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Early Childhood Abuse: Adult Impulsivity and Risky Behavior

Abuso na infância: impulsividade no adulto e comportamentos de risco

Elisabete Castelon Konkiewitz [1, *], Soraya Seedat [2], Edward Ziff [3]

1) Faculdade de Ciências da Saúde (FCS), Universidade Federal da Grande Dourados (UFGD), Mato Grosso do Sul, Brasil. 2) Department of Psychiatry, Faculty of Medicine and Health Sciences, Tygerberg Campus, Stellenbosch University, Cape Town, South Africa. 3) Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, USA.

Abstract
We review the role of childhood abuse (CA) in the practice of impulsive, risk-taking behaviors during adulthood. CA deregulates the adult response to stress, which in turn disrupts the prefrontal-striatal systems that provide executive control over reward-related behavior. The result is impulsivity and risk-taking, including self-medication with drugs and alcohol and the practice of unsafe sex. These behaviors decrease quality of life and impair the attainment of long-term goals. Risky sexual behavior, in particular, increases the chance of HIV infection and perpetuates the epidemic.

Keywords: childhood abuse, early life stress, impulsivity, risky behavior, reward, HIV.

Resumo
Revisamos o papel do abuso na infância na prática de comportamentos impulsivos e de risco durante a vida adulta. O abuso na infância desregula a resposta do adulto ao estresse, o que, por sua vez, impede os circuitos frontoestriatais de fornecerem o adequado controle executivo sobre comportamentos associados à recompensa. O resultado é a impulsividade e escolhas de risco, incluindo automedicação com drogas e álcool e a prática de sexo inseguro, reduzindo a qualidade de vida e prejudicando o alcance de metas de longo prazo. O comportamento sexual de risco, em particular, aumenta a chance de infecção pelo Vírus de Imunodeficiência Humana e perpetua a sua epidemia.

Palavras-chave: *abuso na infância; estresse na infância; impulsividade; comportamento de risco; recompensa; HIV.*

Introduction

Behavior has a large impact on quality of life, and adverse behaviors can impair the health of the individual and the achievement of long-term goals. Impulsivity and risk taking

[*] **Konkiewitz, E.C. -** E-mail: ecastelon@hotmail.com; **Seedat, S. -** E-mail: sseedat@sun.ac.za; **Ziff, E. -** E-mail: edward.ziff@nyumc.org

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are two such behaviors. Recent research has shown that childhood experiences can influence the incidence of impulsivity and risk taking in the adult (Norman et al., 2012).

Trauma can be understood as an emotionally overwhelming experience that overcomes the ability of the individual to cope and that presents the world as threatening, beyond control and unpredictable (Foa, Zinbarg, & Rothbaum, 1992). Thus, trauma is defined by the character of the experience, by the individual's interpretation of the experience of the event and not by the nature of the facts themselves (Toth, Cicchetti, Macfie, & Emde, 1997). Trauma can arise from a single event; however, it more commonly arises from a repeated pattern of abuse.

The term "childhood abuse" encompasses various forms of sexual, physical and emotional abuse as well as neglect. Of the different forms of abuse, emotional abuse is the most difficult to characterize, precisely because it is most subjective. It can occur through actions or words that imply fear, humiliation, threat, or deprecation (Glaser, 2002). Neglect is defined by the failure of the caregiver to meet the basic needs of the child, such as food, shelter, safety and supervision, or to provide for the child's psychological needs through encouragement, acceptance, warmth, love, and support (Foa et al., 1992; Toth et al., 1997; Glaser, 2002).

In this review, we discuss what constitutes impulsive behavior and how it can have an impact on personal well-being. We discuss the neural systems that are regulated by stress and how childhood abuse (CA) alters the stress response itself. We then relate the impact of such alterations upon an individual's reward system, leading to risky behavior and impulsive acts in adulthood, including enhancing risks for infection by the HIV virus. We conclude with a discussion of the great importance of future research for a better understanding of the pathways linking CA to impulsivity.

1. What constitutes impulsive behavior? Impulsivity and its different forms

Impulsivity has been defined as "predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others" (Hamilton et al., 2015). Impulsive behavior compromises attainment of personal goals and often results in bad consequences. Impulsive actions 'are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and … often result in undesirable consequences (Daruna, 1993). The effects of impulsivity may be transmitted to succeeding generations by social mechanisms, such as when an abused female child becomes an adult mother who exposes her offspring to a stressful childhood. In humans, impaired maternal care takes place when mothers neglect their children (De Bellis, 2005) and in rodents when the mother is separated from her young (Vetulani, 2013). Much of the impairment in the case of humans is rooted in poor lifestyle choices reflecting impulsive behavior (Mitchell & Potenza, 2014).

