes involved in the stress response and the serotonin and immune systems to be partly responsible for the long-lasting effects of early adversity. Further longitudinal studies with biological, environmental and behavioural assessments from birth onwards are needed to elucidate the sequence of events that leads to these long-lasting epigenetic marks associated with early adversity and aggression.

KEY WORDS: Aggression, Physical aggression, Epigenetic, DNA methylation, Early-life stress, Development, Immune system, Serotonin, HPA axis

Introduction

Physical aggression is a crucial component of human and animal behaviour. Our ancestors, as well as most animals, needed this skill in order to eat, to protect themselves and their family against predators, to compete for mating as well as to acquire resources and territory. However, in socially organized species, aggression needs to be self-controlled because aggression can be fatal to other members of the social group and can lead to social exclusion of the aggressor (Barker et al., 2008; Tremblay and Nagin, 2005). Even if the need to use physical aggression on a daily basis in our civilized society has become rare, acts of violence account for 1.43 million deaths worldwide annually and are, in most cases, due to individual acts of aggression.

Exposure to adverse social environments, such as child maltreatment, maternal antisocial behaviour and family dysfunction has been shown to predict chronic physical aggression (CPA) (Campbell et al., 2010; Nagin and Tremblay, 2001; Tremblay et al., 2004). Genetic studies also suggest that the frequency of physical aggression is, in part, inherited (Dionne et al., 2003; Hicks et al., 2004; Lacourse et al., 2014). Moreover, genetic and environmental factors have been shown to interact in the expression of impulsive aggression in monkeys (Bennett et al., 2002) and violence in humans (Caspi et al., 2002). However, the mechanisms responsible for mediating the impact of the early social environment on CPA are unknown. Epigenetic modifications are one of the mechanisms hypothesized to mediate the biological response to adverse environments (Mill and Petronis, 2008; Szyf, 2011; Tremblay and Szyf, 2010). In this review, we describe part of the growing body of evidence identifying epigenetic mechanisms in the long-lasting effects of early-life adverse events on diseases and behaviour, focusing on DNA methylation. In particular, we summarize recent evidence suggesting that such mechanisms are involved in the development of CPA in animals and in humans with an emphasis on the immune system, the hypothalamic–pituitary–adrenal (HPA) axis and serotonin (5-HT).

The development of physical aggression

Aggression has been intensively investigated by scientists from different disciplines, such as biology, psychiatry, psychology and sociology in the past century (Tremblay, 2000). The main operational approach to defining aggression is the number of episodes of physical aggression in agonistic encounters (Restoin et al., 1985). The most basic acts of physical aggression in humans are: hitting, kicking, biting, pushing, grabbing, pulling, shoving, beating, twisting and choking. Threatening and using objects to aggress are also included into this definition (Tremblay, 2010). From an evolutionary perspective, physical aggression can be seen as adaptive in some contexts and maladaptive in others. It is therefore not surprising that throughout history philosophers have highlighted either the ‘innate’ or ‘acquired’ perspectives when addressing the origins of aggression. Hobbes (Hobbes, 1647) argued that a wicked person was simply a child who had not grown up, whereas Rousseau argued (Rousseau, 1986) that humans are created good and become evil through the influence of society. More recently, the psychologist Albert Bandura wrote ‘People are not born with preformed repertoires of aggressive behaviour; they must learn them in one way or another’ (Bandura, 1973). This ‘social learning’ perspective on the developmental origin of human aggression drove much of the research in the past 50 years. Indeed, the US National Research Council’s Panel on Understanding and Preventing Violence (Reiss and Roth, 1993) concluded that ‘aggressive and violent behaviors

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are learned responses' and that 'the learning occurs by observing models of such behaviors'.

The main problem with studies that led to these conclusions was that they focused on physical aggression during pre-adolescence, adolescence and adulthood. Only recently have researchers taken a developmental origins approach to the study of physical aggression. Longitudinal epidemiological studies with birth cohorts have shown that physical aggression is observed as early as 12 months of age and its frequency peaks between 2 and 4 years of age (Côté et al., 2006; Côté, 2007; Tremblay et al., 2004). Further longitudinal studies conducted in Canada, New Zealand and the US, have found that the frequency of physically aggressive acts decreases for the majority of children between 5 and 15 years of age (Broidy et al., 2003; Nagin and Tremblay, 1999). These studies indicate that during development, children learn not to use physical aggression, because it is not a socially accepted behaviour, as opposed to learning to use physical aggression. However, among both boys and girls, a small group of children (3–7%) stand out as exhibiting notably more physically aggressive behaviours (CPA) than their peers throughout childhood and adolescence (Alink et al., 2006; Broidy et al., 2003; Campbell et al., 2006; Kokko et al., 2009; Nagin and Tremblay, 1999; Tremblay et al., 2004; Vaillancourt et al., 2007).

A number of studies have now shown that children exhibiting CPA tend to grow up in adverse family environments (Campbell et al., 2010; Côté et al., 2007; Nagin and Tremblay, 2001; Tremblay et al., 2004), have lower cognitive abilities (Barker et al., 2007), tend to be rejected by their peers from early childhood onwards (Barker et al., 2008) and have numerous physical, mental and social problems, such as accidents, hyperactivity, school failure, substance abuse and unemployment (Broidy et al., 2003; Kokko and Pullkkinen, 2000; Nagin and Tremblay, 1999; Séguin et al., 1999). Longitudinal studies of females with CPA during childhood show that although they do not maintain high levels of physical aggression during adolescence and early adulthood as seen in men, they tend to fail in school, suffer from depression, are likely to mate with men having problematic behaviour, become pregnant during adolescence, smoke during pregnancy and use coercive behaviour towards their children (Fontaine et al., 2008; Serbin et al., 1998).

