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Stress, alcohol and infection during early development: a brief review of common outcomes and mechanisms

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Abstract: Although stress is an adaptive physiological response to deal with adverse conditions, its occurrence during early stages of life such as infancy or adolescence can induce adaptations in multiple physiological systems, including the reproductive axis (HPG), the hypothalamic-pituitary-adrenal (HPA) axis, the limbic cortex and the immune system. These early changes have consequences in adult life, as seen in the physiological and behavioral responses to stress. This review highlights the impact of several stress challenges incurred at various stages of development (peri-natal, juvenile, adolescent periods) and how developmental timing of early life stress confers unique physiological adaptations that may persist across the lifespan. In doing so, we will emphasize how intrinsic sex differences in the stress response might contribute to sex-specific vulnerabilities, the molecular processes underlying stress in the adult, and potential therapeutic interventions to mitigate the effects of early stage stress, including the novel molecular mechanism of SUMOylation as a possible key target of HPA regulation during early life stress.

Introduction

Although originally cast in relation to gestational effects, the concept of developmental vulnerability to early life insults and its relationship to subsequent health-related outcomes is well-established in the Developmental Origins of Health and Disease hypothesis [1], which states that stress during development increases the risk of diseases in adult life. A rich literature has therefore examined the influence of threats imposed during the prenatal, early postnatal and childhood periods on subsequent health outcomes in adulthood [2]. The past decade, however, has witnessed increasing recognition that developmental vulnerability to such threats extends into adolescence in humans, with many of these developmental vulnerabilities being aptly modeled in pre-clinical model organisms [3]. Considering that early stages of development are periods of profound neural and behavioral change, during which developing organisms transition to adult-like functioning [4], it is crucial for ongoing studies to examine developmental vulnerabilities in these periods.

Importantly, early stages of development often include exposure to major life stressors, acute infection, and the initiation of alcohol consumption. Although most studies tend to segregate these seemingly independent challenges, stress, alcohol and infection share a wide range of immediate, over-lapping physiological consequences. For instance, stress, alcohol and infection all produce robust activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased circulating corticosteroids (corticosterone in rat and mouse; cortisol in humans) and subsequent activation of glucocorticosteroid receptors (GR), (e.g., [5]). Furthermore, all 3 challenges significantly increase expression of pro-inflammatory cytokines in both brain and blood, and can elicit sickness-

like behavioral responses as a consequence [6]. Finally, and perhaps most importantly, exposure to stress, alcohol or infection during early development has been shown to produce alterations in HPA axis activation and cytokine reactivity that persist into adulthood [7], and perhaps across the lifespan. Thus, examination of common physiological outcomes and mechanisms between early life stress, alcohol exposure and immune challenge has the potential to rapidly advance our understanding of developmentally-entrained alterations in multiple health and disease-related outcomes.

Early life consequences of alcohol, infection and stress: a common role for inflammation?

i. Alcohol consumption:

Alcohol consumption during pregnancy and developmental disorders with consequences in adult life have been linked during the last few decades, however, studies are increasingly being focused on adolescence, which is a critical cognitive and neuroimmune developmental period and one where alcohol intake usually begins in humans. A recent study in rats demonstrated that adolescent males at postnatal day (PND) 28-32 displayed severely blunted cytokine changes across the central nervous system (CNS) when challenged with alcohol or lipopolysaccharide (LPS) relative to young adults (PND 70-74) [8]. These findings are consistent with other studies suggesting functional immaturity of microglia in adolescence [9], and could suggest that the lack of a mature, functional neuroimmune response in adolescence may be critical to certain adolescent vulnerabilities. Several studies have demonstrated that alcohol consumption during adolescence leads to adult phenotypes in adulthood, including the further responses to an immunological challenge [3]. For instance, adult male rats with a history of adolescent binge-like alcohol exposure [10] showed suppressed expression of pro-inflammatory cytokines by circulating immune cells in response to an immunological stressor such as LPS, with no changes in plasma corticosterone (CORT) whatsoever [7]. On the contrary, adult female rats exposed to alcohol during adolescence did not show the pro-inflammatory cytokine suppression in response to LPS, but rather displayed a sensitized CORT response. Importantly, these patterns of immunosuppression in males were observed when rats with a history of intermittent alcohol exposure were challenged as adults with restraint or LPS (but not with adult alcohol challenge), suggesting long-term functional changes in immune reactivity as a result of adolescent alcohol exposure. Thus, adolescent alcohol exposure led to profound, sex-specific outcomes indicating that the systems influenced by adolescent alcohol were completely different for males and females [7], a scenario which should be taken into account in future studies dealing with the effects of adolescent alcohol exposure.

ii. LPS challenge

It has been demonstrated that an immune challenge during early stages of life induces reprogramming events at the CNS level which manifest into adulthood [11]. Cytokine expression during early life stages has been associated with further development of neuropsychiatric disorders in adulthood. Neonatal LPS administration has been demonstrated to increase hypothalamic, hippocampal and prefrontal cortex (PFC) levels of interleukin (IL)-4 and decrease IL-6 levels in both adolescence and adulthood of males and females, and these changes may induce behavioural profiles resembling autism spectrum disorders [12]. Also, it has been demonstrated that immune

challenge during neonatal periods can modify further responses to different types of stress. For example, neonatal treatment with LPS enhanced hippocampal IL-1 β induced by restraint stress in adulthood in both male and female rats, and also tumor necrosis factor- α (TNF α) levels in males [13]. On the other hand, LPS-challenge in neonatal male rats subsequently treated with the same dose of the endotoxin during adulthood showed no changes in plasma TNF α and IL-1 β compared to adult saline-treated rats, but showed reduced LPS fever response [14]. However, neonatal immune challenge enhanced the effect of adult LPS exposure on the expression of the hypothalamic cytokines IL-1 β and TNF α in male rats, and these effects were associated with body weight regulation systems [15]. Focusing on the sex specific effects of an early immune challenge on the CNS, it has been shown that typical colonization by microglia occurs much earlier in males than females in regions including the hippocampus and neocortex [16]. The morphology of microglia can change during development, since adult microglia are known to possess a small cell body with thin and long processes, but during injury can be activated, changing their morphology to an amoeboid and round shape. Males exhibit a greater number of amoeboid microglia during early development (PND 0-4). This early amoeboid shape in males could indicate that these microglia are hypersensitive, thereby making them more reactive to stressors during the juvenile period of development. Interestingly, female microglia display a more amoeboid phenotype in adolescence, when males no longer display this distinct morphology. These sex specific differences in microglial colonization and activation state could indicate that males are preferentially susceptible to long-lasting effects of early-life immune challenge compared to females [9].