From the perspective of making decisions and taking actions, impulsivity may take several forms (Dalley & Robbins, 2017). An impulsive individual may choose a smaller, immediate apetitive stimulus rather than a larger, delayed one, a choice called *temporal discounting*. Or a person may prefer a smaller, more likely reward over a larger, less likely one, a preference called *probabilistic discounting*. Or one may make a rapid decision, before all factors pertinent to the decision are known and evaluated, called *reflection impulsivity*. Or one may engage in inherently risky acts, which is the performance of *impulsive motor activity*.

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2. Neural systems for impulsivity

Acting impulsively represents a failure to make the better choice when presented with alternative courses of action. The brain's reward system, located in subcortical regions of the brain, controls motor cortex and the performance of acts that lead to the experience of reward. These systems also provide feelings of pleasure associated with rewarding acts (Berridge & Kringelbach, 2015). The prefrontal cortex restrains the performance of such acts by estimating the relative benefits of alternative actions and suppressing those acts that are risky and enhancing the ones that are beneficial (Figure 1). Specifically, the striatum (Str) and nucleus accumbens (NAc) drive the execution of reward-related behavior, while the executive, decision-making functions of the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) provide top-down control of reward-related motor activity (Sharpe et al., 2018). The PFC/ACC and Str/NAc signal to one another by multiple inter- and intra-regional connections, and when PFC/ACC control of this signaling is disrupted, impulsive actions gain the upper hand and self-regulation fails. As an example, during control of the desire to eat unhealthy food, the ventromedial PFC (vmPFC) calculates the basic, immediate payoffs of the different options for food consumption (e.g., the sweetness or tastiness of individual choices), while the dorsolateral PFC (dlPFC) estimates the more abstract, long term factors, such as healthiness. Signals from the dlPFC inhibit vmPFC function to delay gratification in favor of health (Hare, Camerer, & Rangel, 2009). This modulation is required for effective delay discounting (appreciating the long-term value of healthy eating), and for the fulfilment of long-term dietary goals, such as establishing proper nutrition.

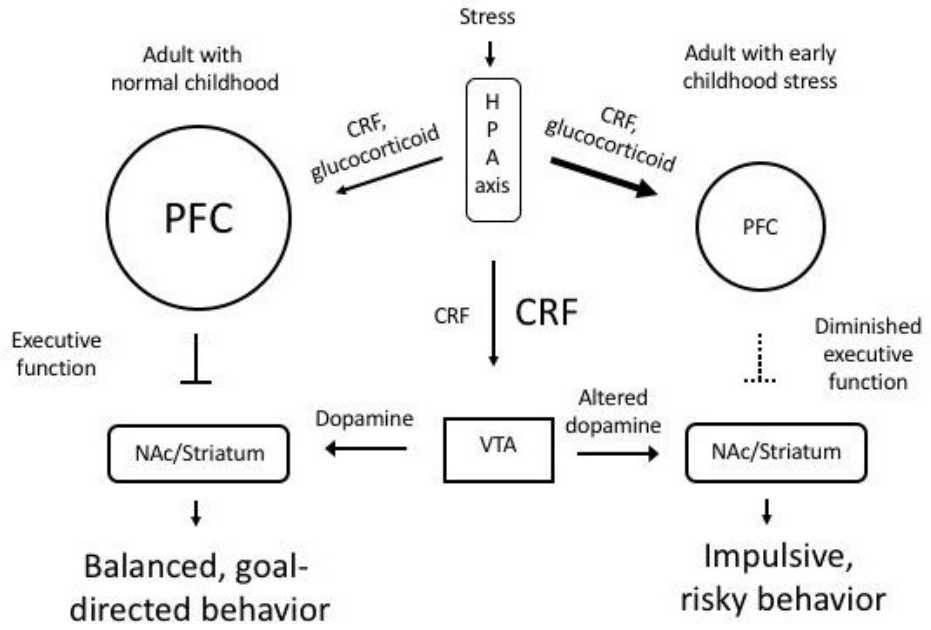

Figure 1- Model for the dysregulation of the HPA axis by childhood abuse. a) In an adult with a normal childhood, stress activates the hypothalamus (H) to express corticorophin releasing factor (CRF), which stimulates the pituitary (P) to express ACTH, which stimulates the adrenal medulla (A) to release glucocorticoids, which in turn regulates various body functions to provide the response to stress. b) With time, glucocorticoids interact with glucocorticoid receptors (not shown) to repress expression of CRF and ACTH, leading to a decrease in glucocorticoids and a termination of the stress response. c) In adults who experienced childhood abuse, expression of the glucocorticoid receptor is diminished by an epigenetic mechanism (not shown – see text),

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leading to a failure of the negative feedback loop and continued expression of CRF and ACTH and glucocorticoids and the stress response. Such individuals exhibit impulsive, risky behavior.

