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Review article

The body keeps the score: The neurobiological profile of traumatized adolescents

Daniela Laricchiuta [a,*], Anna Panuccio [b,c], Eleonora Picerni [b,d], Daniele Biondo [e], Benedetto Genovesi [e], Laura Petrosini [b]

[a] Department of Philosophy, Social Sciences & Education, University of Perugia, Perugia, Italy
[b] Laboratory of Experimental and Behavioral Neurophysiology, IRCCS Fondazione Santa Lucia, Rome, Italy
[c] Department of Psychology, University Sapienza of Rome, Rome, Italy
[d] Department of Neuroscience Imaging and Clinical Sciences, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy
[e] Italian Psychoanalytic Society, Rome, Italy

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ABSTRACT

Trauma-related disorders are debilitating psychiatric conditions that affect people who have directly or indirectly witnessed adversities. Experiencing multiple types of traumas appears to be common during childhood, and even more so during adolescence. Dramatic brain/body transformations occurring during adolescence may provide a highly responsive substrate to external stimuli and lead to trauma-related vulnerability conditions, such as internalizing (anxiety, depression, anhedonia, withdrawal) and externalizing (aggression, delinquency, conduct disorders) problems. Analyzing relations among neuronal, endocrine, immune, and biochemical signatures of trauma and internalizing and externalizing behaviors, including the role of personality traits in shaping these conducts, this review highlights that the marked effects of traumatic experience on the brain/body involve changes at nearly every level of analysis, from brain structure, function and connectivity to endocrine and immune systems, from gene expression (including in the gut) to the development of personality.

Trauma comes back as a reaction, not a memory

(Bessel Van Der Kolk)

1. Introduction

Trauma-related disorders are highly debilitating psychiatric conditions, with immeasurable social and economic costs. They affect more than 4 % of the population who have witnessed events involving direct or indirect exposure to aversive, threatening or fearful situations (Duncan et al., 2018). These pathological disorders, once considered anxiety disorders, include post-traumatic stress disorder (PTSD), reactive attachment, acute stress, and adjustment disorders (American Psychiatric Association, 2013).

Experiencing multiple types of traumas appears to be common during childhood, and even more during adolescence, which is arguably the second largest shift in development (following early life) due to concurrent changes across multiple domains of behavior and neurobiology (Dahl et al., 2018). Each stage of life depends on what preceded it, and young people certainly do not enter adolescence as "blank slates". Rather, adolescent development is partly a consequence of earlier life experiences. Changes occurring during adolescence are strictly associated with a prolonged period of plasticity in order to prepare individuals for independence, but they also render the adolescent system highly vulnerable to the effects of trauma exposure. About two-thirds of young people are exposed to domestic and community violence, war and terrorism, bullying, motor vehicle accidents, and neglect (Box 1). In a more concise way, and in the framework of dimensional models of trauma, adversities are distinguished (although very often coexisting) in two main dimensions, namely threat and deprivation, with unique emotional, cognitive, and neurobiological correlates relevant to the emergence of psychopathology (Sheridan and McLaughlin, 2016; Cisler and Herringa, 2021; Silveira et al., 2021; Panuccio et al., 2022). The personality developed in the presence of early traumas is not well adapted to adult life. Traumatized adolescents face fundamental problems in basic trust, independence, and initiative, and they handle the

* Correspondence to: Department of Philosophy, Social Sciences & Education, University of Perugia, Piazza G. Ermini 1, 06123 Perugia, Italy.
E-mail address: daniela.laricchiuta@unipg.it (D. Laricchiuta).

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tasks of early adulthood whilst being burdened by impairments in self-care, cognition, memory, identity, and in the ability to form stable relationships. During adolescence, affective, cognitive, and behavioral symptoms related to trauma that causes significant impairment or suffering can be classified within the internalizing and externalizing domains (Hofstra et al., 2002; King et al., 2004; Reef et al., 2010). Internalizing problems are those having mood or emotion as their primary feature and include symptoms such as anxiety, depression, anhedonia, and withdrawal, while externalizing problems are those such as aggressiveness, delinquency, oppositional defiant disorder, and conduct disorder (Achenbach et al., 1991; Kovacs and Devlin, 1998).

Thus, given the serious consequences of exposure to trauma, combined with a growing awareness that many of these effects are not observed until adolescence (Kessler et al., 2005; Lee et al., 2014; Gee and Casey, 2015), researchers focused bio-psycho-social consequences of trauma on adolescence (Tottenham and Galván, 2016; Colich et al., 2017). Living with a history of chronic trauma or experiencing exposure to acute trauma during the development may have different, and sometimes even more pronounced, effects on the brain/body than trauma exposure occurring in adulthood (Birn et al., 2014). The occurrence of trauma can be preadolescence-limited (i.e., early life trauma – ELT - in infancy or childhood) or adolescence-limited, with behavioral and brain/body effects related to trauma being measured in adolescence (Table 1 shows the ages for specific life periods of the analyzed samples in literature).

This review starts builds on the crucial assumption that the symptomatology of trauma-related disorders very often reflects the long-lasting response to adversities that were a previously encountered (McLaughlin et al., 2013), and analyzes the effects of trauma on adolescents by examining the relations among neuronal, endocrine, immune, and biochemical signatures of trauma and internalizing and externalizing behaviors, including the role of personality traits in shaping these behaviors. The effects of traumatic experience on the brain/body involves changes at nearly every level of analysis, from cellular signalling to behavioral expression. In this framework, brain structure, function and connectivity (Fig. 1), endocrine and immune systems, genetics/epigenetics, and gut microbiome undergo marked changes following trauma exposure. In order to address trauma-related alterations at those levels of analysis, it was initially necessary to introduce the developmental trajectories characterizing the adolescent brain/body in the absence of traumatic experiences.

2. Adolescence as an open window on the environment: reorganization of neuronal and endocrine systems

Humans have one of the slowest rates of brain development of all species, needing years to reach maturity (Thompson and Nelson, 2011; Landers and Sullivan, 2012; Ho and King, 2021). The upside of their long adolescent period is an intense developmental plasticity, whilst the downside is a significant vulnerability of the systems to internal/-external inputs. In fact, developmental brain is not an immature version of adult brain, but rather exhibits specific functional adaptations suited for the demands of life (Opendak and Sullivan, 2019). One of the adaptive values of a long adolescence is a prolonged period of synaptogenesis and dendritic/synaptic pruning, neuroplasticity, and neuronal connectivity (Houston et al., 2014; Ho and King, 2021).

Box 1

Life traumatic events for children and adolescents. Traumatic events are frightening, dangerous, or violent events that pose a threat to an individual's life or bodily integrity. Even witnessing a traumatic event that threatens life or physical security of a loved one can be traumatic for children and adolescents, since their sense of safety depends on the perceived safety of their attachment figures.

What experiences might be potentially traumatic for children and adolescents?

- **Physical abuse**: a parent or caregiver commits an act that results in physical injury to a child/adolescent.

- **Sexual Abuse**: any interaction between a child/adolescent and an adult (or another child/adolescent) in which the subject is used for the sexual stimulation of the perpetrator or an observer.

- **Psychological abuse and neglect**: child/adolescent's exposure to severe traumatic events - often of an invasive, interpersonal nature, such as abuse or profound neglect. They usually occur early in life and can disrupt many aspects of the development and the formation of a sense of Self.

- **Sex trafficking**: giving or receiving of anything of value (money, shelter, food, clothing, drugs, etc.) to any person in exchange for a sex act with someone under the age of 18.

- **Natural disasters**: effects of hurricanes, earthquakes, tornadoes, wildfires, tsunamis, and floods, as well as extreme weather events such as blizzards, droughts, extreme heat, and wind storms.

- **Terrorism and violence**: effects of mass violence, acts of terrorism, or community trauma in the form of shootings, bombings, or other types of attacks.

- **Community and school violence:** exposure to intentional acts of interpersonal violence committed in public areas by individuals who are not intimately related to the victim.

