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Diplôme d'État
par

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ÉPIGÉNÉTIQUE ET VIOLENCE :
QUEL IMPACT DES VIOLENCES SUBIES SUR LE MATÉRIEL GÉNÉTIQUE ?
UNE REVUE DE LA LITTÉRATURE

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Épigénétique et violence : quel impact des violences subies sur le matériel génétique ? Une revue de la littérature

RÉSUMÉ

Introduction : La prise en charge des victimes de violences est devenue un problème de santé publique. Mieux connaître les conséquences de la violence sur l'état de santé des victimes permet d'envisager des actions à visée préventive et thérapeutique. Parmi les conséquences potentielles, des études sur le matériel génétique de l'animal puis de l'Homme ont suggéré que la violence agirait comme un facteur environnemental modifiant l'expression de certains gènes. L'objectif principal de cette revue de la littérature était de s'intéresser aux modifications épigénétiques induites par l'exposition à la violence : gènes cibles, transmissibilité aux générations suivantes et conséquences fonctionnelles conduisant à une sensibilité accrue à certaines maladies ou au contraire à la résilience. **Matériel et méthodes :** 180 articles ont été analysés dans le cadre de ce travail, recueillis sur les bases de données MEDLINE® (Pubmed), Web of Science® Core Collection, et GoogleScholar® pour étudier les liens entre violence et épigénétique. **Résultats - Discussion :** Les résultats des études étaient parfois contradictoires, ce qui n'est pas surprenant étant donné la complexité de l'épigénétique, le grand nombre de facteurs de confusion existant dans cette approche, et les limitations inhérentes à l'expérimentation humaine. Actuellement, bien que certaines pistes thérapeutiques encore en cours d'exploration semblent prometteuses, il est prématuré de conclure à l'utilisation des « marqueurs épigénétiques » comme biomarqueurs pour la caractérisation et le suivi des victimes de violence.

Mots clés : violence, épigénétique, gènes cibles, transmissibilité, résilience, applications médico-légales

Does violence injure DNA: what do we know? A literature review

ABSTRACT

Introduction: Taking care of victims of violence had become a public health problem. A better understanding of violence consequences on victims' health may lead to preventive and therapeutic interventions. Among potential consequences, studies on animal genetic material then in human's suggested that violence will modify some gene expression as an environmental factor. The main aim of this literature revie as to identified genetic modifications induces by violence exposure: target genes, next generation transmission and functional consequences leading to an increased disease-susceptibility or on the contrary to resilience. **Material and methods:** for this revie , 180 publications ere gathered in scientific literature data bases MEDLINE® (Pubmed), Web of Science® Core Collection, and Google Scholar® were analyzed to study violence and epigenetic association. **Results - Discussion:** Results were sometimes contradictory, as expected, regarding epigenetic complexity, numerous confounders and humans' experimental limitations. Presently, although some therapeutic researches, it's too early to use epigenetic marks as biomarkers for characterization and the follow-up of victims.

Keywords: violence, epigenetic, target genes, inheritance, resilience, medico-legal applications

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,

de mes chers condisciples

et selon la tradition d'Hippocrate,

je promets et je jure d'être fidèle aux lois de l'honneur et de la probité

dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,

et n'exigerai jamais un salaire au-dessus de mon travail.

Admise dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe,

ma langue taira les secrets qui me seront confiés

et mon état ne servira pas à corrompre les mœurs

ni à favoriser le crime.

Respectueuse et reconnaissante envers mes Maîtres,

je rendrai à leurs enfants

l'instruction que j'ai reçue de leurs pères.

Que les Hommes m'accordent leur estime

si je suis fidèle à mes promesses.

Que je sois couverte d'opprobre

et méprisée de mes confrères

si j'y manque

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"On ne saurait aller trop loin dans la connaissance de l'homme."

Emile Zola / Livres d'aujourd'hui et de demain

ABBRÉVIATIONS

5-HT3A-R: serotonin type 3 receptor

ACTH: AdrenoCorticoTropic Hormone

AVP: Arginine VasoPressin

BDNF: Brain-derived neurotrophic factor

CNS: Central Nervous System

CpGs: Cytosine-Guanine dinucleotides

CRH: Corticotropin Releasing Hormone

DM-PFC: dorsomedial prefrontal cortex (DM-PFC)

DNA: DeoxyriboNucleic Acid

DNAm: DNA methylation

DRD2: Dopamine Receptor D2

DRD4: Dopamine Receptor D4

EWAS: Epigenome-Wide Association study

FKBP5: FK506 Binding Protein 51

GC: GlucoCorticoid

GR: Glucocorticoid Receptor

HPA: Hypothalamic-Pituitary-Adrenal

IL-PFC: InfraLimbic-PreFrontal Cortex

IPV: Intimate Partner Violence

MAOA: MonoAmine Oxidase A

miRNA: micro RNA

MR: Mineralocorticoid Receptor

mRNA: messenger RNA

NR3C1: Nuclear Receptor Subfamily 3-Group C-Member 1 PFC: PreFrontal Cortex

PL-PFC: PreLimbic-PreFrontal Cortex

POMC: PropioMelanoCortin

PTSD: Post-Traumatic Stress Disorder

RNA: RiboNucleic Acid

SLC6A4: Solute Carrier Family 6 Member 4

VM-PFC: ventromedial prefrontal cortex

WRVH: World Report on Violence and Health

NB : par convention, chez l'Homme le nom d'un gène s'écrit en lettres majuscules et en italique ; le nom de la protéine associée est simplement écrit en majuscule. Chez l'animal, le nom du gène est en lettres minuscules et en italique ; le nom de la protéine associée est simplement en minuscule.

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Avant-propos : contexte de l'étude

La violence est aujourd'hui largement considérée comme un problème de santé publique, même si ses répercussions ne sont pas encore vraiment reconnues sur le plan sanitaire. Il est difficile d'évaluer l'ampleur et les conséquences de la violence aussi bien au niveau individuel que sociétal, car les définitions des phénomènes de violences sont multiples.

La communauté scientifique s'interroge sur les conséquences physiques et psychologiques des violences sur l'état de santé des victimes. Parmi les thèmes de recherche, celui de l'effet des violences sur le phénotype c'est-à-dire sur l'ensemble des caractéristiques observables d'un individu, émerge depuis plusieurs années.

Les caractéristiques du phénotype reposent d'une part sur le patrimoine génétique, mais aussi sur la modulation de l'expression de celui-ci par l'environnement. C'est grâce à l'épigénétique, c'est-à-dire l'étude des modifications de l'expression des gènes par l'environnement, que ce type d'impact a pu être étudié.

L'objectif principal de ce travail était de réaliser un état des lieux des connaissances actuelles sur les liens entre violence et épigénétique en effectuant une revue de la littérature internationale sur ce sujet.

L'objectif secondaire était de déterminer s'il serait possible, au vu des connaissances actuelles, d'utiliser l'épigénétique comme moyen de prévention, voire une aide aux soins, dans la prise en charge des victimes de violences.

I. Definition and generalities

I.1.Typology of violence

Violence is defined in the World report on violence and health (WRVH) as: "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment, or deprivation."[1]

The WRVH typology of violence (while not uniformly accepted) distinguishes four modes in which violence may be inflicted: physical, sexual, psychological and deprivation. According to the victim-perpetrator relationship, general definition of violence can be also divided into three sub-types:

i) **Self-directed violence** refers to violence in which the perpetrator and the victim are the same individual and is subdivided into *self-abuse* and *suicide*.

ii) **Interpersonal violence** refers to violence between individuals and is subdivided into *family and intimate partner violence (IPV)* and *community violence.* The former category includes child maltreatment; intimate partner violence; and elder abuse, while the latter is broken down into *acquaintance* and *stranger* violence and includes youth violence; assault by strangers; violence related to property crimes; and violence in workplaces and other institutions.

iii) **Collective violence** refers to violence committed by larger groups of individuals and can be subdivided into social, political and economic violence.

In figures, reports from the World Health Organization (2002) indicate that about 20% of women and 5 to 10% of men are exposed to sexual and or physical child abuse and that an approximately 20% of children are neglected worldwide.

A comprehensive review of population-based studies in developed countries concluded that 5 to 35% of children were physically and 5 to 30% of them were

sexually abused, while 10 to 20% had witnessed domestic violence, across the duration of childhood.

In France, epidemiology of violence data is scarce.
An annual survey based on the national victimization inquiry “Cadre de vie et sécurité» conducted by (« Institut national de la statistique et des études économiques-Insee », « Observatoire national de la délinquance et de la réponse pénale- ONDRP » and « Service statistique ministériel de la sécurité intérieure (SSMSI) ») is based on phone interviews of 16 000 household people over 14 years of age, provides some statistics. According to this survey, between 2011 and 2017, in France, each year, 2,5% (1 of 40) people of the population aged from 18 to 75 were victims of physical or sexual violence (Rapport d'enquête CVS 2018)[2]. Regarding children, the “Observatoire National de la protection de l’enfance” gathers data from « Direction de la recherche, des études, de l’évaluation et des statistiques (DREES) », « Direction de la protection judiciaire de la jeunesse (DPJJ) », « 119 » annual statistics, Justice Ministry, National Education Ministry and Interior Ministry (SSMSI) [3].

In a 2006 report, 8,7 % of women and 2,8 % of men had said to have been victim of rape or attempt of rape before the age of 18. Moreover, 1,5 ‰ of girls and 2,1 ‰ of boys under 10 years old were victim of physical violence. 1,5 ‰ of girls and 0,6 ‰ of boys under 10 years old were victim of sexual violence[3].

I.2. Overview of the epigenome: Introduction to Epigenetics

As long ago as 1942, even prior to the discovery of DNA (DeoxyriboNucleic Acid), Waddington coined the term “epigenetics” (*epi* is from the Greek prefix that means “over,” “outside of,” or “around”) to describe how genes might interact with their surroundings to produce a phenotype. The main epigenetic changes playing an active role in gene expression regulation are represented by: DNA methylation, histone modification and non-coding RNAs (RiboNucleic Acid).

I.2.A. DNA methylation

DNA methylation is the most studied epigenetic change. The DNA molecule itself can be modified through the alteration of the methyl molecule patterns on nucleotide bases. DNA methylation is carried out by three active isoforms of the DNA methyltransferase family (DNMT-1, -3a and -3b) able to transfer residues of methyl groups from the S-adenosylmethionine (SAM) to unmethylated cytosines at cytosine-guanine dinucleotides (CpGs) sequences (but not exclusively) in mammals[4–7]. DNMT-3a and -3b perform *de novo* methylation of unmethylated CpGs and produce new DNA methylation marks[8]. This d*e novo* methylation mainly occurs in the early embryonic cells[9].

DNA can be actively methylated or demethylated mostly in response to environmental triggers[10–14] ; but genomic DNA methylation also plays an important role in the maintenance of genome integrity and heterochromatin formation[15–17] during mitosis in daughter cells. Most CpGs are grouped in specific loci of the genome, "the CpG islands", which are located into promoters, exons and (to a lower extent), introns[18,19]. Most work on DNA methylation has focused on CpG islands, which are defined (but debated)[20] as short, 1kb CpG-rich regions that are present in roughly half of the genes in vertebrate genomes. CpG islands are overrepresented in promoter regions, where methylation levels are very low, leaving surrounding DNA and transcription start site unwrapped and accessible for transcription. DNA methylation is globally associated with repressed gene expression[21] and decreased transcriptional activity[22], and the strength of this general rule has been recently confirmed in the brain at the genome-wide level[23] although there are documented exceptions (such as the corticotropin releasing hormone CRH-R2 gene). Whereas DNA methylation located within the gene body, enhancer, and intergenic regions[5,24–26] correlates both negatively and positively with gene expression[27–29].

I.2.B. Post-translational histone (proteins that serve to pack DNA) modifications

Post-translational histone modifications are covalent modifications of the amino-terminal tails of the histones including acetylation, phosphorylation, methylation, and

ubiquitylation. Such modifications influence the interaction between DNA and histones (mainly through electrical charges), thus modifying the chromatin compacting state[30]. These modifications can be either activatory[48] or repressive[31] for transcription.

I.2.C. Post-transcriptional regulation by non-coding RNAs such as microRNAs

Gene expression can be affected by noncoding RNA (including micro-RNA (miRNA), small interfering RNA (siRNA), and piwi-interacting RNA (piRNA).
These promote RNA degradation, inhibit translation, restructure chromatin and regulate gene expression overall[32,33] through post-transcriptional binding to the 3′UTR of mRNA (messenger RNA)[34], by directly binding to promoters and interfering with polymerases[35], or by localizing transcriptionally repressive complexes onto the heterochromatin[36].
Thus, they can block gene expression either temporarily, though the mRNA translational repression, or permanently, through the mRNA cleavage.

I.3. Violence and epigenetic

Adversity during prenatal stage and infancy may alter the physiologic response to stress. It has been posited that changes to the stress response system may underlie the connection between early adversity and damaged learning, behavior, and health across a lifespan[37–40].
By the year 2000, researchers began to reconcile prevailing biomedical and biopsychosocial models of disease causation, with new ideas about the dynamic role of varying psychological and social factors, the developmental timing of life course influences and the variable expression of genetic and epigenetic mechanisms[41–43] .
The life course health development (LCHD) model provided a “conceptual bridge” examining these influences from a developmental perspective, that covers the importance of early relationships, addresses the unique aspects of different life stages (early childhood, adolescence), incorporates emerging ideas from biological systems theory[44] and epigenetic mechanisms, that may influence health development[45–54].

