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Molecular impacts of childhood abuse on the human brain

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ABSTRACT

Childhood abuse (CA) is a prevalent global health concern, increasing the risk of negative mental health outcomes later in life. In the literature, CA is commonly defined as physical, sexual, and emotional abuse, as well as neglect. Several mental disorders have been associated with CA, including depression, bipolar disorder, schizophrenia, and post-traumatic stress disorder, along with an increased risk of suicide. It is thought that traumatic life events occurring during childhood and adolescence may have a significant impact on essential brain functions, which may persist throughout adulthood. The interaction between the brain and the external environment can be mediated by epigenetic alterations in gene expression, and there is a growing body of evidence to show that such changes occur as a function of CA. Disruptions in the HPA axis, myelination, plasticity, and signaling have been identified in individuals with a history of CA. Understanding the molecular impact of CA on the brain is essential for the development of treatment and prevention measures. In this review, we will summarize studies that highlight the molecular changes associated with CA in the human brain, along with supporting evidence from peripheral studies and animal models. We will also discuss some of the limitations surrounding the study of CA and propose extracellular vesicles as a promising future approach in the field.

1. Introduction

Childhood abuse (CA) is a prevalent global health concern that strongly associates with and increases the risk of negative mental health outcomes later in life (Afifi et al., 2008). CA can take several forms, including sexual, physical, and emotional abuse, as well as neglect (Teicher et al., 2016). According to the American Psychological Association, sexual abuse involves sexual activities elicited without the victims' consent. Physical abuse consists of intentional physical harm to a victim, while emotional abuse involves causing negative feelings in the victim. Witnessing domestic violence is also a common form of emotional abuse (Teicher and Samson, 2013). Physical neglect is when the basic physical needs of the victim are not met, whereas emotional neglect is when caregivers fail to provide emotional support, such as failing to respond to a child's distress at school with homework or classmates (Teicher and Samson, 2013). According to a review that investigated global rates of CA, it is estimated that 5–35% of children experience physical forms of abuse (Gilbert et al., 2009). Additionally, rates of emotional abuse and neglect ranged from 4 to 9% and 6–12% respectively (Gilbert et al., 2009). A meta-analysis of studies conducted globally estimated that 9% of boys and 25% of girls experience sexual abuse (Andrew et al., 2004).

CA is associated with higher risks of obesity, diabetes, cardiovascular disease, cancer, as well as psychopathology (Berens et al., 2017; Danese et al., 2009; Kelly-Irving et al., 2013). It is estimated that approximately 25.9–28.6% of adult-onset and 44% of childhood-onset psychiatric disorders can be explained by CA (Green et al., 2010). Specifically, CA accounts for 54% of the population attributable risk (PAR) for depression, which is one of the leading causes of disability worldwide according to the World Health Organization (2020), and importantly, depressed individuals have a 20-fold higher risk of dying by suicide when compared to the general population (Chesney et al., 2014). CA also accounts for 67% of the PAR for suicide attempts (Dube et al., 2003), and life expectancy is reduced by 20 years in adults who were exposed to six or more traumatic life events during childhood (Brown et al., 2009). In addition, there is a well-established relationship between CA and other psychiatric disorders such as post-traumatic stress disorder (PTSD), borderline personality disorder (BPD), and schizophrenia in adulthood (Heim and Nemeroff, 2001; Read et al., 2005; Westphal et al., 2013). For instance, from a cohort that reported

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sustained sexual abuse, 39% of the females and 29% of the males subsequently developed PTSD in adulthood (Molnar et al., 2001). Of 57 patients who screened positive for BPD, 83% reported a history of abuse, and although interpersonal trauma during adulthood was as strongly associated with BPD as that experienced during childhood, non-interpersonal trauma was associated with BPD only if it had occurred during childhood (Westphal et al., 2013). Moreover, an in-patient study found that 75% of those who had suffered physical abuse and 76% of those who had suffered sexual abuse during childhood had one or more of the DSM's characteristic symptoms for schizophrenia (Read and Argyle, 1999).

CA constitutes an environmental exposure, the effects of which may be preventable, and as such, developing strategies to intervene and possibly reverse the effects of CA might help reduce the rates of depression and suicide. Developing such strategies requires a deeper understanding of how CA can contribute to higher risks of MDD and suicide, and how CA can affect the brain in general. Brain structure, volume, and integrity have been shown to be compromised by the various types of CA. For example, the thickness and volume of brain regions that receive sensory stimuli from the environment were found to be affected by exposure to parental verbal abuse as well as witnessing interparental violence (Choi et al., 2009, 2012, 2012; Tomoda et al., 2011, 2012). The anterior cingulate cortex (ACC), orbitofrontal cortex, and hippocampus all have reduced volumes in children who have been maltreated (Cohen et al., 2006; Hanson et al., 2010; Opel et al., 2014). In addition, functional connectivity and network changes occur in several brain regions of individuals who experienced maltreatment during childhood, including the prefrontal cortex, ACC, hippocampus, and amygdala (for a review, see Teicher et al., 2016).

Although it is well-known that CA has substantial effects on brain structure, function, and connectivity, the specific molecular mechanisms through which childhood trauma leaves long-lasting marks that persist in adulthood and cause subsequent pathology remain unknown. In this review, we included articles that provide evidence of molecular changes occurring in the brains of individuals with a history of CA, as well as articles that provide supporting evidence from morphometrics, peripheral, and animal model studies (See Table 1 for a summary of studies on the molecular impact of traumatic early life events on the brain). The majority of these studies defined CA as sexual, physical, and/or emotional abuse along with severe emotional and/or physical neglect. We will also discuss some of the limitations of these studies and highlight possible future directions for the field.

2. Critical periods and sensitivity to stress

A key question in the field is how emotionally traumatic early-life events occurring during childhood and adolescence can have long-lasting effects on the adult brain, increasing one's lifetime risk for psychopathology. A plausible explanation is the concept of critical periods of brain plasticity. The central nervous system (CNS) is one of the last organ systems to complete its development postnatally, where it continues to develop throughout childhood, adolescence, and up until the mid-20s or even 30s (Gogtay et al., 2004; Petanjek et al., 2011). Critical periods are periods of heightened brain plasticity during which the brain receives various stimuli from the external environment, that in turn affect the development and refinement of neural circuitry, to allow better adaptation to that environment (Nelson and Gabard-Durnam, 2020). In the case of individuals exposed to CA, their stress-response systems may adapt and establish low thresholds of responsiveness to stress (Shonkoff et al., 2009). On the other hand, the lack of exposure to adequate stimuli (as is the case with neglect) can also have profound effects on neurodevelopment (McLaughlin et al., 2017). "Closure" of critical periods occurs through molecular brakes, including perineuronal nets (Reichelt et al., 2019), after which brain plasticity is significantly reduced, and external stimuli no longer affect the established brain circuitry to the same extent (Takesian and Hensch, 2013). Thus, if the

Table 1
Summary of studies highlighting key genes that are dysregulated in the brain by traumatic early-life events.