- **Bullying and Cyberbullying**: deliberate and unsolicited action that occurs with the intent of inflicting social, emotional, physical, and/or psychological harm to someone perceived as less powerful. Bullying can be physical (hitting, tripping, kicking, etc.), verbal (name calling, teasing, threatening, and sexual comments), and social (spreading rumors, embarrassing someone in public, being purposefully exclusive). Cyberbullying includes sending negative, harmful, and/or false content electronically via text messages or email, as well as posting mean text or hurtful pictures online through social media, blogs.

- **Domestic violence**: witnessing events in which an individual purposely causes harm or threatens the risk of harm to familiars loved by the child/adolescent.

- **Refugee and war experiences**: including torture, trauma related to war or persecution that may affect child/adolescent's mental and physical health long after the events have occurred.

- **Serious accidents or life-threatening ill**: psychological and physiological responses of children/adolescents and their families to pain, injury, serious illness, medical procedures, and invasive or frightening treatment experiences. Medical trauma may occur as a response to single or multiple medical events.

Table 1
Ages for specific life periods of the samples analyzed in the reported literature. y: years.

References	Early childhood	Childhood	Early adolescence	Adolescence	Late adolescence	Adult
Agans et al. (2008)				11–18 y		22–61 y
Appel et al. (2011)						20–79 y
Banny et al. (2014)		8–13 y				
Behen et al. (2009)		6–15 y				
Cicchetti et al. (2011)		7–13 y				
Cisler et al. (2013)				12–16 y		
Cohen et al. (2010)		8–12 y		14–19 y		25–30 y
Colich et al. (2017)			9–13 y			
Cowell et al. (2015)		3–9 y				
Dandash et al. (2021)			12 y	16 y	19 y	
Darnell et al. (2019)				13–19 y		
De Bellis et al. (2012)				10–18 y		
Do & Galván (2015)				13–18 y		25–30 y
Eluvathingal et al. (2015)		10.2 y (mean)				
Galvan et al. (2006)		7–11 y		13–17 y		23–29 y
Galván and McGlennen (2013)				13–17 y		23–35 y
Gee et al. (2013)		6–10 y		10–17 y		
Ginsburg et al. (2015)		6–13 y				
Goff et al. (2013)		5–10 y		11–15 y		
Govindan et al. (2010)		7–15 y				
Guyer et al. (2006)		8–14 y				
Hanson et al. (2015)				11–15 y		
Heleniak et al. (2016)				13–17 y		
Herringa et al. (2013)				18.79 y (mean)		
Herringa et al. (2016)				18–19 y		
Ho et al. (2020)				9–16 y		
Jensen et al. (2015)	0–6 y	7–13 y			18–21 y	
Kaufman (1991)		7–12 y				
Kaufman et al. (1997)		7–13 y				
Kaufman et al. (2004)		5–15 y				
Loman et al. (2014)			12–13 y			
Marshall (2016)				13–18 y		
McLaughlin et al. (2012)				13–17 y		
McLaughlin et al. (2013)				13–17 y		
McLaughlin et al. (2015)				13–19 y		
Merikangas et al. (2010)				13–18 y		
Nooner et al. (2022)				12–14 y		
Nooner et al. (2013)				13–17 y		
Pagliaccio et al. (2015)		9–14 y				
Phillips et al. (2021)				12–21 y		
Platt et al. (2016)		7–13 y				
Powers et al. (2021)		8–12 y				
Silveira et al. (2021)				12–22 y		
Somerville et al. (2011)		6–12 y		13–17 y		18–29 y
Suzuki et al. (2014)		7–12 y				
Telzer et al. (2013)				15–18 y		
Whittle et al. (2016)				11–20 y		
Wu et al. (2016)		7–12 y		13–18 y		19–25 y

Accordingly, environmental influences generate distinct effects on brain circuitries due to developmental constraints in sources of input and in mechanisms of plasticity, leading to alearning about the environment, in particular about the social environment (Blakemore, 2008; Ho and King, 2021), and complex behaviors (e.g., executive function, emotion regulation, social cognition, and mentalizing) (Blakemore, 2008; Pfeifer and Allen, 2021). From an evolutionary perspective, adolescents acquire the necessary input for early survival from their caregivers and gain the skills that only "primary relationships" can provide through the attachment system (Ainsworth, 1969; Bowlby, 1977; Piekarski et al., 2017).

The brain develops throughout childhood and adolescence and each brain area has its own developmental trajectory and maturation. The increasing ability to regulate cognitive, emotional and social domains heavily relies on interactions among amygdala (AMY), medial prefrontal cortex (mPFC that encompasses in humans the areas 24, 25, and 32 labelled with Brodmann's numbers), striatum, and hippocampus (Somerville and Casey, 2010; Somerville et al., 2011).

Structural studies show that the basic architecture of the AMY is established at birth and continues during infancy and adolescence (LoPilato et al., 2019; Hanson and Nacewicz, 2021). Such AMY developmental trajectorys is coupled with the even more prolonged development of cortical regions involved in cognitive control and emotion regulation (Merikangas et al., 2010; Marshall, 2016). Again, the maturation of the frontal lobe which is ongoing during and beyond adolescence may be beneficial in terms of learning conventions, including language and social norms (Thompson-Schill et al., 2009), but it may also strengthen the effect of negative social and environmental factors that can have long-term consequences on the brain development and cognitive abilities (Steinberg, 2005).

Functional magnetic resonance imaging (fMRI) studies showed that AMY reactivity to negative faces and images decreases with age during adolescence (Silvers et al., 2017; Constantinidis and Luna, 2019), and is accompanied by a significant structural and functional connectivity with the mPFC (Keding and Herringa, 2016; Silvers et al., 2017; Constantinidis and Luna, 2019). These normative patterns contribute to a decreased reactivity to negative contents and an enhanced ability of regulating emotions gained as adolescence progresses (Herringa, 2017).

Remarkably, during adolescence there are also significant developmental changes in the ventral striatum. Adolescents show a strong activation of the ventral striatum in response to primary (Galván and McGlennen, 2013), secondary (Galvan et al., 2006; Cohen et al., 2010;

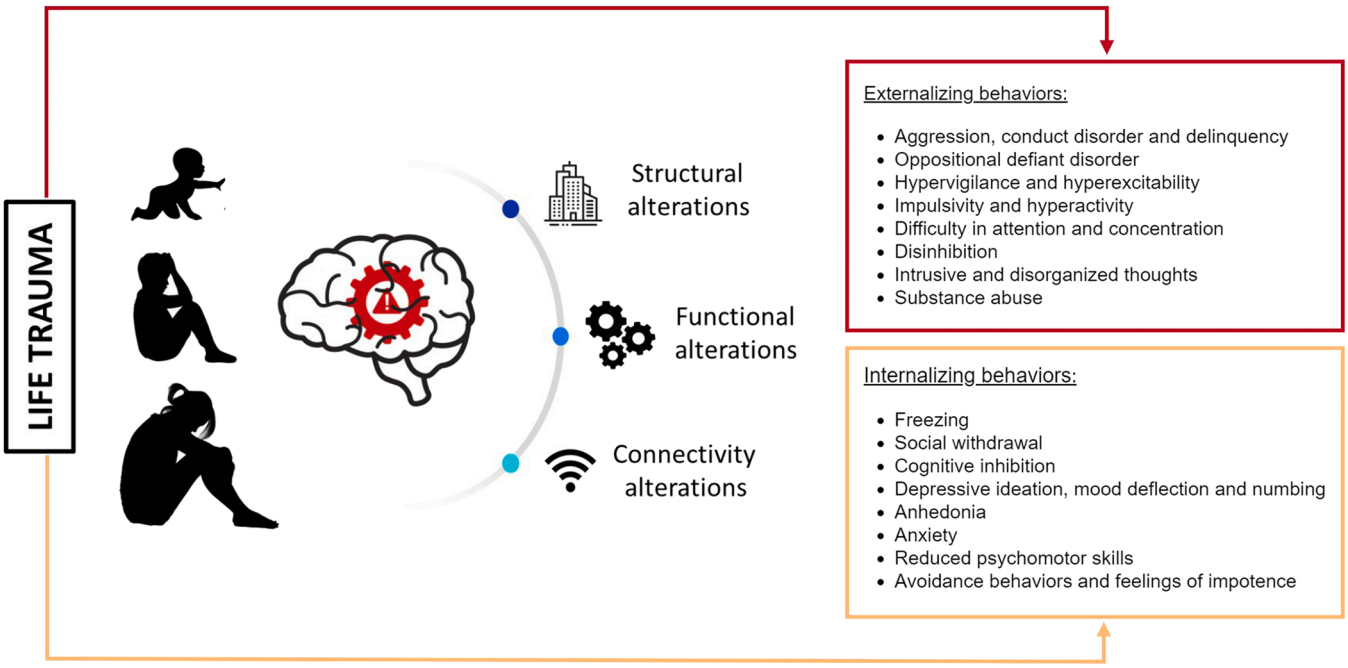

Fig. 1. Life (early and middle childhood, adolescence) trauma elicits brain structural, functional and connectivity alterations and may result in externalizing and internalizing behavioral problems.