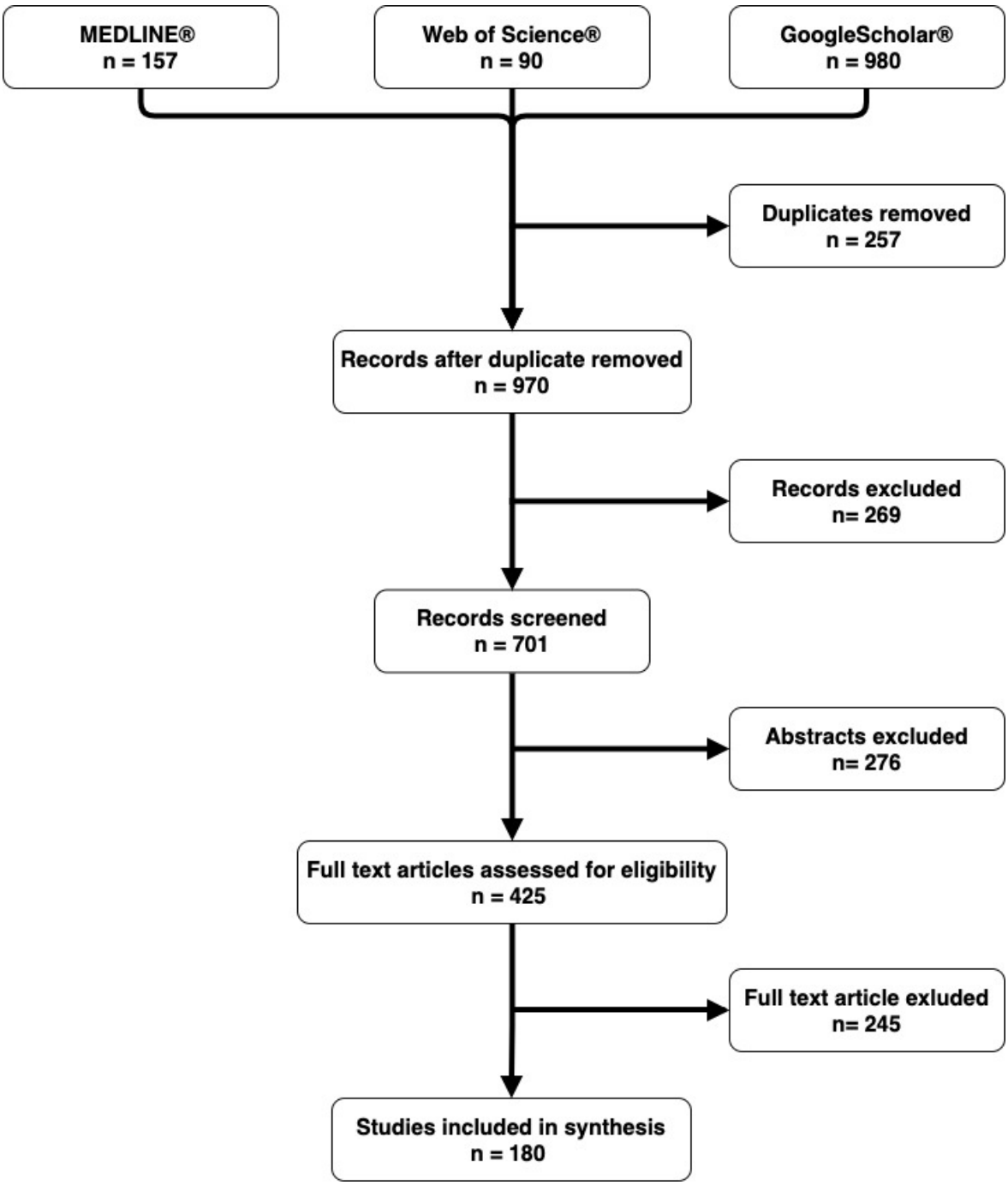
This includes data about neural and endocrine responses to adversity, how evolutionarily adaptive "defensive programming" in utero and in early life may predispose an individual to greater vulnerability to pathogens and future adversity[55–58], and how gene-regulatory and transcriptional networks can be induced into self-perpetuating output, that render an individual susceptible to future maladaptive response patterns. At the same time, evidence is emerging that positive influences in the early environment, including attentive caregiving, warmth and nurturing behaviors, associated to a secure family financial situation can promote more adaptive patterns of neurodevelopment and future positive health[59].

II. **Materiel and Methods**

In order to generate an exhaustive selection of scientific papers, a method developed by Trinquart et *al*., was used to make a step-by-step selection[60]. We performed a systematic search on three databases: MEDLINE® (Pubmed), Web of Science® Core Collection, and Google Scholar® last updated in May 2019.
A search equation with the relevant terms was created using Medical Subject Headings (MeSH) terms and according to recommendations[61,62] . The final search equation is specified below: ("epigenomics"[MeSH Terms] OR "epigenomics"[All Fields] OR "epigenetic"[All Fields]) AND ("violence"[MeSH Terms] OR "violence"[All Fields]).

Two medicolegal physicians independently examined first the titles, then the abstracts, and finally the full-text articles. At each step, reviewers excluded irrelevant articles (based on title, abstract, or full- text) and discussed their selection decision to reach a consensus. Reviewers also searched potential studies not published in academic journals, but which may be of interest, and published in available abstract books and proceedings of notable congresses in the forensic sciences field and forensic anthropology[63,64]: international congresses of the American Academy of Forensic Sciences (AAFS), International Academy of Legal Medicine (IALM), European Academy of Forensic Sciences (EAFS), and Forensic Anthropology Society of Europe (FASE).

The selection process is reported in the flow diagram below. After deleting any duplicates, the search performed through the three databases highlighted 1227 articles. 257 articles were deemed irrelevant according to the titles. Among the 970 articles selected by title, 701 were selected according to their abstracts. The full texts of 425 articles were studied, and 180 scientific papers were included in the systematic review.



Flow diagram

III. **Results**

The first part of our review of literature will focus on the DNA modification found in individuals directly victim of violence. Then, the inheritance of these modifications was studied: from in utero life to transgenerational inheritance.

The functional translation of these molecular modifications will be exposed, on one hand, to understand the neurobiological consequences of epigenetic changes, and on the other hand to offer new insight in the Post-traumatic stress disorder (PTSD).

Effects of epigenetic changes due to violence on other organs are also a search topic.

Therapeutic targets will also be debated.

In the last part, we will discuss the difficulties in establishing a link between violence, and its epigenetic and functional consequences.

III.1. Epigenetic marks induced by personal traumatism

III.1.A. Brain

III.1.A.a. Generalities

In rhesus macaques, the broad impact of maternal rearing in the first year of life on DNA methylation was seen in both the brain and T cells, supporting the hypothesis that the response to early-life adversity is system-wide and genome-wide and persists to adulthood[65]. In the prefrontal cortex (PFC) of these differentially reared monkeys, DNA hydroxymethylation was altered in specific genes involved in neuronal functions that did not show altered DNA methylation patterns[66]. As suspected, this response to early adversity was not limited to DNA methylation; other epigenetic mechanisms were also involved.

Moreover, in rats, histone H3 lysine 9 (H3K9ac) and Histone H4 lysine 5 acetylation (H4K5ac) significantly increased in lateral, basal and centrolateral amygdala after fear conditioning. After fear learning, there was differential H4K5 acetylation in prefrontal cortex, significantly decreasing in infralimbic-prefrontal cortex (IL-PFC) and increasing

in prelimbic-prefrontal cortex (PL-PFC) and in centromedial amygdala[67]. Fear extinction increased H3K9 acetylation in both IL-PFC, and PL-PFC, while H4K5 acetylation increased only in IL-PFC[68]. Neuronal activation followed the same pattern as H3 and H4 acetylation.

More precisely, in mice, early life stress up-regulates the histone acetylation levels of H3 and H4[69] around the promoter regions of the synaptic plasticity genes *Arc* and *Egr1*, resulting in an increased expression of these genes in the mouse hippocampus[69].

In humans, childhood maltreatment widely reprograms the epigenome, mostly in neurons.

Post mortem analysis highlighted sites including genes involved in neuronal plasticity, such as histone cluster 2, H2ab (HIST2H2AB); nuclear receptor subfamily 1, group D, member 1 (NR1D1); and alsin Rho guanine nucleotide exchange factor ALS2 (ALS2)[23].

Exposure to physical abuse was linked with significantly hypermethylated *SHC2*, involved in neurotrophin- activated Trk receptor signaling within cortical neurons and synaptic plasticity in the hippocampus[70], and *IMPACT*[71] encoding a protein that facilitates neurite outgrowth, and modulates kinase activation in neurons[72] . Sexual abuse was associated with *GRIN2D*[71], a gene implicated in Central Nervous System (CNS) plasticity and excitatory synaptic transmission [73]. Physical neglect was associated with *SYNJ2*[71], involved in nervous system development and neuronal vesicle uncoating[74] and *GABBR1,* a GABA class B receptor important for inhibitory synaptic transmission[75].

All three maltreatment types (physical abuse, sexual abuse and neglect) were associated with either hypermethylated, or hypomethylated genes.

Examples of hypermethylated genes are : *HUWE1* (an important regulator of neural proliferation linked to intellectual disability)[76], *WBSCR17* (a gene widely expressed in the brain and associated with neurodevelopmental delay)[77], *CACNA2D4* (identified as a shared risk locus for multiple psychiatric disorders)[78], *LRP4* (involved in neuromuscular junction maintenance), *RER1* (an acetylcholine receptor binding)[79], and *PSEN2*[71] (a gene encoding a presenilin enzyme involved in amyloid precursor protein processing that is robustly implicated in Alzheimer's disease)[80].

Examples of hypomethylated genes are : *TIAM2* (implicated in neurogenesis, in hippocampus and the cerebral cortex)[81], *DNAJB6* (involved in reducing cellular toxicity and acts as a molecular chaperone for neuronal proteins)[82], and *GJD3* (encodes a connexin linked to neuronal excitability)[83].

III.1.A.b. Hypothalamic-Pituitary-Adrenal (HPA) axis

The HPA axis is one of the main systems activated after exposure to a stressor. Thus, genes regulating this system are prime candidates for epigenetic research on the biological embedding of violence.
We will focus on several genes that are particularly relevant in this context: *NR3C1, FKBP5, AVP* and *POMC*.

i) <u>The Nuclear Receptor Subfamily 3-Group C-Member 1 (NR3C1)</u>

The most studied gene is the human Glucocorticoid Receptor (GR) encoded by the *NR3C1* gene, located on chromosome 5q31-32. This gene contains eight translated exons and nine untranslated alternative first exons[84].

In rodents, low levels of maternal care have been linked to three times higher methylation of *nr3c1* in hippocampal samples[85–89], specifically of the region homologous to the human alternative exon 1_F[90] (exon 1_7 GR promoter). Moreover, methylation of exon 1_7 GR promoter is associated with reduced H3K4me3[91,92], H3K9ac[85,90,93], DNA occupancy by the transcriptional regulator NGFI-A[94,95] and *nr3c1* gene expression[90,96–100,] in hippocampus.

Childhood maltreatment, parental loss, and low levels of parental care were associated with increased methylation of *NR3C1* at exon 1_F[84,101–105], 1_B, 1_C, 1_D[104,106], 1_H in hippocampus[94,107] and at cg17860381 in maltreated children[108]. In sexually abused adolescents, same results were found in amplicon 2 ,which covers Exon1_F[109]. However, in another study, the methylation of the exon 1_H promoter was *positively*

correlated with hippocampal GR expression. That study contrasted with other results observed for the other exon 1 regions[110] and previously described for the exon 1_7.

Preschoolers with documented maltreatment showed higher mean baseline methylation at *NR3C1* region 1_D, but not 1_F, in comparison to non-maltreated but demographically similar children. Data indicated that although maltreated children evidenced higher baseline levels of methylation, they also had significant decreases in methylation over time. At the 6-month follow-up their methylation levels were lower than those of non-maltreated preschoolers whose methylation levels remained stable over time[104].

These findings point to the potential for bidirectional relation between transcription factor binding and transcriptional activity one hand and DNA methylation on the other hand[111,112].

A contrario, the hypo-methylation of *NR3C1* promoter region, which translates into augmented inhibitory control of HPA axis, has been shown to be induced by early adverse family environment[113]

Furthermore, some studies observed no gene-wide significant probes associated with victimization within the *NR3C1* gene region[79,114,115].

ii) <u>The FK506 binding protein 51 (FKBP5)</u>

In addition to NR3C1, an important regulator of the GR is FKBP5. This gene mediates an additional negative feedback loop on glucocorticoids.

In the literature, child maltreatment was associated with lower levels of the *FKBP5* intron 7[116,117], 3'UTR site (gene body) and promoter region[113] methylation.

Conversely, in another study, it was suggested, that low childhood socioeconomic status was associated with increased *FKBP5* methylation[118]. However, one explanation could be that low socioeconomic status, in the absence of other adversities, activates the HPA system to initially increase methylation, but does not induce demethylation over time.

In contrast, some authors found no gene-wide significance in relation to childhood polyvictimization[79] (exposure to multiple types of violence or victimization such as

child abuse/neglect, childhood sexual abuse, bullying or cyberbullying, domestic violence, school violence, …).

iii) The arginine vasopressin (AVP)

The AVP gene encodes the neuropeptide vasopressin, also known as antidiuretic hormone (ADH). This central peptide is synthesized in the hypothalamus and secreted by the hypophysis[119].

In mice, prolonged periods of maternal separation alter the methylation of the AVP promotor, increasing hypothalamic AVP synthesis and HPA responses to stress[120].
This epigenetic programming of AVP expression in the parvocellular neurons of the paraventricular nucleus leads to a de-repression of AVP gene transcription[121–123].
This early priming to demethylation could be preceded by the binding of repressive complexes and TET proteins (which had a key role in active DNA demethylation) to the locus[124]. This fits very well with a larger body of evidence linking TET proteins with neuronal activity-dependent DNA demethylation observed in fear conditioning and memory formation paradigms[125–128].

iv) The proopiomelanocortin (*POMC)*

The *POMC* gene encodes for the ACTH (Adreno CorticoTrophic Hormone) pro-hormone: proopiomelanocortin.
Maternal separation of neonatal mice produces an enduring hypomethylation of this gene[129]. This hypomethylation increases *Pomc* mRNA expression and increase basal and CRF (Corticotropin Releasing Factor) -induced levels of ACTH.

Child abuse has been associated with differential hypermethylation in *POMC in 5' CpG island located on* exon 1[130]. Interestingly, methylation of this region has been shown to suppress *POMC* promoter activity in vitro[131].

III.1.A.c. The oxytocinergic pathway

i) The oxytocin Receptor (OXTR)

Oxytocin is a hypothalamic hormone, also known as the ‘‘social neuropeptide’’, that regulates complex social behaviors by promoting attachment and facilitating social interactions[119].

DNA methylation of *OXTR* is an important mechanism linking aversive experiences to susceptibility and to abnormal behavior in adulthood[132–134]. For example, a history of repeated early abuses and traumatic experiences has been correlated to increased *OXTR* methylation in depressed and anxious adults[135,136].

ii) The estrogen receptor (ER)

Child maltreatment-associated differentially methylated CpGs were enriched in genes including multiple steroid hormone receptors, neurohormonal systems (oxytocinergic and HPA, respectively) notably the androgen receptor, the glucocorticoid receptor (NR3C1), estrogen receptor alpha (ESR1), and estrogen receptor beta (ESR2).

The environmental regulation of steroid hormones, that acts on common receptor systems in a wide range of cell types, could explain potential cross-tissue concordance for the effects of child abuse and neglect, on variation in DNA methylation[137].

Methylation levels of the estrogen receptor-alpha (ER-alpha) and the GR gene (i.e., the NGFI-A consensus sequence) are linked with altered cortisol production (in the case of the GR gene) and oxytocin production (in the case of the ER-alpha gene).

These hormonal alterations predict fear response and/or maternal behavior exhibited to offspring later in life[85,138].

III.1.A.d. The serotoninergic pathway

Serotonin is implicated in several physiological function (eating, reward, thermoregulation, cardiovascular regulation, locomotion, pain, reproduction, sleep

wake cycle, cognition and memory, responses to stressors, emotion, aggressiveness, and mood).

i) The serotonin transporter (5-HTT) or solute carrier family 6 member 4 (SLC6A4)

The serotonin transporter (SLC6A4) is involved in neurotransmitter reuptake at serotonergic synapses.