What are the risk factors for the trajectory of chronic physical aggression?

Environmental risk factors

There is now good evidence that parents of children on a CPA trajectory had similar behavioural problems during their own childhood. As parents, they tended to create an early childhood family environment that did not support learning to regulate physically aggressive reactions. Studies focusing on early environmental predictors for childhood CPA have identified four general categories of predictors: maternal characteristics/lifestyle/mental health, family characteristics, maternal parenting and child characteristics (Campbell et al., 2006; Campbell et al., 2010; Côté et al., 2007; Huijbregts et al., 2008; Nagin and Tremblay, 2001; Tremblay, 2010; Tremblay et al., 2004). Maternal smoking, level of education, depression and antisocial behaviour, low family income and dysfunction were all found to be significant risk factors. In addition, perinatal adverse experiences, such as obstetrical complications, were also shown to predict violence in late adolescence in boys who grew up in highly adverse familial environments (Arseneault et al., 2002). Not surprisingly, the characteristics of the child itself, such as high level of hyperactivity and low verbal intelligence (de Souza et al., 2013), were found at the top of the list in predicting CPA. Sex was also found to be a significant risk factor for CPA, with boys being more at risk than girls (Baillargeon et al., 2007; Côté, 2007; Hill et al., 2006).

Childhood adversity such as maltreatment (Caspi et al., 2002), trauma (Weder et al., 2009) and sexual abuse (Beach et al., 2010) in humans have all been shown to increase the risk for antisocial, violent, impulsive and aggressive behaviours in adulthood. In animals, adverse early-life experiences prior to puberty, such as fear induction (Márquez et al., 2013) and maternal separation in rats (Veenema et al., 2006), as well as adverse rearing experiences in rhesus monkey (Barr et al., 2003; Newman et al., 2005) all promote high rates of aggression in adulthood.

Genetic risk factors

Because aggression is an adaptive trait that has been conserved during evolution, it can be expected that genetic factors play a role in this behaviour (Cairns, 1996). Quantitative genetic epidemiology studies that have used twins and adoption designs to investigate the heritability of aggressive behaviour estimate that genetic background accounts for ~50% of the frequency of acts of physical aggression (Arseneault et al., 2003; Brendgen et al., 2008; Brendgen et al., 2005; Dionne et al., 2003; Hicks et al., 2004; Lacourse et al., 2014; Rhee and Waldman, 2002; Tuvblad et al., 2009). Similar results were also found in rhesus monkeys (Bennett et al., 2002).

At the molecular level, genetic association studies have investigated several polymorphisms in essential genes involved in neurotransmission and hormonal regulation in aggressive humans and animals (Pavlov et al., 2011). Most of the research targeted genes involved in the regulation of the neurotransmitters serotonin (5-HT) and dopamine. Indeed, lower cerebrospinal fluid (CSF) and blood levels of 5-hydroxyindolacetic acid (5-HIAA), a terminal metabolite of 5-HT, correlates with high levels of aggressive behaviour in monkeys (Higley et al., 1996) and humans (Coccaro et al., 1997; Tuinier et al., 1995). Studies in mice have also shown that knockout of the 5-HT receptor 1B results in increased aggression (Ramboz et al., 1995). Dopamine is also hypothesized to play a role in aggression because it is involved in the neuronal reward system. CPA may result, in part, from a reduction of this reward system (Chen et al., 2005). Polymorphisms in various genes involved in serotonin and dopamine metabolism were indeed found to be significantly associated with aggression in humans and in animals, such as monoamine oxidase A (*MAOA*), dopamine receptor 2 (*DRD2*) and the serotonin transporter (5-HTT or *SLC6A4*) genes (Pavlov et al., 2011).

It is important to note that only a few of the polymorphisms associated with aggression were found to have an impact on gene expression and function (Pavlov et al., 2011). To date, very few mechanisms have been shown to mediate the impact of a polymorphism on gene expression and phenotype. One hypothesis is that polymorphisms are associated with other marks in the genome that are able to act on gene function. Such associations have been found between genetic variation and DNA methylation, and are called allele-specific methylation (ASM) (Meaburn et al., 2010; Schalkwyk et al., 2010; Shoemaker et al., 2010). These types of association are believed to be involved in complex human diseases and behaviour, and examples are given in the epigenetics section below.

Interactions between genetic and environmental risk factors

It is clear that both the environment and genotype play a role in aggression, but how they interact in the development of the behaviour remains largely unknown. Suomi and colleagues studied rhesus monkeys, a highly aggressive species. Like humans, rhesus

macaques start using physical aggression early in life and need to learn when, how and against whom they must use aggression. As seen in humans, a small proportion (5–10%) of rhesus monkeys in the laboratory and in the wild fail to learn to control their physical aggressions (Steklis et al., 1985; Suomi, 2005). Using early differential rearing environments that induced highly reactive and aggressive monkeys (Barr et al., 2003; Suomi, 1991), Suomi's lab found a significant interaction between rearing environment and a polymorphism in the *SLC6A4* gene on CSF 5-HIAA concentrations; only peer-reared monkeys with the short (S) allele (heterozygote) had lower 5-HIAA concentrations (Bennett et al., 2002). Interestingly, this polymorphism (5-HTTLPR) is functional where the S allele confers lower mRNA expression of the *SLC6A4* gene. These analyses demonstrate a significant gene×environment (G×E) interaction, where rearing of the mother appears to diminish the deleterious effect of the S allele on serotonin metabolism and the development of further behaviour (Champoux et al., 2002).