Van Leijenhorst et al., 2010), and social rewards (Guyer et al., 2008; Telzer et al., 2013). These neuronal findings are mirrored by an increased reward sensitivity, risk taking and motivational behavior in adolescents, as compared to other age groups (Galván and McGlennen, 2013). Interestingly, environmental conditions may exacerbate or diminish these effects, underscoring the flexibility of the mesolimbic system during this crucial period (Do and Galván, 2016).

During development, "activating" and "organizing" effects of adrenal and gonadal hormones on brain plasticity have been reported (Sisk, 2017; Laube et al., 2020). Namely, during puberty increased levels of these hormones have been associated to changes in gray matter (GM) volumes and white matter (WM) connections (Herting and Sowell, 2017; Ho et al., 2020), demonstrating the link between the maturation of these brain regions and behavioral responses to socially relevant stimuli (Pfeifer and Allen, 2021). During adolescence, peers become an especially critical source of environmental input and drive exploratory and approach behaviors. While positive peer relationships can buffer adolescents' responses to negative experiences (Adams et al., 2011), negative peer relationships and an increased social risk taking may became a source of trauma in itself (Vijayakumar et al., 2018; Laube et al., 2020).

According to the "pubertal stress recalibration" hypothesis (Gunnar et al., 2019), neuroendocrine plasticity in puberty allows the more recent positive experiences to remedy the effects of earlier experiences of adversity. Interestingly, the hypothalamic-pituitary-adrenal (HPA) axis undergoes tremendous changes during the transition to adolescence (Netherton et al., 2004; Adam, 2006; Gunnar et al., 2009), both in basal levels and in response to stressful situations (e.g., public speaking, peer rejection or school failures) (Klimes-Dougan et al., 2001; Stroud et al., 2004). Furthermore, during adolescence the massive maturation of the cortical and subcortical regions is highly influenced by cortisol and stress-related hormones (Graf et al., 2013).

This combination of developmental changes has a major influence on the susceptibility to trauma of adolescents, and the effects of developmentally chronic, pre-adolescent or adolescent limited traumas are addressed in the next sections.

3. Trauma-related reorganization of neuronal system in adolescence

The various types of traumatic experiences alter structure, function, and connectivity of the AMY, mPFC, striatum, and hippocampus during adolescence (Tottenham and Sheridan, 2009; Tottenham, 2012). These alterations correspond to increased fear reactivity (Fani et al., 2015), attentional bias towards adversity (Fani et al., 2015; Troller-Renfree et al., 2015), and difficulty with affective regulation (Tottenham et al., 2010), contributing to a risk of externalizing/internalizing behaviors (Fig. 2).

Furthermore, for individuals raised in environments where multiple sources of threat/deprivation are present or long-term survival is uncertain, the "developmental reprioritization" is often marked by an accelerated maturation (in areas such as AMY and mPFC), characterized by an earlier emergence of adult-like phenotypes (Callaghan and Tottenham, 2016; Belsky, 2019), underlying an altered threat processing (Gee et al., 2013a, 2013b; Keding and Herringa, 2016; Wu et al., 2016).

3.1. Brain structural alterations associated with increased an risk of externalizing/internalizing behaviors

Within the neuroimaging studies demonstrating an association between trauma and brain structures, recent findings by VanTieghem et al. (2021) showed that adolescents who suffered early social neglect in institutional care have a reduced growth rate of the AMY. In the same line, increased maternal aggressive behaviors (i.e., expression of anger, contempt, and belligerent or provocative attitude) are associated with adolescent sons' alterations of the superior frontal and lateral parietal cortical thickness (Whittle et al., 2016), which in turn are predictive of functional outcomes such as school performance and academic achievement. Conversely, a high frequency of positive maternal behaviors (i.e., happy and caring affection, and approving or validating comments) predicts an attenuated volumetric growth in the AMY, and an accelerated cortical thinning in orbitofrontal regions (Whittle et al., 2016, 2014) in adolescent sons, suggesting an association between parenting and adolescent brain maturation. In a longitudinal study examining brain structural development in traumatized adolescents

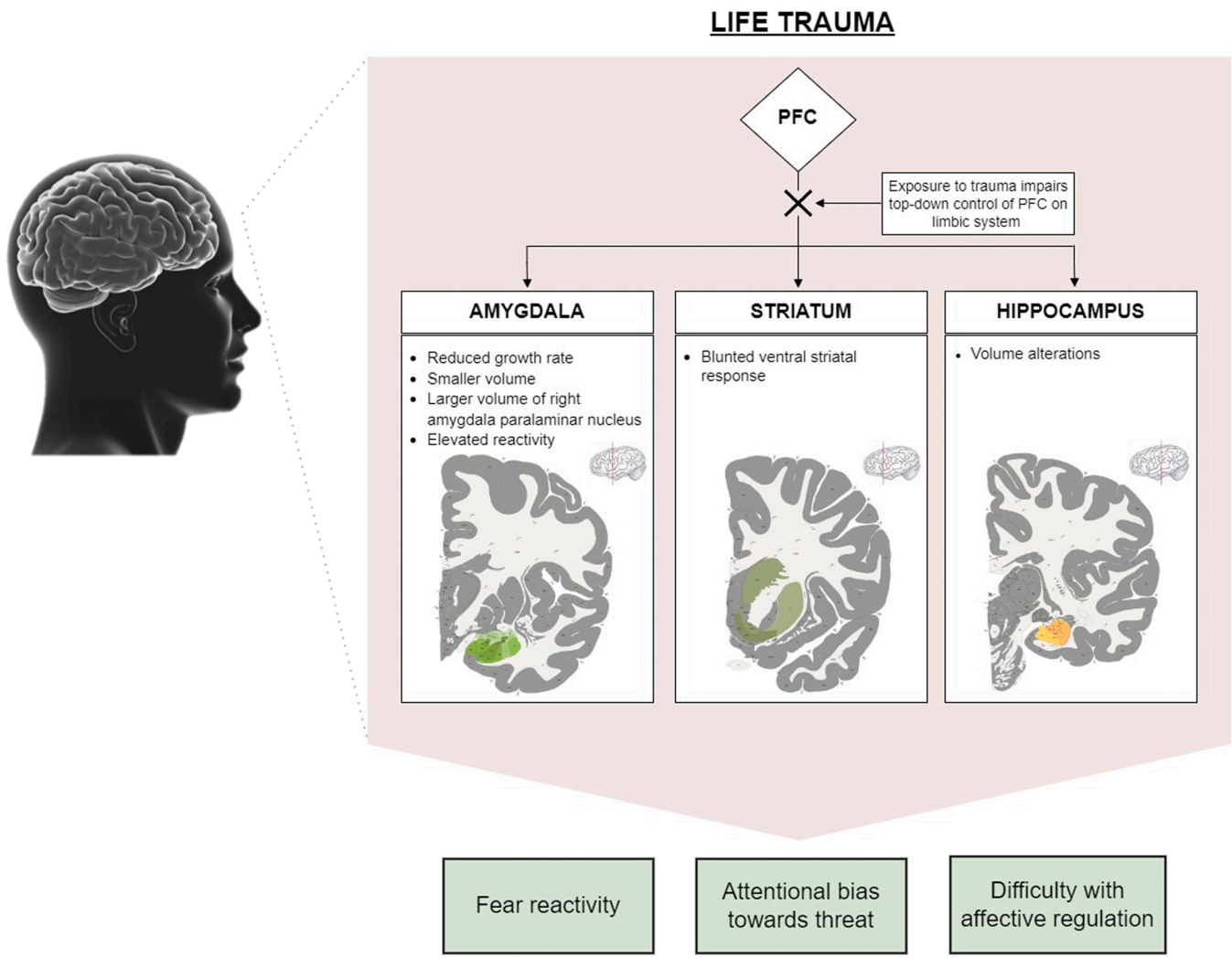

Fig. 2. Trauma-related impairment of connectivity between prefrontal cortex (PFC) and amygdala, striatum and hippocampus results in maladaptive behaviors during adolescence.

compared to not-traumatized adolescents over one year, stable reductions are found in ventromedial PFC (vmPFC) and ventrolateral PFC (vlPFC) volume (Heyn et al., 2019).