In peripheral blood, mononuclear cells from Rhesus macaques interaction was reported between early attachment pattern and the methylation state of the *SLC6A4* promoter, whereby increased methylation in this genomic region was associated with increased reactivity to stress in maternally deprived, but not in mother reared, infants[139].

Several studies have identified relationships between *SLC6A4* methylation patterns and childhood abuse [140–143]. For example, childhood stress and bullying victimization by peers, were linked to increased methylation of *SLC6A4* promoter in the saliva from children aged 5 to 10[144].

Hypermethylation of *SLC6A4* (5-HTTLPR 5′ CpG islands) was found in sexually and/or physically abused men and women from the Iowa Adoption Studies cohort[140,141]. The authors noted significantly higher methylation for two specific CpG loci among female victims only.

Interestingly, an association was also found between changes in *SLC6A4* gene methylation and sexual abuse, but without affecting expression of the SLC6A4[143].

A contrario, several studies of *SLC6A4* methylation found no significant differences between subjects with or without childhood traumatism[113,145–148]

ii) The serotonin type 3 receptor (5-HT3A-R)

The 5-HT3A-R is a cation-selective ion channel expressed in the amygdala, the hippocampus, and the caudate[149].

Significant but divergent associations were found between the percentage of methylation of the *5-HT3A-R* gene and with child maltreatment[150].
Childhood maltreatment and especially physical abuse had a broad impact on *5-HT3A-R* CpG3_II, CpG2_III, CpG5_III methylation levels[150].
On the other hand, methylation of CpG2_III was negatively correlated with maternal verbal and physical aggression and child attachment disturbance. Moreover, the self-endangering behavior, while not significantly associated with maternal PTSD, was strongly and negatively correlated with less methylation of the maternal *5-HT3A-R* particularly at CpG 2_III and CpG 3_III[151] .
Furthermore, childhood emotional neglect was inversely correlated with CpG1_I methylation level[150]. This CpG1_I is located within a GRE element upstream of the *5-HT3A-R* and could thus provide a mechanistic link between stress-induced glucocorticoid levels and the *5-HT3A-R* gene[148].

iii) The monoamine oxidase A (MAOA)

The MAOA plays a key role in the degradation of neurotransmitters such as noradrenaline, dopamine and serotonin.
In a Swedish cohort of depressed subjects with a history of early life adversity, *MAOA* was hypomethylated in its first exon region of female individuals[152].

III.1.A.e. Dopaminergic pathway

Dopaminergic pathways are involved in many functions such as executive function, learning, reward, motivation, and neuroendocrine control.

i) The dopamine receptor D2 (DRD2)

While methylation levels did not differ between bulimia and normal eaters, there was a slight increase in methylation of DRD2 in bulimics with borderline personality disorders, as well as those who reported a history of childhood sexual abuse[153].
Because of its close proximity to DRD2, ANKK1 (ankyrin repeat and kinase domain containing 1) is believed to regulate DRD2[154]. Interestingly, maltreated children with

early onset, but not recent maltreatment, had significantly higher ANKK1 methylation than non-maltreated children[155].

ii) The dopamine receptor D4 (DRD4)

DRD4 methylation levels were significantly different between adults with a chronic-history of physical aggression and those with a low history of physical aggression in childhood and adolescence. But using published Genome Wide Association Study data from the EAGLE consortium (Early Genetics and Lifecourse Epidemiology), and Mandelian Randomization analysis (a genetic variant is used as an instrumental variable to test for the causative effect of an exposure on an outcome), no evidence was found to support causal effects of peripheral DRD4 methylation on aggression[156]. Surprisingly, lower DNAm levels in one region spanning the DRD4 gene was associated with higher physical aggression with strong cross-tissue concordance (both blood and brain tissue)[156].

III.1.A.f. The brain-derived neurotrophic factor (BDNF)

Another candidate gene gaining momentum in childhood trauma research is related to BDNF, a member of the nerve growth factor family[157] with roles in neuronal development, functioning and plasticity[158–162].

Adverse experiences in childhood, even polyvictimisation[79] resulted in enduring methylation changes to the *BDNF* gene body[113], within the PFC[163,164], the hippocampus and the amygdala[165] or the peripheral tissue[79]. Both increase and decrease in BDNF methylation have been associated with stress[166–169]. Sex differentials in methylation may also occur following early adversity like abuse[165,170].

III.1.B. The immune system

Analysis from whole-genome DNA methylation profiles revealed that several highly differentially methylated candidate genes between children with and without early

stress were implicated in immune system functioning, in addition to genes involved in various pathways important for brain development.

Functional annotation clustering analysis regarding the methylation profiles of more than 14,000 genes in individuals who experienced traumatic events leading to PTSD found a strong signature of immune system involvement, including uniquely unmethylated genes from the innate immune system *(TLR1* and *TLR3)*, and genes that regulate innate, adaptive immune system processes *(IL8*, *LTA* and *KLRG-1)*[171,172] .

III.1.C. Metabolism-Regulation

Cellular regulation processes were found to be modulated in victims.

Among 173 genes, differentially methylated across individuals with and without previous placement into foster care, number of genes were identified as involved in negative regulation of transcription, apoptosis and cell death, post-translation protein modifications, regulation of translation, and muscle tissue development[173]. These clusters might have direct as well as indirect effects, which in turn may influence biological factors[137]. Of specific interest were changes in the expression of the promoters in the WNT signaling pathway complex that the authors note to become deregulated in chronic health conditions, such as metabolic syndrome, obesity, diabetes, and cancer[174].

Chromosomal maintenance was regulated with significantly hypermethylated *SMC1A*, a gene involved in DNA repair[175] in response to physical abuse exposure[71]. Sexual abuse was associated to the *MGMT* gene which protein is implicated in DNA repair mechanisms (O-6-Methylguanine-DNA Methyltransferase)[71].

Concerning transcriptional activity, in physically abused subjects, 66 differentially methylated regions (both hyper-methylated and hypo-methylated) were demonstrated to include transcription factor genes such as *NFkB1*, *NFAT5* and *STAT6* genes[176].

Moreover, childhood maltreatment was associated with increased hippocampal methylation in the promoter region of the small (40S) ribosomal sub-unit, leading to a decreased transcriptional activity[177].
Finally, genes involved in histone regulation were identified, including *SETDB1* (histone methyltransferase), *JADE1* (histone acetyltransferase), *HIST1H1A* (H1 histone family, member 1)[71] and *ALKBH5* (RNA demethylase)[79] in childhood victimization such as physical neglect[71].

Cellular metabolism was also found to be susceptible to abuse.
Child abuse and physical neglect were associated with methylation of the cell growth regulators gene *AHRR* (Aryl-Hydrocarbon Receptor Repressor)[137] and with demethylation of *EVPL* (epidermal growth) gene[71]. *NOTCH3* has been associated with life time PTSD risk on a nominal level in survivors of the Rwandan genocide[178].

Moreover, child abuse was found to impact cellular metabolism through DNA methylation of *CFTR* (cystic fibrosis transmembrane conductance regulator)[179] and GRB10 (insulin modulator)[71] or demethylation of *RPTOR* (a gene involved in cell growth regulation by climatic factors, nutrient and insulin levels)[180] in response to three maltreatment types : physical abuse, sexual abuse and neglect[71].
Finally, childhood adversity has also been associated with DNA methylation of *PM20D1* (energy homeostasis regulation)[174], *OPRK1* (Opioid Receptor Kappa 1)[181], *CYP2E1* (cytochrome p450 family 2 subfamily e member 1)[182], and *PPP1R3G* (glucose homeostasis and glycogenesis in liver)[179].

III.1.D. Whole genome methylated DNA (DNAm)

Epigenetic reprogramming as a result of early-life adversity may occur on a much larger scale than hypothesis-driven specific genes approaches. Indeed, epigenetic indicators of stress tolerance are not dependent on a single a CpG, but instead on averages information across genomes. As such, genome-wide studies seem better equipped to investigate disorders of complex genetic and epigenetic heterogeneity. Such methodological approaches allow for a more comprehensive overview of the

molecular pathways potentially involved, and of the relationships between specific sites and nearby genomic regions. An epigenome-wide analysis overlooks cumulative evidence about the biological plausibility of specific candidate genes.
For example, post mortem explorations in the human brain hippocampus of a 6.5 million base pair region surrounding the GR[183], and to the genome-wide level, identified 362 sites that were differentially methylated (248 hypermethylated and 114 hypomethylated) in suicide completers with a history of childhood maltreatment, in comparison to psychiatrically normal controls[23].

In peripheral blood samples of 14 institutionalized and 14 children raised by their biological parents, 914 of the 26,214 sites tested were differentially methylated in both groups including genes implicated in cellular signaling, immune responses and brain function. These differences were mostly due to increased DNA methylation (90% were hypermethylated) in the genomes of institutionalized children[184]. For example, hypermethylation of a locus in the Kit ligand gene (KITLG) showed the strongest association with cortisol stress reactivity, thus mediating its relationship with childhood maltreatment, and was associated with programming reactivity in the human brain[185].

On peripheral tissue, 2868 CpG sites showed significantly different methylation values between maltreated children (96 maltreated children who were removed from their parents due to neglect or maltreatment) and matched controls[186].
Individuals with and without prior placement into foster care showed differential methylation of 180 CpG sites localized in 173 genes : higher levels of methylation in 72 genes, and significantly lower levels of methylation in 101 genes[173].

Concerning miRNA specifically, an analysis of the promoter methylation of over 20,000 genes and 489 micro-RNAs identified 997 differentially methylated gene promoters associated with parentally inflicted verbal, emotional, or sexual child abuse; 311 of them were hypermethylated, 686 hypomethylated and 31 miRNAs were hypermethylated in a sample of control adult males (40 males at age 45) exposed to

childhood abuse. The hypermethylated state for 6 of these miRNAs was consistent with an hypomethylation status of their target genes[174].

A recent study of high-risk inner-city youth (*n*=124, 68% of whom reported at least one form of maltreatment) identified differentially methylated probes for physical abuse (34 probes), sexual abuse (7 probes) and physical neglect (118 probes). No differentially methylated probes were identified for emotional abuse or neglect[71].

In an extensive study, associations between exposure to each of the six victimization types (*i.e.* physical abuse, physical neglect, emotional abuse/neglect, sexual abuse, intimate-partner violence, and bullying victimization) and DNA methylation was performed. A total of 48 array-wide significant associations were observed across four of the six victimization types (physical abuse, emotional abuse/ neglect, sexual abuse, and intimate-partner violence). None of these probes were shared between victimization types, and none of them were identified in the Epigenome-Wide Association study (EWAS) of childhood polyvictimization. Interestingly, 39 of these 48 probes were associated with childhood sexual victimization but not observed in relation to sexual victimization in adolescence[79].

III.2. Epigenome and neurobiological mechanisms

As suggested in a review of human studies by Lutz *et al*., DNA methylation is important for mediating neurobiological consequences of childhood trauma throughout life. The DNA methylation can increase dysfunctional behavioral patterns and the risk of psychopathology by making a form of molecular memory that may exert an effect on brain function over long-term periods[187].

The functional implications of DNA methylation in non-promoter regions ("shores" of CpG islands, gene bodies, intergenic regions) remain comparatively less understood than in promoter regions[5,24] . However, most data reveal a neuron-specific negative correlation between gene bodies CpG methylation states and gene expression[188,189], suggesting epigenetic regulatory mechanisms specific to the brain tissue.

III.2.A.HPA axis

Upon activation of the HPA axis, CRH and AVP are released and stimulate the production of ACTH which in turn is released into the blood. This results in glucocorticoid (GC) (cortisol in humans and corticosterone in rodents) secretion. Upon cortisol binding, the GR and the mineralocorticoid receptor (MR) are translocated to 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[190,191]. However, the response of the axis after its activation is limited: the activation of the GR will initiate a negative feedback loop terminating the stress response and therefore reducing 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 a lab assay, increased levels of GR methylation were associated with decreased sensitivity to dexamethasone suppression test[103]. This suggests strongly a functional relationship between peripheral GR methylation and HPA axis activity.

In response to childhood abuse, DNA demethylation in functional GC response elements of *FKBP5*, an important regulator of the GR, resulted in a differential transcriptional activation of its target gene. Demethylation was linked to increased stress-dependent *FKBP5* gene expression followed by a long-term dysregulation of the stress hormone system and a global effect on the function of immune cells and brain areas associated with stress regulation[116]. Overexpression of *FKBP5* reduced the hormone binding affinity and nuclear translocation of GR, thus contributing to increase GR resistance and hypercortisolemia[192]. These changes would result in long-term alterations of HPA axis sensitivity, such as GR hypersensitivity, and would affect further adult response to a new trauma[193].
FKBP5 has also been associated with depression, anxiety and current PTSD[194–197] but not in life time PTSD in people within a cohort following the 9/11 attacks in New York City who developed PTSD compared to similarly exposed controls who did not[198].

While antenatal GC are critical for the proper maturation of vital organs and tissues during pregnancy, especially in the third trimester[199], pathologically increased levels

of fetal GC are suspected to impair normal development with long-term adverse consequences such as dysregulation of the infant's HPA axis and neurobehavioral changes[200–203]. For example, among neonates, placental methylation of *FKBP5* at intron 7 was associated with higher levels of arousal during a physical examination[204].

Another example is the *SKA2* gene encoding a protein that regulates mitotic anaphase (a component of the microtubule-binding complex) and important for enabling glucocorticoid receptor nuclear transactivation[205]. Epigenetic variation influencing levels of *SKA2* gene expression may be important for modulating the sensitivity of the HPA axis : in facilitating GR nuclear transactivation and anticorrelated relationship with gene expression[206,207]. This epigenetically driven decrease in *SKA2* may inhibit the ability of GR to properly suppress the natural stress response by moderating the suppression of cortisol release subsequent to a stress[206].
A study of military veterans who had been exposed to at least one lifetime trauma event found that higher methylation of SKA2 was associated with higher rates of disorders such as depression, dysthymia, generalized anxiety, phobia, obsessive-compulsive disorder, and panic disorders, current suicidal ideation and suicidal behaviors but not with substance use disorders, antisocial personality disorder or PTSD[208]. Moreover, *SKA2* methylation in the mostly African-American urban population of a cohort named the “Grady trauma project” was observed to be significantly associated with suicidality and childhood trauma[209]. It was also demonstrated that higher DNA methylation predicted lower SKA2 expression in the prefrontal cortex of suicide completers[206], along with lower levels of microRNA-301a in the cortex of depressed suicide completers[210].

III.2.B. Corticolimbic system

Childhood traumatism exposure has been repeatedly related to epigenetic changes and altered gene expression profiles, particularly in the CNS (*e.g.,* hippocampus, amygdala), thus affecting stress responses and memory consolidation[211–214]. The brain serotonin concentration is regulated by SLC6A4 that controls its reuptake from the synaptic cleft, and by MAOA that catabolizes serotonin[215].

Structural and functional findings have consistently appeared in the circuitry of the frontal and limbic regions of the brain, which include structures such as the amygdala, prefrontal cortex, orbitofrontal cortex, anterior cingulate gyrus and hippocampus.