Inspired by these results, Caspi and his group reported a specific G×E interaction involving a polymorphism in the *MAOA* gene, which encodes an important neurotransmitter-metabolising enzyme, and adverse early social experiences in a birth cohort from a New Zealand hospital (Caspi et al., 2002). Indeed, a functional polymorphism in the gene was found to moderate the effect of childhood maltreatment. Maltreated children with the polymorphism conferring high levels of *MAOA* expression were less likely to develop antisocial problems such as violence compared with those with the genotype conferring low MAOA activity. Following this publication, a number of independent studies have tried to replicate the results and reported mixed findings. In contrast, meta-analyses grouping most of these studies were able to confirm a significant MAOA×child abuse interaction that predicts antisocial behaviour in men, whereas these results turned out to be less consistent in women and this requires further investigation (Byrd and Manuck, 2014; Kim-Cohen et al., 2006; Taylor and Kim-Cohen, 2007).

These studies provide evidence that specific gene polymorphisms can moderate children's sensitivity to environmental insults. However, the mechanisms responsible for mediating these interactions remain unclear. In the past decade, there is increasing evidence that epigenetic marks are likely to play a major role in the molecular mechanisms underlying the long-lasting effect of early adversity on adult health in animals (Darnaudéry and Maccari, 2008; Gudsnuk and Champagne, 2012) and in humans (Klengel et al., 2014; Mill et al., 2008; Sasaki et al., 2013; Szyf, 2012).

Overview of the epigenome

The main functions of the epigenome are to regulate gene transcription and compaction of the DNA into the cell nucleus. Several distinct epigenetic marks come together to achieve this, including DNA methylation and hydroxymethylation, histone modifications, ATP-dependent chromatin remodelling and non-coding RNAs. DNA methylation is a covalent modification of the DNA at cytosine residues that are located primarily at CpG dinucleotide sequences in mammals. Increased DNA methylation in the promoter region or in the first exon is usually associated with repressed gene expression (Bird, 1986), whereas DNA methylation found within the gene body, enhancer and intergenic regions (Ball et al., 2009) correlate both negatively and positively with gene expression (Jiang et al., 2013; Jjingo et al., 2012; Mehta et al., 2013). DNA methylation patterns are copied and maintained by DNA methyltransferases (DNMTs) (Jeltsch, 2008) whereas DNA demethylation processes are achieved through more complex DNA excision/repair-based mechanisms (Barreto et al., 2007; Guo et al., 2011a; Morgan et al., 2004; Schmitz et al., 2009; Wu and Zhang, 2014). Together, these epigenetic mechanisms have been shown to be involved in the immune response to pathogens as well as in neuronal activity and also underlie the mechanism of learning (Busslinger and Tarakhovsky, 2014; Day et al., 2013; Garden, 2013; Guo et al., 2011b; Ma et al., 2009; Quintin et al., 2014; Russ et al., 2013).

Epigenetics, early-life adversity and physical aggression

The main reasons why the epigenome is expected to play a role in the development of disease and behaviour, are that it can program the genome at different time points during development, it can register environmental input onto the genome, and it can mediate the effect of genetic polymorphisms on phenotypic variations. DNA methylation is the most studied mark for such a biological response mediated by the environment, because it is thought to be a relatively stable mark and is therefore hypothesized to play a role in the development of aggression (Tremblay, 2010; Tremblay and Szyf, 2010). In this section, we describe the evidence related to the role of DNA methylation in the biological embedding of early adversity, and its association with aggressive behaviour.

Epigenetic programming by early-life adversity

The first study reporting epigenetic programming in response to early-life stress was performed by Weaver et al., who show that DNA methylation patterns of the glucocorticoid receptor (*Nr3c1*) gene, a key player in the regulation of the stress response, can be altered after birth in response to maternal care (Weaver et al., 2004). The study identified higher DNA methylation and lower histone acetylation profiles, leading to decreased expression of the *Nr3c1* exon 1_7 (human exon 1F) gene in the hippocampus of offspring of mothers displaying decreased levels of pup licking and grooming over their first week of life. These pups exhibited higher behavioural and endocrine responses to stress in adulthood. Although these differences were maintained until adulthood in the untreated rat, they could be prevented by cross-fostering or reversed by central infusion of a histone deacetylase inhibitor. Moreover, the study also demonstrated that DNA methylation changes in response to the environment are triggered by a molecular signalling cascade. They show that maternal care could activate, through the 5-HT signalling pathway, *Nr3c1* promoter transcription factor (NGFI-A), which recruits histone acetyltransferase protein (CBP) and, in turn, triggers DNA demethylation that confers proper *Nr3c1* transcription (Weaver et al., 2007; Weaver et al., 2004). These results illustrate how an environmental stimulus can lead to epigenetic programming that influences life-long behavioural trajectories. The basic concepts of this study were repeated in several other animal models of early-life adversity and found similar epigenetic alterations in genes such as the *Bdnf* (Roth et al., 2009), *Avp* (Murgatroyd et al., 2009), *Crh* (Elliott et al., 2010), *Crhr2* (Franklin et al., 2010), *Gad1* (Zhang et al., 2010b) and *Olfr151* (Dias and Ressler, 2014).