Importantly, in a recent longitudinal study Phillips et al. (2021) measured the effects of ELT and alcohol use, an externalizing conduct, on the developmental trajectories of the AMY and the volumes of hippocampal subregions in adolescents. The effect of ELT at baseline is associated with a larger right CA3 head hippocampal volume. Whereas younger adolescents with greater trauma exposure at baseline have smaller volumes of left hippocampal subiculum and molecular layer hippocampal head, older adolescents with greater trauma exposure at baseline have a larger volume of right AMY paralaminar nucleus, and a smaller volume of whole AMY. Lastly, adolescents who reported greater alcohol use with greater baseline trauma show smaller volumes of right hippocampal CA1 head, yet larger whole hippocampus volume. Thus, concurrent trauma and alcohol use affect volume and trajectory of hippocampal and AMY structures, supporting the hypothesis that AMY and hippocampus do not homogeneously respond to trauma.

Finally, associations between ELT, internalizing symptoms during childhood and early adolescence, and brain structures in late adolescence were investigated in a community-based birth cohort (Jensen et al., 2015). Early adversity is directly associated with smaller volumes in the anterior cingulate cortex (ACC) and greater volumes in the precuneus, as well as higher levels of internalizing symptoms are associated with smaller superior frontal gyrus volume.

3.2. *Brain functional alterations associated with an increased risk of externalizing/internalizing behaviors*

Evidence from fMRI studies showed that trauma exposure impairs top-down control of PFC on limbic system (De Bellis, 2002; Crews et al., 2016). Adolescents who have experienced high ELT levels exhibit heightened activation of brain regions (AMY, anterior insula, dorsal ACC) involved in processing salient stimuli, when exposed to emotionally evocative faces and images (Garrett et al., 2012; Suzuki et al., 2014; Marusak et al., 2015). Adolescents with a history of physical abuse and neglect/deprivation (De Bellis and Hooper, 2012) or exposure to family violence (McCrory et al., 2011) exhibit elevated AMY reactivity in response to highly arousing emotional faces, even when pre-attentively presented (McCrory et al., 2013). Elevated AMY reactivity to emotional faces has also been observed in adolescents who experienced deprivation, such as low parental warmth (Casement et al., 2014) or severe neglect and institutional care during infancy (Maheu et al., 2010; Tottenham et al., 2011; Gee et al., 2013a). Moreover, the observation that traumatized adolescents more likely exhibit AMY developmental trajectory similar to adolescents with significant familial risk for depression (Swartz et al., 2015) suggests that AMY hyperactivity in adolescence may be an important biomarker for mental illness, associated with

affective dysregulation and internalizing symptoms. Notably, it has been reported that only adolescent females, and not males, exhibit positive associations between ELT and vlPFC activation during implicit emotion regulation, between ELT and internalizing problems, and between activation in these regions and internalizing problems (Colich et al., 2017). In accordance, among females, ELT has been found to be a relevant risk factor for the development of major depressive disorder (Ge et al., 2001; Rudolph and Flynn, 2007). Females also differ from males in their perception of adverse life events (Raffaelli et al., 2016), in biological responses to acute and chronic stressors, and in neuronal response to negative stimuli (Novais et al., 2017). Given the striking sex differences in the incidence of internalizing disorders, there may be sex-specific mechanisms (as sex-specific effects on corticolimbic circuitry) through which ELT contributes to vulnerability for internalizing problems in adolescence (Teicher et al., 2003). In this context, the age at which sex differences in internalizing disorders become most pronounced corresponds to the complex developmental period of puberty that is typically experienced earlier in females than in males (Negriff and Susman, 2011).

In a study on adolescents with history of child maltreatment, McLaughlin et al. (2015) found a bias toward negative stimuli and, relatively to non-maltreated adolescents, greater recruitment of PFC during cognitive reappraisal to achieve comparable reduction of AMY activity. In this study, maltreated and non-maltreated adolescents demonstrate comparable emotional regulation abilities via AMY modulation, but maltreated adolescents employ more executive resources to do it, and this would reduce their availability to regulate subsequent distress (Muraven and Baumeister, 2000). In parallel, traumatized adolescents show increased activation in superior frontal gyrus and frontal pole when downregulated their negative affect to a negative image, (McLaughlin et al., 2015). Similarly, adolescents exposed to child trauma exhibit elevated dorsolateral PFC (dlPFC) activation when performing an emotional conflict task (Marusak et al., 2015). It has been also reported that positive maternal behavior in early adolescence is associated with lower activation in the left parietal cortex and dlPFC during a task activating cognitive and attention brain networks (Karlsgodt et al., 2018).

Like the AMY and mPFC, in adolescence the ventral striatum is highly influenced by aversive experiences. Adolescents with a history of deprivation (institutional caregiving) exhibit blunted ventral striatal response, and specifically they do not differentiate reward predicting cues (Mehta et al., 2010). Goff et al. (2013) showed that group differences in ventral striatal responses to positive facial emotions between individuals with a history of institutional care and typically-raised subjects emerge in adolescence. Furthermore, adolescence is the time when depression symptoms significantly increase, and ventral striatal hypoactivity correlates with depressive symptomology in the adversity-exposed group.

Consistently with the blunted ventral striatal reactivity, adolescents with a history of early adversity (institutional caregiving, maltreatment) and a diagnosis of depression less likely engage in risky behaviors (Guyer et al., 2006; Loman et al., 2014). These findings fit the assumption that ELT may render the adolescent vulnerable to internalizing behaviors just because of the effect of trauma on ventral striatal development during this sensitive time (Auerbach et al., 2014; Goff and Tottenham, 2015).

3.3. Brain functional connectivity alterations associated with an increased risk of externalizing/internalizing behaviors

A way to measure functional connectivity is to employ resting state fMRI measures, which assay spontaneous regional interactions occurring when the subject is not performing any explicit task and provide an index of the integrity of functional connections between regions of interest.

Adolescents with a history of child maltreatment (Herringa et al., 2013) or trauma (Pagliaccio et al., 2015; Thomason et al., 2015) exhibit weaker connectivity between AMY and mPFC regions and AMY and hippocampus (Nooner et al., 2013, 2022). The nature of AMY-mPFC resting state connectivity has implications for mental health. In fact, in adolescence weaker AMY-mPFC connectivity is associated with increased anxiety (Kim et al., 2011; Pagliaccio et al., 2015). Furthermore, Burghy et al. (2012a) provided compelling evidence that developmental trauma increases the risk for internalizing problems, and this relation is mediated by alterations to AMY-mPFC functional connectivity.

Notably, traumatized adolescents paradoxically show lower AMY reactivity, greater dmPFC activation, and greater AMY-vmPFC connectivity at younger ages, a pattern which reverses by late adolescence and is independent from trauma onset (Gee et al., 2013b; Vink et al., 2014).

ELT predicts resting state functional connectivity of inferior frontal gyri and, in turn, the altered connectivity of inferior frontal gyrus predicts the presence of externalizing symptoms in early adolescence (Barch et al., 2018a). Furthermore, a thinner inferior frontal gyrus in early adolescence predicts drinking and externalizing psychopathology in late adolescence (Brumback et al., 2016), reinforcing the notion that the connectivity of the inferior frontal gyrus may be associated with impulsivity (Herz et al., 2014; Wang et al., 2016). Importantly, child neglect is negatively associated with resting-state functional connectivity of the dorsal ACC to brain regions within the cingulo-opercular network, a well-known executive function network that underlies control of attention and self-regulation, and this connectivity pattern mediates the association between neglect and externalizing behaviors (Silveira et al., 2021).