Corticostriatal circuits are components of yet larger cortico-striato-thalamo-cortical (CSTC) loops that control reward-related behavior. These circuits convey information from cortex through striatum to thalamus, and back to cortex (Berner & Marsh, 2014). The CSTC loops provide executive functions that enable the attainment of particular goals (Funahashi & Andreau, 2013). A model for CTSC function proposes that the striatum, acting within these circuits, provides action selection, which is the choice between two or more different courses of action that contend for execution (Redgrave, Prescott, & Gurney, 1999). The striatum lies in the path between cortical command systems that dictate motor behaviors and the motor systems that carry them out. The tonic inhibitory output from the striatum to the thalamus prevents the execution of motor behaviors. Selective relief of tonic inhibiton is necessary to release the execution of any given motor act while maintaining repression of other competing ones, as is appropriate. Thus the model suggests that commands for different motor behaviors can be disinhibited selectively. This relases the execution of one action while continuing to repress others. Selectivity is particularly important when the system is presented with commands for actions that are incompatible, such as speaking and swallowing water. The action selection function of the striatum gathers sensory and body state information relevant to the alternative actions and selects the one that is optimal for the time, for example drinking water rather than speaking if one is thirsty. The action selection function of the striatum is particularly significant when the alternative actions have very different relative benefits, such as is the case in which temporal discouting (taking a smaller but sooner reward) or probabilistic discounting (taking a smaller but more likely reward) is invoved. There are at least five such CSTC loops (Alexander, DeLong, & Strick, 1986; Peters, Dunlop, & Downar, 2016) that neuroanatomically lie parallel to one another. Three loops are particularly significant for impulsivity. One is the dorsolateral prefrontal cortex (dlPFC) CSTC loop that initiates within the dlPFC and projects through the striatum and thalamus back to the dlPFC. This loop provides top-down regulation of goal-directed behavior (Furman, Hamilton, & Gotlib, 2011) Malfunction of this loop can lead to making impulsive choices.

Release of the neurotransmitter, dopamine, by midbrain mesocortical and mesolimbic dopamine systems into frontostriatal regions of the CSTC loop provides a neurochemical representation of both the anticipation of reward and the hedonic experience of reward (Schultz, 2016). Dopamine interacts with dopamine receptors of cortical and striatal neurons to enable the past experience of reward and the anticipation of future reward to influence our choice of behaviors (Baik, 2013). The functions of these regulatory pathways are disrupted by ECS.

3. The body's response to stress: Function of the HPA axis

The body employs two major pathways to respond to stress and threat. The more rapidly acting stress pathway, the sympathoadrenomedullary (SAM) response (Ulrich-Lai & Herman, 2009), also known as the flight or fight response, responds in seconds to minutes to acute stressors. The second, the hypothalamic-pituitary-adrenal medullary (HPA) axis pathway (Pariante & Lightman, 2008), is slower and more prolonged in its function than the SAM response, normally lasting minutes to hours. However, under prolonged stress conditions, the response may persist for days or longer (Smith & Vale, 2006). In the function of the HPA axis pathway, perception of stressors by the brain stimulates the paraventriclar

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nucleus (PVN) of the hypothalamus to release the peptide, corticotrophin releasing factor (CRF), also called corticotropin releasing hormone (CRH). The PVN also releases arginine vasopressin (AVP). CRF and AVP activate the pituitary to produce ACTH, which stimulates the adrenal medulla to release glucocorticoids (GCs), which in humans is cortisol (Figure 2a) (Juruena, 2014). GCs elevate blood pressure and the production of glucose from glycogen, and improve emotional memory and vigilance.

GCs bind to GC receptors (GRs), which are members of the nuclear receptor superfamily of ligand-dependent transcription factors that reside in the cytosol until activated. Binding of GCs to the GR activates the receptor, which translocates to the nucleus where it regulates gene transcription (Weikum, Knuesel, Ortlund, & Yamamoto, 2017). Significant for this review, activated GRs repress the CRF gene in hypothalamic corticotrophs of the PVN (Dostert & Heinzel, 2004; Malkoski & Dorin, 1999). Thus, during the normal HPA axis response to stress, CRF levels rise and then fall, limiting pituitary production of ACTH and the release of new GC by the adrenal medulla (Figure 2b). The activated GR also represses the gene for pro-opiomelanocortin (POMC), the precursor to ACTH (Keller-Wood, 2015). Activated GRs shut down the immune response as well by inactivating NF-kB, a transcription factor that controls immune function by regulating the expression of inflammatory cytokines and antimicrobial agents, as well as genes that control the development and proliferation of cells of the immune system (Glass & Saijo, 2010; Hayden, West, & Ghosh, 2006; Ratman et al., 2013). Thus, the activated GR represses both the response to stress via the HPA axis and the response via the immune system. Given these roles for the GR, it is apparent that reduction of GR expression will augment or prolong the stress response by relieving the HPA axis from its GR-dependent negative autoregulation (Figure 2c) (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Kitraki, Karandrea, & Kittas, 1999; Pariante & Lightman, 2008; Raison & Miller, 2003). Loss of GR function also relieves the immune response from negative regulation, placing individuals in a state of chronic inflammation.