Some of these results have also been translated to humans, using post-mortem brains. Methylation and expression of the human *NR3C1* exon 1F gene showed altered profiles in the hippocampus of victims of suicide exposed to child abuse (McGowan et al., 2009). Analysis of the DNA methylation status in a large genomic locus containing the *NR3C1* gene identified additional numerous regions such as the protocadherin (*PCDH*) gene cluster that also displayed differences in DNA methylation associated with both maternal care in rats and child abuse in humans (Suderman et al., 2012). Moreover, genome-wide studies identified differential DNA methylation in many gene promoters in the hippocampus involved

in cellular/neuronal plasticity associated with severe childhood abuse (Labonté et al., 2012).

The use of peripheral tissues in DNA methylation association studies

Most of the current clinical and epidemiological work with humans cannot include brain samples. Thus, human epigenetic studies have used peripheral tissue, such as blood and buccal cells, and were able to identify numerous epigenetic associations with early-life stress and various disease states. These associations can either be seen as simple potential biomarkers, but they might also be causally involved in the disease state through, for example, their action on stress and the immune system (Miller and O'Callaghan, 2005).

Indeed, previous studies have shown associations between DNA methylation in blood and epithelial cells, and various types of environmental exposure (Kinnally et al., 2011; Klengel et al., 2013; Mehta et al., 2013; Naumova et al., 2012; Ressler et al., 2011; Smith et al., 2011; Tobi et al., 2009). In a recent study, Suderman et al. identified a specific DNA methylation signature in peripheral blood that associates with childhood abuse (Suderman et al., 2014). Childhood experiences such as lower socioeconomic position were also shown to associate with specific DNA methylation profiles in adult peripheral tissue (Borghol et al., 2012). Alterations in DNA methylation, not only blood cells, but also in buccal epithelial cells, are associated with parental stress in adolescents (Essex et al., 2013) and victimization/bullying in monozygotic (MZ) discordant twins (Ouellet-Morin et al., 2013).

Epigenetic modifications could be one of the mechanisms underlying G×E interactions in aggression. Evidence for such a mediating effect has been reported in patients with post-traumatic stress disorder (PTSD). Analysing DNA of cells from whole blood, Binder and colleagues found that allelic-specific DNA demethylation of the FK506 binding protein 5 (*FKBP5*) gene, which encodes an important regulator of the stress hormone system, is associated with long-term dysregulated response to stress and an increased risk for PTSD in individual victim of child abuse (Klengel et al., 2013). Additional allele-specific changes in DNA methylation following early-life adversity were also described by other groups (Gertz et al., 2011; Gibbs et al., 2010; Kerkel et al., 2008; Meaburn et al., 2010; Zhang et al., 2010a). Together, these studies indicate that the DNA sequence itself also encodes information on its methylation status, thereby offering a potential mechanism by which G×E interactions alter disease state later in life.

These studies also support the hypothesis that differences in DNA methylation in response to social adversity are system wide and are not limited to the brain. These effects in peripheral blood cells may be mediated, in part, by the bilateral relationship of the HPA axis and the immune system – the main brain and blood communication system. It is also possible that similar genes or members of similar pathways as those affected in the periphery are affected in the brain. Studying maternal deprivation in rhesus macaques, we tested this hypothesis using whole-genome promoter mapping of DNA methylation profiles of the prefrontal cortex and T cell DNA (Provençal et al., 2012). We observed altered DNA methylation patterns in specific genes as well as organized genomic clusters, and biological functions in both cells type. Interestingly, most of these changes were tissue specific, where only a small fraction of genes, genomic clusters and biological functions were found to be affected in both tissue types. These data suggest that the response to early-life adversity is genome- and system-wide, and targets mostly tissue-specific functions in both the brain and the periphery, further supporting the use of peripheral immune cells in the study of behaviour. Moreover, this response to early-life maternal deprivation was not limited to DNA methylation alone, other epigenetic mechanisms were involved. We observed altered DNA hydroxymethylation profiles in the prefrontal cortex of these differentially reared monkeys in specific genes involved in neuronal functions that did not show altered DNA methylation patterns (Massart et al., 2014).

These data are of particular interest in relation to aggression, because the frontal cortical region, in particular the prefrontal cortex, was shown to play a crucial role in the regulation of aggressive behaviour (Miczek et al., 2007; Siever, 2008). For example, prefrontal cortical lesions result in disinhibited aggressive behaviour in humans (Damasio et al., 1994). Moreover, as mentioned above, the maternal deprivation model used here induces a high level of aggressive/impulsive behaviour in the offspring (Barr et al., 2003). Therefore, it is possible that these epigenetic alterations in the prefrontal cortex play a role in the neurobiology of aggression.