In traumatized adolescents, the altered functional connectivity has been demonstrated not only through the above-reported resting state analyses, but also through tasks involving effortful emotional regulation. In a sample of traumatized adolescents performing an emotional conflict task that involves categorizing facial emotions and ignoring the overlying emotional words, marked trauma-related alterations emerge in AMY and PFC (Marusak et al., 2015). Specifically, the trauma-exposed adolescents exhibit AMY-PFC connectivity patterns consistent with poor emotional regulatory function.

It has been reported that adolescents exposed to ELT show stronger negative AMY-PFC connectivity - a more mature, adult-like pattern of connectivity - while viewing negative facial expressions (Goff et al., 2013; Wolf and Herringa, 2016). The magnitude of this effect is associated with avoidance behaviors (Wolf and Herringa, 2016). Similarly, during an aversive learning paradigm, adolescents with a history of deprivation (institutional care) more likely exhibit adult-like patterns of AMY-PFC connectivity (Silvers et al., 2017). All these findings reflect adaptive functioning in the face of adversity and indicate that adolescents exposed to ELT may develop adult-like patterns of connectivity at an earlier age in order to deal more effectively with environmental adversity. In fact, Gee et al. (2013a) showed that in previously institutionalized adolescents, negative pattern of AMY-mPFC functional connectivity is associated with lower levels of separation anxiety, pointing out that adult-like pattern may be protective against early adversities. However, it has to be considered that the early development of adult-like pattern also represents the premature end of the sensitive period of childhood, suggesting a potential acceleration linked to trauma in the development of the circuitry that supports socio-emotional processing and regulation. The long-term consequences of this earlier maturation are still unclear as are ELT effects on the developmental trajectories of AMY-mPFC circuitry from childhood to adulthood. Decreased AMY-mPFC connectivity in relation to family adversity and maltreatment mediates the occurrence of some risk for adolescent internalizing symptoms (Gilmore et al., 2010; Raznahan et al., 2011). Child adversity predicts increased fronto-AMY connectivity in response to negative, but not positive, images, only in adolescents with low internalizing behaviors, and also predicts increased fronto-hippocampal connectivity in response to negative images, even if not moderated by internalizing

conducts (Herringa et al., 2016). Taken together, these findings argue that adaptation to child adversity is associated with enhanced activity of fronto-subcortical circuits, specifically for negative emotional stimuli. Conversely, poor enhancement of fronto-AMY connectivity, with increased AMY reactivity, may represent the neural signature of vulnerability for internalizing behaviors by late adolescence. Neuronal mark of adaptation to child adversity involves augmentation of functional connectivity in fronto-AMY and fronto-hippocampal pathways, important routes in the regulation of fear and anxiety.

Given the early maturation of the AMY within the hierarchical brain development, it is possible that the extent of connectivity of AMY with PFC regions in adolescence depends on its earlier emerging function (Gee et al., 2013b). That is, trauma-induced AMY hyperreactivity might increase the risk for its atypical (in nature, timing, or both) connections with the PFC.

In addition to the changes in AMY-mPFC circuitry, adolescence is also featured by changes in the neuronal correlates of reward sensitivity and cognitive regulation (Steinberg, 2005). Specifically, the ventral striatum supports reward-related processes, such as reward-based learning (Fiorillo et al., 2003), through reception of dopaminergic inputs from the ventral tegmental area and substantia nigra (Haber, 2011). The dopamine system, which undergoes significant maturation during adolescence (Andersen and Teicher, 2009, 2008; Spear, 2009), is very sensitive to the effects of adversity (Starcke and Brand, 2012). Researches independently performed by Hanson et al. (2015) and Schneider et al. (2012) have shown that even few extreme forms of caregiving adversity (as low maternal affiliation or emotional neglect) are associated with alterations in ventral striatal areas. Importantly, Hanson et al. (2015) reported that a history of emotional neglect was associated with decreased functional connectivity (perhaps even negative) between AMY and ventral striatum in response to reward, advancing a possible process linking elevated AMY reactivity to blunted ventral striatum functioning in adolescents with a history of adversity. The low responsivity of ventral striatum during adolescence following ELT may predict the emergence of internalizing symptoms in reward-related paradigms.

Finally, the trauma-associated alterations in fiber tracts have been recently investigated by using diffusion tensor imaging (DTI). DTI indices, encompassing fractional anisotropy (FA) and mean diffusivity (MD), provide estimates of microstructural changes in WM pathways, allowing for a more nuanced understanding of WM differences, when compared with traditional volumetric methods. Numerous studies on children internationally adopted after previous histories of deprivation (institutional rearing) show reduced integrity (lower FA and higher MD) of limbic and para-limbic (Eluvathingal et al., 2006; Govindan et al., 2010; Kumar et al., 2011; Hanson et al., 2013) and fronto-striatal (Behen et al., 2009; Kumar et al., 2014) circuitries. Even the trauma-associated alterations in the external capsule and corpus callosum might explain, at least partially, the link between institutional rearing and internalizing symptoms in early adolescence (Bick et al., 2017), considering that WM tracts involved in circuitries supporting emotion and stress regulation may be particularly implicated in risk for internalizing symptoms.

4. Trauma-related reorganization of endocrine and immune systems in adolescence

Exposure to a single abrupt traumatic event or series of chronic traumatic events can lead to repeated activation of the HPA axis, physiological system of stress response (Tarullo and Gunnar, 2006; Trickett et al., 2010; De Bellis and Zisk, 2014; Cross et al., 2017). Such a system is made up of different sub-systems working together to protect the individual against environmental adversities and to shift metabolic resources from homeostasis toward "fight, flight or freeze" reaction (Cannon, 1939; Chrousos and Gold, 1992). The traumatic stressors are processed by cortical structures that directly or indirectly (via the thalamus) activate the AMY. In the presence of fear signals processed by AMY, hypothalamus, hippocampus, and mPFC, the cortisol levels increase and, in turn, increase the activity in the locus coeruleus and sympathetic system. In accordance, Burghy et al. (2012a) reported that early traumatic events are associated in childhood with increased cortisol levels, which in adolescence predict altered functional connectivity between AMY and mPFC as well as internalizing problems. These effects are observed only in females, suggesting a possible hormonal basis for the commonly observed sex differences in risk for internalizing problems. Conversely, inefficient cardiovascular responses to stress are positively associated with externalizing symptoms (Heleniak et al., 2016).

Cortisol activates glucocorticoid and mineralocorticoid receptors located and expressed throughout the brain. Glucocorticoid receptors act as transcription factors and regulate gene expression for metabolism and immune function (Lupien et al., 2009). Namely, increased levels of cortisol turn off the immune system and gluconeogenesis, inhibit its own secretion via negative feedback on hippocampal glucocorticoid receptors (Chrousos and Gold, 1992), and have neurotoxic effects (Lupien et al., 2016). In fact, in traumatized youths elevated levels of corticotropin releasing hormone (CRH), whose main function is the stimulation of the cortisol synthesis, lead to pituitary hypertrophy, most pronounced during very early childhood and puberty (Thomas and De Bellis, 2004).

This idea agrees with McEwen's theory of allostatic load (McEwen, 2007), defined as the phenotypic consequences of chronic activation of stress response systems, including neural adaptations to environmental inputs combined with endocrine and immune responses (McEwen and Stellar, 1993; Lupien et al., 2007). While the physiological changes that attend exposure to adversity are helpful in the short-term by allowing the body to maintain homeostasis in spite of changing environmental conditions, over time these initially adaptive responses produce "wear and tear" on regulatory systems. On one hand, acute exposure to adversity promotes the secretion of hormones (e.g., cortisol) and pro-inflammatory cytokines that drive changes in structural plasticity of the AMY and hippocampus to enhance learning for similar traumatic events (McEwen et al., 2016). On the other hand, through these same hormonal and immune mediators the chronic exposure to adversity elicits glutamatergic excitotoxicity and atrophy in the AMY and hippocampus provoking impaired memory and other behavioral and cognitive symptoms, commonly found in internalizing behaviors (McEwen, 2004).