Considering the inflammatory pattern observed in CNS induced by an early immune challenge and its influence on further development of neuropsychiatric disorders, it is worthwhile highlighting the role of the endocannabinoid system, since it has been demonstrated that the expression of the cannabinoid CB2 receptor is enhanced in CNS during inflammatory conditions [17]. Particularly, neonatal cortical microglial cells exposed to LPS showed increased levels of pro-inflammatory cytokines, but cannabinoid administration prevented this effect [18]. Also, an *in vivo* experiment of neonatal LPS exposure in male rats indicated decreased cannabinoid CB1 receptor binding in adulthood in the CNS [19], suggesting a potentially important role for the endocannabinoid system in linking immune challenge in early life stages with neuropsychiatric disorders during adulthood.

iii. Maternal separation

Maternal separation (MS) in rats is used as a model of postnatal stress that induces adult neurodevelopmental changes. MS entails separation of pups from their mother for 3-4 hrs per day during the first 2-3 weeks of life, which disrupts the mother-infant relationship via disorganized maternal behavior [20], [21], and imposes direct infant stress when the pups are isolated during the separation [22]. In contrast to the consequences of stress exposure in adulthood, developmental exposure to stress can affect the trajectory of actively maturing systems that may manifest in atypical function after a seeming latent period [23]. For example, it has been suggested that MS induces long-lasting alterations in the developing immune system [24], [25], though the mechanistic underpinnings of these effects is still not well understood. MS exposure produces changes in baseline circulating levels of cytokines that are first apparent in early adolescence - two weeks after the stress paradigm was terminated [26]. These findings indicate that adolescence is a critical period when developmental events can evoke immunological dysfunction that can manifest into adult behavioral disorders.

Animal models have shown various immunological responses to MS, often with sex-specific effects. Particularly, it has been demonstrated that although MS induced no changes associated to age or sex in plasma levels of the pro-inflammatory cytokine IL-1 β or the modulatory cytokine IL-4, males previously exposed to MS for 4 hrs/day from PND 2-20 displayed a transient drop in the modulatory cytokine IL-10 in early adolescence (PND 35) [26]. This decrease in IL-10 occurred at an age that correlated with the initiation of puberty [26], [27] and with a concurrent decrease in circulating testosterone levels, compared to control males [28]. Interestingly, the effects of MS on IL-10 levels in male rats during puberty may be under testosterone influence, since this hormone induces IL-10 expression in male T-cells [28] during puberty [26], [29], [30]. Taken together, early life experiences may affect immune signalling in male adolescents indirectly via differential development of the HPG axis, as further described below.

The immune adaptive responses are in part driven by T-helper cells, and since they have different types of responses, they are classified into different cellular subtypes. T_H1 cytokine responses are associated with intracellular responses, whereas T_H2 cytokine responses are linked with extracellular responses and self-cell tolerance. The importance of IL-10 in the regulation of the immune system has been demonstrated since it can modulate both T_H1 and T_H2 responses in different scenarios [31], [32]. Thus, the consequences of MS on circulating IL-10 in males should be interpreted in the context of its potential influence on associated immune signals [33]. IL-10 is an essential component of the immune regulatory response needed to inhibit pro-inflammatory cytokine synthesis, decrease reactive oxygen species, and suppress cytotoxic T-cell responses [33]. Therefore, decreases in IL-10 that were observed in adolescent males following MS may exacerbate pro-inflammatory signaling mechanisms, with neuro-behavioral consequences. Finally, it should be noted that the endocannabinoid system is another potential target for inflammatory deregulation induced by MS, since the inhibition of endocannabinoid inactivation was shown to prevent increased CORT levels and astrocyte number in the hippocampus - which is associated with oxidative stress processes, induced by MS [34]. Further studies are needed to fully understand the potential benefits of endocannabinoid modulation in the context of these detrimental processes in early life stages. Overall, it is becoming clear that immune activity during critical developmental periods is an important mechanism to consider as underpinning long-term effects of early life stress.

iv. Cytokine production: common features

Taken together, reports indicate that early-life insults evoke further changes in the adult immune system. Particularly, one of the most interesting links between early insults and adult cognitive disorders are cytokines, since their imbalance is associated with depression and schizophrenia. Studies indicate that MS evokes changes in IL-10, IL-6, and TNF α [24], [25], [35], ethanol exposure during adolescence alters IL-1 β , IL-6 and TNF α [8], and neonatal LPS affects IL-1 β , IL-4, IL-6, and TNF α in the CNS [12], [15], and all these cytokines have been related to further adult cognitive disorders. IL-1 β is a pro-inflammatory cytokine with detrimental effects on cognitive dysfunction [36]. Its negative effects are known to synergize with other cytokines such as TNF α and IL-6, to induce neuron damage [37], and its detrimental effects are also associated with an increase craving for alcohol [38]. IL-6 is a modulatory cytokine induced by IL-1 β and TNF α , and its increase during early stages of development is associated with autism, and its decrease with higher aggression and emotionality [39], [40]. IL-4 is also a modulatory cytokine able to downregulate IL-1 β and TNF α production [41], but also with a pro-inflammatory potential [42], and its deregulation is associated with autism disorders [12], [43]. Finally, and as explained previously, IL-10 is also a modulatory cytokine regulating the immune response, and its deregulation correlated with cognitive dysfunction [26]. Table 1 summarizes the principal responses of each cytokine during adulthood, triggered by early life insults.

Interactions with neuroendocrine systems: the HPA and HPG axes

i. HPA

a. Physiological and developmental outcomes

The HPA axis is formed by several populations of hormone-secreting cells. One of these populations is composed by hypothalamic neurons located in the paraventricular nucleus, which secrete corticotropin releasing hormone (CRH) to the adenohypophysis, where another population of cells - corticotrophs - are located. Corticotrophs can respond to the hypothalamic neuropeptide by releasing adrenocorticotrophic hormone (ACTH), which is the stimulus for the third population of the axis, the endocrine cells in the zona fasciculata of the adrenal cortex. Adrenal cortical cells respond to ACTH by synthesizing glucocorticoid hormones which are released into the circulation, and among other effects they can inhibit the release of CRH and ACTH, by a direct feedback inhibition. As previously mentioned, stress, alcohol and infection are known to activate the HPA axis, increasing circulating CORT and subsequently activating GR (eg., [5]). Notably, adolescent alcohol exposure differently affects further responses to stress in adulthood depending on the sex of the animals, since male alcohol exposure during adolescence (PND 30-32) evoked no changes in adult CORT responses to stress, whereas females displayed an enhanced CORT response [7]. It can be noted, however, that adolescent intermittent ethanol has previously been shown to have little effect on the normal progression of puberty, suggesting that the effects observed here may be independent of pubertal hormones [44]. Sexually dimorphic CORT responses were also found in adult rats exposed to an adolescent single session of inescapable footshock (~2 hr of intermittent stress), where a robust and time-dependent expression of pro-inflammatory cytokines in the CNS was found (e.g., [45]) after footshock exposure. However, as adults, male rats displayed symptoms of increased anxiety in the light-dark box, whereas other behavioral tests (social interaction, exploration of a novel environment) yielded no effects of adolescent stress history. Interestingly, these males also exhibited normal CORT responses as adults. In contrast, females with a history of adolescent footshock displayed very few behavioral signs of anxiety, but once again displayed a modestly exaggerated CORT response as adults (Lovelock & Deak, in prep). Nevertheless, the finding that distinct challenges imposed on females during adolescence consistently yielded exaggerated CORT responses in adulthood suggests that adolescence in females (but not males) may be a developmentally critical or sensitive period during which HPA axis reactivity is entrained. These findings may therefore have implications for the development of sex-biased outcomes in numerous disease states, as well as defining sex-specific interventions for health-related problems that emerge during adulthood [46].