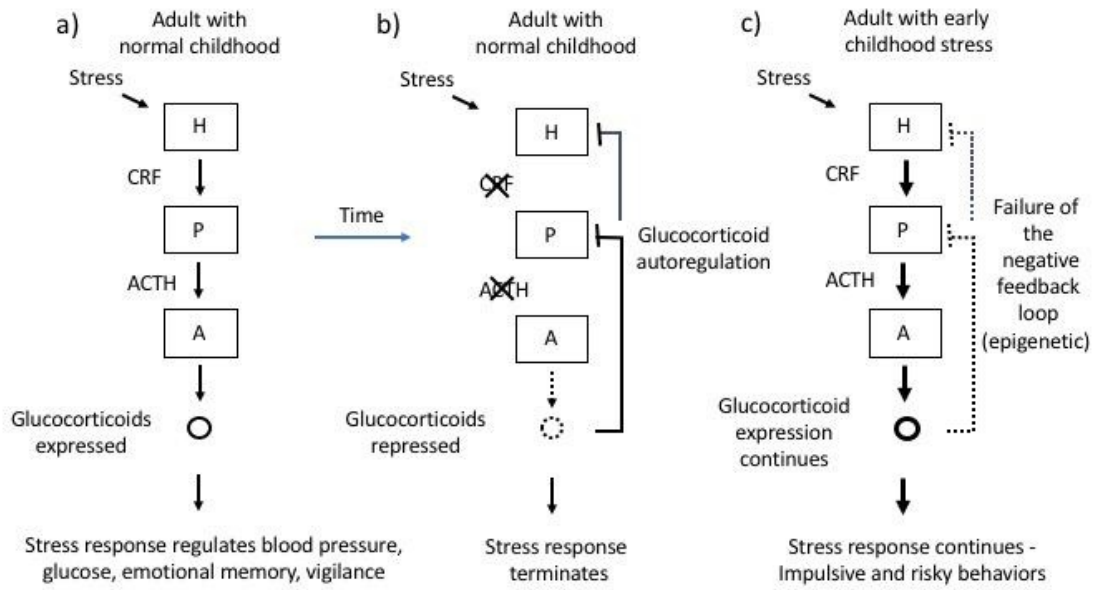

Figure 2 – Model for the dysregulation of 65rea65x65ntal 65rea65x (PFC), nucleus accumbens and striatum (Nac/Striatum) and ventral tegmental 65rea (VTA) by childhood abuse leading to impulsive behavior in the adult.

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Reward-seeking behavior is driven by the nucleus accumbens and striatum (NAc/Striatum) but is limited by executive functions provided by the prefrontal cortex (PFC). The result is the performance of balanced goal-directed behaviors. In adults who experienced childhood abuse, development of the PFC is altered, diminishing its capacity to provide executive functions and capacity to regulate reward-seeking behavior driven by the NAc/Striatum. Overexpression of glucocorticoids can also cause PFC atrophy, which limits executive functions provided by the PFC. The result is the performance of impulsive, risky behaviors. In the adult with childhood abuse, expression of CRF by the hypothalamus and of dopamine by the ventral tegmental area (VTA) are modified (see text) compounding impulsivity.

4. How HPA axis function is altered by stressful, early childhood experiences

The level of stress experienced in early childhood adjusts the adult response to stress and reward, and when childhood stress is severe or repeated, it may shift a stress pathway's homeostatic set-point in the adult (Juruena, 2014). Repeated, extreme levels of stress in childhood can result in exaggerated stress response and diminish responses to rewarding stimuli in adult (Juruena, 2014; Matthews & Robbins, 2003).

CA alters the regulation of expression of the GR by epigenetic mechanisms, causing malfunctions that can culminate in impulsivity (Anacker, O'Donnell, & Meaney, 2014; Heim & Binder, 2012; McGowan, 2013; Oberlander et al., 2008; Weaver et al., 2004). In general, epigenetic mechanisms control the activities of genes by introducing epigenetic marks, specifically by methylating DNA or by modifying histones, or by inducing expression of non-coding RNAs (Chen, Li, Subramaniam, Shyy, & Chien, 2017). Epigenetic regulation, however, leaves the DNA nucleotide sequence of the gene itself intact. Epigenetic marks can be induced by environmental influences, and in some cases are heritable. In the case of CA in rat and human, stress elevates the introduction of repressive methyl marks in the promoter of the gene that encodes the GR, the NR3C1 gene, and these methyl marks repress GR expression (McGowan et al., 2009; Palma-Gudiel, Cordova-Palomera, Leza, & Fananas, 2015; Turecki & Meaney, 2016). This results in a decline in the levels of the GR, which relieves HPA axis auto-regulation, releasing the HPA axis to continue to function in a pathological fashion.