However, in some individuals exposed to ELT, lower (and not higher) cortisol levels and attenuated cortisol reactivity (i.e., HPA axis downregulation) have been reported, with the onset of such a downregulation typically occurring during adolescence (Trickett et al., 2010). Downregulation of the HPA axis follows a period of chronic upregulation and may be the result of increased sensitivity of glucocorticoid receptors leading to blunted stress reactivity and lower baseline cortisol levels, potentially acting as a compensatory strategy. One of the most robust findings of an interesting meta-analysis by Miller et al. (2007) states that the longer is the time by the trauma, the lower are the levels of adrenocorticotropic hormone (ACTH) and postdexamethasone cortisol, as well as the lower are the levels of morning cortisol.

Activation of the immune system elicits the production of cytokines, promoting the inflammatory reaction. The increasing levels of pro-inflammatory cytokines in response to acute or chronic trauma elicit hyperactivation of the HPA axis that, in turn, leads to a further rise in levels of cytokines through positive feedback (Janssen et al., 2010; Eyre and Baune, 2012). In particular, IL-1, IL-6, TNF-a and IFN-a increase the CRH release and disrupt glucocorticoid receptor function. These mechanisms are particularly relevant during adolescence, when brain structures are susceptible to adverse effects of prolonged periods of excessive amounts of corticosteroids with consequent atrophy of the apical dendrites of the hippocampal pyramidal cells (McKittrick et al., 2000).

The cytokines also affect biological pathways associated with depression, crucial component of internalizing behavior. The cytokine theory in depression can be viewed as complimentary rather than competitive to other hypotheses on depression etiology, such as the

monoaminergic theory (Ruhé et al., 2007). Increased levels of cytokines lead to depressive symptoms by reducing serotonin levels and stimulating neuronal damage (Goebel et al., 2000; Madrigal et al., 2002; O'Connor et al., 2003; Deinzer et al., 2004). Interestingly, Pouget et al. (2022) provided preliminary evidence that common variation in IL-6 may be associated with depressive symptoms in children and adolescents, and that common variation in interleukin genes may sensitize individuals to the internalizing effects of traumatic life experiences.

5. Genetic and epigenetic signatures of externalizing/internalizing behaviors after trauma

The adolescents experiencing threat and deprivation display great variability in the physiological, neurobiological, and behavioral outcomes after trauma. Such a variability is affected by environmental (e.g., type of trauma) and genomic factors, influencing individuals'vulnerability and resilience (Spear and Silveri, 2016). Genomic, epigenomic, and transcriptomic studies, aimed to understand why some individuals are more likely than others to develop certain traits or psychopathology after experiencing trauma, are emerging areas of research (Layfield et al., 2021; Gladish et al., 2022).

While it has become clear that the effects of individual genetic variants on behavior are too small to be reliably detected (Kendler, 2013), burgeoning genome-wide association studies (GWASs) are now informing on the development of polygenic scores - aggregate indices of genetic influences - that can be used to more directly examine the role of genomic influences in responding to trauma (Harden and Koellinger, 2020; Layfield et al., 2021).

A large GWAS was able to assess genomic factors that could influence exposure to ELT (Dalvie et al., 2020). Two genome-wide significant loci rs142346759 and rs10262462 (annotated to genes *FOXP1* and *FOXP2*, respectively) are significantly associated with early maltreatment. A significant genetic overlap has been found between early maltreatment and internalizing/depressive symptoms, suggesting there may be shared underlying mechanisms of predisposition.

In a transcriptome-wide study, Minelli et al. (2018) compared gene expression in subjects who experienced ELT (sexual abuse, physical abuse, emotional abuse, and emotional neglect) with and without depression diagnosis. A specific association has been found between neglect and *MED22* gene, encoding for a protein that contributes to coordination of transcription and cell lineage development.

These genome/transcriptome-wide studies follow gene × environment candidate gene studies focusing on single genetic polymorphisms as moderators for the trauma effects. Although, these studies must be taken with some caution until replicated in larger samples, they still provide important insight into how biological effects of trauma may be related to molecular (genetic and epigenetic) factors.

Some studies investigated polymorphisms in genes associated with monoamine neurotransmitter regulation and externalizing/internalizing outcomes in response to trauma. Meta-analyses revealed that the association between ELT and the short version of the *MAOA* gene (which codes for an enzyme that selectively degrades the dopamine, serotonin, and norepinephrine after reuptake from the synaptic cleft) results in mental health problems, antisocial behavior, attentional problems, and hyperactivity in boys (Kim-Cohen et al., 2006). Adolescent boys with the short *MAOA* allele who were exposed to maltreatment or deprivation exhibit more alcohol-related problems than maltreated boys with the long *MAOA* allele (Nilsson et al., 2007). Young people who were homozygous for the short allele of the serotonin transporter gene promoter polymorphism (*5- HTTLPR*) display elevated vulnerability to internalizing behaviors, but only in the presence of ELT, even if the presence of positive supports reduced their vulnerability (Kaufman et al., 2004). Furthermore, interaction of the short alleles of *5-HTTLPR* and trauma predicts early use of alcohol in young people (Francis et al., 2000). Having two short-short alleles of the *5-HTTLPR* gene moderats the association between bully victimization and emotional problems, such that bullied children are at an increased risk, as adolescents, for depression or anxiety; the short-long and long-long genotypes do not confer an increased risk (Sugden et al., 2010).

In a prospective study on the *FKBP5* gene, which inhibits glucocorticoid receptor-mediated glucocorticoid activity (Wochnik et al., 2005), only the adolescents who were homozygous for the minor alleles show an increased incidence of depression after ELT, suggesting that the minor allele of the *FKBP5* polymorphism and trauma interact to predict internalizing behavior later in life (Zimmermann et al., 2011). Three variants in the *FKBP5* gene (rs4713916, rs1360780, and rs3800373) are associated with a failure of cortisol responses to return to baseline in traumatized subjects, suggesting a genotype-dependent risk of chronically elevated cortisol levels as possible mechanism for the increased risk for trauma-related disorders (Ising et al., 2008). Cross-sectional studies have also found such an interaction in adults who carried the minor *FKBP5* allele and have histories of ELT, as they have increased rates of internalizing behavior (Appel et al., 2011).

In addition to the presence of certain genes affecting the response to trauma, the experiences of adversity may influence genetic expression through epigenetic mechanisms, such as DNA methylation and hydroxymethylation, posttranslational histone modifications, and non-coding RNAs (Yehuda and LeDoux, 2007; Champagne, 2013; Turecki et al., 2014). Epigenetic signatures are responsive to environmental factors and are stable over long periods of time and across generations to persistently modify gene transcription. In fact, epigenetic perturbations may facilitate the process whereby life experiences (both negative and positive) alter gene expression patterns (Bjornsson et al., 2004; Malan-Müller et al., 2014), providing a link between environment and transcriptome (Binder et al., 2008; Champagne, 2008; Franklin et al., 2010). In this framework, epigenetic modifications may explain the individual variability in resilience or predisposition to trauma-related diseases (Yehuda and Bierer, 2009; Bowers and Yehuda, 2016). Fujisawa et al. (2019) demonstrated greater methylation of *OXTR* gene coding for oxytocin receptor in adolescents with maltreatment histories in comparison to controls, and found that *OXTR* gene methylation is negatively associated with volume in the left orbitofrontal cortex.

Similar to GWASs, the large-scale epigenome-wide association studies (EWASs) move away from hypothesis-driven approach. Although, EWASs have limitations similar to those of candidate gene studies, they can assess higher-level biological processes beyond individual genes. Specifically, evidence for epigenetic changes in the pathways associated to immune system, neural, developmental and cardiovascular processes, and stress responses have been reported more consistently after childhood maltreatment (Uddin et al., 2010; Cecil et al., 2020).

Recently, it has been demonstrated that in traumatized adolescent girls, an intensive 1-week residential group program reduces trauma-related symptoms, and in parallel epigenetically modulates 49 methylated loci annotated to genes linked to neural, immune, and endocrine pathways, as well as cancer and cardiovascular disease (Kaliman et al., 2022). Furthermore, biological and environmental risk for trauma-related externalizing conducts in female adolescents is associated with complex epigenetic changes involving the neurite regulator *SLITRK5* (Chiocchetti et al., 2022).