The endocannabinoid system has been implicated in anti-stress mechanisms during adulthood [47]. Considering the influence of the endocannabinoid system in early development, it was demonstrated in a mouse CB1 knockout model that this receptor modulates the stress response during early life stages, since the lack of CB1 increased vulnerability to acute (swimming) and chronic (repeated bell) stress, inducing greater and prolonged freezing behaviour and decreased ultrasonic vocalizations [48]. In another study, early life stress resulted in diminished levels of CB1 and increased GR levels in the CNS of male and female rats, but these effects were prevented with late adolescence administration of a CB1 agonist, WIN55,212-2. Also, the CB1 agonist prevented impaired performance, induced by early life stress, in adult short-term memory in spatial location and social recognition tasks [49]. Considering that the CB1 receptor mediates CORT effects [50], it is possible that decreased CB1 expression during early life stress resulted in a blunted HPA axis response, increasing GR expression which might also impact short-term memory in adulthood. These results indicate that the endocannabinoid system participates in the early events of neural development, modelling further responses to stress, and its modulation might be a target in the treatment of stress- and anxiety-related disorders.

b. SUMO conjugation as a possible mechanism underlying stress related challenges

Protein SUMOylation is a post-translational modification (PTM) regulating multiple cellular pathways and consists of the covalent attachment of one or many small ubiquitin-like modifiers (SUMO) to target proteins [51], [52]. The consequences of SUMO conjugation vary with different substrates and may include alterations in protein stability, protein interaction and subcellular localization. Importantly, in the CNS, SUMOylation is related to the modulation of many aspects of neuronal functions, is essential for emotionality, cognition and memory, and is also important in the regulation of the inflammatory response mediated by astrocytes [53], [54].

The adrenal gland from the HPA axis is responsible for the release of glucocorticoids (GCs) in response to stress. Its binding to GR induces nuclear translocation and transcriptional modulation of different genes related to the immune system, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and the Activator protein 1, among others [55], [56]. GC binding, GR translocation, and transcriptional modulation [57], in turn, depends on its proper folding by a chaperone complex, including the Heat shock protein (Hsp) 90 and Hsp70, and immunophilins, such as the FK506 binding protein (FKBP) 51 and FKBP52 [58]. The fine-tuning for GR nuclear translocation is mediated by these immunophilins since FKBP52 promotes nucleus migration favoring GR transcriptional activity and FKBP51 prevents it [59], [60]. In particular, GR transcriptional activity is controlled by its own response, since it induces FKBP51 transcription [61], which inhibits GR action in the nucleus. This mechanism seems to be crucial to the correct HPA responses to stress, since deregulation of FKBP51/FKBP52 balance has been related to a dysfunctional activity of the HPA axis and stress disorders, such as depression and bipolar disorders, among others [62], [63]. These immunophilins could be a reasonable target for the treatment of stress-related disorders, but also for immune system disorders since GR also controls NF- κ B transcription and the activity of other key inflammatory transcription factors [62].

It has been reported that GR activity is modulated by SUMOylation [64], [65], and is important for fine-tuning GR activity under cellular stress conditions [66], [67]. Also, FKBP51 is a target of SUMO conjugation [68] and SUMOylation of FKBP51 was suggested to be necessary for the inhibition of GR activity. SUMO conjugation to FKBP51 favors FKBP51 interaction with Hsp90 and its recruitment to the chaperone complex, thereby inhibiting GR hormone binding and migration to the nucleus [68]. Since over-expression of FKBP51 is associated with deregulated GR activity and pathological adrenal responses [63], the inhibition of FKBP51 SUMO conjugation could be an interesting approach to modulate deregulated inflammatory and stress-related responses [69].

SUMO conjugation has been shown to be affected by environmental stressors such as heat-shock and hypoxia, which are present in the development of certain inflammatory processes [67], but also, pro-inflammatory stimuli have been shown to activate the SUMOylation pathway and modulate the inflammatory response. Thus, different environmental stressors such as the early developmental challenges discussed in this review, might affect specific players of the HPA axis response and, therefore, might be a novel mechanism by which HPA axis regulation is altered. Furthermore, it cannot be ruled out that SUMOylation might be the common feature shared by these early insults, which would signify a major step forward in the study of alternative approaches to deal with these adverse conditions.

ii. HPG

The HPG axis is mainly composed of 3 cell populations. A neuronal population is located in the preoptic area, and releases gonadotropin releasing hormone (GnRH) to the adenohypophysis, where another population of cells, the gonadotrophs, are located. These cells respond to GnRH by releasing gonadotrophins into the circulation, such as luteinizing hormone (LH) and follicle stimulating hormone (FSH). The last population of cells are located in the gonads, and can respond to gonadotrophins by releasing steroids into the circulation, which in turn can modulate the release of GnRH and LH differently, depending on the sex of the organism. It has been shown that neonatal immune challenge can interfere with reproductive physiology in adult rats by impairing sexual performance, diminishing testosterone in males and estradiol in females [70], [71], as well as LH [72], and GnRH release [73]. In particular, the effects of immune challenge on the suppression of the reproductive axis associate with an impaired hypothalamic function, since LPS inhibits LH release by decreasing GnRH pulse frequency in the hypothalamus [74], [75]. Furthermore, the hyporesponsive hypothalamic activity due to LPS was reported to be mediated by TNF α and IL-1 β augmentation [76], but also by the influence of the HPA axis [77].

Considering early life exposure to immune challenge on HPG activity, Munkhzaya *et al.*, injected LPS at different PND and evaluated the reproductive axis state 3 hours later, finding diminished LH levels only after PND 25, suggesting that, as with the HPA axis, the HPG axis displays stress hyporesponsive periods (SHRP) after PND 25 [78]. Long lasting effects of LPS were shown in females at different PNDs, where, prior to PND 7, LPS delayed puberty onset by altering hypothalamic reproductive function [79]. Another study considered the consequences of early life immune challenge in males by injecting LPS or saline on PND 10 (during the SHRP of both HPA and HPG axes) and evaluating a further response to LPS on mid-late adolescence (PND 49). LPS inhibited LH levels in adolescence of rats treated with saline during early life, but this inhibition was prevented when rats were given LPS neonatally [80]. It is possible that this effect was due to endotoxin tolerance, since adult LPS rats also showed diminished hypothalamic immunological markers (such as TNF α and IL-1 β) when neonatally-treated with LPS. These results also demonstrated that LPS challenge during SHRP somehow locks in this phenotype into future developmental stages, making the HPG hyporesponsive to further immunological challenge. The mechanisms underlying these effects seems to be mediated at least in part by a lack of LPS signaling due to diminished levels of the LPS receptor, TLR4 [81].