III.2.B.a. Amygdala

The amygdala is a key structure for processing emotional information including memory formation, and post-traumatic stress disorder[216].

Actually, studies have reported conflicting results, including increased[217], decreased[218,219] and unaltered amygdala volume[220] in maltreated subjects.
A number of studies suggested a moderating effect of *FKBP5*[221–223] and MR genotypes[224] on amygdala volume, reactivity and connectivity of early life stress exposed adults, thus implicating HPA axis-related genes in brain development. Hence, the genetic susceptibility may represent a crucial factor leading to related structural and functional trajectories of early life stress on brain development[225].

A dynamic system has been presented: (i) initially, childhood maltreatment may cause an increase in amygdala volume and activity. This hypothesis derived from rodent studies showing increased dendritic arborization in the amygdala, in response to stress [226,227], potentially leading to a volume increase. Then, over time, it may be followed by (ii) neurodegeneration and reduced volume of the amygdala in maltreated subjects[219]. Indeed, the amygdala has many GC receptors [228] and high GC levels (prolonged stress) have been associated with degeneration of amygdala cells in adult rats [229] and decreased amygdala volume in humans[230].
Moreover, serotonin pathway seemed also to be involved : long-lasting SLC6A4 hypermethylation (see serotonin pathway section) results in lower cortical thickness[231,232] and alters amygdala reactivity[233].
Concerning *BDNF* participation on brain volume, it appeared to be modulated by its allelic version (see polymorphism section)[234].

In a rat model, the exposure to peripubertal stress affected the connectivity between amygdala and orbitofrontal cortex accompanied by a parallel increase of *MAOA* expression in the frontal cortex in adulthood. Interestingly, an increased H3 acetylation of *MAOA* was observed in the prefrontal cortex of these individuals suggesting that the aversive experience had induced a stable epigenetic regulation of the transcription of this gene (histone acetylation opens chromatin conformation to promote transcription)[235].

In humans, since peripheral methylation levels of *MAOA* have been shown to predict activity levels of the enzyme in the brain[236], the *MAOA* promoter hypomethylation in peripheral DNA of depressed individuals would in theory correlate with an abundance of brain MAOA. This excess in brain MAOA levels could, in turn, catabolizes serotonin at a higher rate.

III.2.B.b. Mesencephalon: prefrontal cortex (PFC), cingulate gyrus, anterior cingulate cortex (ACC)

These cortical brain regions are involved in emotion and arousal regulation.

Child abuse may lead either to hyper- or to hypomethylation of genes in the cingulate cortex and in the hippocampus[23].
Post mortem brain studies (of individuals who committed suicide vs individuals with other cause of death) indicated that early-life adversity ,such as child abuse, was associated with profound epigenetic and transcriptomic alterations that affect oligodendrocytes located in the cingulate cortex gray matter[237]. The three most significantly differentially methylated regions intersected with genes directly related to myelin and oligodendrocytes were *LINGO3* (of the LINGO family of proteins implicated in myelination)[238]; *POU3F1* (a transcription factor controlling myelination)[239]; and *ITGB1*(one of the integrins that mediate interactions between oligodendrocytes and axons)[240]. Child abuse, in contrary to suicide or depressive psychopathology, accounted for oligodendrocyte-lineage specific decreased DNA methylation in

LINGO3 and *POU3F1* genes, suggesting oligodendrocyte-specific epigenetic reprogramming as a consequence of child abuse.
Nevertheless, oligodendrocyte-specific differential methylation of these two genes had no detectable effect on their transcriptional activity at the whole tissue level (RNA sequencing data). Because of the dynamic relationship between DNA methylation and gene expression during brain development[241], it is possible that these two adaptation responses represent, in fact, epigenetic "traces" of child abuse that do not impact gene expression in adulthood. However, individuals abused during childhood had decreased expression of a large collection of myelin-related genes in the cingulate cortex, suggesting a strong impairment in oligodendrocyte function. This global downregulation was completely absent in a sample of individuals who had committed suicide but who had no history of child abuse.

A Swiss study of mothers in controlled stressful parenting situations found that maternal *BDNF* methylation in saliva was positively correlated with higher levels of maternal anxiety and greater childhood exposure to domestic violence. Brain activity measured by fMRI was positively correlated with *BDNF* methylation in both the ACC and the ventromedial prefrontal cortex (VM-PFC)[242].

Reduced maternal emotional regulation capacities were associated to methylation of the maternal *5-HT3A-R* at CpGs 2 III and reduced maternal dorsomedial prefrontal cortex (DM-PFC) activation[151]. Methylation of CpG2_III has been suggested to repress transcription[243].
In response to menacing relational stimuli[151], *5-HT3A-R* methylation at "CpG2_III" site was linked to decreased medial prefrontal cortical (DM-PFC and VM-PFC) activity. Moreover, neural activity was found to be negatively and significantly associated with maternal IPV-PTSD severity[244] : in PTSD, demethylation of CpG2_III may possibly increase transcription [151] but it remains to be determined.

As far as the orbitofrontal cortex is concerned, ventromedial-frontal lesions and hypo-functioning of serotonin neurotransmission has been linked to higher risk of aggressive behaviors in Vietnam War Veterans[245–247]. Brain expression of SLC6A4 was

reduced in aberrant impulsive-aggressive individuals[248]. Moreover, morphological asymmetry of orbitofrontal cortex has been associated with higher aggressivity[249].
The potential role of the serotonin system in the pathophysiology of affective disorders[250] was highlighted by the *5-HT3A-R* CC genotype (see polymorphism section) and its association with alterations in brain structures central to emotion processing, particularly when exposed to stress.
In males, an *in vivo* study, using positron emission tomography, found a link between physical abuses experienced in childhood and *SLC6A4* hypermethylation in peripheral white blood cells (T cells and monocytes), correlated with lower orbitofrontal cortex serotonin synthesis[251,252].
A contrario, despite of relatively low serotonin synthesis neither groups (childhood maltreatment or not) differed markedly in adulthood in their levels of aggressive behavior, nor in their behavioral, neurocognitive and psychosocial outcomes[252].

III.2.B.c. Hippocampus

Nonhuman animal model studies suggested that the regulation of BDNF in the hippocampus might be influenced by epigenetic modifications[253]. The BDNF protein levels are a key mediator of brain plasticity and can modulate learning and memory in response to stress[254]. Given that, stress promotes changes in *BDNF* expression through effects on the hippocampus[255,256]. Therefore, disruption of BDNF expression during sensitive periods in development may alter neural development and functioning, possibly contributing to either vulnerability for psychopathology, or resilience[257].
In contrast to previous findings of decreased hippocampus volume in carriers of the BDNF met-allele[258,259], no evidence for structural changes in the hippocampus of maltreated subjects or a relationship between BDNF and hippocampal volume was found[234]. However, meta-analysis suggest that initial findings may be non- existent and were related to publication bias[259,260].

Moreover, lower *SLC6A4* (*AluJb)* methylation is associated with lower hippocampal gray matter volumes[261]. Booij et *al.,* demonstrated that adults with childhood trauma

experience had an increase of peripheral serotonin transporter methylation and smaller volume of the hippocampus[262].

A significant association also emerged between sex abuse and overall DNA methylation of the CpG island at the promoter region of the SLC6A4 gene, among females[140], as well as a higher risk of developing long-lasting antisocial personality disorders[141].

III.3. Could victim- induced epigenetic marks be inherited?

III.3.A. Intergenerational transmission

The intergenerational transmission of epigenetic modifications, *i.e.* of changes in gene expression without changes in DNA sequences, is defined as observable epigenetic changes that are transmitted from one generation to the next, or from parent's generation, named the zero filial generation (F0), to the offspring's generation, named the first filial generation (F1)[263].

Mammalian cells possess two alleles, one from each parent. In some genes, called "imprinted genes", one allele is silenced by methylation depending on its parental origin in a process called imprinting. In germ lines, a single copy of the gene is present, and a demethylation process occurs. In fact, two developmental periods have been identified in which global demethylation is followed by global remethylation of DNA. The concept of transgenerational epigenetic inheritance has been established, proposing that epigenetic modifications can be transmitted into the next generations[264,265].

III.3.A.a. Animal model

Roth et *al,.* exposed male and female rat neonates (F0) to, either a stressed-abusive mother (maltreatment), or a care-giving mother (cross-fostered care) and compared these animals with rats exposed to normal care. The authors reported an increase in methylated *bdnf* DNA and a reduced *bdnf* gene expression in the adult prefrontal cortex specific to maltreatment (F0). The maltreated female rats showed abusive maternal behavior toward their own offspring. Prefrontal and hippocampal tissues of

the male and female offspring (F1) also presented increased methylation of the *bdnf* gene compared to offspring derived from normal-treated females[163].

Combining in vivo and in vitro programming and reprogramming studies, Cantone and Fisher proposed a model in mouse.
During the passage from one generation to the next, the great majority of the DNA methyl marks are erased. This includes the "physiological" methyl marks that are established in each generation during development and in adulthood and the "accidental" methyl marks induced by environmental factors. The DNA methylation erasure or "reprogramming" occurs in two major waves affecting two different cell types. The first major wave of demethylation begins just after the fertilization of the oocyte by a spermatozoon, resulting in a zygote that contains the two pro-nuclei of biparental origin[266]. The second major wave of reprogramming is a sequential demethylation occurring before meiosis in primordial germ cells (precursors of spermatogonia and oogonia)[267] and independent from the TET enzymes[268].
Therefore, a genome-wide loss of DNA methylation occurs following fertilization.

However, if methylation in the DNA inherited from maternal and paternal stem cells is erased in the very first stage of development and reprogrammed across next stages, why can parental methylation traces be found in the offspring after birth like in Roth et al. study[163]? Are the observed methylation patterns in offspring truly inherited or do they appear as a consequence of a modified parenting model, due to the adversities the parents went through?

It has to be pointed out that transmission of adaptive epigenetic marks to the next generation can occur via two possible routes of transmission:

i) behavioral or social transmission. It occurs when parental behavior affects the phenotype of the offspring through several generations. For example, the mother experiences traumatic event that could both cause her epigenetic changes, and an increased risk of a traumatic event that alters the child's epigenome-independent of the mother transmitting her epigenome to her child.

or

ii) germline transmission, the transmission of epigenetic marks through either the male or female germline[269–272].

In rats, offspring that were derived from stressed fathers presented reduction of DNA methylation in the frontal cortex among females only, and increased DNA methylation in the hippocampus in both males and females[273].

Several studies reported epigenetic transmission across generations suggesting incomplete erasure of methylation marks in the germline. Epigenetic effects were frequently not transmitted, or were only occasionally transmitted then lost, and, at best, only rarely stably transmitted to the subsequent lineage[263,274]. It has been shown that epigenetic modifications occurring in a germline cell can become stable in the next generation, if fecundation occurs[275]

III.3.A.b. Role of the sperm

Childhood abuse may lead to adulthood exposures that affect the sperm epigenome during spermitogenesis[276] : sperm DNAm varies by experiences of childhood abuse[277].

In mice, transmission through the paternal lineage excludes confounds associated with maternal transmission, such as the intrauterine environment or maternal behaviors, and implicates gametic epigenetic mechanisms[278]

Epigenetic marks present and detected in sperm include : noncoding RNAs, such as miRs and piRNAs, histone modifications (for the few retained histones in sperm), and DNA methylation[279].

Histone modifications can be stabilized by protamine marks and transmitted to the next generation through the germ line[280]. MicroRNAs have been shown to alter gene expression post-fertilization, suggesting that these changes in the sperm microRNA content could impact the offspring development[281–283]. Chronic preconception stress either during adolescence or adulthood can increase the expression of specific miRNAs in sperm [284]. Presumably non-coding RNAs or chromatin structure modifications could store the information to later guide the methyltransferases and define where to add methyl groups to the DNA[285].

Early gestational period seems to be vulnerable to prenatal stress epigenetic programming of the male germline[286].

In Dias and Ressler work, adult mice (F0) were subjected to fear conditioning to a specific odor prior to conception. DNA methylation levels in the olfactory receptor gene responsible for the detection of the specific odor (acetophenone), the *Olfr151* gene locus, were shown to be altered in the sperm. This significant decrease in DNA methylation (~10 to 20%) seen in the F0 generation persisted in the F1 generation[287].

III.3.B. In utero prenatal stress

In the case of maternal to offspring transmission, with *in utero* exposure to a stressor, F1 embryos growing into F0 pregnant mothers already contain germ cell precursors that will generate the F2 individuals. Thus, F0, F1, F2 cells are exposed to the initial stressor. Transgenerational inheritance in these cases has therefore been strictly considered to begin only from the third filial generation (F3) onwards.

Another specificity of in utero exposure is the placenta. Indeed, placenta is at the interface between maternal and the embryo.

A key enzyme controlling the placental transfer of maternal glucocorticoids to the fetus is the 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2)[200]. During gestation in rats, chronic restrain stress increased in DNA methylation of the *11β-HSD2* promoter[288]. In parallel, 11β-HSD2 mRNA levels were shown to decrease[289,290].

III.3.B.a. From animal discoveries to human's exploration

In an experiment conducted in pregnant rats which were exposed to stressor, 336 miRNAs were differentially expressed in their offspring. When a miRNA binds to its mRNA-target, it represses expression through degradation of the mRNA[291]. The putative gene targets for miRNA that appeared differentially expressed were related to neurotransmission, neurodevelopment, brain pathologies and stress responsivity. This indicates that the developing brain is particularly vulnerable to stress exposure during gestation[292].

Prenatal stress exposure is associated with postnatal epigenetic modifications in brain, including *NR3C1* site-specific methylation patterns among offspring[166,293], *FKBP5*[294] hypomethylation of *SLC6A4*[295], hypermethylation of *OXTR*[296].

Maternal stress during pregnancy is an overwhelmingly common event, with 70,2% of women reporting the occurrence of a stressful life event in the year preceding the birth of their child, including pregnancy-specific stress, intimate partner violence, and natural disasters[297].

Project Ice Storm followed up with women who were pregnant around the time of an ice storm in Quebec. This study examined the methylation profiles of 36 offspring willing to provide blood samples around thirteen years of age. They found that 1675 CpG sites were associated with objective maternal stress levels, though no sites were significantly associated with subjective maternal stress[298].

In three tissues (maternal blood, placental tissue, and umbilical cord blood) collected at the time of birth, human *BDNF* methylation was significantly associated with prenatal maternal extreme traumatic stress (war) exposure[299]. Most of the significant CpG sites were located upstream of exons 1 through 4 in maternal blood, upstream of exon 8 in placenta tissue and upstream of exon 2, exon 4 and exon 9 in cord blood. Interestingly, methylation upstream of exon 2 has previously been associated with child maltreatment[113]. Other studies of more "mild" prenatal stress have not shown notable associations with offspring methylation, at least when tested in cord blood[300]. Maternal exposition to war or rape during pregnancy[301,302] , or depressed maternal mood in the third trimester[303] has been associated with increased neonatal methylation of the *NR3C1*promoter region.