	Species	Brain region	Gene/Pathway	Reference
HPA Axis	Human	Hippocampus	*NR3C1*/GR ↓Expression,↑ DNA methylation	McGowan et al. (2009) Takahashi et al. (2018)
	Human	Hippocampus	GR variants 1_B, 1_C, and 1_H ↓Expression	Labonté et al. (2012b)
	Rat	Hippocampus	$GR1_7$ ↑DNA methylation	Weaver et al. (2004)
Myelination	Human	Anterior Cingulate Cortex	*LINGO3* and *POU3F1* ↓DNA methylation	Lutz et al. (2017)
	Human	Ventromedial Prefrontal Cortex	*MASH1* ↑Expression *OLIG2* ↓ Expression	Tanti et al. (2018)
	Rat	Medial Prefrontal Cortex	Hdac1, Hdac2 ↓ Expression ↑ Wnt Signaling	Yang et al. (2017)
	Mouse	Prefrontal Cortex	ErbB3, neuregulin-1 ↓Expression and signaling	Makinodan et al. (2012)
Opioid Signaling	Human	Anterior Insula	KOR ↓Expression,↑ DNA methylation	Lutz et al. (2018)
	Mouse	Amygdala	*Oprl1* Dysregulated expression	Andero et al. (2013)
Growth Factors and Plasticity	Rat	Prefrontal Cortex	*Bdnf* ↓Expression,↑ DNA methylation	Roth et al. (2009)
	Rat	Hippocampus	*Bdnf* ↓Expression,↑ H3K9 methylation	Suri et al. (2013)
	Mouse	Ventral Tegmental Area	*Otx2* ↓Expression,↓ Binding to *Sema3 and Wnt1*	Peña et al. (2017)
Excitatory and Inhibitory Signaling	Rat	Hippocampus	*Gad1* ↓Expression,↑ DNA methylation,↓ H3K9 acetylation	Zhang et al. (2010)
	Rat	Locus Coeruleus Nucleus of Solitary Tract Amygdala	$GABA_A$ receptor ↓ Levels γ2 Subunit ↓Expression	Caldji et al. (2000)
	Rat	Ventral Tegmental Area	*Akap* ↓ Signaling	Authement et al. (2015)
	Rat	Hippocampus	*Grin2a, Grin2b, Grin1* ↑ Expression *mGlur1* ↑ Expression,↓ DNA methylation,↑ H3K9 acetylation,↑ H3K4 methylation	Bagot et al. (2012a) Bagot et al. (2012b)
Monoaminergic Signaling	Rat		β1-adrenergic receptor	Torres-Berrío et al. (2019)

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Table 1 (*continued*)

	Species	Brain region	Gene/Pathway	Reference
		Medial Prefrontal Cortex	Dysregulated signaling	
Genome-Wide Studies	Human	Hippocampus	*ALS2* ↓Expression,↑ DNA methylation	Labonté et al. (2012a)
	Human and Rat	Hippocampus	Protocadherin α, β, and γ gene families ↑DNA methylation	Suderman et al. (2012)
	Human	Hippocampus	rRNA genes ↓Expression,↑ DNA methylation	McGowan et al. (2008)

individual adapts to conditions of high levels of stress, which benefits survival in the short-term, the body's initial programming is maintained and persists throughout life, which might not be favorable in the long run (Nelson and Gabard-Durnam, 2020; Shonkoff et al., 2009). In other words, the adaptations that occurred in the brain during critical periods in response to the exposure to emotionally traumatic events will persist throughout adulthood, and this biological embedding could be the reason why individuals who experienced CA are at higher risk of psychopathology, including depression and suicide.

There are several molecular mechanisms and pathways involved in the regulation of brain development, especially during critical periods, that are affected by CA. For instance, the neurotransmitters serotonin and γ-amino-butyric acid (GABA) modulate several developmental processes, such as neuronal differentiation and migration, as well as synaptogenesis (Sodhi and Sanders-Bush, 2004) and have been implicated in CA (Berens et al., 2017). GABA, the main inhibitory neurotransmitter of the CNS, is essential for the excitatory-inhibitory (E/I) circuit balance that triggers critical period onset and that might be disrupted in CA (Takesian and Hensch, 2013). Brain-derived neurotrophic factor (BDNF) can also modulate brain plasticity in several ways including promoting the maturation of GABAergic neurons and accelerating critical periods (Huang et al., 1999), and its dysregulation upon exposure to early-life stress has also been studied (Berens et al., 2017). Moreover, during critical periods, oligodendrocytes which are responsible for myelination undergo maturation, so any disruption in this process could result in abnormal long-range connectivity in the brain (Marín, 2016). Therefore, CA during critical periods of brain plasticity can alter these pathways along with others, which may result in increased sensitivity to stress later in life. More details regarding the effects of CA on these systems will be discussed later in this review.

3. Epigenetics

One way that environmental factors, such as traumatic events, can alter brain function is through epigenetic changes that may lead to long lasting molecular changes increasing risk for psychiatric disorders such as depression (Sun et al., 2013). Accordingly, epigenetic changes have been shown to be associated with CA. In theory, they can be reversible, dynamically responding to environmental stimuli, and it is this interplay between stability and reversibility that makes epigenetic processes a promising area of study and potentially a source of targets for interventions (Burns et al., 2018). The term "epigenetics" refers to mechanisms that regulate gene expression other than the DNA sequence itself; hence, it is "above the genome" (Felsenfeld, 2014). Epigenetic mechanisms include (but are not restricted to) DNA methylation, histone modifications, and non-coding RNA expression (Dupont et al., 2009). Epigenetic mechanisms are particularly amenable for regulation during critical periods (Takesian and Hensch, 2013).

3.1. DNA methylation

DNA methylation is a well-studied epigenetic mark that consists of covalent modifications to the DNA molecule, resulting in the addition of a methyl group at the 5′ position of cytosine (5 mC) residues. This modification is found in 70% of CpG dinucleotides in a normal genome. However, CpG-rich sites, also known as CpG islands, tend to be over-represented in promoter regions and are usually protected from methylation (Strichman-Almashanu et al., 2002). Methylated CpG islands are often associated with transcriptional repression by recruiting methyl-binding proteins which can alter chromatin architecture or physically interfere with the binding of transcription factors (Dupont et al., 2009). However, 5 mC methylation does not always occur at CpG sites and does not always lead to transcriptional silencing, as DNA methylation is also found within gene bodies, leading to transcriptional activation (Maunakea et al., 2010). Non-CpG methylation, or CpH (H refers to A, C, or T) methylation was shown to be particularly important in neurons and regulates transcripts' expression as well as their splicing events (Price et al., 2019). CpH methylation is also important for neurodevelopment and the epigenetic critical period of the first years of postnatal life, and thus, it might be particularly important in psychiatric disorders (Price et al., 2019). CpH methylation signatures were also found to identify distinct neuronal populations in mouse and human frontal cortex (Luo et al., 2017). The enzymes responsible for DNA methylation are the DNA methyltransferases (DNMT) 1, 3a and 3b. Other forms of DNA methylation exist, such as hydroxymethylation of cytosine residues, which is associated with transcriptional activation and carried out via ten-eleven translocation (TET) methylcytosine deoxygenase enzymes (Richa and Sinha, 2014).