It has been recently demonstrated in an *in vivo* model that the inhibitory effects of LPS were mediated by the endocannabinoid system [82] since hypothalamic blockade of the cannabinoid receptor CB1 prevented the inhibitory effects of LPS on GnRH and LH release. The endocannabinoid system is reported to modulate several processes, including reproduction [83] and inflammation [84]. Since the CB1 and CB2 receptors are expressed in microglial cells of the neonatal hypothalamus, endocannabinoid participation in the inflammatory effects of LPS on reproduction cannot be ruled out. Indeed, microglial cells exposed to LPS increased cytokine mRNA expression, and a specific CB2 antagonist enhanced that effect, suggesting that cannabinoids modulate cytokine expression in the hypothalamus through a mechanism involving the CB2 receptor [18]. Further studies are needed to fully characterize the participation of the endocannabinoid system in the early life stage-effects of an immunological challenge in adulthood.

Cognitive function

It is known that both peripheral and central immunological signals influence the responses of the CNS at behavioral and neuroendocrine levels during development [85]. Hence, early life insults can affect behavior of both adolescent and adult animals [24], [86] and humans [87], through immune and neuro-immune changes. Specifically, a pro-inflammatory phenotype has been correlated with severity of disorders with strong cognitive components, such as schizophrenia and

depression, but this association is most robust in patients with a history of childhood trauma compared to those without such history [87]. Cytokines influence cognitive processing via actions on vagal afferents and at the blood-brain barrier [88], which in turn regulate neural activity within critical regions such as the hippocampus and PFC [89]. While lifetime stress can cause atrophy in these regions through inflammatory and endocrine mechanisms, neonatal MS as defined in this article does not reportedly cause atrophy or development of a smaller hippocampus [90] or PFC [91]. However, MS does produce several alterations in microstructural and circuit development within these regions [92]. Moreover, several other models of early-life disturbances such as alcohol [93] or LPS exposure [11], long-term maternal deprivation, [94] or limited nesting [95], result in decreased neurogenesis within the hippocampus, decreased mossy-fiber density, lower dorsal hippocampal volume, and lower PFC volume later in life, with cognitive disturbances. These effects in animals have supported similar findings in humans with histories of childhood maltreatment and related cognitive dysfunction [96], [97].

Rodent models of early life stress have begun to uncover how developmental stress exposure may affect cognitive function via immune signaling. For example, both male and female adolescent rats have displayed significant deficits in the win-shift spatial working memory paradigm after MS, an effect that has been reproduced in several reports of early adversity induced cognitive dysfunction in both rodents [26], [91] and humans [96], [98]. Cognitive dysfunction as measured by errors in the win-shift task correlated with lower circulating levels of IL-10 in PND 35 male rats exposed to MS, while in females no correlation of MS-attributable win-shift errors with cytokine levels was found [26]. One hypothesis to explain this sex-specific correlation is that a convergent behavioral dysfunction may be driven by different mechanisms in males and females, with males more vulnerable to adolescent immune dysfunction following MS. Further supporting a neuro-immune mechanism underlying cognitive deficits after MS, earlier studies also showed that IL-10^{-/-} male mice exhibit higher peripheral levels of the pro-inflammatory cytokines IL-1 β , IL-6 and TNF α and more pronounced learning and memory deficits after an immune challenge with LPS, compared to wild type mice [99]. Moreover, direct administration of IL-10 intracerebroventricularly to male rats in early adolescence prevented the MS-attributable loss of PFC interneurons that are reportedly critical for cognitive function [24]. On the other hand, memory function has been associated with an adequate balance in IL-1 levels, since central alteration of physiological IL-1 β levels showed impaired memory performance [100]. Balanced pro-inflammatory and anti-inflammatory cytokine activity therefore is necessary for cognitive function, and this balance can be influenced by early-life experiences.

A causal relationship between adolescent pro-inflammatory activity after early-life stress and cognitive dysfunction may be mediated by important rate-limiting enzymes in the inflammatory pathway that affect neurotransmitter release. For example, the kynurenine pathway has been found to play important roles in several behavioral sequelae of early-life stress [89]. This pathway is initiated by prostaglandin-induced formation of indoleamine 2,3-dioxygenase and subsequent conversion of tryptophan into kynurenine, which is then converted into kynurenic acid (an NMDA antagonist) or quinolinic acid (an NMDA agonist). Upstream from this pathway is the prostaglandin-synthesizing enzyme cyclooxygenase-2 (COX-2), which is also expressed at higher levels in the PFC of MS-exposed male adolescent rats. The role of COX-2 in cognitive dysfunction after MS was supported using a nonsteroidal anti-inflammatory drug that blocks COX-2; when a COX-2 inhibitor was administered systemically during early adolescence (PND 30-38), MS-exposed males did not commit more errors on the win-shift task than control-reared males.

Converging evidence is unmasking the importance of peripheral immunological markers in early life stages as markers of PFC-related cognitive impairment, which may signify an interesting approach to deal with the effects of early stress instances on behavioral adult responses. It has been found that there is a time lapse between childhood maltreatment and the onset of depression of

about 11.5 years (usually during adolescence) [23]. This may suggest that there could be a critical period for intervention in order to deal with such alterations. Increasing understanding of an immune signaling link between developmental stress and later behavioral dysfunction may lead to strategies of identification and treatment of vulnerable populations.

Concluding remarks

Taken together, the topics of the present review highlight the repercussions of different kinds of threats imposed during early stages of development on further health outcomes during adulthood, including subsequent responses to stress at behavioral and immunological levels, and also the participation of the endocannabinoid system in this context. The common features of different early insults are summarized in Fig 1. The mechanisms underlying these effects remain unknown, but may include the novel influence of SUMOylation on the HPA axis, and should consider the influence of sex differences, since the physiological response to early stress differentially affects several systems such as the HPA axis and the immunological system in a sex-specific fashion.