Radtke and colleagues reported, with caution, a positive correlation between maternal exposure to IPV during pregnancy and the *NR3C1*. DNA methylation level in their adolescent (10–19 year-old) children[304]. However, in their study, IPV preceding or following pregnancy had no effect on *NR3C1* methylation of adolescents.

Thus, these children affected by prenatal stress did not express the same methylome switch than adult women, and *vice versa*. This result indicates that prenatal IPV may have unique epigenome-wide consequences across lifespan (see confounder section).

Similarly, women who were pregnant during the 1995 Rwandan genocide were studied (women in Rwanda versus those out of the country)[305]. Compared to out-of-the-country controls and their children, genocide survivors (20 years after initial exposure to the traumatic event) and their children had higher DNA methylation of the promoter of *NR3C1*.

Methylation of *FKBP5* was correlated in Holocaust survivors and their offspring; survivors showed greater methylation of *FKBP5* whereas the children of these survivors exhibited low levels of methylation in comparison with participants who were not Holocaust survivors[306].

These results bolster the hypothesis that epigenetic changes induced before birth can still be seen into adolescence and possibly beyond.

The study by Essex et al., suggests that parental adversity during a child's first years leads to discernible changes in his or her "epigenome," measurable more than a decade later. DNA methylation was investigated in adolescents whose parents themselves experienced high levels of stress earlier in their child's life. Children whose mothers were highly stressed in the child's first year of life showed significantly higher levels of methylation than those less exposed. These authors also found that fathers' stress level is more strongly associated with DNA methylation in daughters, whereas mothers' stress level had an effect on both sons and daughters[47].

III.3.B.b. Evolution

The Developmental Origins of Health and Disease (DOHaD)[307] and the Predictive Adaptive Hypothesis (PAR)[308], state that the uterine environment, experienced by the mother, prepares the fetus for postnatal challenges. In animals, prenatal stress sometimes leads to general shifts toward what appears to be adaptations in the offspring to the stressful environments[308]. In these studies, outcome is highly dependent on the postnatal environment, where for example prenatal stress in rodents leads to behavioral changes that are beneficial in predator rich environments but not otherwise[309]. Analogies have been reported in several taxa including primates, but in humans they remain speculative in nature[310–313].

Parental PTSD is not only a risk factor for PTSD in the offspring, but also leads to transgenerational effects on the epigenetic level[314].

Differential effects of maternal and paternal PTSD on the methylation of their children's *NR3C1* promoter have been observed. If only the father was diagnosed with PTSD the promoter region was hypermethylated. If both parents suffered from PTSD methylation was significantly decreased[315].

The authors discussed that mothers were the primary care givers in their sample and might have buffered the stress associated with parental PTSD, while PTSD in both parents might lead to unpredictable stress in the offspring, resulting in epigenetic changes mimicking those of individuals with PTSD[315].

III.3.C. Transgenerational transmission

Intergenerational transmission is distinguished from transgenerational transmission, in that the latter implies continuing transmission across generations, from (F1) offspring to their respective offspring or second filial generation (F2), without exposure to the initial environmental stressor.

Animal models show changes in behavior up to two generations after early life trauma, which could affect methylation in their offspring[85,316].

Franklin and colleagues characterized DNA methylation changes induced by maternal separation combined with maternal stress in the germ cells of (F1) and (F2) male mice, and in the cortex of (F2) female mice.

In (F1) males' sperm, either hypermethylation (of endocannabinoid receptors in the brain, or hypomethylation (of the CRH-receptor 2) was observed[317].

Gapp et *al.*, showed alterations in miRNA expression, metabolism and behavior after traumatic stress in early life up to the third generation in mice. In response to maternal stress and unexpected maternal separation, the relative miRNA levels were altered in germ cells, serum and hippocampus of the first generation (F1) males. The resulting offspring (F2) revealed upregulation of several miRNAs in serum, plasma and brain, but interestingly not in sperm. The third generation (F3) showed behavioral symptoms similar to those of the (F1) and (F2) mice despite, and consistently with (F2) animals, no changes in miRNA of the sperm cells. These findings suggest an alternative

mechanism mediating the transfer of adaptive changes to subsequent generations, which might include other epigenetic marks such as histone modifications[316].
Yao and colleagues observed multigenerational inheritance whereby great-grandchildren of gestating female rats exposed to stress. As shown in their work, stress altered miRNA expression patterns in the brain and uterus of F2 mothers[318].

In human, grandchildren whose maternal grandmother was exposed to violence during pregnancy showed differential methylation in genes involved in circulatory system processes, when compared with grandchildren whose grandmothers had no, or few, events of violence during pregnancy[319]. Grandmaternal exposure to interpersonal violence during pregnancy was associated with 27 differentially methylated CpG sites in the children that map to 22 uniquely annotated genes. Within the CpG sites associated with grandmaternal prenatal stress, five had a high-confidence significance[319].

In contrario, in an study on IPV in São Gonçalo (brazilian) female (we will refer to this study several times because the results were particularly interesting), when grandmother were exposed to IPV during pregnancy, no correlation within families (*n*= 115 mother/child pairs) was found for the 31 significant CpGs identified in the children[320], providing evidence against either genetic or intergenerational epigenetic inheritance.

Thus, results are contradictory. An hypothesis could be the increase of confusing factors, particularly other stress factors, that add up through generations (see below, section IV).

III.4. Shaping risk and resilience

III.4.A. Psychiatric risk

Adverse childhood experiences have been associated with increased risk of developing a range of psychiatric disorders later in life, such as mood and anxiety

disorders[321], PTSD[322–331], alcohol or drug use disorders, depression, suicide attempts [332] and antisocial behavior[333].

miRNAs are highly expressed in neural cells and because they are considered as the main regulator of neural plasticity and neurogenesis, they appear to be a strong candidate to lead to neuropsychiatric disorders[334].

The more abundant miRNA in neurons, miR124, is very important for neuronal differentiation and neurogenesis. It closely interacts with the cAMP response element-binding (CREB) protein, a protein involved in the etiology of several psychiatric disorders[335]. miR124 targets two crucial genes in the regulation of the HPA axis (NR3C1 and NR3C2). Upon fear conditioning, miR124 is upregulated in the lateral amygdala of rats[336,337].

In addition, miR137,and other CpGs (cg14035771) near miRNA (miR137) were associated with severity of childhood maltreatment[338].

Early life adverse events, such as childhood mistreatment, were associated with CpGs located within or near genes involved in several biological functions[338] such as KCNQ2 (Potassium Voltage-Gated Channel Subfamily Q Member 2) which is involved in bipolar disorder[339].

Emotional abuse was shown to predict lower LINE-1 methylation in first-episode schizophrenia patients[340]. NT5DC2 (a target of miR137) was previously associated with schizophrenia[341].

In another study, newborns who carried hyper-methylated OXTR had an increased probability of developing callous-unemotional traits[296], indicative of stable and severe aggressive behavior[342].

DNA methylation of BDNF of peripheral cell populations has been shown to predict changes in the brain as well as behavioral vulnerabilities (early detection of psychopathology)[157,343,344]. For example, the BDNF gene differential methylation of CpG islands allows to distinguish major depression patients from healthy controls in a Japanese population [167], while methylation at specific CpG islands of the promoter region is also associated with depression phenotypes among adults[167] and child populations[113].

Conversely, in traumatized children, increased methylation in three genes (NMDA glutamate receptor, GRIN1; inhibitor of DNA binding 3, ID3; and tubulin polymerization promoting protein, TPPP) was associated with reduced rates of depression[113]. Decreasing NMDA expression via trauma-induced gene methylation may affect the maturation process of the glutamatergic system. Increased methylation of one CpG island has also been seen in women with higher levels of childhood exposure to domestic violence[242].

III.4.B. Resistance and resilience

The ability of an individual to keep a stable, efficient maintenance of mental health despite stressors throughout its life like early life adversities, is a dynamic process, named resilience [345–349].

There is accumulating evidence from clinical and animal (non-human primates, and rodents) studies for ‘‘stress inoculation-induced resilience’’. Stress experienced early in life can promote adaptive effects on emotional and cognitive development, resulting in resilience to stressful experiences encountered later in life[350,348,351–360]. These findings indicate that depending on the intensity and timing of stress exposure, early life stress might result in an improved stress coping potential to stressful situations, which can be discussed in the context of “the match/mismatch hypothesis”[359,361].

This hypothesis predicts that after early life stress, if the adult environment is also stressful (match), an improved stress coping behavior and adaptability will develop, whereas a ‘‘mismatch’’ between the anticipated environment in early life and the actual adult environment increases the risk of pathology[359,361–364]. Indeed, if interactions between the prenatal and postnatal environments are important for the shaping mental resilience, this may explain the absence of stress-related mental illness in prenatal stress studies targeting juvenile populations exposed to violence[365]. For example, children living in high violence communities like in São Gonçalo in Brazil seemed more resilient to the epigenome-wide and psychiatric consequences of prenatal IPV reported repeatedly in other studies[366–368]. Similar effects were found in an independent sample of children exposed to war violence. These children presented

the opposite relationships in their epigenetic profiles compared to United States patients with documented history of psychiatric disorders.
Altogether these effects involved hundreds of subjects and thousands of methylation sites, and a clear impact was found in two well established stress response genes, *FKBP5* and *NR3C1.* The *FKBP5* and *NR3C1* findings were consistent with a reprogramming of the HPA-axis, resulting in an enhanced negative feedback and a faster stress recovery in prenatal IPV exposed São Gonçalo children.
Indeed, chronic cortisol exposures in children[369] and endogenous hypercortisolism[370] were associated with similar changes in DNA methylation.

DNA methylation in heterochromatin-like regions would therefore indicate stress resilience. In the stress-susceptible mouse strain Balb/c (but not in the resilient strain C57Bl/6), early life stress elicits biphasic changes in HDAC expression and histone modifications during postnatal development that trigger several post-translational modifications of histone proteins[371].

Exposure to stress related to loss of DNA methylation in repetitive heterochromatin-like regions may in part involve a mechanism that reactivates intact retrotransposons[369,372–375]. These virus-like elements are often found in repetitive genomic regions and are normally silenced by DNA methylation. It is believed that when this epigenetic control mechanism is compromised, these elements may reactivate, spread to other genomic locations, leading to disruption of genome integrity, and increased nuclear instability[374].
As expected, prenatal IPV exposed São Gonçalo children showed more DNA methylation in repetitive heterochromatin-like regions, suggesting that these children may have stronger protection against nuclear instability caused by reactivation of retrotransposons compared to the controls. Specifically, São Gonçalo children whose mothers were exposed to IPV during pregnancy had more DNA methylation in retrotransposons and heterochromatin-like regions. These particularities had previously been associated with slower aging and lower risk of disease[372–375].

III.5. PTSD and epigenetics: new insights

PTSD is a complex psychiatric condition. It is acquired following exposure to a stressor that the individual perceives as threatening to the physical and/or psychological integrity of self.

PTSD is typically diagnosed using clinical criteria from the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). These criteria include exposure to a traumatic stressor with subsequent intrusion symptoms (*e.g.*, flashbacks, nightmares, physiological reactivity), avoidance behaviors, negative mood/thoughts, and/or alterations in arousal (*e.g.*, hypervigilance, exaggerated startle, sleep disturbance).

In the general population, lifetime prevalence is 1,9% to 3,9%[376,377], 12 month prevalence is 0,9 to 2,2%[376] and current PTSD is 0,7 to 0,9 %[376,378]. Because people may have symptoms of PTSD for many years before seeking treatment, or have subsyndromal PTSD, the prevalence of PTSD may be underreported.

Indeed, 5 % of French people who experienced a traumatic event had flashbacks and psychopathologic outcome[378]. Suicide rates are elevated in PTSD patients in most studies; but the statistical relationships are complex, especially since comorbid psychiatric diagnosis are frequently associated. Epigenetic is speculated to be involved in the development and phenotype of PTSD.

III.5.A. Trauma exposure creates long-lasting changes in gene function

PTSD is associated with pathways regulating neuron signaling, inflammation, and multiple aspects of physical health.

III.5.A. a. Brain

Distinct biological pathways may be perturbed in clinical PTSD populations with and without a history of childhood maltreatment, with epigenetic adaptations being more prominent in the group of early abused victims. DNA methylation may exert a much greater impact during early life[29]. Those who had experienced maltreatment in childhood, had gene expression profiles that were almost completely non-overlapping (98%) with those who were suffering PTSD, but did not have a history of childhood

abuse, and, in fact, showed up to 12 times as many differentially expressed transcripts[29].

Increase in methylated DNA reduces neurogenesis, particularly in the right hippocampus[116], which is associated with depression and PTSD[379–381]. A reduction in hippocampal volume is observed among those who experienced sexual abuse between ages 3 to 5, while a reduction is observed in the corpus callosum and frontal cortex during ages of 9 to 10 and 14 to 16 years old, respectively[382]. Moreover, these differential changes in brain development paralleled differences in psychopathology. Depression and PTSD symptoms were more likely to appear among those who experienced abuse respectively between ages of 3 to 6 and 9 to10 years old[382].

Before war service, a higher number of GR in peripheral blood of soldiers has been indicated as a vulnerability factor for PTSD development after deployment[383]. In war combatants diagnosed with PTSD, lower methylation of *NR3C1* was linked to an increased expression of GR in T lymphocytes and in peripheral blood mononuclear cells, accompanied with changes in circulating cortisol compared with controls[384–389]. Recently, Kuan and colleagues reported an hypomethylation of *FKBP5*, *NR3C1*, *BDNF* and *SLC6A4* in men with PTSD in World Trade Center-related disorder[390].

Moreover, Koenen et al., concluded that exposure to a great number of traumatic events was associated with increased risk of PTSD diagnosis, great number of symptoms, and great severity of symptoms at low levels of *SLC6A4* methylation. Whereas high levels of *SLC6A4* methylation and exposure to a large number of traumatic events was associated with resilience to developing PTSD[391].

In patients with a major depressive disorder, higher SLC6A4 promoter methylation status was significantly associated with a range of childhood adversities[142].

Four SNPs in the *FKBP5* locus (rs9296158, rs3800373, rs1360780 and rs9470080) have been shown to interact with the severity of childhood maltreatment, that could predict adult PTSD symptoms[193]

A contrario, pregnant mothers that had been exposed to the Tutsi genocide in Rwanda and their offspring were shown to display increased both PTSD and comorbid depression symptom severity that were associated with increased

methylation of the NR3C1 promoter in the blood and decreased cortisol and NR3C1 plasma levels[305]. Indeed, Perroud and colleagues showed that severity of childhood abuses including sexual abuse and neglect (repetition of abuses, number of types of abuse and neglect, types of abuses) was associated with increased *NR3C1* promoter methylation in the peripheral blood. However, there was no association between *NR3C1* methylation status and past or current PTSD[392].