There is evidence suggesting that DNA methylation, particularly post-natal and environmentally acquired DNA methylation, may be dynamic, as it has been shown to play a critical role in fear conditioning, memory consolidation, and synaptic plasticity (Feng et al., 2010; Lubin et al., 2008; Miller and Sweatt, 2007). However, although there is limited data that demonstrates the stability of DNA methylation throughout the lifespan, some studies have shown that DNA methylation is more plastic during the earlier stages of life, and that changes slow down markedly with aging and may persist over time (Flanagan et al., 2015; Lister et al., 2013; Numata et al., 2012; Price et al., 2019; Talens et al., 2010). Therefore, it may be one mechanism through which CA leads to long-lasting changes throughout adulthood.

3.2. Histone modifications

Histones include H2A, H2B, H3, and H4, where two of each form an octamer around which the DNA double helix is wrapped, and H1 which associates with the linker DNA. Among the most characterized are histone modifications of lysine residues on H3 and H4. Methylation of lysine residues may lead to either transcriptional repression as in the case of H3K9, H3K27, and H4K20, or transcriptional activation as in the case of H3K4, H3K36, and H3K79. Methylation can also be monomeric, dimeric, or trimeric, which dictates the effect of the modification on transcription as well (Dupont et al., 2009; Egger et al., 2004). In addition, lysine residues on H3 and H4 can be acetylated, resulting in transcriptional activation. Other histone modifications exist, but methylation and acetylation are the most characterized. The enzymes involved in regulating these marks include histone methyltranferases (HMTs), histone demethylases (HDMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs) (Koch et al., 2007).

3.3. Non-coding RNAs

Non-coding RNAs (ncRNAs) are RNA molecules that do not code for proteins, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and others. The most studied ncRNA, miRNAs, are small

single-stranded molecules of approximately 22 nucleotides (nt) in length, which incorporate into the RNA-induced silencing complex (RISC) (Bartel, 2018). The RISC complex then targets specific sequences predominantly in the 3' UTR of mRNAs through base-pairing with the "seed region" of the miRNA. Translational repression is then achieved by exposing the mRNA for degradation or by creating a physical hindrance for translation initiation (Bartel, 2018). miRNAs may also regulate gene expression at the transcriptional level by targeting transcription factors and in turn affecting the expression of their target genes (Michalak, 2006).

NcRNAs have been extensively described to play a role in brain development (Mehler and Mattick, 2007), and may also be impacted by CA. We will, however, limit our discussion to miRNAs, as they are the most widely studied type of ncRNA. Many miRNAs are enriched in the central nervous system (CNS), and some are even brain-specific (Lagos-Quintana et al., 2002). In addition to their roles in neuronal development and plasticity, miRNAs have also been highly implicated in the stress response, as they are highly responsive to environmental stimuli. The GR, for example, is heavily regulated by miRNAs (Uchida et al., 2008; Vreugdenhil et al., 2009).

Throughout this review, examples of epigenetic alterations as a function of CA will be discussed.

4. Molecular impacts of CA

4.1. HPA axis and early-life adversity

The hypothalamic-pituitary-adrenal (HPA) axis is the major neuroendocrine stress-response system that allows an organism to adapt to changes in their environment for better survival (McEwen, 2004). Exposure to CA has been shown to dysregulate the stress-response by the HPA axis, which in turn, increases the risk of developing mood and anxiety disorders, such as MDD (Van Voorhees and Scarpa, 2004). HPA axis hyperactivity is a consistent phenomenon observed in individuals with MDD (Pariante and Lightman, 2008), and suicide has also been associated with HPA hyperactivity (Coryell and Schlesser, 2001). Thus, there is a clear link in which early traumatic events may cause long lasting hyperactivity of the HPA stress-response, eventually increasing the likelihood of developing MDD and thus conferring a higher risk of suicide. HPA dysregulation has also been identified in other disorders, including PTSD, BPD, and schizophrenia (Cherian et al., 2019; Heim et al., 2008b; Thomas et al., 2019). Numerous studies, some of which are discussed below, have investigated how CA can alter the function of the HPA axis.

The HPA axis consists of the hypothalamus, pituitary gland, and adrenal cortex. Briefly, the paraventricular nucleus secretes corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), which stimulate the pituitary gland to release adrenocorticotrophic hormone (ACTH). ACTH, in turn, stimulates the adrenal cortex to produce and secrete glucocorticoids, such as cortisol. Glucocorticoid (GR) and mineralocorticoid (MR) receptors can be activated by glucocorticoids and regulate HPA activity by activating a negative feedback loop on the hypothalamus. Interestingly, the hippocampus is a primary target for corticosteroids, and it has complex interactions with the HPA axis that involve both positive and negative-feedback effects (Brown et al., 1999). In addition, FK506 binding protein 5 (FKBP5) binds to GR and prevents GR-mediated transcriptional activation by inhibiting its translocation to the nucleus.

Several studies have shown alterations in HPA axis hormones as a result of CA. For example, in response to psychosocial stress, women with a history of CA exhibit higher circulating levels of ACTH (Heim et al., 2008b). Adults with a history of CA presented with elevated levels of CRF in cerebrospinal fluid (Heim et al., 2008b; Lee et al., 2005). Furthermore, using a test that measures HPA axis hyperactivity, ACTH and cortisol blood levels were increased specifically in men with a history of CA and an MDD diagnosis compared to men with MDD and no history of abuse, as well as to controls (Heim et al., 2008a).

There have also been several studies that demonstrate how CA directly affects HPA regulation through epigenetic modifications to key HPA axis genes. Our group was first to show that individuals who died by suicide with a history of CA show decreased hippocampal mRNA expression of the neuron-specific GR (*NR3C1*), as well as mRNA transcripts bearing the GR 1_F splice variant (McGowan et al., 2009). These alterations in expression may be due in part to hypermethylation of the *NR3C1* promoter and reduced binding of nerve growth factor induced clone A (NGFI-A) transcription factor (McGowan et al., 2009). In post-mortem hippocampal tissue of children exposed to severe physical abuse, hypermethylation was also observed in the 1_F promoter region of the *NR3C1* gene (Takahashi et al., 2018). Additionally, our group revealed that hippocampal expression of other GR variants 1_B, 1_C, and 1_H was also decreased in individuals who died by suicide with-versus those without a history of CA and controls (Labonté et al., 2012b). Site-specific methylation in promoter sequences of the 1_B and 1_C variants was negatively correlated with total GR as well as $GR1_B$ and $GR1_C$ mRNA expression (Labonté et al., 2012b). However, methylation at the 1_H promoter positively correlated with GR expression. These findings further support the notion that CA can alter DNA methylation patterns in GR promoters, leading to altered GR expression in the hippocampus (Labonté et al., 2012b). Findings from other studies, conducted in both animals and humans, have been mostly consistent with the aforementioned findings (Turecki and Meaney, 2016). Interestingly, in a different study, hippocampal $GR1_F$ expression was reduced in MDD subjects, but this was not in the exon 1_F promoter region, which could suggest that the molecular mechanisms regulating $GR1_F$ expression in CA and MDD are different and that these two phenotypes are similar yet with different molecular underpinnings (Alt et al., 2010). In addition, a functional polymorphism in the *FKBP5* gene was found to be associated with childhood trauma-dependent DNA hypomethylation in individuals with PTSD and depressed mood (Klengel et al., 2013). This study suggested that hypomethylation in risk allele carriers is associated with increased expression of *FKBP5* by GR activation, which enhances the negative-feedback loop and increases glucocorticoid resistance (Klengel et al., 2013). This effect is consistent with the observation of decreased hippocampal GR expression in individuals with a history of CA. Furthermore, although this was a peripheral study, morphological changes in the brain were associated with the hypomethylation, which shows that there could be a link between peripheral methylation changes in HPA axis genes and effects in the CNS (Klengel et al., 2013). Another peripheral study found hypermethylation in the *NR3C1* gene in peripheral samples from adolescents exposed to stress (Van Der Knaap et al., 2014). Cumulatively, these studies show that CA can result in epigenetic alterations to the HPA axis through altered gene expression, which in turn affects responsiveness to stress as well as susceptibility to psychopathology.