References

- [1] D. Barker, "The fetal and infant origins of disease," *Eur. J. Clin. Invest.*, vol. 25, no. 7, pp. 457–463, 1995.
- [2] B. R. H. Van den Bergh *et al.*, "Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy," *Neurosci. Biobehav. Rev.*, 2017.
- [3] L. P. Spear, "Consequences of adolescent use of alcohol and other drugs: Studies using rodent models," *Neurosci. Biobehav. Rev.*, vol. 70, pp. 228–243, 2016.
- [4] S. B. Johnson, R. W. Blum, and J. N. Giedd, "Adolescent Maturity and the Brain: The Promise and Pitfalls of Neuroscience Research in Adolescent Health Policy," *J. Adolesc. Heal.*, vol. 45, no. 3, pp. 216–221, 2009.
- [5] R. L. Spencer and T. Deak, "A users guide to HPA axis research," *Physiol. Behav.*, vol. 178, pp. 43–65, 2017.
- [6] T. Deak, A. Kudinova, D. F. Lovelock, B. E. Gibb, and M. B. Hennessy, "A multispecies approach for understanding neuroimmune mechanisms of stress," *Dialogues Clin. Neurosci.*, vol. 19, no. 1, pp. 37–53, 2017.
- [7] A. S. Vore, T. Doremus-Fitzwater, A. Gano, and T. Deak, "Adolescent Ethanol Exposure Leads to Stimulus-Specific Changes in Cytokine Reactivity and Hypothalamic-Pituitary-Adrenal Axis Sensitivity in Adulthood.," *Front. Behav. Neurosci.*, vol. 11, no. May, p. 78, 2017.
- [8] T. L. Doremus-fitzwater, A. Gano, J. E. Paniccia, and T. Deak, "Male adolescent rats display blunted cytokine responses in the CNS after acute ethanol or lipopolysaccharide exposure," *Physiol Behav.*, vol. 148, pp. 131–144, 2015.
- [9] S. D. Bilbo and J. M. Schwarz, "The Immune System and Developmental Programming of Brain Front Neuroendocrinol Author Manuscript and Behavior," *NIH Public access*, vol. 33, no. 3, pp. 267–286, 2012.
- [10] M. Buck, C. Hueston, C. Bishop, and T. Deak, "Enhancement of the hypothalamic-pituitary-adrenal axis but not cytokine responses to stress challenges imposed during withdrawal from acute alcohol exposure in Sprague-Dawley rats," *Psychopharmacol.*, vol. 218, no. 1, pp. 203–215, 2011.
- [11] A.-L. Dinel *et al.*, "Inflammation early in life is a vulnerability factor for emotional behavior at adolescence and for lipopolysaccharide-induced spatial memory and neurogenesis alteration at adulthood," *J. Neuroinflammation*, vol. 11, no. 1, p. 155, 2014.
- [12] C. S. Custódio *et al.*, "Neonatal Immune Challenge with Lipopolysaccharide Triggers Long-lasting Sex- and Age-related Behavioral and Immune/Neurotrophic Alterations in Mice: Relevance to Autism Spectrum Disorders," *Mol. Neurobiol.*, pp. 1–14, 2017.

- [13] A. K. Walker, T. Nakamura, and D. M. Hodgson, "Neonatal lipopolysaccharide exposure alters central cytokine responses to stress in adulthood in Wistar rats," *Stress. Int. J. Biol. Stress*, vol. 13, no. 6, pp. 506–515, 2010.
- [14] F. R. Walker, N. A. Hodyl, K. M. Krivanek, and D. M. Hodgson, "Early life host-bacteria relations and development: Long-term individual differences in neuroimmune function following neonatal endotoxin challenge," *Physiol. Behav.*, vol. 87, no. 1, pp. 126–134, 2006.
- [15] T. Iwasa *et al.*, "Neonatal LPS injection alters the body weight regulation systems of rats under non-stress and immune stress conditions," *Int. J. Dev. Neurosci.*, vol. 28, no. 1, pp. 119–124, 2010.
- [16] J. Schwarz, P. Sholar, and S. Bilbo, "Sex differences in microglial colonization of the developing rat brain," *J Neurochem.*, vol. 120, no. 6, pp. 948–963, 2012.
- [17] M. Roche and D. P. Finn, "Brain CB2 receptors: Implications for neuropsychiatric disorders," *Pharmaceuticals*, vol. 3, no. 8, pp. 2517–2533, 2010.
- [18] R. A. Puffenbarger, A. C. Boothe, and G. A. Cabral, "Cannabinoids inhibit LPS-inducible cytokine mRNA expression in rat microglial cells," *Glia*, vol. 29, no. 1, pp. 58–69, 2000.
- [19] K. Zavitsanou, V. S. Dalton, A. K. Walker, C. S. Weickert, L. Sominsky, and D. M. Hodgson, "Neonatal lipopolysaccharide treatment has long-term effects on monoaminergic and cannabinoid receptors in the rat," *Synapse*, vol. 67, no. 6, pp. 290–299, 2013.
- [20] R. L. Huot, M. E. Gonzalez, C. O. Ladd, K. V. Thirivikraman, and P. M. Plotsky, "Foster litters prevent hypothalamic-pituitary-adrenal axis sensitization mediated by neonatal maternal separation," *Psychoneuroendocrinology*, vol. 29, no. 2, pp. 279–289, 2004.
- [21] J. P. Aguggia, M. M. Suárez, and M. A. Rivarola, "Early maternal separation: Neurobehavioral consequences in mother rats," *Behav. Brain Res.*, vol. 248, pp. 25–31, 2013.
- [22] B. Zimmerberg, A. J. Rosenthal, and A. C. Stark, "Neonatal social isolation alters both maternal and pup behaviors in rats," *Dev. Psychobiol.*, vol. 42, no. 1, pp. 52–63, 2003.
- [23] M. H. Teicher, J. A. Samson, A. Polcari, and S. L. Andersen, "Length of time between onset of childhood sexual abuse and emergence of depression in a young adult sample: a retrospective clinical report.," *J. Clin. Psychiatry*, vol. 70, no. 5, pp. 684–91, 2009.
- [24] A. Wieck, S. L. Andersen, and H. C. Brenhouse, "Evidence for a neuroinflammatory mechanism in delayed effects of early life adversity in rats: Relationship to cortical NMDA receptor expression," *Brain. Behav. Immun.*, vol. 28, pp. 218–226, 2013.
- [25] C. H. do Prado, T. Narahari, F. H. Holland, H.-N. Lee, S. K. Murthy, and H. C. Brenhouse, "Effects of early adolescent environmental enrichment on cognitive dysfunction, prefrontal cortex development, and inflammatory cytokines after early life stress," *Dev. Psychobiol.*, vol. 58, no. 4, pp. 482–491, 2016.
- [26] R. Grassi-Oliveira, J. Honeycutt, F. Holland, P. Ganguly, and H. Brenhouse, "Cognitive impairment effects of early life stress in adolescents can be predicted with early biomarkers: Impacts of sex, experience, and cytokines," *Psychoneuroendocrinology*, vol. 71, pp. 19–30, 2016.
- [27] C. S. Vetter-O'Hagen and L. P. Spear, "Hormonal and physical markers of puberty and their relationship to adolescent-typical novelty-directed behavior," *Dev. Psychobiol.*, vol. 54, no. 5, pp. 523–535, 2012.
- [28] Y.-Z. Zhang, X.-W. Xing, B. He, and L.-X. Wang, "Effects of testosterone on cytokines and left ventricular remodeling following heart failure.," *Cell. Physiol. Biochem.*, vol. 20, no. 6, pp. 847–52, 2007.
- [29] S. M. Liva and R. R. Voskuhl, "Testosterone Acts Directly on CD4+ T Lymphocytes to Increase IL-10 Production," *J. Immunol.*, vol. 167, no. 4, pp. 2060–2067, 2001.
- [30] K. J. Bodensteiner, N. Christianson, A. Siltumens, and J. Krzykowski, "Effects of early maternal separation on subsequent reproductive and behavioral outcomes in male rats," *J. Gen. Psychol.*, vol. 141, no. 3, pp. 228–246, 2014.