African-American patients from a large, urban area were assessed for childhood maltreatment, PTSD and total life stress exposure. While differential methylation genes were associated with PTSD and total life stress, no significant finding was reported for childhood maltreatment. PTSD was associated with hypermethylation in *CLEC9A* (activation receptor on myeloid cells), *ACP5* (glycoprotein with elevated expression in leukemias), *TLR8* (pathogen recognition and innate immunity activation) and hypomethylation in *TPR* (involved in trafficking across the nuclear membrane) and *ANXA2* (calcium-regulated membrane-binding protein involved in signal transduction and cellular growth).Moreover, increased methylation in *CXCL1* and *BDNF* was associated with PTSD and comorbid total life stress[171].

III.5.A. b. Immune system

A genome-wide gene expression study of 12 PTSD subjects and 12 trauma-exposed without-PTSD controls found 3989 genes significantly upregulated in PTSD and three downregulated differences in DNA methylation. Among those, gene expression of the immune system was upregulated[393]. Increased methylation of other immune-related genes, such as (TPR, CLEC9A, ANXA2, TLR8, tartrate- resistant acid phosphatase (ACP5), and neuropeptide FF receptor 2 (NPFFR2), were also found to be associated with PTSD[171].

However, other studies have found results in favor of a down regulation of immune system genes.
A compromised immune response was suggested both clinically and epigenetically in adult PTSD subjects obtained from a population sample of a large, industrial city in

the United States (Detroit, MI)[172]. Compared to healthy controls, PTSD subjects had significantly less methylated genes related to immune (innate and adaptative) and inflammatory response, and a possible marker of compromised immune systems: cytomegalovirus antibodies were significantly higher in PTSD subjects. Among those, *MAN2C1* was demonstrated to modify the risk of PTSD in the context of cumulative trauma[394] in association with the implication in PTSD pathology of accumulation of misfolded proteins, alterations in apoptosis[395] and specially death of leukocytes[396].

A contrario, Kuan and colleagues did not confirm the immune system genes implicated in prior studies of DNA methylation in PTSD in World Trade Center-related disorder, suggesting that links between individual methylation sites and these conditions are too subtle to be detected in such sample[390].

III.5.B. Trauma exposure affects biological development and mental illness through the life course.

Trauma-exposed military veterans have been assessed for DNA methylation, and PTSD was associated with significantly accelerated cellular age as measured by DNA methylation rates. Trauma-associated increased DNA methylation was also associated with a higher probability of all-causes mortality during the 6,5 year follow-up period[397].

Epigenetic mechanisms are critical in the acquisition and modification of traumatic memories[398]. The dentate gyrus is the hippocampal area receiving the excitatory neuronal input, especially for novel situations and memory formation.
Rodent models revealed that novel environments increased H3 acetylation in the dentate gyrus[399] and that fear conditioning caused hippocampal H3K14 (histone H3, lysine 14) acetylation[400].
Benzodiazepines inhibit H3ac[399] and HDAC (histone deacetylase) inhibitor administration modified memory extinction[400] and enhanced fear memory[401].
Moreover, in rats that undergo through fear extinction after fear training, H3 acetylation was unaffected by immediate (10 minutes) extinction training but was

significantly increased in the infralimbic prefrontal cortex but not in prelimbic prefrontal cortex after delayed (24 hours) extinction training[68].
Interestingly, inhibition of the DNA methyltransferase blocks long-term potentiation and memory consolidation in rat hippocampi[402].

In humans, histone trimethylation differences have been found at various lysine sites in the peripheral blood monocytes of human PTSD subjects and some of these histone modifications were associated with the differential methylation of couples of genes and miRNA expression[403].
The drugs cocaine and Ayahuasca (Amazonian shamanic plant) activate the stress-responsive receptor SIGMAR1 (endoplasmic reticulum protein involved in lipid transport). SIGMAR1 interacts with the histone deacetylases HDAC1/2/3, and this interaction is enhanced by cocaine[404] .This mechanism has been hypothesized to contribute to the traumatic memory-retrieval for PTSD patients using Ayahuasca[405].
Moreover, the differential expression of ncRNA has been implicated in altered synaptic plasticity after cocaine administration[398].

III.6. Organ targets

Differential methylation between the mistreated and comparison children concerns genes involved not only in biological processes relevant to psychiatric and substance use disorders (*e.g*., neurogenesis, axonal guidance), but also heart disease (e.g., cardiac development), stroke (development of blood vessel morphogenesis), respiratory disease (*e.g*., interleukin regulation), diabetes (e.g., leptin signaling), and cancer (*e.g*., WNT signaling, NOTCH signaling)—all medical illnesses that have been associated with a history of adverse childhood experiences[186].

III.6.A. Cardiovascular disorders

Changes in organs other than the brain due to childhood maltreatment may be linked to the increase in risk for cardiovascular and metabolic disorders[52].

The HPA axis is also known to interact with the immune system[406], which is another pivotal mechanism mediating the relationship between adversity and cardiometabolic disease. In a twin study, Zhao and colleagues observed an association between methylation of the promoter region of the *NR3C1* gene in peripheral blood leukocytes and subclinical atherosclerosis. This association was independent of genetic, family environment and other coronary risk factors[407].
Besides epigenetic alternations of the *NR3C1* gene, an association of BDNF genotype and promoter methylation with acute and long-term stroke outcomes was also found in an East Asian cohort[408].

An increasing number of studies has now documented that stress exposure leads to proinflammatory immune profiles in adulthood[409] as risk factor for cardiovascular disease and increases in body mass index. It is also and likely associated with an increased in metabolic risk profiles[410].

III.6.B. Endocrine disorders

Child mistreatment may confer risk for obesity through eight methylation sites in genes previously associated with obesity risk[411–417].
This genes are involved in glucose metabolism with *PCK2* (involved in glucose metabolism)[418] and *MADD* (implicated in type 2 diabetes)[419] or in lipid metabolism with *PRDM16* (involved in the differentiation of brown adipose tissue)[420], *BCAT1* (candidate risk gene for obesity)[421], *HIDI* (associated with preadipocyte number and adipocyte size in rats)[422], *CXCL10* (chemokine CXCL10 correlates with visceral fat area in obese children)[423], OSBPL9 (encodes an intracellular lipid receptors)[424], PXDN (associated with early onset obesity)[425,426] and GALE (encodes UDP-galactose-4- epimerase)[427].

In neuroendocrine targets, BDNF plays an important role in regulating energy homeostasis and body weight [428,429] and FKBP5 gene expression in subcutaneous adipose tissue was correlated to markers of insulin resistance [430].
Epigenetically deregulated neuroendocrine and neurotransmitter receptor pathways were evident in both high prenatal stress mothers and children, while in children,

calcium- and WNT-signaling involved in lung maturation were epigenetically deregulated, potentially explaining the increased risk of repeated wheeze[431].

III.6.C. Aging: the lifetime theory

This evolutionary-developmental perspective suggests that exposure to harsh environments should favor the development of life history traits consistent with faster maturation. Growing literature suggests that exposure to early life adversity may contribute to accelerated development[432–444].
Other authors state that exposure to deprived environments (including neglect, food insecurity, and an absence of cognitive stimulation) should favor the development of life history traits that conserve resources and delay reproduction[441,443 445,446], but are not associated with accelerated aging[440].

"Horvath's clock" aggregates DNA methylation at 353 CpG sites to quantify DNAm age. Epigenetic age acceleration represents variance in DNAm age, that is not accounted for by the chronological age. Positive values suggested accelerated cellular aging, meaning that an individual is biologically older than expected.
Experienced, but not witnessed, violence was associated with greater DNAm age acceleration[439].
Epigenetic aging has been observed in youth, young adults and adults with childhood trauma[447], early institutional care[448] and in harsh discipline[449].
More precisely, sexual abuse was associated with DNA methylation age acceleration of approximately 3 years in analysis of data from the mothers of the ALSPAC (Avon Longitudinal Study of Parents and Children) study[450].
Some authors found that higher cumulative stress and trauma increased epigenetic aging in children[439], in adults[451] and specially with PTSD hyperarousal symptoms[452] (but trauma exposure and total PTSD severity were not).
Moreover, recent findings show that war-veterans with PTSD can show epigenetic age-deceleration[453,454].
Accelerated cellular aging has been linked to all-cause mortality; some cancers, cardiometabolic disease, lower lung function, cognitive function and physical

capability[455]. A 5-year difference between chronological and methylation age is associated with a 21% higher risk of mortality[456].

Conversely, other authors showed that maternal NFP (Nurse Family Partnership targets mothers at risk for abusive parenting) participation or history of childhood trauma did not predict epigenetic age acceleration[137,453].

III.6.D. Could whole-genome epigenetic reprogramming predict gravity of disorders?

In a rodent model of maternal abusive behaviors[163], peripheral levels of DNA methylation in the *BDNF* promoter increased as a function of the number of childhood trauma. Of note, this study found no correlation between DNA methylation state and expression level of BDNF in the plasma[457].
These results suggested the possibility of interactive relationships between the type of childhood adversity, site of methylation, and clinical outcome.

Extreme psychosocial stressors in pregnant women, as observed in the Democratic Republic of Congo, was associated with an high rate of methylation of the *NR3C1* promoter in the newborn, which was proportional to the degree of stress during intrauterine life[301]. These findings are consistent with other studies where methylation status of the *NR3C1* gene promoter was closely correlated with both the frequency and severity of maltreatment[94,103,105,152,392] or emotional abuse experienced during childhood[458].
In the same line, the mean percentage of methylation of the promoter region of the *5-HT3A-R* gene in salivary DNA was significantly and convergently associated with : maternal history of exposure to childhood maltreatment and subsequent violent victimization, related IPV-PTSD, maternal aggressive behavior and child attachment disturbance[151].Exploratory works found that higher *5-HT3A-R* methylation levels were associated with childhood physical abuse, a greater severity of suicide attempts, a more important number of hospitalizations, and mood disorder episodes, whereas

childhood emotional neglect was inversely correlated with CpG1 I methylation levels[150].

Moreover, methylation changed in CpG sites in *ID3 (*DNA Binding Protein Inhibitor ID-3), *GRIN1* and TPPP (Tubulin Polymerization Promoting Protein)[113]. These three genes have been implicated in stress response[459,460461,462], neural plasticity[463], and neural circuitry[464–466].

Regarding PTSD, Marinova et *al.*, found a correlation of DNA methylation modifications with complex posttraumatic sequelae in elderly individuals exposed to prolonged and complex childhood trauma.

Positive correlation for DNA methylation in the body of carnosine synthase 1 (*CARNS1*, known also as *ATPGD1*) was associated with trauma complexity[467] and DNA methylation profiles were significantly associated with complex posttraumatic sequelae in the symptom dimensions dissociation, tension reduction behavior and dysfunctional sexual behavior.

Positive correlation of DNA methylation with the scale tension reduction behavior was detected in *RANBP* (RAN binding protein 2)[468] and negative correlation was found for methylation changes in *HAP1* (Huntington associated protein 1)[469,470] and dissociation symptoms severity[467].

Separately, associations between intensity of *SLC6A4* DNA methylation and PTSD or AntiSocial Personality Disorders (ASPD), depression symptomology severity with an history of childhood abuse were found[142,471,472].

III.7. Therapeutic targets

Epigenetic marks have long been thought to be fixed in post-mitotic cells, but rodent studies indicated that DNA methylation can be reversed in adult brain. Epigenetic mechanisms are temporally dynamic, adjusting in the short- and long-term to environmental influences. Gene and environment interactions can influence clinical phenotypes, and these interactions can be further modified by inherited or environmentally induced epigenetic changes.

Although methylation is thought to be the most stable form of epigenetic modification, there is evidence that gene methylation may be plastic during childhood and into adulthood. Then, therapeutic interventions could alter methylation patterns and reduce the biologic risk engendered by early life adversity[473].

MRI studies have suggested that early-life adversity may be associated with structural alterations in white matter[474]. Interventions, such as placement in high-quality foster care, may partly counteract some of these effects, suggesting that white matter deficits could be reversed to alleviate lifelong consequences of early-life adversity[475]. Thus, it is possible that drugs or even psychotherapeutic approaches could reverse epigenetic effects of life stress.

III.7.A. Drug

The first evidence that prenatal environmental exposures may remodel epigenetics came from a mouse study.

Maternal methyl-rich diet during pregnancy can change the offspring's coat color and growth phenotype in agouti mice, and this was mediated by DNA methylation of a transposable element[476]. The methyl-rich diet increases the availability of methyl groups in the offspring and therefore increases the DNA methylation capacity for DNA methyltransferases. Moreover, treatment with methionine, a compound that is known to increase gene methylation, suppressed gene expression in rats with high levels of early life maternal care and was associated with increased depressive and anxious behaviors[48].

The DNA methylation inhibitors zebularine and 5-aza-2-deoxycytidine reverse DNA methylation and block synaptic long-term potentiation in mouse hippocampal slices[477], as well as fear memory formation[402]. In rats, treatment with trichostatin A (HDAC I and II inhibitor) reversed the decreased gene expression that was imparted by neglect in early life. This reversal was associated with decreased behavioral phenotypes of depression and anxiety[48].

In humans, several drugs can alter methylation patterns across the lifespan : the so-called ‘epigenetic drugs’ are being developed for a range of disorders, most notably cancer [478]. Interestingly, many currently-used psychiatric medications have effects on

the epigenome [479]: clozapine, sulpiride, and valproic acid have been shown to actively promote demethylation in cell culture [480,481] and in mouse brain [482,483]. Fluoxetine treatment in traumatized mice significantly reduces several miRNAs, most notably mmu-miR-1971, compared to untreated traumatized mice [484] but increases the histone modifications[371,485].

Concerning monoamine oxidase inhibitors (MAOIs), peripheral methylation levels of *MAOA* predict activity levels of the enzyme in the brain[236]. So, the *MAOA* hypomethylation in peripheral DNA of depressed individuals should in theory be correlated with an abundance of brain MAOA. This excess in brain MAOA levels could, metabolize amines (such as dopamine and serotonin) at a higher rate. The latter sequence of events is in line with the therapeutic mechanism of MAOIs.

Another potential therapeutic approach is to modify the cellular environment with antioxidant.

In a single-prolonged stress model of PTSD in rats, grape powder through suspected antioxidant properties prevented stress-induced corticosterone increases, BDNF decreases, significantly increased hippocampal and amygdalic H3 acetylation and HDAC5[486].

Furthermore, dietary supplementation with carnosine has shown positive effects on cognition on veterans suffering from Gulf War illness [487]. The formation of carnosine and homocarnosine, which are compounds with anti-oxidant properties [488] is catalyzed by CARNS1. As shown by Marinova *et al*., *CARNS1* methylation was positively correlated with PTSD[467].

However, drugs that target the epigenome globally can have unexpected (and potentially pathogenic) effects on the transcription of genes which are not the desired target. It may be an obstacle to their development.