Epigenetic associations with aggressive behaviour

Using DNA from monocytes and T cells in peripheral blood, we recently reported an association between childhood CPA in men and differential DNA methylation in the regulatory regions of cytokine and transcription factor genes (Provençal et al., 2013a). Moreover, these cytokines were also shown to be repressed in men with CPA compared with men on a normative developmental trajectory of aggressive behaviour (Provençal et al., 2013b). Interestingly, one of these downregulated cytokines in men with CPA, interleukin-6 (IL-6), was previously shown to be involved in aggressive behaviour in mice, because its knockout (IL-$6^{-/-}$) resulted in an 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., 2011; Koo and Duman, 2008; von Känel et al., 2007), as well as aggression (Marsland et al., 2008; Suarez et al., 2002). Moreover, studies in rodents have shown that cytokines play an important role in early brain development (Deverman and Patterson, 2009). Early-life stress such as social isolation and prenatal anxiety as been found to alter the immune system, including cytokines (Barreau et al., 2004; Danese et al., 2007; O'Connor et al., 2014; 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 peripheral nervous system. Maternal deprivation in rhesus macaques (Provençal et al., 2012), early-life socioeconomic position (Borghol et al., 2012), child abuse (Suderman et al., 2014) and PTSD (Mehta et al., 2013; Smith et al., 2011; Uddin et al., 2010), were all found to associate with DNA methylation in promoters regulating genes in immune-response pathways. Together, these results suggest that immunoregulators are responsive to early-life stress. Alterations in immunoregulators might lead to alterations in brain development, which, in turn, may affect the regulation of aggression. DNA methylation and histone modifications could be mechanisms that mediate the association between the early environment and brain and behavioural outcome. Immunoregulators may influence brain circuitry and behaviour directly, or via interactions with other biological systems. Of particular interest in the context of early adversity and physical aggression are the HPA axis and the serotonin system. These systems will be discussed in greater detail below.

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 cortisol are mediated by its binding to the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which 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 induced by lower maternal care (Weaver et al., 2004), for example, is generally associated with an increase in the response to stress due to an impaired negative feedback. Activated GR can also act as a potent repressor of pro-inflammatory protein and cytokine genes through its binding to glucocorticoids response elements (GREs) in regulatory regions. As describe above, GREs have been shown to be epigenetically altered after exposure to stress such as child abuse or dexamethasone exposure (Klengel et al., 2013). Thus, the effects observed on the immune system in relation to aggression could also be due to a dysregulated HPA axis and therefore alterations in the cortisol release and actions, through GR binding, on immune system genes. Similarly, administration of cytokines, such as IL-1 and IL-6, to animals could stimulate the HPA axis (Dunn, 2000), suggesting a reciprocal interaction.

In general, correlations have been found between reduced cortisol levels and increased aggression in boys, adolescents and young men (Loney et al., 2006; Popma et al., 2007; Shirtcliff et al., 2005). In contrast, a longitudinal study on aggressive behaviour reported elevated salivary cortisol levels in boys with conduct disorder (CD) compared with boys without CD, where boys with an aggressive form of CD had even higher levels of cortisol (van Bokhoven et al., 2005). A strong correlation was also observed between reactive aggression and elevated cortisol in this study. Another important study investigating the type of aggression and cortisol reactivity reported higher cortisol reactivity in children with patterns of reactive aggression compared with children with no aggression or proactive aggression (Lopez-Duran et al., 2009). These mixed findings might reflect the inconsistency in the types of aggression studied and lack of longitudinal data, including basal and reactive cortisol levels at many time points through development (Tarullo and Gunnar, 2006). Overall, different subtypes of aggression are more likely to be characterized by differential HPA axis regulation where hyperactivity of the axis is more likely to be seen in individuals with reactive aggression and HPA hypoactivity in individuals with proactive aggression.

Maltreatment in childhood can lead to high levels of aggression in adulthood, and is known to induce long-lasting alterations of the HPA axis and cortisol levels in children and adults (Veenema, 2009). The true nature of this relationship is definitely complex, involving interactions with many other biological systems. Indeed, excessive release of glucocorticoids following early-life stress could specifically alter the neuronal structure of glucocorticoid-sensitive areas of the brain and induce epigenetic alteration of various genes either through direct binding of GR to GREs, or through activation of neuronal signaling pathways regulating various epigenetic proteins such as MeCP2 (Murgatroyd et al., 2009). Indeed, activated GR has been shown to induce stable DNA demethylation in and around GREs, leading to increased transcriptional sensitivity of the target gene (Thomassin et al., 2001).