All together, these findings advance that the gene (predisposition) × environment (traumatic experience) interplay may produce various emotional, behavioral, and neurobiological outcomes. Furthermore, a traumatic event may also alter epigenetic patterns potentially associated with neural plasticity, and endocrine/immune regulation. Even if it remains unclear if the variations in the genome and epigenome are a mechanism linking trauma to mental disorder, or are biomarkers of vulnerability, it is important to research in these new, active, and cutting-edge fields.

6. Interaction between microbiome and trauma: suggestions from human and animal studies

It has become increasingly evident that environmental and epigenetic factors interact with gut microbial flora, the microbiota (i.e., the nonpathogenic microorganisms, including bacteria, viruses, and fungi and other single-celled organisms, colonizing the gastrointestinal tract) and its entire habitat, the microbiome (including the microbial genetic patrimony and products), having thus a strong impact on the health (Bhat and Kapila, 2017). Interestingly, the gastrointestinal microbiome is increasingly recognized as important for brain function and mental health, and vice versa (Fig. 3). For example, gastrointestinal bacteria produce neurochemicals essential for brain function and emotional behaviors, such as the precursor to serotonin, which then reach the central nervous system through humoral and vagal nerve pathways (bidirectional communication channels between the brain and gut) (Cryan and Dinan, 2012). Despite the technical advances provided by molecular biology have identified the molecular signatures of the microorganisms hosting our guts, only a little fraction has been cultured to date, rendering questionable the cause-and-effect relationships between microbioma and disordered mental health. Thus, the body of evidence that is emerging in experimental researches using rodent models (which specific taxa are known and less numerous), and beginning to emerge clinically, has to be taken into account.

Animal studies have indicated that modifications of the gastrointestinal microbiome affect neurogenesis (Möhle et al., 2016), cortical myelination (Hoban et al., 2016), blood-brain barrier function (Braniste et al., 2014), microglia maturation (Erny et al., 2015) as well as fear learning, stress-related responses, and social behavior (He et al., 2017; Hoban et al., 2017; Lu et al., 2018). In addition, the microbiome influences immune and inflammatory pathways (Belkaid and Hand, 2014), in turn directly associated with anxiety and depression (Vogelzangs et al., 2013, 2016). Manipulations of such bacteria influence anxiety levels in adult humans (Messaoudi et al., 2011; Collins et al., 2013) as well as fear behaviors in developing rodents (Callaghan et al., 2016; Cowan et al., 2016). It has been recently advanced that the mechanism through which the intestinal microbiome influences the fear learning is the modulation of excitatory neurons of the mPFC (Chu et al., 2019).

Interestingly, growing evidence indicates that the trauma-related microbial profile is involved for the trauma-related phenotype and suggests that the microbial ecology may serve as additional biological memory of ELT (Leclercq et al., 2016). Conversely, physical and emotional trauma in early life damages not only organ/tissue development (e.g., brain, gut, immune system) but also microbiome status. Importantly, Zhang et al. (2022) suggested that depressed patients with ELT show different gut microbiome, which might have a mediating effect on the influence of early maltreatment on depressive symptoms.

In many ways, physical and emotional "toxicity" for the microbiome has been understudied and potentially underappreciated in the adult population in general, and in the adolescent population in particular. The microbiome of adolescents (11–18 years old) is distinguishable from those of adults (22–61 years old) by specific taxa and relative abundance of taxa in the gut (Agans et al., 2011). Once again, the rodent models offer the possibility of advancing that the adolescence is a critical window during which the gut microbiome impacts on trauma-associated brain network. In fact, the microbiome changes prior to the end of adolescence can be a unique opportunity to shape neuronal development (Foster and McVey Neufeld, 2013; McVey Neufeld et al., 2016; Flannery et al., 2019). Disrupted development of several neuronal networks involved in emotional functioning, including the AMY, mPFC, and hippocampus, has been observed in germ-free animals (Ogbonnaya et al., 2015; Hoban et al., 2016, 2017, 2018), and these neuronal alterations can be lifelong if microbial reconstitution does not occur

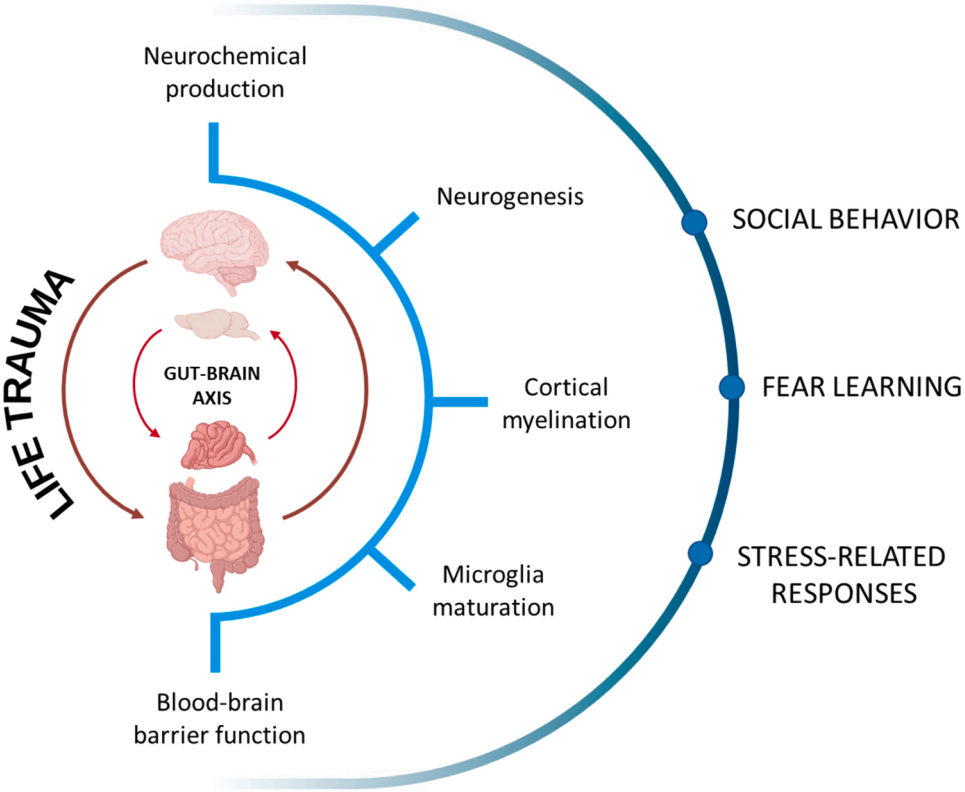

Fig. 3. Gut microbiome and brain interact in modulating life trauma effects in both humans (larger red circle) and mice (smaller red circle). Gut microbiome affects neurochemical production, neurogenesis, cortical myelination, microglia maturation, blood-brain barrier function, as well as fear learning, stress-related responses, and social behavior.

before adolescence. Antibiotic depletion of the gut microbiome during adolescence leads to wide changes in concentrations of various neuromodulators and metabolites (Desbonnet et al., 2015).

Callaghan et al. (2020) explored associations between mood and gastrointestinal distress by utilizing data from a population of adolescents raised with their biological parents or exposed to ELT. Adverse care is associated with increased incidence of gastrointestinal symptoms, and gastrointestinal symptoms are associated with internalizing behaviors and anxiety. Interestingly, previous trauma is associated with changes in microbial communities, and, in turn, bacteria levels are correlated with PFC activation to emotional faces.

Overall, the gut microbiome may be viewed as a determinant in modulating the risk for psychiatric disorders. It is therefore possible to propose that the adolescence is a susceptible period for the communication between microbiome and brain. Building a mechanistic understanding of the pathways through which trauma might affect both microbiome and behavioral symptoms is an important step to identify high-risk target groups for early interventions.

7. Interpersonal and personality traits influence trauma-related externalizing/internalizing behaviors in adolescence

The analysis of the interpersonal and personality traits that influence the responses to trauma in adolescence allows interesting reflections.