Histone modifications in HPA axis genes also associate with CA, although studies investigating this relationship have only been performed in animal models so far. One well known animal model, albeit not of CA but rather of natural variation of early-life environment, is that of the maternal care in rats in which the frequency of licking/grooming (LG) of pups by their mother varies. This natural variation in maternal care affects HPA responsiveness to stress in adulthood (Anacker et al., 2014). In fact, hypermethylation was detected at the exon 1_7 GR promoter (ortholog of 1_F GR in humans) in the hippocampus of pups receiving low LG compared to those of high LG (Weaver et al., 2004), which is in agreement with human findings of decreased hippocampal $GR1_F$ expression (McGowan et al., 2009). Early experiences and maternal care also result in histone modifications. Increased levels of H3K9 acetylation as well as H3K4 trimethylation at the 1_7 GR promoter were found in the hippocampi of pups receiving high levels of maternal care, and these levels were positively correlated to each other and to transcriptional activation (Zhang et al., 2013). Whether CA induces histone modifications in HPA axis genes in the human brain remains to

be deciphered and is open to further investigation.

4.2. Myelination

As mentioned earlier, myelination is an important process during critical periods of brain development, as it plays a role in halting critical periods (Hensch, 2005), and thus any disruption may cause malfunctions in brain circuitry, potentially leading to psychopathology. A study conducted by our group used post-mortem human brain samples from depressed individuals who died by suicide with CA versus those without a history of CA, as well as controls, to investigate possible effects of CA on myelination (Lutz et al., 2017). Using a genome-wide approach followed by cell type-specific validation, we showed that cell type-specific changes in DNA methylation of oligodendrocyte genes are associated with a history of CA, leading to a global impairment in the myelin-related transcriptional programs. For instance, the leucine rich repeat and Ig domain containing 3 (*LINGO3*) and POU class 3 homeobox 1 (*POU3F1*) were characterized with decreased DNA methylation in oligodendrocyte lineage cells. *LINGO3* is a member of the LINGO family of proteins which are implicated in myelination by oligodendrocytes (Mi et al., 2005), and *POU3F1* expression is critical for proper myelination (Ryu et al., 2007). Thinner myelin sheaths were also observed around small-diameter axons in individuals with a history of CA. These changes were not found in individuals who died by suicide without a history of CA (Lutz et al., 2017). Another study showed that CA might result in a bias of oligodendrocyte-lineage cells toward a more mature phenotype in the ventromedial prefrontal white matter, which also might cause long-term connectivity changes within the fromto-limbic network (Tanti et al., 2018). Alterations in the expression of oligodendrocyte transcription factor 2 (*OLIG2*), and mammalian achaete scute homolog-1 (*MASH1*), two transcription factors involved in oligodendrocyte-lineage differentiation, were also reported (Tanti et al., 2018).

Imaging studies have shown effects of different forms of CA on myelination and white matter integrity. For instance, early life neglect has been associated with the microstructural integrity of the corpus callosum body as well as tracts involved in limbic and sensory circuitry in institutionally reared children (Bick et al., 2015). Observing domestic violence has been associated with diminished myelination in a key fibre tract that connected the visual and limbic systems (Choi et al., 2012). Moreover, adolescents that were exposed to CA and subsequently developed MDD or substance use disorder exhibited altered white matter integrity in the right cingulum-hippocampal projection, showing that disruptions in white matter might increase vulnerability to psychopathology such as depressive and substance use disorders (Huang et al., 2012). Dysregulation of gene expression in oligodendrocytes is likely to be the main cause of such morphological abnormalities, which would further suggest the impact CA may have on the brain.

Animal models also provide evidence that early-life adversity (ELA) may affect myelination and oligodendrocyte regulation and in turn have long-lasting effects. Maternal separation (MS), a rat model of neglect, has previously been shown to affect myelination in the medial prefrontal cortex through decreased HDAC1 and HDAC2 expression across the lifespan, altered Wnt signaling, and impaired oligodendrocyte development (Yang et al., 2017). A different study showed that social isolation of mice reduces oligodendrocyte expression of ErbB3 receptors and their ligand neuregulin-1, impairing neuregulin-1/ErbB3 signaling and prefrontal cortex function and myelination (Makinodan et al., 2012). Although other studies have found that myelination, Wnt signaling, and neuregulin signaling may be transiently altered in response to acute stress exposure (Cathomas et al., 2019; Chen et al., 2017; Maguschak and Ressler, 2011; Pan et al., 2020), it has been shown that ELA in animals can lead to molecular changes in pathways that are similar to those altered in post-mortem human brain samples of individuals with a history of CA (Weaver et al., 2004). These rodent studies use maternal separation or early social isolation, followed by molecular analyses in adulthood. In these studies, all variables are controlled between groups except for the distal exposure to ELA.

Collectively, these studies provide evidence that CA can affect myelination in the brain at the structural, functional, and molecular level, and these effects can persist throughout adulthood.

4.3. Opioid signaling

Opioids are considered critical period modulators through their action on opioid receptors in the CNS (Nelson and Gabard-Durnam, 2020), and they are also tightly related to stress responses (Lutz et al., 2018). Our group found that the kappa opioid receptor (KOR) was downregulated in the anterior insula of individuals who had a history of CA. Specifically, there was decreased methylation in the second intron of the *KOR* gene, which acts as a genomic enhancer that the glucocorticoid receptor can bind to and thus regulate KOR expression (Lutz et al., 2018). Selective reduction in the DNA hydroxymethylation levels within this intron associated with CA, providing further evidence of epigenetic alterations caused by CA (Lutz et al., 2018).

Animal studies have also implicated the opioid system in stress. The expression of the opioid receptor-like 1 (*Oprl1*) gene was found to be altered in the amygdala of mice that were exposed to a behavioral paradigm that induces PTSD-like behavior in mice. Activating the receptor encoded by this gene impaired fear memory consolidation (Andero et al., 2013). Interestingly, a single nucleotide polymorphism (SNP) rs6010719 within this gene in humans was associated with a self-reported history of CA and PTSD. This SNP also associated with amygdala-insula functional connectivity (Andero et al., 2013).