III.7.B. Non-drugs therapies

Given the potential “reversibility” of epigenetic modifications shown in rodent models[489], it is tempting to speculate that, even beyond the critical developmental periods of childhood, social environmental “recalibration” of gene expression may be

possible. For example, negative methylation marks at specific sites can be at least partially reversed by supportive environment[490–493]. The increases in NGFI-A induced by higher levels of maternal care are hypothesized to stimulate transcription and thereby increase glucocorticoid receptor mRNA[494].

In the fish known as the three-spined stickleback, only fathers take care of the offspring. One study showed that paternal care reduced offspring anxiety as well as the expression of Dnmt3a in the whole-brain, responsible for *de novo* DNA methylation[495].
In animal models, exercise modulates changes DNA methylation in brain associated with stress exposure[496–498], suggesting that physical activity interventions may have a role in modifying the effects of early adversity on gene methylation.

Thus, maybe in patients with trauma, psychotherapy could exert a biological effect. Some epigenetic marks might represent predictors of psychotherapy success[499].
For example, the assessment of promoter region methylation of *NR3C1* and *FKBP5* in combat veterans with PTSD undergoing prolonged exposure therapy found that, pretreatment methylation of the *NR3C1,* but not *FKBP5* promoter predicted treatment response[499]. In responders, the methylation of the *FKBP5* promoter region decreased, while it increased in non-responders. FKBP5 expression increased in association with recovery[499].
In children, *FKBP5* DNA methylation was significantly associated with treatment response to a cognitive behavioral therapy-based intervention for anxiety disorders[500]. Children with a smaller reduction in symptoms showed an increase in DNA methylation, while children with a larger symptom reduction showed a decrease in DNA methylation.

Borderline personality disorder subjects had a higher *BDNF* methylation status than in controls, an association that may be the consequence of child maltreatment. After a 4-week course of intensive dialectical behavior therapy (a type of cognitive-behavioral therapy), responders showed a reduction in methylation status over time[457].

IV. Discussion: confounders

The methylome switch relies on broad epigenome signatures, making it less affected by populational structure and measurement artifacts, such as fluctuations in cell-type heterogeneity. When used properly, this marker allows for epigenome studies in relation to more stochastic models of stress and aging, such as the allostatic load[501] and epigenetic drift[375] concepts.
In such models, it is expected that broad genomic mechanisms, such as a loss of genome integrity, can disassociate the impact of stress at single CpGs[374].

IV.1. Complexity of epigenome

First, there is a debate as to whether 5-hmC (hydroxy methyl cytosine) solely represents a transient state in the process of demethylation, or whether this mark be itself associates with specific functional consequences[125]. The latter hypothesis implies that 3 epigenetic states are possible at CpGs (unmethylated cytosine, 5-mC or 5-hmC), thus increasing the encoding capacities of DNA. While 5-mC is associated with decreased transcriptional activity, 5-hmC is associated with the opposite effect.

Then, the extremely high diversity of cell types encountered may well be associated with a similar diversity in epigenomes. Epigenetic mechanisms controlling transcriptional activity may be cell-type, and even gene-specific[189]. Applying fluorescence-assisted cell sorting to human post-mortem tissues, notably in the study of childhood maltreatment[23,110,502] or developing new methodologies (such as the visualization of histone modifications at single genomic loci with single-cell resolution)[503] will be required to assess epigenetic heterogeneity across cell types and genomic loci.

Eventually, this is a big challenge to integrate these reviewed findings into broad epigenetic organizational and regulatory domains.

IV.2. Methodological limitations and challenges

Differentiating the genetic and environmental origins of changes to the human epigenome has been less clear than in other animal models and the confirmation of transgenerational inheritance encounter substantial methodological challenges.
Examining human populations to clarify questions may be complicated by a number of factors : additional risk factors during assessments, including enquiring about the transgenerational effects of trauma, the nature and number of abuse, the importance of demographic profiles, and the effect of psychiatric comorbidities, contributory genes, risk versus protective alleles, and superimposed epigenetic effects.

Research on epigenomic changes in humans occurring in response to early-life adversity is considerably limited, and the results are often difficult to interpret given the biological, technical and methodological issues inherent in how the studies have been implemented[94,103,140,504].
For example, the hypothesized causal effect of violence exposure on health can not be confirmed by experimental designs exposing children to violence (which are unethical) or by longitudinal designs taking biomarker measurements before and after violence exposure to use each child as his own control (which are impractical, though not impossible). This causal hypothesis could also be tested by comparing the stress biomarker status of siblings who are discordant for the experience of violence exposure. Twins are particularly good for this contrast, though in most twin pairs studied as young children, when one twin is maltreated, so is the other. As a result of these research limitations, we may never be able to rule out the possibility that biomarker abnormalities observed in violence-exposed children were caused by some other kind of adversity.
Because of the difficulty of testing children with functional activation paradigms, most studies of children have reported only structural MRI measures[505,506]. Moreover, because of challenges in undertaking neuroimaging of young children, most studies focused on adult patients with trauma-related psychiatric conditions[382,507], or adults who retrospectively reported maltreatment[508,509].

IV.2.A. Violence characterization

Another obstacle facing cross-species comparisons is the high rate of exposure in humans to multiple types of abuse. For instance, 60% of the mothers who had experienced IPV as adults had experienced physical abuse as children[151].

Under the label of "adversity," studies have focused on a diverse mix of exposures spanning maternal psychiatric disease[295], early parental loss[510], institutionalization[182], indentured child labor[511], child abuse[140], the Holocaust[306] and war trauma included such experiences as being kidnapped, raped, having family members killed, and being a refugee.

Additionally, different populations face exposure to different types and rates of trauma (urban versus rural populations, wartime versus peace, and military versus civilian).
For example, military populations are frequently used as a source of PTSD subjects, but it is possible they are not comparable to PTSD cases in the general population[512]. Exposure to life-threatening trauma can be both significantly more severe and frequent than in a typical civilian population, and social cohesion can be lost on return to civilian life. Additionally, combat veterans have higher rates of physical and traumatic brain injury[513]. The higher rates of comorbid brain injury increases the risk of PTSD in this population[514].

Definition of violence of violence and trauma may also vary.
Presence of trauma (physical and sexual abuse, neglect, deprivation) are documented on the basis of different types of reporting (self-report, family- and school-report).
In order to unify these definitions, validated and robust instruments have been developed, such as the Childhood Experience of Care & Abuse (CECA) questionnaire[515,516], Childhood Trauma Questionnaire (CTQ)[517] which explore five subscales (three assessing abuse : emotional, physical and sexual and two assessing neglect : emotional and physical),Parent–Adolescent Relationship Questionnaire (PARQ),parental separation, Hegarty Intimate Partner Violence score even instruments to assess the risk of maltreatment[518].

IV.2.B. Host of other environmental factors

IV.2.B.a Socioeconomic status

Findings suggested that early-life socioeconomic status (SES) was associated with genome-wide DNA methylation in adult [519], [520], whereas concurrent adult SES was not reliably related[49] [521].

Family income-per-dependent in early childhood, as well as parental education and family psychosocial adversity, were each associated with children's DNA methylation marks in middle childhood[522].

Moreover, prenatal neighborhood disadvantage (poverty) was associated with significantly higher methylation of *LINE-1* and *MEG3* in newborn umbilical cord blood[523,524]. *LINE-1* methylation has been implicated in neuropsychiatric conditions such as depression[525].

Other studies have shown that children from low socioeconomic environments present a greater risk of brain development problems, but only if the family environment has serious deficits[526,527]. For example, US children growing up in poverty had reduced volumes of their hippocampus[528] and in a Canadian study[529] and a Romanian study[530],poor maternal care in early childhood leads to an enlarged amygdala volume in children.

IV.2.B.b. Toxins (*e.g.* tobacco smocking)

When smoking pack-years was added as a covariate to the adolescent polyvictimization EWAS, no probes remained significantly associated with DNA methylation, for example at three differentially methylated positions of AHRR[79] which were associated with tobacco smoking[531] .

Epigenetic analyses of umbilical cord blood showed an association between maternal smoking during pregnancy and DNA methylation[532533534535536537]. The duration and intensity of smoking during pregnancy also led to a dose-dependent response and longitudinal analysis revealed that some methylation sites were persistently perturbed[532538] whereas others showed reversibility[539].

IV.2.C. Timing

There is some evidence that the timing of childhood maltreatment might be important in determining the severity of epigenetic alterations[540] [541]. As epigenetic patterns appear to vary over the life course, the effects of adversity timing may have gene specific consequences[448,542,543].

Perinatal stress coincides in time with neurogenesis, migration of progenitors and establishment of circuits and synapses[544,545]. Thereby, periods of greater HPA axis plasticity may represent specific periods of greater vulnerability [546–548] while mounting evidence suggests a differential impact of early life stress on HPA axis activity according to the specific developmental age of exposure[549].

Pregnancy is the first critical period for neurodevelopment in the offspring[550] and transient environmental conditions in very early pregnancy seem to result in persistent changes in epigenetic information, contributing to fetal programming[551].

In studies from Swedish famine periods, males exposed to famine prior to or during the "slow growth" period prior to the start of puberty passed on health and disease risks to their children and grandchildren, suggesting that there is machinery present and able to reprogram epigenetic marks in the germ cell at this stage[552]. Famine experienced outside this window diminished the transgenerational impact.

Similar results have been reported in studies examining generational outcomes in exposures during the "Dutch Hunger Winter". The individuals exposed to prenatal famine displayed altered DNA methylation patterns: periconceptional exposure to famine was associated with lower methylation of the *IGF2* DMR six decades after the initial exposure. This outcome was distinct from those who were prenatally exposed later in gestation and did not show a change in methylation at this locus as adults[553].

The early development represents a particularly sensitive period to epigenetic modification of the genome[540]. Infancy and early childhood (age 0 to 5 years old) represent a vulnerable period in brain development[351,366,548,554]. Exposure in the first 2 years of life, when the brain doubles its volume and a massive synaptogenesis occurs is associated with high risk of aggressive behavior in childhood[555,556], and with prolonged cortisol reactivity to acute social stressors among adolescents[557,558]. This could partly rely on important interactions of GC-signaling with oxytocin pathways[559].

Exposure in very early childhood was associated with DNAm differences for nearly all adversity types[560]. In contrast, the effects of exposure in middle childhood were largely detected only for arguably the most severe forms of adversity exposure (e.g., sexual or physical abuse)[47561–564].

It has been shown that the intensity of DNA methylation of the *FKB5* gene is most pronounced in early life period and that childhood trauma can induce persistent epigenetic changes[565].
Some longitudinal studies suggest that stress responsivity in early childhood decreases with age throughout the preschool period[548,566–568], suggesting a potential social buffering of the HPA axis by a nurturing caregiver, who may operate as a safety signal[569–571].

In addition to prenatal and early postnatal life, adolescence also represents a time-window particularly sensitive to external and environmental events, as in this period the brain concludes its maturation process[572]. Some retrospective studies have shown that adolescent DNAm patterns are more strongly associated with life stress during adolescence than earlier periods[573].
The onset of gonadal hormone production plays a vital role in stress and HPA axis reactivity, since estrogen secretion influences GC hyperactivity[574]. Therefore, adolescents are victimized by a more diverse set of actors across a wider range of environments than any other age group, and exposure to multiple types of victimization (including relational aggression, sexual victimization, and serious violent crim) peaks during adolescence[575].
Conversely, some studies on early life stress during adolescence reported lower baseline cortisol[576] and blunted cortisol responses to psychosocial stress[577], accordingly suggesting an opposite effect of early life stress on HPA axis basal activity and reactivity than in infancy and early childhood.

Eventually, gene expression can physiologically be altered by aging.
For example, community and domestic violence are associated with decreased DNA methylation of *BDNF* and *CLPX* in adolescents and during middle adulthood (mothers)

but not during late adulthood (grandmothers). In fact, BDNF is known to modulate age-related changes in hippocampal function[578], and its levels in peripheral blood decrease significantly with increasing age[579]. Reduced levels of serum BDNF were linked with hippocampal shrinkage and memory decline in late adulthood[580,581].

IV.2.D. Allelic profile

While animal experiments mostly use genetically identical animals, environmental exposure in humans falls on a genetically diverse background, leading to large differences in the long-term behavioral/psychiatric outcomes[582,583].
Genetic factors can give a predisposition to the effect of childhood trauma in a given subject. They can interact with the occurrence of childhood trauma to produce various negative clinical phenomena in adulthood. Interaction of several genes has been demonstrated.

IV.2.D.a. Polymorphism

Environmentally-induced epigenetic changes may have sequence specific effects, with an individual carrying the genetic predisposition being more sensitive to long-lasting epigenetic alterations.

Thus, careful consideration of the intersection of DNA methylation with allelic variation is necessary to determine what fraction of epigenetic variation is genetic, environmental, therefore suggesting the involvement of both “gene and gene”, and “gene and environment” interactions[533 116,584,585].
In addition, genetic variation can affect epigenetic changes. DNA sequence itself encodes information on its methylation status in cis (local genotype that is associated with DNA methylation on the same DNA molecule)[96,586–591].

i) FKBP5

Specific *FKBP5* alleles enhance the effects of acutely released cortisol following early life stress on *FKBP5* mRNA expression. That abnormal *FKBP5* expression would lead

to maladaptive changes in GR sensitivity in the presence of five high-risk *FKBP5* polymorphisms and these are further exacerbated by DNA demethylation[116]. People carrying the minor allele for each of these five polymorphisms and who were exposed to severe trauma showed higher level of adult PTSD symptoms[193,592], depressive and anxiety symptoms[593,594], stress-related psychiatric disorders[595–597], suicide[193,598–604] and drug abuse[116,193,197,597,600,605].
Heterozygous individuals carrying one risk allele did not differ from homozygous risk allele carriers. This emphasizes the effects trauma severity on *FKBP5* demethylation in risk-allele carriers, but not in protective genotype carriers.

Conversely, other findings suggest that epigenetic alterations of the *NR3C1* gene, but not the *FKBP5* gene even when considering the presence of a risk-allele, may contribute to the finding of both increased morning cortisol levels in depression and early life adversity[458]

ii) Serotonin pathway

SLC6A4

Highly studied are genetic variations of SCL6A4 which functions to modulate serotonergic activity through the reuptake of secreted serotonin from the synaptic cleft.
Serotonin system dysregulation is critical in pathogenesis of internalizing disorders[606]. *SLC6A4* and its polymorphic promoter region are indeed linked with changes in transporter gene expression, and thus, functional effects on serotonin transport and subsequent pathogenesis[607].

Promotor polymorphism of the *SLC6A4* gene, with allele variants of allele "s", short[608] and allele "l", long[609] repeats have been implicated in moderation effects[610]. These effects may be mediated by altered DNA methylation[611].
In healthy carriers of “s” allele, strong evidence was found for an association between the “s” allele and increased stress sensitivity following the childhood trauma[610,612–614],

mainly sexual abuse[615,616] and higher risk of developing depressive symptoms, diagnosable depression, and suicidality[610,617–620].