In addition, early stress also affects multiple neurotransmitter systems such as serotonin, noradrenaline and dopamine. The role of 5-HT is of particular interest, given that it is among the neurotransmitters most consistently and frequently associated with aggression (see above), and also plays a very important role in early brain development (Booij et al., 2014). There is convincing evidence from both animal and human studies that prenatal adversity (e.g. maternal smoking and maternal exposure to antidepressants during pregnancy), as well as early-life stressors, could have a long-term impact on 5-HT neurotransmission (Booij et al., 2014). For instance, in rodents, maternal separation was shown to associate with altered concentrations of 5-HT and its metabolite 5-HIAA in the dorsal raphe nucleus in adulthood (Arborelius and Eklund, 2007). As mention above, maternal deprivation in monkeys is associated with altered 5-HIAA concentrations in the CSF but also with reduced 5-HTT and 5-HT_{1A} binding in the frontal-limbic regions (Ichise et al., 2006; Spinelli et al., 2010). Interestingly, serotonergic alterations in these brain regions have also been associated with impulsive/aggressive behaviours (Booij et al., 2010; Siever, 2008). In humans, we found that maternal smoking during pregnancy was associated with lower brain 5-HT synthesis in the orbitofrontal cortex (OBFC) in adults (Booij et al., 2012). Notably, prenatal exposure to nicotine is one of the early environmental predictors of physical aggression in children (Huijbregts et al., 2008). Methylation in the *SLC6A4* transporter gene has been found to correlate with early adversity. For instance, Beach et al. recently proposed that methylation of the promoter of *SLC6A4* may contribute to diminished serotonergic system responsiveness to child abuse by decreasing expression of the serotonin transporter (SERT), thus creating potential for impulsive/aggressive behaviour that, in women, could lead to antisocial personality disorder (ASPD) (Beach et al., 2011). They identified an association between female victims of child sexual abuse and overall hypermethylation of the *SLC6A4* promoter region. In addition, they observed a significant association between DNA methylation in the *SLC6A4* promoter with symptoms of ASPD in women that was also partly mediated by 5-HTTLPR polymorphism. Thus, child sexual abuse may create long-lasting epigenetic changes in the *SLC6A4* gene promoter leading to female antisocial behaviour.

Although different signatures in response to early-life events are observed in different tissues, epigenetic changes in peripheral tissues may also correlate to some extent with measures in the brain. We previously found a significant association between aggression during childhood and adult DNA methylation profiles in the *SLC6A4* gene promoter in DNA from peripheral blood cells (T-cells and monocytes) (Wang et al., 2012). Notably, even though the observed differences in DNA methylation between those with high levels of aggression in childhood and those who had low levels were relatively small (5–8%), higher *SLC6A4* methylation was associated with lower *in vivo* brain serotonin synthesis in the lateral left and right orbitofrontal cortex. Interestingly, these specific brain regions were also shown previously to have lower serotonin synthesis in those individuals with higher levels of aggressive behaviour during childhood (Booij et al., 2010).

It could be speculated that epigenetic alterations in 5-HT in the frontal-limbic regions are an underlying mechanism of how early environmental adversities translate into an increased risk for physical aggression. However, systematic studies investigating causal mechanisms of this potential association are lacking. In

addition to the role of 5-HT on risk for aggression and brain development, is clear that the serotonin system has widespread interactions with other biological systems. These include, but are not limited to, the immune system and the HPA axis; and the interactions are highly complex. For instance, a number of experimental studies in animals have shown that cytokines can alter serotonin turnover (Capuron and Miller, 2011). One of the mechanisms by which this association occurs is through stimulating the tryptophan metabolising enzyme indoleamine-2,3-dioxygenase (IDO) (Capuron and Miller, 2011; Myint and Kim, 2003; Tsao et al., 2006), which, in turn, decreases brain 5-HT synthesis. In addition, a number of *in vivo* and *in vitro* studies have shown that cytokines can activate the expression and activity of serotonin transporters (see Capuron and Miller, 2011). The interaction between cytokine and serotonin has been proposed as mechanism for the etiology of depression (Myint and Kim, 2003). It could be speculated that it may also be true for aggression.

As mentioned above, exposure to maternal stress during gestation in mammals was 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 behaviour through alterations of the HPA axis and the serotonin system (Ahmed et al., 2014). Reduced hypothalamic levels of GR protein and *CRH* mRNA levels accompanied by an increase in DNA methylation in the GR and CRH gene promoters were observed in the chicks, whereas no changes in GR mRNA levels were observed. These chicks also displayed lower TPH1 and higher 5-HT_{1A} and MAOA mRNA levels accompanied with a decreased whole-blood 5-HT concentration. Here, prenatal cortisol exposure caused altered expression levels and epigenetic reprogramming of critical genes that, in turn, altered the HPA axis and serotonin system, brain development, and consequently, enhanced aggressive behaviour. Unfortunately, methylation levels of only GR and CRH were analyzed in the study. It is unclear whether serotoninergic genes also undergo epigenetic remodelling as a result of cortisol exposure and how these influence behavioural outcome.

In rats too, exposure to early adverse life experiences was shown to induce high and sustained rates of increased aggressive behaviour in adulthood. In their model, Márquez et al. found that peripubertal exposure to stress (fear-induction experiences) induces pathological aggression in male rats (Márquez et al., 2013). These peripubertal stressed rats 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 prefrontal cortex 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. Histone acetylation is known to promote gene transcription by increasing the accessibility to binding of active transcription regulators (Kuo and Allis, 1998) and histone 3 acetylation in particular, has been shown to play a role in regulating long-term changes in gene expression (Tsankova et al., 2007). These findings, together with previous work on the *MAOA* gene, support the hypothesis that either hypo- or hyperactivity of MAOA contributes to pathological aggression (Nelson and Trainor, 2007), possibly through epigenetic programming.