4.4. Growth factors and plasticity

BDNF is a well-known regulator of brain plasticity and critical periods (Hensch, 2005) and has also been extensively studied in the context of stress responses and depression in both humans and animal models (Castrén and Rantamäki, 2010; Kang et al., 2013; Keller et al., 2010). The Val66Met variant of the *BDNF* gene has been implicated in the gene-environment interaction, whereby individuals with this polymorphism are more susceptible to negative outcomes as a result of CA (Chen et al., 2006, 2008; Gatt et al., 2009). In one study, this polymorphism modified the risk of depression as a function of CA (Kaufman et al., 2006). It has been shown that adult carriers of the Val66Met polymorphism with depression had reduced serum BDNF levels when exposed to CA, and those with higher levels of trauma had lower BDNF mRNA levels (Aas et al., 2014; Elzinga et al., 2011). However, there have been inconsistent results regarding the association between the Val66Met polymorphism and CA, and this might be due to several factors, such as age, sex, and ethnicity (Tsai, 2018). One study showed that in one sample, Val allele carriers with CA were more vulnerable to psychotic experiences, while the same was true for Met allele carriers with CA in another sample (de Castro-Catala et al., 2016).

Epigenetic alterations in BDNF expression as a function of CA have been identified, as the methylation status of *BDNF* CpG exons I and IV in plasma was found to be positively correlated with the frequency of CA events in subjects with BPD (Perroud et al., 2013).

Although studies of the *BDNF* gene-CA interactions in humans are limited to peripheral studies, there are several animal studies that provide evidence of such interactions in the brain. For instance, in the prefrontal cortex of adult rats that were exposed to stressed caregivers during infancy, changes in *Bdnf* DNA methylation and Bdnf expression were detected (Roth et al., 2009). Furthermore, hippocampal H3K9 di-methylation at the *Bdnf* IV promoter was increased, followed by decreased hippocampal Bdnf expression in adult rats that were exposed to early stress (Suri et al., 2013). Therefore, these studies show that BDNF is another key factor that is affected by CA, with effects lasting throughout adulthood. Post-mortem human brain studies aimed at investigating CA associated epigenetic regulation of *BDNF* expression

are needed to complement current findings from the periphery.

The orthodenticle homeobox 2 (OTX2) gene is another gene that has been found to be relevant to CA. OTX2 is involved in brain plasticity and critical period regulation and onset, especially through its tight link with parvalbumin (PV) cells and perineuronal nets (Takesian and Hensch, 2013). In a rodent model, juvenile and not adulthood knockdown of *Otx2* in the ventral tegmental area (VTA) was found to increase stress susceptibility and mimic ELA, while its overexpression reversed the effects of early stress (Peña et al., 2017). Reduced expression of Otx2 was associated with reduced binding to genes involved in VTA development, such as *Sema3* and *Wnt1*, indicating that ELA can cause lifelong disturbances of transcriptional programming in the VTA by acting on OTX2 (Peña et al., 2017). In a subsequent human study, in which DNA samples from maltreated children were collected from saliva, a genome-wide DNA methylation assay revealed a hypermethylation in the *OTX2* gene in maltreated children (Kaufman et al., 2018). *OTX2* methylation and maltreatment history predicted depression in the children, and the methylation was associated with increased functional connectivity between key brain structures implicated in depression (Kaufman et al., 2018).

4.5. Excitatory and inhibitory signaling

GABAergic neurons play an essential role in the timing of critical periods, as their onset seems to be regulated by GABAergic maturation. Enhancing GABA transmission and tonic GABA release can bring forward critical periods and trigger an eventual closure of the brain plastic state (Hensch, 2005). GABAergic neurons are also involved in the assembly of neuronal circuits during critical periods (Marín, 2016). Moreover, perineuronal nets (PNNs) have heightened affinity to PV-expressing GABAergic interneurons, and PNN formation and condensation is thought to coincide with the closure of critical periods (Reichelt et al., 2019). New evidence suggests that CA might be associated with increased recruitment and maturation of PNNs in human ventromedial prefrontal cortex as well as with upregulated expression of canonical components of PNNs in oligodendrocyte progenitor cells (Tanti et al., 2020). Despite these findings, it has been demonstrated that PNNs may also be dynamically regulated in adulthood, in processes such as learning and memory formation (Banerjee et al., 2017; Carulli et al., 2020). Nonetheless, GABA transmission is a good candidate mediator of CA effects on the brain and subsequent psychiatric disorders.

In a post-mortem human brain study, different subunits of the $GABA_A$ receptor were reduced in the frontopolar region of individuals who died by suicide. The study also found that the subunits' expression in cortical regions is highly correlated, but this correlation is lost in those who died by suicide (Merali et al., 2004). The authors suggested that this disturbed coordination between subunits might contribute to depression and/or suicidality (Merali et al., 2004). A subsequent study reported increased methylation in the $GABA_A$ receptor α1 subunit promoter region in the frontopolar cortex of suicides, which might explain the reduced expression of this subunit (Poulter et al., 2008). Additionally, somatostatin, an inhibitory neuropeptide localized to a subset of GABAergic neurons, exhibits downregulated mRNA expression in the dorsolateral prefrontal cortex, subgenual anterior cingulate cortex, and the lateral and basomedial nuclei of the amygdala in MDD, which further suggests that GABAergic function might be altered in depression (Guilloux et al., 2012; Sibille et al., 2011; Tripp et al., 2011). Although the subjects' history of trauma was not assessed in these studies, it is still an interesting observation given the high frequency of CA among individuals with depression and/or who died by suicide.

Animal studies have also shown direct involvement of GABA transmission in the mediation of effects of the early environment. Hippocampal glutamic acid decarboxylase 1 (Gad1), the enzyme involved in GABA synthesis, of rats reared by high-LG dams displayed higher expression, decreased cytosine methylation, and increased H3K9 acetylation at the *Gad1* promoter when compared to those of low-LG dams (Zhang et al., 2010). The latter was associated with increased binding of NGFI-A at the promoter (Zhang et al., 2010). These results suggest that maternal care influences epigenetic regulation of the GABA system, and that natural variations in maternal care might disrupt the development of this system. Animals that were not handled or that were exposed to maternal separation exhibited reduced $GABA_A$ receptor expression in the locus coeruleus and the nucleus of the solitary tract, along with reduced levels of the γ2 subunit of the receptor in the same brain regions as well as in the central and lateral nuclei of the amygdala (Caldji et al., 2000). This was accompanied with altered response to various forms of stress in adulthood, further validating how early-life stress can disrupt the GABAergic system with long-lasting effects in adulthood (Caldji et al., 2000). Furthermore, maternal separation disrupted GABAergic synapses onto the VTA dopamine (DA) neurons, an effect that was reversed by an HDAC inhibitor that normalized the expression levels of A-kinase anchoring protein 150 (known to regulate $GABA_A$ receptor trafficking in VTA DA neurons) (Authement et al., 2015).

Interestingly, there is evidence of concordant changes in GABAergic regulation and the GR system in animals during stress. For instance, one study in which mice who were exposed to chronic early-life stress and then to acute-swim stress in adulthood showed that GR-binding genes and GABA-related genes exhibited similar patterns of response to stress (Marrocco et al., 2019). Another study demonstrated that dexamethasone, a synthetic glucocorticoid, increases GABA release, $GABA_A$ receptor responsiveness, and GABAergic neuron excitability in the amygdala, showing a link between the stress response and GABAergic signaling (Wang et al., 2016). Interestingly, glucocorticoids affect mRNA expression levels for hippocampal $GABA_A$ receptors (McEwen, 2000). Since there are concordant GR and GABAergic alterations in mice exposed to ELA, and since GR dysregulation is also established in humans with a history of CA, it is feasible to hypothesize that similar GABAergic dysregulation might be induced by CA in the human brain.