- [31] F. Cottrez, S. D. Hurst, R. L. Coffman, and H. Groux, "T regulatory cells 1 inhibit a Th2-specific response in vivo.," *J. Immunol.*, vol. 165, no. 9, pp. 4848–4853, 2000.
- [32] G. Trinchieri, "Interleukin-10 production by effector T cells: Th1 cells show self control," *J. Exp. Med.*, vol. 204, no. 2, pp. 239–243, 2007.
- [33] K. N. Couper, D. G. Blount, and E. M. Riley, "IL-10: The Master Regulator of Immunity to Infection," *J. Immunol.*, vol. 180, no. 9, pp. 5771–5777, 2008.
- [34] R. Llorente *et al.*, "Gender-dependent cellular and biochemical effects of maternal deprivation on the hippocampus of neonatal rats: A possible role for the endocannabinoid system," *Dev. Neurobiol.*, vol. 68, no. 11, pp. 1334–1347, 2008.
- [35] J. J. Dimatelis, N. S. Pillay, A. K. Mutyaba, V. A. Russell, W. M. U. Daniels, and D. J. Stein, "Early maternal separation leads to down-regulation of cytokine gene expression," *Metab. Brain Dis.*, vol. 27, no. 3, pp. 393–397, 2012.
- [36] N. Terrando *et al.*, "The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction," *Crit. Care*, vol. 14, no. 3, 2010.
- [37] S. M. Allan, P. J. Tyrrell, and N. J. Rothwell, "Interleukin-1 and neuronal injury," *Nat. Rev. Immunol.*, vol. 5, no. 8, pp. 629–640, 2005.
- [38] F. Kiefer, H. Jahn, M. Schick, and K. Wiedemann, "Alcohol intake, tumour necrosis factor-alpha, leptin and craving: factors of a possibly vicious circle?," *Alcohol Alcohol*, vol. 37, no. 4, pp. 401–404, 2002.
- [39] H. Wei *et al.*, "IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation," *J. Neuroinflammation*, vol. 8, no. 1, p. 52, 2011.
- [40] E. Alleva *et al.*, "Behavioural characterization of interleukin-6 overexpressing or deficient mice during agonistic encounters," *Eur. J. Neurosci.*, vol. 10, no. 12, pp. 3664–3672, 1998.
- [41] P. H. Hart, G. F. Vitti, D. R. Burgess, G. A. Whitty, D. S. Piccoli, and J. A. Hamilton, "Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor alpha, interleukin 1, and prostaglandin E2.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 86, no. 10, pp. 3803–7, 1989.
- [42] J. Major, J. E. Fletcher, and T. A. Hamilton, "IL-4 Pretreatment Selectively Enhances Cytokine and Chemokine Production in Lipopolysaccharide-Stimulated Mouse Peritoneal Macrophages," *J. Immunol.*, vol. 168, no. 5, pp. 2456–2463, 2002.
- [43] P. E. Goines and P. Ashwood, "Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment," *Neurotoxicol Teratol*, vol. 36, no. 916, pp. 67–81, 2013.
- [44] E. Varlinskaya, C. Vetter-O'Hagen, and L. Spear, "Puberty and Gonadal Hormones: Role in Adolescent-typical Behavioral Alterations," *Horm. Behav.*, vol. 64, no. 2, pp. 343–349, 2013.
- [45] C. M. Hueston and T. Deak, "The inflamed axis: The interaction between stress, hormones, and the expression of inflammatory-related genes within key structures comprising the hypothalamic-pituitary-adrenal axis," *Physiol. Behav.*, vol. 124, pp. 77–91, 2014.
- [46] T. Deak, M. Quinn, J. A. Cidlowski, N. C. Victoria, A. Z. Murphy, and J. F. Sheridan, "Neuroimmune mechanisms of stress: sex differences, developmental plasticity, and implications for pharmacotherapy of stress-related disease," *Stress*, vol. 18, no. 4, pp. 367–380, 2015.
- [47] P. N. Surkin, S. L. Gallino, V. Luce, F. Correa, J. Fernández-Solari, and A. De Laurentiis, "Pharmacological augmentation of endocannabinoid signaling reduces the neuroendocrine response to stress," *Psychoneuroendocrinology*, vol. 87, no. June 2017, pp. 131–140, 2018.
- [48] E. Frider, R. Suris, J. Weidenfeld, and R. Mechoulam, "Differential response to acute and repeated stress in cannabinoid CB1 receptor knockout newborn and adult mice," *Behav. Pharmacol.*, vol. 16, no. 5–6, pp. 431–440, 2005.
- [49] S. Alteba, N. Korem, and I. Akirav, "Cannabinoids reverse the effects of early stress on neurocognitive performance in adulthood," *Learn. Mem.*, vol. 23, no. 7, pp. 349–358, 2016.
- [50] M. Scerif *et al.*, "CB1 receptor mediates the effects of glucocorticoids on AMPK activity in the hypothalamus," *J. Endocrinol.*, vol. 219, no. 1, pp. 79–88, 2013.