5. Study of CA negative regulation of GR expression with animal models

Much of the evidence for the effects of CA on the HPA axis comes from studies of animal models. In the maternal separation (MS) early life stress model, pups are removed from the mother for 3 hours per day (Bailoo, Jordan, Garza, & Tyler, 2014; Vetulani, 2013). In the naturalistic early life stress model (Raineki, Cortes, Belnoue, & Sullivan, 2012), pups are housed with limited nesting or bedding material (Avishai-Eliner, Gilles, Eghbal-Ahmadi, Bar-El, & Baram, 2001; Gilles, Schultz, & Baram, 1996; Ivy et al., 2010), which decreases the mother's ability to construct a nest, leading pups to spend less time nursing. The lack of bedding also causes stress in the mother leading her to maltreat the pups. In both of these models, GR expression in the pups decreases (Lutz & Turecki, 2014; Meaney & Szyf, 2005; Zhang, Labonte, Wen, Turecki, & Meaney, 2013). Significantly, when the mother provides more extensive care in the form of perinatal pup licking and grooming and arched-back nursing, GR promoter methylation declines and GR expression increases, in the hippocampus, limiting the HPA-axis stress responses observed when the offspring grew to be adult (van Hasselt et al., 2012; Weaver et al., 2004). As the pup received greater maternal care, the expression of

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hypothalamic CRF mRNA was reduced (Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997; Weaver et al., 2004), consistent with maternal care limiting HPA axis activity. Thus, a less maternal care increased stress pathway activity, while greater maternal care decreased this activity, all by controlling GR expression. In rhesus monkeys, stress of a pregnant mother increased HPA axis function in the offspring, when they matured into adults (Clarke, Wittwer, Abbott, & Schneider, 1994). In humans, CA also reduced the expression of the GR, as was seen in suicide victims (McGowan et al., 2009) and persons with a history of early life abuse (Romens, McDonald, Svaren, & Pollak, 2015). Thus in rodents, non-human primates and humans, maternal behavior programs GR gene expression in the offspring to control HPA axis function (Pariante & Lightman, 2008).

6. Effects of deregulation of the stress response on reward system function

CA is a risk factor for people to carry out impulsive actions in adulthood, without forethought or regard for long-term consequences (He et al., 2018; Lovallo et al., 2013). But, mechanistically, how could the experience of CA have such consequences?

CA modifies reward-related behavior by directly or indirectly altering the circuits that control the responses to reward (Dalley & Robbins, 2017). First, CA has been shown to exert many effects on the brain including changes in gene expression, alterations in the sensitivity of the brain to reward- and stress-related cues, as well as behavioral patterns (Kim et al., 2017). CA can induce changes in dopamine expression that can alter reward-related behavior. CA can also induce changes in oxytocin expression that alter responses to social cues. Changes in GC and CRF expression also take place in individuals exposed to CA that can alter amygdala function and the response of the HPA axis to stress (Kim et al., 2017). Significantly, these effects may also be closely interrelated such that changes in HPA axis function can also regulate the responses of frontostriatal circuits to reward (Arnsten, Raskind, Taylor, & Connor, 2015). As we have discussed, by diminishing HPA axis negative feedback, CA renders the HPA axis more readily activated in adulthood by stressful events (Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008), as was shown by high stress-induced ACTH levels (Heim et al., 2000).

The more ready activation of the HPA axis leads to chronic release of cortisol, which in turn deregulates the control of fronto-striatal signaling, creating both reward surfeits and reward deficits (Marinelli & Piazza, 2002; Oswald et al., 2005; Pruessner, Champagne, Meaney, & Dagher, 2004; Rodrigues, Leao, Carvalho, Almeida, & Sousa, 2011; Vaessen, Hernaus, Myin-Germeys, & van Amelsvoort, 2015; Wand et al., 2007). HPA axis deregulation thereby alters one's motivation to seek and to experience reward.

7. Deregulation of dopamine release

Unregulated HPA axis activity drives the persistent release of CRF within the mesocortical and mesolimbic dopamine systems, which can deregulate dopamine transmission. CRF released by PVN neurons that project to cell bodies of dopaminergic neurons of the VTA (Nemeroff, 2004) stimulates NMDA receptor-dependent glutamatergic signaling onto the VTA dopamine neurons, which increases the release of dopamine into the ventral striatum. Rats raised post-weaning in social isolation exhibited increased firing of VTA neurons as determined electrophysiologically, indicating elevated release of dopamine (Fabricius et al., 2010). Likewise, in rats raised in social isolation, increased levels of dopamine were released into the nucleus accumbens and dorsomedial striatum, as detected by

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voltammetry in brain slices (Yorgason et al., 2016). By this mechanism, social stress enhanced conditioning to reward-related sensory inputs (Polter & Kauer, 2014; Tovar-Diaz, Pomrenze, Kan, Pahlavan, & Morikawa, 2018; Rodaros, Caruana, Amir, & Stewart, 2007).