Glutamatergic pathways have also been implicated in MDD pathogenesis and more recently, targeted for rapid-acting treatment (Mathews et al., 2012; Sequeira et al., 2009), but only a few studies have examined the effect of CA on glutamatergic signaling. In a peripheral study in humans, saliva was collected from individuals with or without a history of CA and either with or without depression. The methylation status of the ionotropic glutamate receptor NMDA type subunit 2B (*GRIN2B*) gene was determined in these samples, and the study revealed that CA was associated with increased methylation of *GRIN2B* in adulthood, indicating possible glutamatergic disruption induced by early stress (Engdahl et al., 2020). Animal studies also suggest alterations in glutamatergic signaling as a function of early-life environmental variation, as low-LG offspring exhibited increased expression of Grin2A, Grin2B, and Grin1 in the hippocampus (Bagot et al., 2012a), while another study by the same group showed increased type I metabotropic glutamate receptor (*mGluR1*) mRNA and protein expression in the hippocampus of high-LG offspring (Bagot et al., 2012b). The study also showed decreased DNA methylation, increased H3K9 acetylation, and increased H3K4 trimethylation at the same locus, associating with positive transcription (Bagot et al., 2012b).

4.6. Monoaminergic signaling

Serotonergic dysfunction is well known for its involvement in MDD, as selective serotonin reuptake inhibitors (SSRIs) are one of the first-line antidepressant drugs used in the treatment of MDD. The serotonergic system displays several changes that are associated with depression and suicide (Celada et al., 2013), such as decreased serotonin transporter (presynaptic) and increased serotonin receptor (postsynaptic) binding sites (Arango et al., 1995). Serotonin (5-HT) is known to be involved in developmental processes, including critical periods of brain plasticity, as fluoxetine (an SSRI) can restore plasticity in the adult visual cortex (Vetencourt, 1991). SSRIs can also accelerate fetuses' perceptual development (Weikum et al., 2012). Several studies have shown how the

serotonergic system interacts with components of the HPA axis. For instance, one study provided direct evidence that CRF innervates serotonergic neurons in the midline raphe (Ruggiero et al., 1999). This suggests that 5-HT could be involved in the stress response and is linked to the HPA axis, which substantiates its relevance to CA. An extensively studied polymorphism (5-HTTLPR) in the serotonin transporter *SLC6A4* gene was also linked to HPA hyperactivity after early deprivation in non-human primates (Barr et al., 2004), and this polymorphism was found to strongly moderate the relationship between depression and stress (Karg et al., 2011). Hypermethylation of the GR promoter (and related genes) was induced by altered 5-HT signaling in rats exposed to less favorable maternal care (Meaney and Szyf, 2005), which is consistent with the hypermethylation of the GR promoter that has also been reported in humans with a history of CA (McGowan et al., 2009).

Apart from its link with the HPA axis, 5-HT has been extensively studied in the context of CA. Indeed, the 5-HTTLPR polymorphism mentioned above was found to interact with early family environment, and individuals with the low expressing variant showed greater depressive symptomatology if they had experienced early adversity (Caspi et al., 2003; Taylor et al., 2006). Although this effect has been replicated in a few studies (Kaufman et al., 2004; Kendler et al., 2005), findings have not always been consistent (Culverhouse et al., 2018). In addition, a different polymorphism in the promoter of the monoamine oxidase A (*MAOA*) gene, which is involved in 5-HT degradation, was also found to mediate the association between CA and antisocial behavior in adulthood (Caspi et al., 2002). Of interest, a recent finding from our group indicates that individuals who died by suicide present differential methylation in the promoter region of a locus that codes for MAALIN, a long non-coding RNA. This transcript, which is lowly abundant and primarily expressed in the nucleus, is increased in individuals who died by suicide, negatively regulates the expression of MAOA, and increases latency to attack, a measure of impulsive-aggressive behavior in animals (Labonté et al., 2020).

Epigenetic changes in the 5-HT system have also been investigated in human peripheral samples. CA was found to be associated with peripheral 5-HT transporter methylation in adulthood (Booij et al., 2015; for a review, see Provenzi et al., 2016). For instance, sexual abuse during childhood significantly increased methylation at the *SLC6A4* promoter in lymphoblasts of female adults, and this methylation had a significant effect on symptoms of antisocial personality disorder (Beach et al., 2011). Another interesting study revealed increased *SLC6A4* DNA methylation in T cells and monocytes in males who had high aggression and antisocial behavior during childhood, which is associated with CA, and the methylation was negatively correlated with in vivo levels of serotonin in the orbitofrontal cortex (Wang et al., 2012). It remains to be determined whether similar epigenetic effects occur in the brain of individuals who were exposed to CA.

Although less studied, the adrenergic system might be another system affected by CA. In a study employing guanfacine, which is an α_{2A}-adrenorecoptor agonist, therapeutic effects were demonstrated in children and adolescents with a history of traumatic stress and with symptoms of PTSD (Connor et al., 2013), suggesting that adrenergic dysregulation might be yet another candidate that is affected by CA. In rats, rewarding maternal contact induced β_1-adrenergic receptor gene hypomethylation, enhancing noradrenergic signaling in the medial prefrontal cortex of adult rats (Torres-Berrío et al., 2019), which is another example of long-term effects of early experience in the adult brain.

4.7. Genome-wide studies

In addition to the systems mentioned above, several studies have shed light on other possible molecular outcomes of CA. Epigenome and transcriptome-wide studies are crucial for the identification of novel gene candidates that may be impacted by CA. Labonté et al. (2012a) conducted a study using hippocampal tissue from individuals with a history of severe CA and who died by suicide, with the aim of investigating genome-wide promoter methylation alterations induced by CA. Results showed that 248 promoters were hypermethylated, while 114 promoters were hypomethylated (Labonté et al., 2012a). Later validation indicated that the main differences occurred in neuronal fractions, and the most significantly differentially methylated genes were involved in neuronal plasticity. In particular, the gene Alsin (*ALS2*), which is a GTPase activator, was the most significant finding (Labonté et al., 2012a). A later study that employed a genome-wide DNA methylation approach, while also probing for different histone modifications in the human amygdala identified that CA associates with methylation changes equally in CAC and CpG sites, and that small GTPases and immune system processes are critical pathways associated with CA (Lutz et al., 2021). Moreover, a cross-species investigation was performed to compare the hippocampal DNA methylation profile of the 6.5 million base pair region centered at *NR3C1* in humans to the analogous region in rats. ELA associated with DNA methylation differences that clustered by genomic location in both species, and these differences seemed to target gene promoters, specifically those of protocadherin α, β, and γ gene families (Suderman et al., 2012).

Aberrant regulation of the protein synthesis machinery was identified in the hippocampus of individuals who had a history of CA or severe neglect and who died by suicide (McGowan et al., 2008). Hypermethylation was detected in the promoter and 5' regulatory region of the ribosomal RNA (rRNA) genes, consistent with reduced rRNA expression in the hippocampus (McGowan et al., 2008).