The epigenetic association studies presented above mainly focus on candidate genes involved in the HPA axis and the serotonin pathways that either were suspected or previously shown to be involved in aggression. Another approach that has been used successfully in the past to find significant association with diseases and behaviour is an unbiased genome-wide approach. Using this approach to analyse male T-cell genomes, 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 report their colocalization 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 an aggressive phenotype in humans (Guo et al., 2007; Våge et al., 2010; Vaughn et al., 2009) and animals (Ferris et al., 2006; Hammock et al., 2005). As anticipated from our previous study of cytokine genes (Provençal et al., 2013a), the inflammatory and immune biological functions of specific signalling pathways, such as cytokine signalling between immune cells, IL-6 and IL-10 signalling was found enriched with genes differentially methylated in men with CPA. Specific cytokines and receptors, such as IL1R1 and IL1RN, which are involved in these pathways were previously shown to be involved in aggression and human mood disorders (Hassanain et al., 2005; Pesce et al., 2011). Together, these findings suggest a well-defined, genome-wide epigenetic pattern associated with CPA in men.

Aggressive behaviour was also studied in women for associations with DNA methylation. 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 gender-independent fashion. The almost perfect overlap between functional categories represented by both male and female signatures provides further evidence that they are, at least in part, associated with aggression rather than confounding factors. Here also, specific genes involved in serotonin metabolism and regulation of the HPA axis, which were previously shown to be involved in aggression, were found to be differentially methylated in women with childhood CPA. These HPA-regulating genes (*NR3C1* and *CRHBP*) were found differentially methylated only in women with CPA. This may be explained, in part, by the fact that negative-feedback control of the HPA axis has 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.

Conclusions

There is increasing evidence that epigenetic mechanisms play an important role in the association between early-life adversity and long-term health and well-being. This review summarises the evidence that the early-life environment, including prenatal and postnatal stress, may play a crucial role in the development of chronic physical aggression in animals and in humans. Results from the studies discussed suggest that early adversity produces acute and long-lasting epigenetic alterations. These alterations may influence brain development and the ability to learn to control aggressive behaviour. In the context of early-life adversity and physical aggression, epigenetic alterations in genes regulating cytokines, the HPA axis and 5-HT are of particular interest.

In addition to the epigenetic alterations in these systems and the putative effects on brain development, the systems may also interact. For instance, alterations in cytokine production induced by early adversity may lead to alterations in SERT signalling in the 5-HT

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system, which, in turn, has consequences for brain development. Similarly, cytokine alterations may affect GR production, which, in turn, could affect the formation of certain brain structures involved in the regulation of aggressive behaviour. To complicate things further, it is reasonable to assume that these effects are bidirectional. Moreover, the influence of other neurotransmitters, such as dopamine and noradrenalin cannot be ignored. Together, these findings suggests a dynamic model of the role of the immune system on physical aggression, that interacts with multiple factors other than the factors considered here, including other biological systems, timing of adversity in development, resilience factors and sex. The specific consequences ultimately depend on the complex interplay between these various factors. In addition, genetic resistance to epigenetic alterations could explain, in part, why some children will be resilient to the deleterious effects of early-life adversity (Fig. 1).

Longitudinal and preventive experimental studies initiated during the prenatal period and combining genetic, epigenetic, brain imaging and environmental assessments are needed to clarify the developmental mechanisms that lead to chronic physical aggression. The understanding of these mechanisms will not only increase our knowledge on the developmental mechanisms but also, and more importantly, will help prevent them to occur because we know that they can be remodelled (Szyf, 2014; Weaver et al., 2004; Yehuda et al., 2013). The tissues available to perform such studies are peripheral tissues, such as blood and saliva. Both tissue and cell-specific changes will probably be apparent in the context of early-life adversity and aggression, as well as system-wide effects that are most likely in response to stress hormones (Klengel et al., 2014; Provençal and Binder, 2014; Szyf, 2013). Neural activity and stress hormone receptors have been shown to induce epigenetic changes following postnatal stress exposure, leading to long-term changes, not only in the brain, but also in peripheral tissues (Klengel et al., 2013; Provençal et al., 2012). Indeed, the increased release of glucocorticoids observed following early-life stress, for example, could simultaneously target similar genes across diverse tissues because its receptors are present in most tissues. Subsequently, changes in DNA methylation could be induced in several tissues by these activated hormones and receptors in response to early-life