In some circumstances, CA may diminish the functions of dopamine releasing-and-responding systems (Novick et al., 2018). Notably, one study of early social isolation reported *increased* dopamine turnover in nucleus accumbens but *decreased* dopamine turnover in medial prefrontal cortex (Heidbreder et al., 2000). Thus, dopamine function may be elevated by CA in some brain regions and lowered in others, with each change having the potential to modify reward-related behavior (Rodrigues et al., 2011). The stage of brain development at the time stress is experienced may determine the specific effect on dopamine release, and it is likely that both increases and decreases can adversely affect reward-related behavior selection (Boecker et al., 2014). In this regard, it has been proposed that hyper-dopaminergic function increases the rewarding properties of drugs of abuse, while hypo-dopaminergic function increases drug seeking behavior (Rodrigues et al., 2011), both representing disruption of reward system homeostasis (Febo et al., 2017).

8. Impact of CA on adult conduct and consequences of risky behavior and impulsive acts

CA can manifest itself in many ways neurophysiologically and psychologically in the adult. CA may cause deficits in reward, alter cognition and learning, modify PFC function, deregulate emotions, and impair self appraisal. The associated risk-taking behavior can have significant adverse consequences for well-being, such as increasing the risk of HIV transmission.

9. Reward Deficiency Syndrome: CRF connects CA and the HPA axis to dopamine and the reward system

In keeping with CA exerting a range of effects , one CA outcome is an increased drive to seek reward because of alterations in reward processing that cause a state of reward deficit, referred to as Reward Deficiency Syndrome (RDS) (Blum et al., 2000). RDS is a hypodopaminergic state that may be overcome by drug seeking acts and other forms of impulsivity that elevate dopamine release (Bowirrat & Oscar-Berman, 2005). With RDS, deficits in reward system-dependent release of dopamine suppress normal feelings of well-being (Blum, Gardner, Oscar-Berman, & Gold, 2012). This increases the subcortical drive to engage in impulsive acts that compensate for reward deficit (Febo et al., 2017). Indeed, drug use arising from CA can reduce an individual's capacity to experience natural reward, a form of antireward, leading to reward deficit that stimulates compulsive drug taking and addiction (Koob, 2017).

In animals with CA, ventral striatum-related functions that control reward responsiveness and the willingness to expend effort to secure rewards (approach motivation), and reward seeking-related motor activity were altered (Novick et al., 2018). Notably, the nature of the change depended upon the stage of development at which stress was experienced. Stress experienced at a very early stage diminished ventral striatum-related functions, while stress at later times in development enhanced them. The impulsive escape behavior that compensates for depression following CA has been compared to the enhanced drug-seeking behavior of addicts who have withdrawn from cocaine administration and have entered "the dark side" of addiction, a state of reward deficit. In this depressed, "dark side" state, a CRF-dependent mechanism enhances cocaine seeking (Roberto, Spierling, Kirson, &

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Zorrilla, 2017) and indeed, a CRF receptor antagonist, administered to the VTA, reduced binge alcohol consumption in animals that had experienced maternal separation (Gondre-Lewis et al., 2016).

10. Deficits in cognition and learning

During the period of vulnerability to CA and maltreatment, children acquire fundamental cognitive and learning skills. As described by Gregorowski and Seedat (Gregorowski & Seedat, 2013), these include, during the first two years, acquisition of symbolism, basic language skills and awareness of the self as an agent that can take actions based on personal knowledge. During the third and fourth years, development continues to make possible the ability to discriminate emotions from intentions and impulses, and the ability to integrate new information and to anticipate the consequences of future events based on past experiences. It has been proposed (Gregorowski & Seedat, 2013) that early childhood trauma disrupts the brain development that provides these developmentally-acquired capacities. This disruption focuses the individual's attention on avoidance of potential threats, and the emergence of hypervigilance and refusal to rely on caregivers. These are distortions in the categorization of new information, creating a bias that all new encounters are menacing and potentially traumatic.

Traumatic experiences in childhood may thereby teach a person to be hypervigilant and to see the world as a dangerous place. The person may interpret neutral cues as threatening. This is reflected by increased amygdala activity upon seeing faces or other normally neutral cues (Lupien, McEwen, Gunnar, & Heim, 2009; Pervanidou & Chrousos, 2018). Traumatic experiences in turn increase cortisol, which is toxic for the hippocampus and for the PFC. The PFC normally downregulates amygdala responses, but in traumatized people, it fails to do so.

11. Prefrontal cortex dysfunction

The PFC is particularly vulnerable to stress (Arnsten, 2009, 2015) and expresses high levels of GRs that are activated by GCs released during stressful periods to stimulate glutamatergic afferents to the VTA, which in turn release high levels of dopamine back in the mPFC (Butts & Phillips, 2013; Butts, Weinberg, Young, & Phillips, 2011). The PFC also expresses CRF receptors (Butts et al., 2011) enabling CRF to modulate the PFC response to stress (Jaferi & Bhatnagar, 2007). Furthermore, the continued activity of the HPA axis is neurotoxic to the PFC (Lupien, Juster, Raymond, & Marin, 2018), further impairing the executive functions that limit impulsivity. Significantly, higher impulsivity and depression in 7-21 year old's was associated with decreased cortical thickness, in particular for ventromedial PFC/medial OFC, consistent with a role for these regions in constraining impulsivity and associated depression (Sivaramakrishnan, Gordon, Halliday, & Herman, 2018).