Telomere length has been associated with early life adversity in children that experienced severe social deprivation during institutionalization. For instance, one study found that children who were institutionalized for longer periods had shorter relative telomere length in middle childhood (6–10 years old) (Drury et al., 2012). The authors suggest that these results may support the hypothesis that CA can impact health outcomes through altering cellular aging (Drury et al., 2012).

Human studies that link miRNA dysregulation with CA are not numerous, but there are a few studies that shed light on the importance of further investigating this molecular species. In a study that used blood samples from participants with or without a history of CA, microarray analysis revealed 80 miRNAs that were differentially expressed between the two groups (Cattane et al., 2019). For example, miR-29b-3p, miR-29c-3p, and miR-16-5p were upregulated, while miR-200b-5p and miR-125b-1-3p were downregulated (Cattane et al., 2019). Some of the most significant pathways altered in association with CA and targeted by the differentially expressed miRNAs were those involved in neurodevelopment, GABAergic synapses, axon guidance, and glutamatergic synapses. The study also found that miR-125b-1-3p was downregulated in patients with schizophrenia who self-reported CA when compared to patients without CA (Cattane et al., 2019). Since miRNAs themselves can be epigenetically regulated, another study examined DNA methylation changes in blood of individuals who experienced CA. 31 miRNAs had hypermethylation in their promoters which was associated with abuse, and the target genes of 6 of these miRNAs (miR-514, let-7d, miR-520c, miR-215, miR-519a, and miR-519e) exhibited promoter hypomethylation in abused subjects (Suderman et al., 2014). In addition, a study using blood leukocytes identified that methylation in the promoter region of miR-124-3p was associated with severity of childhood trauma in individuals with BPD (Prados et al., 2015). MiR-124-3p targets several genes that are thought to play a role in BPD, including *NR3C1* (Prados et al., 2015).

Although numerous studies using animal models have highlighted dysregulation of miRNA as a function of early-life adversity, human studies are limited to the periphery. Post-mortem human brain tissue studies should be conducted as they help provide a snapshot of central processes dysregulated in CA.

4.8. Discussion: the bigger picture

With the current state of the literature, it is clear that there are many different avenues that need to be explored before we can fully understand the molecular impacts of CA. However, the knowledge gathered so far allows us to assemble some pieces of the puzzle. The first piece revolves around the importance of critical periods of brain plasticity, during which CA can have deleterious effects. Many of the pathways and factors that regulate the onset and timing of critical periods have been found to be affected by CA. Most evidence, despite some inconsistencies, point toward a decrease in BDNF levels in individuals exposed to CA and in animals exposed to ELA (Aas et al., 2014; Chen et al., 2006, 2008; Elzinga et al., 2011; Gatt et al., 2009; Kaufman et al., 2006; Perroud et al., 2013; Roth et al., 2009; Suri et al., 2013). BDNF plays an important role in the regulation of the maturation of GABAergic neurons, a process that determines the onset of critical periods (Takesian and Hensch, 2013). The reduction of GABAergic signaling in animals exposed to ELA may be due in part to alterations in BDNF signaling (Authement et al., 2015; Caldji et al., 2000; Zhang et al., 2010). Future research is needed to clarify the link between CA, BDNF, GABAergic signaling, and critical periods in humans. Interestingly, OTX2 has also been shown to regulate the maturation of PV-expressing GABAergic interneurons and affect the onset of critical periods (Sugiyama et al., 2008). As mentioned previously, OTX2 also seems to be reduced as a function of ELA (Kaufman et al., 2018; Peña et al., 2017). In addition, myelination, which is considered a "molecular brake" that induces closure of critical periods (Nelson and Gabard-Durnam, 2020), has been found to be reduced in individuals exposed to CA (Bick et al., 2015; Choi et al., 2012; Huang et al., 2012; Lutz et al., 2017). On the other hand, CA has also been shown to associate with a more mature phenotype in oligodendrocyte-lineage cells, however, myelin content was still found to be reduced in this investigation (Tanti et al., 2018). Finally, other factors affected by CA, such as serotonergic, glutamatergic, and opioid signaling have also been implicated in the regulation of critical periods (Hensch, 2005; Nelson and Gabard-Durnam, 2020). Collectively, the impacts that CA has on each of these molecular pathways may converge to influence the timing, onset, duration, and/or closure of critical periods.

Another link between the pathways affected by CA is through their regulation of the HPA axis. The hyperactivity of the HPA axis, observed in depression, suicide, and CA, may be due in part to elevated levels of the stress hormones ACTH, CRF, and cortisol (Heim et al., 2008a, 2008b). Reduced negative feedback, as well as GR resistance, has also been shown to consistently associate with CA (Klengel et al., 2013; McGowan et al., 2009). Interestingly, some studies have provided evidence that myelination might be linked to HPA activity. Oligodendrocyte-lineage cells express glucocorticoid receptors, where glucocorticoids regulate certain stages in their development (Chetty et al., 2014; Matsusue et al., 2014). In a non-human primate model of infant maltreatment, impaired white matter integrity was correlated with plasma cortisol levels (Howell et al., 2013). The HPA axis has also been implicated in multiple sclerosis and the occurrence of comorbid mood disorders (Melief et al., 2013). Moreover, in Fkbp5 knockout mice, myelination was reduced in the cortex and corpus callosum, indicating that increased expression of Fkbp5 might enhance myelination (Choi et al., 2021). Concordantly, an FKBP5 SNP that confers increased FKBP5 expression has been found in individuals with PTSD and depressed mood with a history of CA (Klengel et al., 2013). There have also been several studies that show a link between BDNF and HPA axis activity (Alexander et al., 2010; Kunugi et al., 2010). As mentioned earlier, this is true for GABAergic signaling as well, where both GABA-related and GR-regulated genes were reduced in response to stress (Marrocco et al., 2019), and these results are consistent with what has been found previously in relation to CA. In terms of serotonergic signaling, although there is a well-known link between 5-HT and HPA axis activity, the findings seem to be less consistent. In many instances, elevated levels of 5-HT signaling have been associated with stress and CA, whereas reduced 5-HT has been linked to reduced GR in animals receiving low LG (Meaney and Szyf, 2005), and it is reduced GR that is associated with CA. Other pathways that have been found to be affected by CA are also implicated in HPA axis regulation, including glutamatergic signaling (Evanson and Herman, 2015), adrenergic signaling (Bugajski et al., 1995), and opioidergic signaling (Fountas et al., 2018). Altogether, the aforementioned work is suggestive of CA impacting molecular pathways that converge on similar biological functions, collectively increasing the vulnerability to mental disorders (Fig. 1).

5. Limitations

Despite the fact that the studies discussed above, along with many others, helped us gain some insight into molecular mechanisms that might be implicated in CA, these studies are not without limitations. One frequent limitation found in studies that investigate the impact of CA is that of the experimental designs used. First, some studies used relatively small sample sizes, thus decreasing statistical power to detect significant results. Second, identifying CA based on self-reports is limited, as recall biases are thought to play a role (Maughan and Rutter, 1997), where some subjects may have difficulty recalling negative events, may prefer not disclosing certain events, may not be aware that certain events are classified as CA, or may recall certain events and not others based on their mood state (Hardt and Rutter, 2004). For example, depressed patients tend to over-report negative events (Jorm and Henderson, 1992). Third, most of the studies follow a cross-sectional design, which poses a problem in determining causality. The temporal relationship between molecular changes and the onset of psychopathology is unclear; thus, whether the molecular changes were induced by CA or by the psychopathology itself is difficult to disentangle in this type of design. Forth, even if the study design is longitudinal, which can clarify the temporal order of effects, such designs usually employ peripheral tissue to study molecular and epigenetic alterations. The extent to which molecular dysregulation in peripheral samples, such as blood and saliva, are reflective of the actual state within the brain remains to be investigated.