- [51] R. T. Hay, "SUMO: A history of modification," *Mol. Cell*, vol. 18, no. 1, pp. 1–12, 2005.
- [52] R. Geiss-friedlander and F. Melchior, "Concepts in sumoylation: a decade on," *Nat Rev Mol Cell Biol*, vol. 8, no. 12, pp. 947–956, 2007.
- [53] L. Wang *et al.*, "Neuron-specific Sumo1-3 knockdown in mice impairs episodic and fear memories," *J. Psychiatry Neurosci.*, vol. 39, no. 4, pp. 259–266, 2014.
- [54] J. M. Henley, T. J. Craig, and K. A. Wilkinson, "Neuronal SUMOylation: Mechanisms, Physiology, and Roles in Neuronal Dysfunction," *Physiol. Rev.*, vol. 94, no. 4, pp. 1249–1285, 2014.
- [55] A. C. Liberman *et al.*, "The activated glucocorticoid receptor inhibits the transcription factor T-bet by direct protein-protein interaction.," *FASEB J.*, vol. 21, no. 4, pp. 1177–88, 2007.
- [56] A. C. Liberman, J. Druker, D. Refojo, F. Holsboer, and E. Arzt, "Glucocorticoids inhibit GATA-3 phosphorylation and activity in T cells," *FASEB J.*, vol. 23, no. 5, pp. 1558–1571, 2009.
- [57] I. Grad and D. Picard, "The glucocorticoid responses are shaped by molecular chaperones," *Mol. Cell. Endocrinol.*, vol. 275, no. 1–2, pp. 2–12, 2007.
- [58] W. B. Pratt and D. O. Toft, "Steroid receptor interactions with heat shock protein and immunophilin chaperones," *Endocr Rev*, vol. 18, no. 3, pp. 306–360, 1997.
- [59] G. M. Wochnik, J. Rüegg, G. A. Abel, U. Schmidt, F. Holsboer, and T. Rein, "FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells," *J. Biol. Chem.*, vol. 280, no. 6, pp. 4609–4616, 2005.
- [60] D. L. Riggs *et al.*, "The Hsp90-binding peptidylprolyl isomerase FKBP52 potentiates glucocorticoid signaling in vivo," *EMBO J.*, vol. 22, no. 5, pp. 1158–1167, 2003.
- [61] V. Paakinaho, H. Makkonen, T. Jääskeläinen, and J. J. Palvimo, "Glucocorticoid receptor activates poised FKBP51 locus through long-distance interactions.," *Mol. Endocrinol.*, vol. 24, no. 3, pp. 511–525, 2010.
- [62] C. Storer, C. Dickey, M. Galigniana, T. Rein, and M. Cox, "FKBP51 and FKBP52 in signaling and disease," *Trends Endocrinol Metab*, vol. 22, no. 12, pp. 481–490, 2011.
- [63] E. B. Binder, "The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders," *Psychoneuroendocrinology*, vol. 34, no. SUPPL. 1, pp. 186–195, 2009.
- [64] Y. Le Drean, N. Mincheneau, P. Le Goff, and D. Michel, "Potentiation of glucocorticoid receptor transcriptional activity by sumoylation," *Endocrinology*, vol. 143, no. 9, pp. 3482–3489, 2002.
- [65] S. Tian, H. Poukka, J. J. Palvimo, and O. A. Janne, "Small ubiquitin-related modifier-1 (SUMO-1) modification of the glucocorticoid receptor," *Biochem J*, vol. 367, no. Pt 3, pp. 907–911, 2002.
- [66] A. Carbia-Nagashima *et al.*, "RSUME, a Small RWD-Containing Protein, Enhances SUMO Conjugation and Stabilizes HIF-1a during Hypoxia," *Cell*, vol. 131, no. 2, pp. 309–323, 2007.
- [67] D. Tempé, M. Piechaczyk, and G. Bossis, "SUMO under stress," *Biochem. Soc. Trans.*, vol. 36, no. 5, pp. 874–878, 2008.
- [68] M. Antunica-Noguerol *et al.*, "The activity of the glucocorticoid receptor is regulated by SUMO conjugation to FKBP51," *Cell Death Differ*, vol. 23, no. 10, pp. 1579–1591, 2016.
- [69] L. Ni, C.-S. Yang, D. Gioeli, H. Frierson, D. O. Toft, and B. M. Paschal, "FKBP51 promotes assembly of the Hsp90 chaperone complex and regulates androgen receptor signaling in prostate cancer cells.," *Mol. Cell. Biol.*, vol. 30, no. 5, pp. 1243–53, 2010.
- [70] A. K. Walker, S. A. Hiles, L. Sominsky, E. A. McLaughlin, and D. M. Hodgson, "Neonatal lipopolysaccharide exposure impairs sexual development and reproductive success in the Wistar rat," *Brain. Behav. Immun.*, vol. 25, no. 4, pp. 674–684, 2011.
- [71] J. Laroche, L. Gasbarro, J. P. Herman, and J. D. Blaustein, "Enduring influences of peripubertal/adolescent stressors on behavioral response to estradiol and progesterone in adult female mice," *Endocrinology*, vol. 150, no. 8, pp. 3717–3725, 2009.

- [72] X. F. Li *et al.*, "Neonatal lipopolysaccharide exposure exacerbates stress-induced suppression of luteinizing hormone pulse frequency in adulthood," *Endocrinology*, vol. 148, no. 12, pp. 5984–5990, 2007.
- [73] M. Yoo, M. Nishihara, and M. Takahashi, "Tumor Necrosis factor- α Mediates Endotoxin Induced Suppression of Gonadotropin-Releasing Hormone Pulse Generator Activity in the Rat," *Endocr. J.*, vol. 44, no. 1, pp. 141–148, 1997.
- [74] D. Refojo, P. Arias, J. Moguilevsky, and C. Feleder, "Effect of bacterial endotoxin on in vivo pulsatile gonadotropin secretion in adult male rats," *Neuroendocrinology*, vol. 67, no. 4, pp. 275–281, 1998.
- [75] Y. Takeuchi, H. Nagabukuro, O. Kizumi, and Y. Mori, "Lipopolysaccharide-Induced Suppression of the Hypothalamic Gonadotropin-Releasing Hormone Pulse Generator in Ovariectomized Goats," *J. Vet. Med. Sci.*, vol. 59, no. 2, pp. 93–96, 1997.
- [76] H. Watanobe and Y. Hayakawa, "Hypothalamic Interleukin-1 β and Tumor Necrosis Factor- α , but Not Interleukin-6, Mediate the Endotoxin-Induced Suppression of the Reproductive Axis in Rats," *Endocrinology*, vol. 144, no. 11, pp. 4868–4875, 2003.
- [77] C. L. Jasoni, M. G. Todman, S. Han, and A. E. Herbison, "Expression of mRNAs Encoding Receptors That Mediate Stress Signals in Gonadotropin- Releasing Hormone Neurons of the Mouse," *Neuroendocrinology*, vol. 82, no. 5–6, pp. 320–328, 2005.
- [78] M. Munkhaya *et al.*, "The suppressive effect of immune stress on LH secretion is absent in the early neonatal period in rats," *Int. J. Dev. Neurosci.*, vol. 46, pp. 38–43, 2015.
- [79] A. M. I. Knox *et al.*, "Neonatal lipopolysaccharide exposure delays puberty and alters hypothalamic kiss1 and kiss1r mRNA expression in the female rat," *J. Neuroendocrinol.*, vol. 21, no. 8, pp. 683–689, 2009.
- [80] T. Iwasa *et al.*, "Neonatal lipopolysaccharide exposure attenuates the homotypic stress-induced suppression of LH secretion in adulthood in male rat," *Int. J. Dev. Neurosci.*, vol. 27, no. 4, pp. 345–349, 2009.
- [81] T. Iwasa *et al.*, "Developmental changes in hypothalamic toll-like-receptor 4 mRNA expression and the effects of lipopolysaccharide on such changes in female rats," *Int. J. Dev. Neurosci.*, vol. 40, pp. 12–14, 2015.
- [82] P. Surkin *et al.*, "Participation of hypothalamic CB1 receptors in reproductive axis disruption during immune challenge," *J Neuroendocr.*, vol. 29, no. 8, p. doi: 10.1111/jne.12499., 2017.
- [83] J. Fernández-Solari *et al.*, "Alcohol inhibits luteinizing hormone-releasing hormone release by activating the endocannabinoid system.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 101, no. 9, pp. 3264–8, 2004.
- [84] A. De Laurentiis, J. Fernandez-Solari, C. Mohn, B. Burdet, M. A. Zorrilla Zubilete, and V. Rettori, "The hypothalamic endocannabinoid system participates in the secretion of oxytocin and tumor necrosis factor- α induced by lipopolysaccharide," *J. Neuroimmunol.*, vol. 221, no. 1–2, pp. 32–41, 2010.
- [85] A. H. Miller, V. Maletic, and C. L. Raison, "Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression," *Biol Psychiatry*, vol. 65, no. 9, pp. 732–741, 2009.
- [86] A. H. Veenema, S. O. Reber, S. Selch, F. Obermeier, and I. D. Neumann, "Early life stress enhances the vulnerability to chronic psychosocial stress and experimental colitis in adult mice," *Endocrinology*, vol. 149, no. 6, pp. 2727–2736, 2008.
- [87] U. Dennison, D. McKernan, J. Cryan, and T. Dinan, "Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype," *Psychol. Med.*, vol. 42, no. 9, pp. 1865–1871, 2012.
- [88] V. Chesnokova and S. Melmed, "Minireview : Neuro-Immuno-Endocrine Modulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis by gp130 Signaling Molecules," *Endocrinology*, vol. 143, no. 5, pp. 1571–1574, 2002.