12. CA leads to emotional dysregulation

The ability to regulate one's behavior and emotions is essential for maintaining personal well-being. Self-regulation makes harmonious social interactions, the achievement of goals and "making the better choice" possible when presented with alternative courses of action. Self-regulation provides the ability to control impulses and to limit actions that are risk-taking and harmful to one's well-being, such as smoking, substance abuse, binge eating and

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unprotected sex. Self-regulation requires a balance between the drive to commit impulsive acts that provide immediate reward and the restraint and self-control that enable us to delay actions for the sake of long-term benefits.

If one cannot regulate one's emotions or affect - if one cannot stop being angry, or extremely sad - then one may take an action that, although harmful, for some reason brings relief and enhances the feeling of being alive, and may be necessary because normal experiences cannot bring these rewards. Such actions may be enhanced because CA has altered brain development, for example by impairing the function of the dopamine system so as to create a barrier to the experience of reward that gives rise to reward deficit syndrome (Febo et al., 2017).

Persons with CA often experience persistent depression, anxiety about threats and a lack of trust in others. They form unrewarding social relationships and may employ impulsive acts to escape from these inadequacies (Miller, Chen, & Parker, 2011). In general, CA reduces transmission of PFC regulatory signals to the Str/NAc (Watt, Weber, Davies, & Forster, 2017), which in turn unleashes the execution of unhealthy behaviors. Furthermore, persons with adverse childhood experiences (ACE) often perceive that others have negative attitudes towards them, which is another source of depression (Salokangas, From, Luutonen, & Hietala, 2018). The balance of executive functions versus reward drive provides a buffer that protects us from extremes of emotion as well as from extremes of reward-seeking actions (Dalton, Wang, Phillips, & Floresco, 2016; Wallis, 2007). This buffer keeps one in an emotional steady-state and makes it possible for one to bring one's self back into emotional balance after having been enraged, or frustrated. When this intrinsic buffering system does not function well, individuals may try to overcome the emotional imbalance by seeking reward from outside.

Stress, negative emotional feelings, depression and exposure to overwhelming temptations deplete self-regulatory resources and disrupt the balance between subcortical drive and prefrontal constraint (Devilbiss, Spencer, & Berridge, 2017; Gee et al., 2018; Park & Moghaddam, 2017; Park, Wood, Bondi, Del Arco, & Moghaddam, 2016). From the perspective of affective neuroscience, early childhood trauma disrupts the balance between the individual's SEEKING and SADNESS networks, resulting in emotional dysregulation and leading to depression and addictive behaviors (Fuchshuber, Hiebler-Ragger, Kresse, Kapfhammer, & Unterrainer, 2018). Such imbalances in reward valuation are evident on fMRI while subjects are making reward-related choices (Dalley & Robbins, 2017; Mason, O'Sullivan, Montaldi, Bentall, & El-Deredy, 2014).

13. CA shapes cognitive appraisal of life and self

When considered from a cognitive perspective, we may expect that people who have had bad experiences in childhood will develop a pessimistic and distrustful appraisal of life. Childhood abusive experiences will have taught a young adult that life is not fair, that good behavior does not lead to success, that one can be betrayed, and that one should take what one has now (seek an immediate reward) and not expect much from the future. The future might not come, and thus long-term benefits or rewards are not worth sacrificing short-term pleasures for. In this line of reasoning, risky behavior means that the person does not really care (i.e., exhibits failure to strive for healthy, long-term goals). Persons raised in environments with few resources are more likely to fear that they will be taken advantage of and will be maltreated. The negative feelings may arise from cognitive processes: beliefs about life and about one's self, namely what one thinks life is about and what one believes one to be, one's self-esteem, what one deserves and what one has the right to expect from life. Young

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black American men raised in a resource-poor rural setting and exposed to neglect, family violence and other forms of childhood adversity expressed mistrust of the motives of romantic partners, were cynical of close relationships and had difficulties in forming strong attachments upon entering adulthood (Kogan, Cho, & Oshri, 2016).

Adolescent girls who were subject to sexual abuse displayed impulsive behavior (Kendler et al., 2000), and the greater the severity of the abuse, the greater their sexual vulnerability and sexual at-risk factors and the likelihood of pregnancies in adolescence (den Hartog & Lotens, 2004; Fergusson, Horwood, & Lynskey, 1997; Noll, Shenk, & Putnam, 2009; Senn, Carey, Vanable, Coury-Doniger, & Urban, 2007). If a child is sexually abused by a trusted adult, he/she is likely to develop a sense of betrayal, and may engage in sexual risk-taking if they believe it will secure affection. Ultimately, the child may develop a sense of powerlessness.