Another frequent limitation is confounding factors. In studies that examine effects of specific types of CA and not others, such as focusing on sexual abuse for example, it would be difficult to claim that the effects observed are due to sexual abuse alone, as it is possible that other forms of adversity were experienced but not accounted for. On the contrary, in studies that define CA in general terms, the specific effects of each type of adversity might be lost, for it is also possible that different types of trauma can have different biological consequences. It is worth

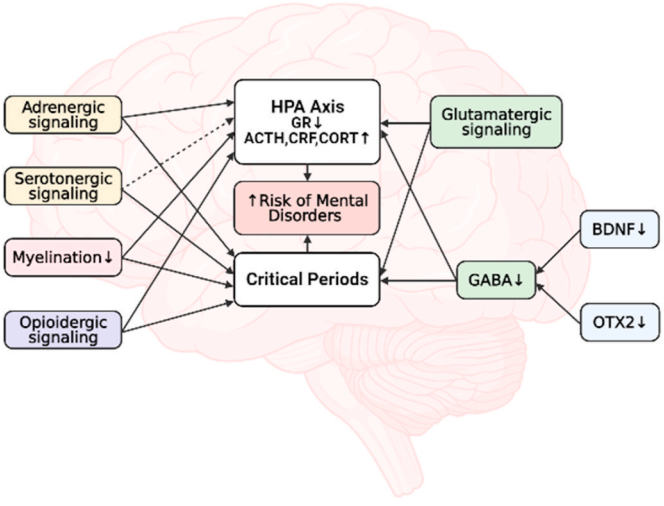

Fig. 1. Converging molecular pathways through which CA increases susceptibility to mental disorders in adulthood (Created with BioRender.com).

mentioning that while most studies examining the effects of CA define it as sexual, physical, and/or emotional abuse, and physical and/or emotional neglect, other forms of childhood adversity exist. Some examples include caregiver psychopathology, exposures to crime and discrimination, as well as bullying. It is thus important to distinguish between abuse and adversity when defining inclusion criteria for studies, as this will enhance the replicability of the findings and the soundness of interpretations. Underlying psychiatric disorders may also be a confounding factor. Subjects from large community studies may have mental illnesses that have been either undetected or undiagnosed. Dissecting whether an observed effect is due to CA *per se* or whether the psychiatric diagnosis also mediates the effect can be challenging as well. This is especially relevant in post-mortem studies where attributing molecular findings to distal factors such as CA or proximal factors such as depression may be difficult. However, some post-mortem studies employ experimental designs that allow the differentiation between the effect of CA and the immediate effect of underlying psychiatric disorders. Moreover, medication and substance use history, both of which can alter molecular regulation in the periphery and brain, can confound the obtained results.

Lastly, there are limitations in how results are often interpreted. First, generalizing the findings of a sample to the population may not always be plausible, as some studies employ stringent inclusion/exclusion criteria to select their subjects. Population stratification might also cause certain findings to be applicable only to a specific population and not to humans in general. Epigenetic alterations that are found to be associated with CA might not actually be a long-lasting effect of CA, as epigenetic processes can be dynamic. This is a major problem with studying post-mortem brain tissue which only provides a snapshot of the brain near the time of death (Burns et al., 2018). In addition, different cell types may be affected by CA differently, so the analysis of bulk tissue may mask epigenetic alterations occurring in specific cell types, which may be crucial for the pathogenesis of the psychopathology.

Despite the limitations surrounding studies that aim to identify the molecular basis through which CA could mediate the development of psychopathology, such as depression and suicide, many efforts are being made to enhance our understanding. Although some individuals who are exposed to CA are resilient to later-life psychopathology, devising helpful intervention methods for those who were abused as children and that develop mental illnesses later on is essential for facing the disabling burden that CA creates on society.

6. Future directions: the promise of extracellular vesicles

Emerging technological advancements will allow investigators to conduct research in the field of childhood trauma with more precision. Using bulk tissue analyses may mask the specific molecular changes occurring in different cell types, and it is likely that neurons, astrocytes, oligodendrocytes, and microglia respond to stressors in a different manner. Refining the molecular alterations detected and assigning them to a single cell type are crucial to better understand the molecular impacts of CA on the brain. This will also help better define a target for developing effective treatment and prevention measures. Single cell or single cell-type technologies, which are increasingly being employed to study psychiatric disorders and CA, offer a solution to the problem posed by using bulk brain tissue homogenates.

Another important limitation, as mentioned earlier, in human studies is the use of peripheral tissue, as the relevance of the findings to what actually takes place in the brain and is the cause of the psychopathology is not clear. Extracellular vesicles (EVs) are a good candidate to solve this problem. EVs carry cargo from their cell of origin, and they are thus a partial reflection of the state and nature of that cell. EVs have been found in various body fluids, such as blood, urine, saliva, breast milk, semen, and cerebrospinal fluid (CSF) (Colombo et al., 2014). Moreover, EVs are released from all the different brain cell types (Zhang and Yang, 2018) and cross the blood-brain barrier (Alvarez-Erviti et al., 2011; Zhuang et al., 2011), so it is thus plausible that brain-derived EVs circulate in peripheral blood. Enriching neuron-derived EVs from blood is an already implemented technique (Hornung et al., 2020) and could provide a direct link between the CNS and peripheral findings.

The question that remains is whether EVs can reflect a long-lasting molecular change that was initiated in childhood as a result of trauma and that persists until adulthood. Given the evidence discussed in this review and elsewhere (Burns et al., 2018; Lutz et al., 2015; McGowan and Roth, 2015) that CA can have long-lasting effects on epigenetic gene expression, whether the product of this gene is a protein or miRNA, and because the composition of EVs depends on the cell of origin, it is possible that the dysregulation of a gene product can be reflected in the produced EVs that are sent from the brain to the periphery. In that way, investigating brain-derived blood EVs from adult subjects who were exposed to CA and comparing them to those individuals without a history of CA could provide another layer of information that has been overlooked previously. It may also help refine the findings by looking specifically at peripheral markers that we know originated from the brain rather than other organs. Finally, performing such studies may help identify potential biomarkers that would have predictive value and be used to initiate immediate intervention methods to prevent subsequent psychopathology.

In conclusion, we might still be looking at perfunctory evidence when it comes to the molecular impact early life adversity may have on the brain and how it may predispose individuals to devastating outcomes such as depression and suicide. With some of the emerging new techniques discussed above, we will be better equipped to identify alterations that have been masked before and that will likely be essential for therapeutic developments and prevention measures.

CRediT authorship contribution statement

Pascal Ibrahim: Writing – original draft, preparation, Writing – review & editing. **Daniel Almeida:** Writing – review & editing. **Corina Nagy:** Writing – review & editing. **Gustavo Turecki:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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