Regarding behavioral modeling, caregivers are a vital source of information on numerous domains as social cognition, emotion regulation, and threat-safety discrimination. On such a basis, caregiver's modeling has a major impact on risk for trauma-related disorders in adolescents. For example, parental anxiety can be directly transmitted to adolescent offspring (Eley et al., 2015) and can be mitigated by parental coaching (Ginsburg et al., 2015). Parental anxious rearing also mediates the effects of adversive life events on adolescents (Platt et al., 2016). Namely, parental psychological disorders are associated with offspring's distress, behavioral problems, and altered HPA axis functioning, particularly when parent and young are exposed to interpersonal violence (Leen-Feldner et al., 2013; Lambert et al., 2014). Furthermore, maternal emotion dysregulation increases risk for offspring's trauma-related symptoms (Powers et al., 2020), while lower levels of parent distress following young's trauma predict more favorable outcomes for the young (Pine and Cohen, 2002). Finally, improvements in parental distress mediate broad improvements in internalizing and externalizing symptoms in traumatized youths (Pine and Cohen, 2002; Yasinski et al., 2016).

It appears also likely that ELT destroys individuals' secure attachment and self-esteem, impairs homeostatic regulation, peer relationships, and stress resilience (Cicchetti and Lynch, 1995; Lowell et al., 2014), as well as reduces school achievements during adolescence (Greger et al., 2016). Importantly, Vejnović et al. (2019) reported that traumatized adolescents have difficulties in the development of personality (character and temperament dimentions). Traumatized adolescents show low co-operativeness, self-direction and persistence, which may be related to the difficulty of setting goals for themselves, to achieve an independent identity, to be self-confident, as well as to be persistent and tolerant of the frustrations.

Particular personality traits are closely associated with internalizing/externalizing dimensions (Kotov et al., 2010; Fletcher et al., 2016). Internalizing behaviors are associated with high levels of negative emotionality that characterizes personality traits linked to avoiding dimension, such as neuroticism and harm avoidance. Conversely, externalizing behaviors are associated with high levels of disinhibition that characterizes personality traits linked to approaching dimension, such as extraversion and novelty seeking.

Personality traits critically impact on the association between ELT and psychopathology observed later in life, such as depression (Clark and Diamond, 2010; Rosellini and Brown, 2011; Hayashi et al., 2015; Hovens et al., 2016). According to the five-factors model of personality, while in traumatized youngs higher neuroticism levels are accompanied by depressive symptom in adulthood (Huang et al., 2016), extraversion, conscientiousness, and emotional stability are protective factors for depression severity (Rosellini and Brown, 2011; Hayashi et al., 2015; Hovens et al., 2016; Lee and Song, 2017). These findings indicate that ELT may lead to unfavorable personality traits and cognitive styles that likely support the development of internalizing symptomatology.

Similar to the findings reported in studies on adult subjects, Rudolph and Klein (2009) described that in adolescents higher depressive symptoms predict higher depressive personality traits. Oshri et al. (2013) found that adolescents with childhood maltreatment have a compromised personality organization, and an increased risk for psychopathology. Once more, Zhang et al. (2018) examining the relationship between ELT, personality traits, and depressive symptoms in Chinese adolescents indicated that personality style may mediate the association between child trauma and internalizing behaviors.

Furthermore, there is a general consensus that ELT when combined with specific personality temperaments (namely high harm avoidance that corresponds to neuroticism and novelty seeking that corresponds to extraversion) may be predictive of the development of adolescent externalizing conducts, as borderline personality disorder (for a review see Bozzatello et al., 2021).

However, it must be noted that the impact on personality development exerted by the ELT is not homogeneous and causative and the combinations of ELT and personality traits may be numerous in developing internalizing or externalizing symptoms.

8. Conclusions

Research has demonstrated that early trauma is not constrained to a moment, but it comes out during adolescence and lingers over the entire lifetime with pervasive long-term ramifications (Cowell et al., 2015). However, older ages (as a transition phase to adolescence) may be a sensitive period to trauma as well (Pechtel et al., 2014). In any case, it cannot be excluded that the age of greatest impact will vary depending on the domain of functioning. The adolescent brain/body is vulnerable to environmental perturbations, and traumatic experiences occurring before or during this period have an increased saliency in affecting the cognitive and emotional domains, and in enhancing the risk of adolescent externalizing/internalizing behaviors.

Trauma determines a constellation of neuronal, endocrine, immune, and epi/genetic signatures at nearly every level of analysis, from cellular signaling to behavioral expression. Trauma-induced alterations impact on trauma-sensitive regions (AMY, mPFC, hippocampus, and ventral striatum) and on the development of the targets which they project to as well.

Trumatized adolescents show a stronger negative AMY-mPFC functional connectivity - a more mature, adult-like pattern of connectivity – (with increased AMY reactivity) associated with internalizing behaviors, such as avoidance and depression (Burghy et al., 2012a; Goff et al., 2013; Hanson et al., 2015; Wolf and Herringa, 2016), while the connectivity of the inferior frontal gyrus may be associated with externalizing behaviors, such as impulsivity (Herz et al., 2014; Wang et al., 2016; Barch et al., 2018a).

Thus, in the face of trauma adolescents may develop adult-like patterns of connectivity, that play a protective role against adversities. However, this protective strategy comes at a great cost, paid with the premature end of the sensitive childhood period. This accelerated maturation blocks the prolonged synaptogenesis and dendritic/synaptic pruning, neuroplasticity, and the neuronal connectivity that is typical of adolescents.

Notably, in traumatized adolescents (especially in females) the altered functional connectivity between AMY and mPFC associated with internalizing problems is predicted by increased cortisol levels (Burghy et al., 2012a), as well as common variation in IL-6 may sensitize adolescents to the internalizing effects of trauma (Pouget et al., 2022).

Modern large-scale approaches to understanding genomics, epigenetics, and transcriptomics have transformed our understanding of biomarkers and biological factors that differentiate risk vs. resilience in the aftermath of trauma. This review analyzed some of the different examples in recent years that have examined specific trauma-related pathways mediating threat and deprivation effects, as well as the new findings emerging from the largest multi-omic studies (Minelli et al., 2018; Dalvie et al., 2020). This significant genetic sharing between trauma and internalizing/depressive symptoms may represent a mechanism of predisposition to post-traumatic psychopathology.

In this context, the growing field of epigenetics provides a conceptual framework that adds insights into the mechanisms of trauma, potentially leading to novel preventive, diagnostic, and therapeutic approaches (Dunn et al., 2019; Keverne and Binder, 2020). Specifically, decoding the trauma epigenetic mechanisms in adolescence is crucial to unveal how early experiences are embedded in biological systems and exert influence on development and health throughout the lifespan.

Another promising approach recently employed to address the consequences of trauma in adolescence is the sudy of gut microbiome, given the adolescence is a susceptible period for the communication between gut and brain. Traumatized adolescents show changes in microbial communities, a correlation between gut bacteria levels and PFC activation, as well as gastrointestinal symptoms associated with internalizing behaviors and anxiety (Callaghan et al., 2020).

Elucidation of the biology of adversities and its effects in adolescence is certainly only part of the equation for reducing the consequences of the unfortunate experiences. Future studies should ideally capture both parental modeling as well as temperamental dispositions to fully understand trauma effects and risk for internalizing/externalizing behaviors in adolescence.

Overall, it is possible to advance that traumatic experiences leave a sign on personality development, increasing the probability to have negative personality traits, which may further influence traumatized subject's future wellbeing. For example, high neuroticism that corresponds to negative emotion, and low extraversion that corresponds to avoid social interaction and inhibit emotional expression, may enhance the occurrence of depressive symptoms in adolescents which could benefit from prevention strategies based on personality re-organization (Rosellini and Brown, 2011; Hayashi et al., 2015; Hovens et al., 2016; Huang et al., 2016; Lee and Song, 2017).

Finally, we would like to conclude on a note of hope. Life experiences, even if traumatic, are not determinative and with ineluctable consequences, since the adaptive plasticity of adolescence marks it as a window of opportunity for change through mechanisms of resilience, recovery, development and health promotion.

Declaration of Competing Interest

The authors report no declarations of interest.

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