- [89] D. J. Allison and D. S. Ditor, "The common inflammatory etiology of depression and cognitive impairment: A therapeutic target," *J. Neuroinflammation*, vol. 11, no. 1, pp. 1–12, 2014.
- [90] M. I. Zalosnik, A. Pollano, V. Trujillo, M. M. Suárez, and P. E. Durando, "Effect of maternal separation and chronic stress on hippocampal-dependent memory in young adult rats: Evidence for the match-mismatch hypothesis," *Stress*, vol. 17, no. 5, pp. 445–450, 2014.
- [91] H. Brenhouse and S. Andersen, "Nonsteroidal Anti-Inflammatory Treatment Prevents Delayed Effects of Early Life Stress in Rats," *Biol Psychiatry*, vol. 70, no. 5, pp. 434–440, 2011.
- [92] S. A. J. Reincke and I. L. Hanganu-Opatz, "Early-life stress impairs recognition memory and perturbs the functional maturation of prefrontal-hippocampal-perirhinal networks," *Sci. Rep.*, vol. 7, no. February, pp. 1–16, 2017.
- [93] V. Tiwari and K. Chopra, "Resveratrol prevents alcohol-induced cognitive deficits and brain damage by blocking inflammatory signaling and cell death cascade in neonatal rat brain," *J. Neurochem.*, vol. 117, no. 4, pp. 678–690, 2011.
- [94] R. A. Sarabdjitsingh, M. Loi, M. Joe, R. M. Dijkhuizen, and A. van der Toorn, "Early life stress-induced alterations in rat brain structures measured with high resolution MRI," *PLoS One*, vol. 12, no. 9, pp. 1–14, 2017.
- [95] J. Molet *et al.*, "MRI Uncovers Disrupted Hippocampal Microstructure That Underlies Memory Impairments After Early-life Adversity," *Hippocampus*, vol. 26, no. 12, pp. 1618–1632, 2016.
- [96] L. Mothes, C. H. Kristensen, R. Grassi-Oliveira, R. P. Fonseca, I. I. de Lima Argimon, and T. Q. Irigaray, "Childhood maltreatment and executive functions in adolescents," *Child Adolesc. Ment. Health*, vol. 20, no. 1, pp. 56–62, 2015.
- [97] J. Bick and C. A. Nelson, "Early adverse experiences and the developing brain," *Neuropsychopharmacology*, vol. 41, no. 1, pp. 177–196, 2016.
- [98] P. Pechtel and D. Pizzagalli, "Effects of early life stress on cognitive and affective function: an integrated review of human literature," *Psychopharmacology (Berl.)*, vol. 214, no. 1, pp. 55–70, 2011.
- [99] A. F. Richwine, N. L. Sparkman, R. N. Dilger, J. B. Buchanan, and R. W. Johnson, "Cognitive deficits in interleukin-10-deficient mice after peripheral injection of lipopolysaccharide," *Brain Behav Immun*, vol. 23, no. 6, pp. 794–802, 2009.
- [100] I. Goshen *et al.*, "A dual role for interleukin-1 in hippocampal-dependent memory processes," *Psychoneuroendocrinology*, vol. 32, no. 8–10, pp. 1106–1115, 2007.

Figure legend

Table 1: Cytokine response during adulthood in animal models of early life stress.

Fig 1: Common outcomes induced by early insults. Different developmental challenges such as MS, alcohol consumption and immune challenges can induce changes in the immune system, which in turn affects the adult neuroendocrine response, probably by endocannabinoid rearrangement, and brain development. Some of the effects inducing major neurological diseases in adulthood could be mediated by FKBP51 SUMOylation mechanism.

Table 1. Cytokine responses in adulthood

Cytokine	Effect	Adolescent alcohol consumption	Neonatal LPS	Maternal separation
TNF α	Pro-inflammatory	Males: blunted response to further stress (7) Females: no changes (7)	Males: enhanced response to restraint stress (13) Females: no changes to restraint stress (13)	Males: increased baseline levels (25) Females: no baseline changes (25)
IL-1 β	Pro-inflammatory	Males: blunted response to further stress (7) Females: no changes (7)	Males: enhanced response to restraint stress (13) Females: enhanced response to restraint stress	Males: no baseline changes (26) Females: no baseline changes (26)
IL-6	Modulatory	Males: blunted response to further stress (7) Females: no changes (7)	Males: suppressed baseline levels (12) Females: suppressed baseline levels (12)	Males: increased baseline levels (24)
IL-4	Modulatory		Males: increased baseline levels (12) Females: increased baseline levels (12)	Males: no baseline changes (26) Females: no baseline changes (26)
IL-10	Modulatory			Males: decreased baseline levels (26)