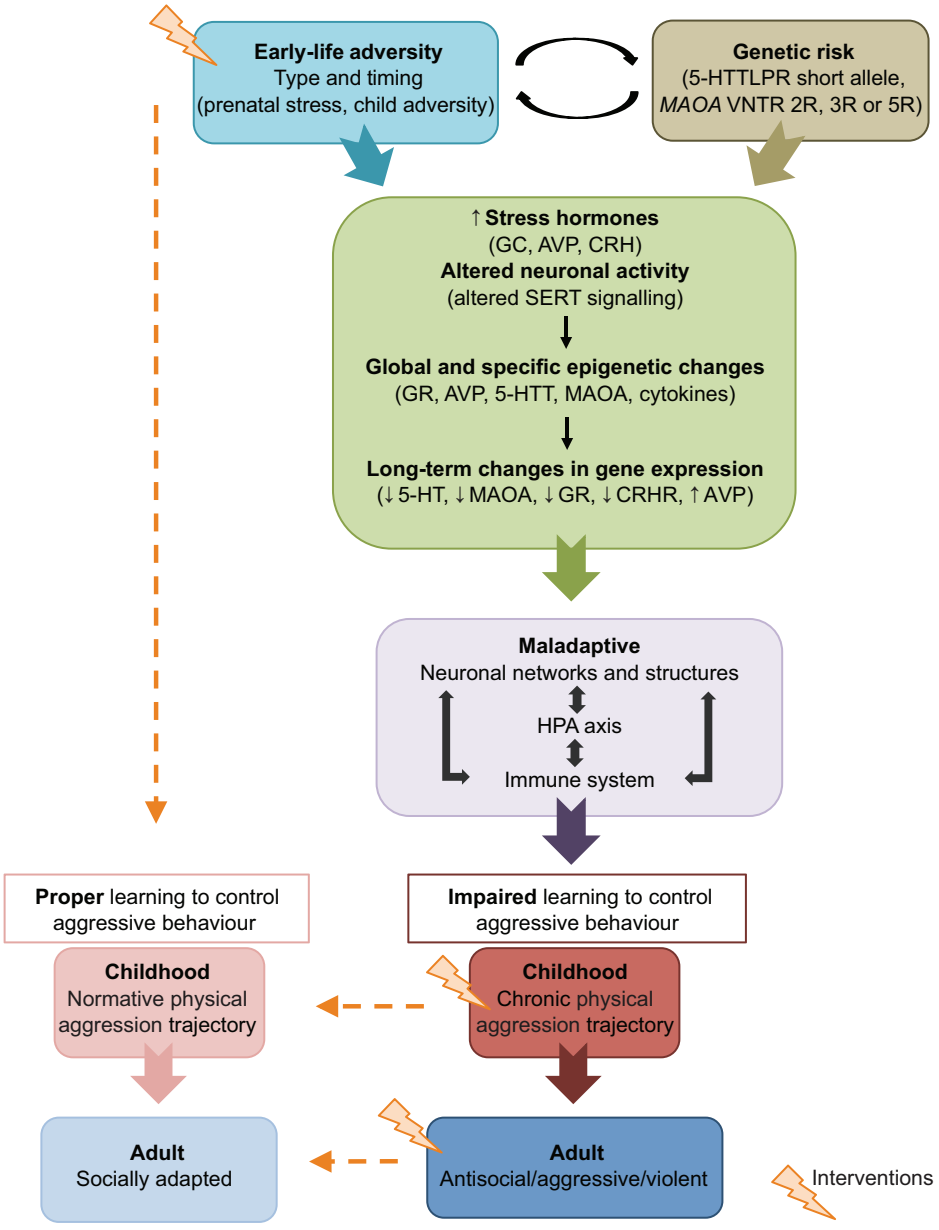

Fig. 1. Developmental mechanisms underlying the association between early-life adversity and the development of chronic physical aggression. Early life adversity is believed to produce acute and long-lasting epigenetic alterations that influence gene expression profiles in many systems, such as the HPA axis, neuronal networks, as well as the immune and endocrine systems that will, in turn, alter an individual's ability to learn to control physically aggressive behaviour. Genetic factors will probably moderate these effects of early-life stress on the epigenome and influence the risk or resilience to develop maladaptive behavioural outcomes. Because epigenetic alterations are potentially reversible by either drug or environmental interventions, these negative outcomes may be avoided. Biological, psychological and social interventions at different points during development could possibly reverse the phenotype by inducing global as well as specific epigenetic changes, allowing a resetting of the dysregulated systems (represented by dashed orange arrows) and potentially facilitating learning of alternatives to physical aggression. Interventions are likely to be more effective if put in place during pregnancy prior to the establishment of long-lasting epigenetic marks and the development of key neuronal networks and structures. 5-HTT, 5-hydroxytryptamine transporter (also known as *SLC6A4*); 5-HTTLPR, serotonin-transporter-linked polymorphic region, a degenerate repeat polymorphic region in *SLC6A4*; AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; CRHR, CRH receptor; GC, glucocorticoid; HPA, hypothalamic–pituitary–adrenal; *MAOA*, monoamine oxidase A; SERT, serotonin transporter 5-HTT; VNTR 2R, 3R, 5R, alleles of the variable number tandem repeat.

stress (Provençal and Binder, 2014; Szyf, 2009; Szyf, 2013). An example is the study by Klengel et al. described above that identified a G×E interaction associated with demethylation in the *FKBP5* gene in blood cells. Interestingly, they also found similar DNA methylation changes after glucocorticoid exposure in human progenitor hippocampal neuronal cells, suggesting that in both tissues, similar epigenetic mechanisms could be at play in response to an increase in cortisol. Moreover, these epigenetic effects were only seen in response to childhood trauma and not adult trauma, as well as only when the progenitor hippocampal neuronal cells were treated during their proliferation and differentiation periods, suggesting that there are critical periods during development for these changes to have long-lasting effects (Klengel et al., 2013; Mehta et al., 2013).

The studies discussed here are consistent with the hypothesis that the response to early-life social adversity and aggression has an immune component. There is strong evidence of a crosstalk between the immune system and the brain through the HPA axis and the 5-HT system that could in part explain these observations. Actions of GR following activation of the HPA axis occur in most tissues and are known to affect expression of various immune system genes. Thus, the immune system might play a role in the overall response to social adversity and in the development of chronic physical aggression through epigenetic mechanisms. This suggests that T-cells will be useful for future studies, to investigate not only immune-specific genes that are associated with the HPA axis but also genes that are involved in brain function, as in our rhesus macaque study (Provençal et al., 2012). Further longitudinal studies with biological, environmental and behavioural assessments from birth onwards, are needed to elucidate the sequence of events that leads to these long-lasting epigenetic marks associated with early adversity and aggression.

Competing interests
The authors declare no competing or financial interests.

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