14. Effects of impulsivity on HIV transmission and the continuation of the AIDS epidemic

Finally, we consider a special health-related case of the effects of impulsivity and risk taking behavior: increase in the chance of transmission of HIV and the resulting continuation of the AIDS epidemic. Despite having the means for diagnosis, prevention and treatment of HIV infection, individuals continue to engage in impulsive, risk-taking behaviors such as unsafe sex, needle sharing and non-adherence to Combined Antiretroviral Therapy (CART), thereby increasing the chance of HIV transmission and propagating the AIDS epidemic. If we are to contain and eventually eliminate the epidemic, we need to understand why intelligent, young, well informed people engage in these unhealthy behaviors and risk infection with HIV.

For a long time, it has been known that people living with HIV/AIDS (PLHIVA) have high rates of childhood trauma (Bensley, Van Eenwyk, & Simmons, 2000; Boroughs et al., 2015; Hein, Dell, Futterman, Rotheram-Borus, & Shaffer, 1995; Kimerling, Armistead, & Forehand, 1999; Mimiaga et al., 2009; Pao et al., 2000; Pence et al., 2012; Reif, Geonnotti, & Whetten, 2006). This raises the question of whether there is a link between early life experiences and the behavior associated with risk of HIV infection. As we have discussed, studies show that CA, such as caused by neglect and exposure to violence and sexual abuse in childhood, has a large, adverse impact on the adult, and is often associated with impulsivity and risk-taking behaviors (Juruena, 2014; Lovallo, 2013). Moreover, experiencing a resource-poor childhood environment, such as being reared in a home lacking effective parent-child contact and encouragement, can have effects similar to overt adversity and can, in turn, lead to an inability to form healthy romantic relationships as well as to engage in risk-taking sexual behavior (Kogan et al., 2016). Significantly, for people with disorders of depression, anxiety and substance abuse, the age of onset for these disorders is earlier for those with childhood maltreatment (Dubey, Raza, Sawhney, & Pandey, 2013). The risk for drug taking is increased 3-fold by non-genital sexual abuse and nearly 6-fold as much with abuse involving intercourse. Adults with five or more adverse childhood events are also 7-10 times more at risk for drug abuse than those without such events.

The great majority of HIV infections arise by transmission of the virus via risk-taking, impulsive acts (https://www.cdc.gov/hiv/risk/estimates/riskbehaviors.html; accessed July 18, 2018), including forms of unsafe sex and needle-sharing during drug injection. Because the chance of infection increases with the frequency of these acts, impulsivity arising from CA may have a great impact on the likelihood of viral transmission.

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15. Importance to society of secure and trauma-free rearing of children

Childhood experiences have a large impact on adult behavior, and the capacity for early life stress to induce risky behavior and impulsivity in adult life significantly impacts personal well-being. Substantial evidence supports our argument that CA increases impulsive behaviors that place individuals at greater risk for HIV infection or transmission of the virus (Devieux et al., 2002; Latimer, Fleckman, Wallace, Rountree, & Theall, 2017; Semple, Zians, Grant, & Patterson, 2006). Multiple neural systems and processes contribute to behavior formation, including frontostriatal circuits for executive control of reward-related behaviors, and the HPA axis and stress-response pathways, plus related immunological systems. These systems are all highly interconnected and their functions are calibrated (and re-calibrated) during brain development into adolescence and beyond to adjust the adult response to stress (Tottenham & Galvan, 2016). Although we do not fully understand how these pathways become misadjusted, their malfunction is likely to be common, given the high prevalence of mood and anxiety disorders in our society (Ferrari et al., 2013). Understanding how is stress perceived at the neurophysiological level, and what constitutes a constructive fine adjustment of threat perception versus a pathological one is therefore relevant to well-being including the risk of HIV transmission and the AIDS epidemic. To reduce the impact of CA, we must determine whether the effects of stress can be readily reversed after they are experienced, for example through pharmacological or psychotherapeutic interventions. Recent studies of memory consolidation and reconsolidation (Treanor, Brown, Rissman, & Craske, 2017) may be helpful here, as could knowledge of mechanisms of PTSD (Kelmendi et al., 2016). The role of epigenetics in these processes and in human behavior in general is receiving great attention and could also suggest novel interventions.

To understand these mechanisms will require application of the most modern techniques of genetic and optogenetic nervous system experimentation in rodents in parallel with longitudinal studies in humans, including functional imaging of persons who are at risk for early life stress. Also, we must not neglect the societal, economic, political and ecological factors that distort childhood experiences and trigger maladaptive behavioral development. Together, such studies promise not only benefit for individuals at risk for health impairments, including HIV exposure, but they may also provide a more general understanding of the basics of human development. The goal is to protect us from harmful childhood influences so that in adulthood we may lead healthy, constructive, balanced and personally satisfying lives.

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