Individuals with the s/s genotype had more depressive symptoms if they had encountered early or current stress but fewer depressive symptoms if they declared a supportive early environment or recent positive experiences than the subjects with the "s/l "or "l/l" genotype[621]. It has been hypothesized that in the carriers of the "s" allele ,abnormalities of serotonergic neurotransmission connected with stress reaction could cause disturbances in emotional processing and increased susceptibility for the development of mood disorders following negative childhood experiences[622].

However, no differences of *SLC6A4*methylation in self-reported neighborhood crime was found whatever allele variants[623] but an indirect effect of neighborhood crime on depressive symptoms through *SLC6A4* methylation was witnessed when the respondents carried the "s" allele[623].

A contrario, recent findings did not find a strong interaction between stress and *SLC6A4* genotype in the development of depression. The authors concluded that if an interaction exists in which "s" allele increases risk of depression it must be of modest effect size and observable only in limited situations[624,625].

The serotonin 3 A receptor

5-HT3A-R is known to interact with childhood trauma in the development of various psychopathologies.

The 5-HT3A-R "CpG2_III" is localized just before rs1062613 polymorphism (T>C).

Patients carrying the CC risk-genotype showed the highest levels of methylation at CpG2 III (compared to T allele carriers). Since C allele has been also associated with a lower expression levels of *5-HT3A-R* increased methylation, due to exposure to childhood maltreatment, could lead to a further decrease in the expression of mRNA[150].

Furthermore, the CC genotype group (compared to the T carriers), demonstrated comparative loss of grey matter in hippocampal structures, which extended to the

frontal cortices for those CC genotype individuals also exposed to early life stress. Additionally, the interaction between 5-HT3A-R genotype status and childhood maltreatment predicted a depressed mood[626].

Others found only a significant interaction in those with a history of childhood sexual abuse, not other types of childhood trauma.
Findings indicate that people with the 5-HT3A-R CC genotype may show increased impulsivity and have a higher suicide risk compared with T carriers when they have history of childhood sexual trauma[627,628]. Authors suggested that CC genotype could be a genetic risk factor for low central serotonergic function[628,629]. In contrast, individuals with the T allele, in particular the TT genotype, may be more protected from such alterations combined with minimal exposure to early life stress events[250] or child sex abuse[628].

iii) The dopamine active transporter, DAT, SLC6A3

The *SLC6A3* promoter allelic variation has been associated with increased lifetime rates of PTSD (particularly the 9R allele), only in the presence of highly methylated promoter locus[630].

iv) MAOA

Early parental death was associated with hypermethylation of the *NR3C1* gene proximal to an NGFI-A biding site, as assessed in child saliva samples. A regression analysis revealed that this association may be mediated by a well-characterized genetic polymorphism in the *MAOA* promoter. Indeed, individuals with history of physical and sexual abuse[631,632] carrying the low-activity allele, were more likely to develop antisocial-personality disorder and commit violent crimes in adulthood[585,633–635] compared to the high-activity allele carriers.
Some studies confirm that *MAOA* polymorphism enhance depressive symptoms but only among extensively maltreated young individuals (three or four maltreatment subtypes)[615].

v) BDNF

Studies have predominantly focused on a specific valine (Val)- methionine (Met) polymorphism to the *BDNF* gene, which may have negative effects on human memory as well as on hippocampal functioning[636].

First, the magnitude of amygdala atrophy has been significantly associated with the BDNF Val66Met genotype[234]. It was suggested that the met-allele may increase vulnerability to child maltreatment related morphological changes in the amygdala due to decreased activity- dependent secretion of BDNF[636]. However, in van Velzen's study, BDNF gene expression levels were not significantly lower in maltreated subjects, suggesting that the effect of the Val66Met gene on amygdala volume could not be explained by BDNF gene expression in maltreated subjects. Thus, there is a positive relationship between BDNF gene expression and volume of the amygdala in subjects without a history of maltreatment, and this relationship was absent in maltreated subjects.

Given the role of the amygdala in emotion processing, decreased amygdala volume may underlie emotion regulation impairments in maltreated subjects [637,638]. This lack of an association between BDNF gene expression levels and amygdala volume might suggest an absence of a neuroprotective effect of BDNF in maltreated subjects probably predisposing to aggressive behavior[234].

History of childhood trauma or being a Met carrier of the *BDNF* polymorphism was associated with significantly reduced BDNF mRNA level and met carriers with highest levels of childhood trauma had the lowest BDNF mRNA levels[639].

While previous meta-analyses show no general link between this *BDNF* polymorphism with adult psychopathology, such as depression[640,641], a recent meta-analysis shows the potential modulating effects of *BDNF* polymorphism on associations between early adversity and depression[642]. Other studies also replicate these findings among youth populations[643,644] and young adults[645].

Combined with the *5-HT3A-R* polymorphism, individuals with both "Met" and CC genotypes, and early life stress exposure demonstrated elevated emotion elicited heart rate and right frontal hyper-activation with right parietotemporal hypoactivation on EEG[250].

Moreover, combined with the *SLC6A4* polymorphism, *BDNF* polymorphism interacted with an unfavorable early environment to predict depressive symptomology[646] and to significantly moderate the association between childhood abuse and positive dimension of psychotic-like experiences[647]. Depressive symptomology was most common in carriers of either the "ll + Met" or the "ss/sl + Val/Val" genotypes in the presence of a history of early-life adversity[644] or "Met" and "s" carriers concerning child sexual abuse[648].

vi) Immune system

Dysfunction of the immune system can also cause a genetic link between childhood trauma and mood disorders.

The effect of sexual abuse on the early onset of bipolar disorder could be connected with polymorphism of the Toll-like receptor gene associated with the activity of immune system[649].

Plus, an interaction between childhood maltreatment and polymorphism of genes for inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) genes was described[650]. These inflammatory markers show an association with the pathogenesis of depression[651].

IV.2.D.b. Geographic contributory genes

A recommendation suggested accounting for confounding genetic variation within epigenome-wide analyses[652]. Indeed, there can be geographic differences in allele frequency that may affect chromatin confirmation independently of histone or DNA modification. Ancestry is one of the stronger predictors of variation in DNA methylation[519,521,653–656] suggesting that ancestry- specific genetic background may play a role in shaping the epigenetic landscape of the human genome in ways similar to polymophism[657].

For example, a recent study in Singapore of 237 newborns and their parents showed that their DNA methylation profile could differentiate their ethnic origin and was correlated with a number of prenatal environmental characteristics such as maternal

smoking and depression that have been associated with the development of antisocial behavior problems[533].

In European-Americans, childhood maltreatment resulted in several sites of increased DNA methylation in both alcohol dependent and non- dependent subjects that had a history of childhood maltreatment. In contrast, in African-Americans, childhood maltreatment -associated DNA methylation changes in dependent patients were not observed in non-dependent controls[658].

Specifically, for *NR3C1* among African-American children, maltreated children evinced much lower methylation than non-maltreated children, and among maltreated children, African-American children had lower methylation than children who were not African-American[155].

Some risk alleles were found to alter chromatin conformation (and thus gene transcription) relative to protective alleles without geographic effect. Indeed, childhood trauma, with its associated epigenetic modifications, was significantly associated with DNA demethylation of *FKBP5* in risk alleles than in protective alleles and the effects of childhood trauma on DNA demethylation were consistent across European and African-American ethnic groups[116]

IV.2.E. Sex differences

Preclinical behavioral work illustrates that exposure to prenatal stress may lead to sex biases in offspring reactivity to stressors related to depressive symptomology[659] and DNA methylation changes occur in a sex-specific manner[471].

The interaction between the HPA-axis and SCL6A4 has been shown to be influenced by not only gene variations but also early-life stress and sex[660–662]. Similar result have been found for the CRHR1 (corticotropin- releasing hormone type 1 receptor) gene and its polymorphism (G>A,C) on the relationship between negative childhood experiences and the occurrence of depression during adulthood[663].

In men, a protective effect of the “A-allele" against developing depression after childhood trauma was found, and the “A- allele” was connected with lower cortisol response in the dexamethasone/CRH test. No such findings were obtained in women. Among the A-allele carriers, women with negative childhood experiences had higher cortisol response than men[664,665].

Gender is significant in determining whether functional genetic variation in the mineralocorticoid receptor (MR) gene is favorable or unfavorable following childhood maltreatment. The “CA” haplotype can be advantageous for women to depression , while the “GA” and “CG” haplotype – for men to vulnerability[666].

One study examined and identified possible sex-specific interactions with the *BDNF* polymorphism by predicting a small but significant increase in depression risk among men, related to possible interactions with early life events [641]. More emerging evidence strengthens this theory, showing the role of environment and *BDNF* polymorphism interactions in predicting risk of anxiety among Korean adult male (not female) victims of childhood abuse[667].

In another study, significantly higher methylation of an histone deacetylase 4 gene (*HDAC4*) was also associated with lower blood estradiol in PTSD cases compared to healthy controls[668]. And, in mouse amygdala, fear conditioning (as an animal PTSD model) was associated with higher *HDAC4* expression and was modified by estrogen levels[668].

Effects of prenatal stress are sex-specific with male offspring being more sensitive than female offspring as they displayed a long-term increase in HPA axis reactivity not seen in females[669,670].

Moreover, prenatal stress might affect multiple genes and microRNAs through its epigenetic alteration of OGT expression and O-GlcNAcylation profiles[669]. OGT, an X linked gene, plays an important role in the regulation of chromatin remodeling proteins such as histones like O-GlcNAcylation. The sex- specific effect on the phenotype may be explained by the fact that OGT is less expressed in males.

IV.2.F. DNA exploitation

IV.2.F.a. DNA material origin

Most animal models are able to directly examine brain tissue, while most human studies require peripheral tissues for the indirect assessment of epigenetic modifications occurring in the CNS. Though peripheral epigenetic markers frequently reflect central epigenetic changes[671], this is not always the case.

This further complicates the interpretation of gene associations and epigenetic markers as most peripheral tissue findings have not been replicated in human brain samples. Several studies suggest that methylation differences across tissues are substantial[672–675]. However, the effect of trauma, mediated through stress hormones or cytokines, appears to affect the epigenome in a wide range of cell and tissue types[676]. Thus, methylation evoked by adverse experiences could be preserved across tissues.

Several studies suggest that blood is a useful surrogate tissue[677–680].

Tyrka *et al.,* demonstrated a cross-sectional relation between trauma-related whole-blood GR-1$_F$ methylation with decreased negative feedback of the HPA axis[103]. Also, increased GR-1$_F$ methylation in peripheral blood cells has consistently been linked to (early life) adversity[84]. Furthermore, differential DNA methylation of the *SLC6A4* gene promoter in T cells and monocytes was also found associated with in vivo measures of human brain serotonin synthesis[251].

The question of generalizability of methylation patterns across tissues also pertains to measurement in peripheral blood mononuclear cell (PBMC), instead of whole blood[681].

Methylation profiles appear to be tissue-specific[674,675], and several studies indicated a clear separation of samples derived from saliva and blood[130,682–684].

On the opposite, other works indicate that DNA methylation levels in saliva are similar to those in peripheral blood, skin fibroblasts, and buccal swab DNA, but it may not reflect the epigenome of adipose tissue, muscle, pancreas, gastrointestinal system, or the pituitary-tissues[685–687]. One of its advocates, Talens *et al.,* compared epigenetic

profiles of candidate loci in blood and buccal cells and found that DNA methylation was the same for more than half of the sites in both tissues[677].
Data suggests that DNAm in buccal cells may be a useful tool for the investigation of brain-based phenotypes, as they are derived from the same ectodermal layer as brain cells during development, and have been shown to correlate with CNS methylation more strongly than other commonly examined peripheral tissues, such as blood[682].
Moreover, it was found that several loci in both blood and buccal cell samples, repeatedly collected from the same individuals (age 14–62 years old) over a period of up to 20 years, generally remain stable[677].

Another difficulty of limited CNS tissue availability from humans is that it is difficult to directly study epigenetic changes over the course of human development.

IV.2.F.b. Tools to explore DNA methylation

Target gene study alone seems to be too stringent to reflect complexity of DNA methylation.

Using some array, appears to visualize more complete and complexe profile which is not without technical limitation. Indeed, according to O'Donnell and colleagues, the 450K array (Illumina Infinium HumanMethylation450K BeadChip) describes <3% of the DNA methylome and provides limited coverage of enhancer regions[137], which play an important role in transcriptional regulation and mental health[688].

V. **Conclusion**

In this literature review of “violence and epigenetic”, we highlighted dozens of papers mostly done during the past ten years.

Firstly, implicated in neurobiological mechanisms through mental diseases studies in victims, further researches showed that violence-induced epigenetic marks can modulate many other human physiological pathways. Then, based on animals’ models, human studies demonstrate inheritance of these epigenetic marks. However, epigenetic can shape risk but also resilience to violence-linked pathological issues.

As a dynamic phenomenon, epigenetic marks were shown to be reversible and thus potential therapeutic targets.

Unfortunately, this comprehensive and extended analysis of literature provided lots of contradictory results. Indeed, because of epigenomic complexity, a high number of confounders, the well-known human experimental limits as well as the ever-evolving definition of violence, it may be difficult (perhaps impossible?) to obtain causal and unidirectional evidence linking violence to altered DNA transcription and subsequent disease. `

Thus, in spite of some promising therapeutic experimentations, it seems premature to conclude.

Nevertheless, considerable interest in epigenetic research in both the scientific and popular press has been raised, stimulating construction of optimal research methods. It appears that the less unrealistic promise lay on using specific epigenetic contributions in human populations as a tool to monitor therapeutic surveillance and efficiency in the treatment of psychiatric consequences of violence.

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Résumé :

Introduction : La prise en charge des victimes de violences est devenue un problème de santé publique. Mieux connaître les conséquences de la violence sur l'état de santé des victimes permet d'envisager des actions à visée préventive et thérapeutique. Parmi les conséquences potentielles, des études sur le matériel génétique de l'animal puis de l'Homme ont suggéré que la violence agirait comme un facteur environnemental modifiant l'expression de certains gènes. L'objectif principal de cette revue de la littérature était de s'intéresser aux modifications épigénétiques induites par l'exposition à la violence : gènes cibles, transmissibilité aux générations suivantes et conséquences fonctionnelles conduisant à une sensibilité accrue à certaines maladies ou au contraire à la résilience. **Matériel et méthodes :** 180 articles ont été analysés dans le cadre de ce travail, recueillis sur les bases de données MEDLINE® (Pubmed), Web of Science® Core Collection, et GoogleScholar® pour étudier les liens entre violence et épigénétique. **Résultats - Discussion :** Les résultats des études étaient parfois contradictoires, ce qui n'est pas surprenant étant donné la complexité de l'épigénétique, le grand nombre de facteurs de confusion existant dans cette approche, et les limitations inhérentes à l'expérimentation humaine. Actuellement, bien que certaines pistes thérapeutiques encore en cours d'exploration semblent prometteuses, il est prématuré de conclure à l'utilisation des « marqueurs épigénétiques » comme biomarqueurs pour la caractérisation et le suivi des victimes de violence.

Mots clés : violence, épigénétique, gènes cibles, transmissibilité, résilience, applications médico-légales

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