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Review

Stress in adolescence as a first hit in stress-related disease development: Timing and context are crucial

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ABSTRACT

The two-hit stress model predicts that exposure to stress at two different time-points in life may increase or decrease the risk of developing stress-related disorders later in life. Most studies based on the two-hit stress model have investigated early postnatal stress as the first hit with adult stress as the second hit. Adolescence, however, represents another highly sensitive developmental window during which exposure to stressful events may affect programming outcomes following exposure to stress in adulthood. Here, we discuss the programming effects of different types of stressors (social and nonsocial) occurring during adolescence (first hit) and how such stressors affect the responsiveness toward an additional stressor occurring during adulthood (second hit) in rodents. We then provide a comprehensive overview of the potential mechanisms underlying interindividual and sex differences in the resilience/susceptibility to developing stress-related disorders later in life when stress is experienced in two different life stages.

1. Introduction

Exposure to stress is a predominant environmental risk factor for the development of stress-related diseases, including anxiety and post-traumatic stress disorder (PTSD) (De Kloet et al., 2005; McEwen, 2003). The most deleterious stress-induced effects occur when stressful events are experienced during critical developmental windows, such as during gestation, and early postnatal and adolescent periods (Bagot et al., 2014; Burke et al., 2017; Chen and Baram, 2016). Adolescence, representing the transition between childhood and adulthood, is a stage of development during which profound behavioral and brain structural changes occur (Spear, 2000). Adolescents across many animal species are characterized by increased exploratory, risk-taking, sensation-seeking, and social behaviors, all activities that support their efforts to gain independence from parental caretakers (Casey et al., 2008; Spear, 2000). Notably, social interactions with peers are extremely important during adolescence, and their alteration could induce detrimental changes over the long-term (Buwalda et al., 2011; Spear, 2000). During adolescence, key stress-sensitive brain areas involved in the regulation of emotional and cognitive processes, including the amygdala, hippocampus, prefrontal cortex, and components of the hypothalamic–pituitary-adrenal axis (HPA), are still immature (Eiland and Romeo, 2013; McCormick et al., 2010; Romeo and McEwen, 2006). These behavioral features and ongoing structural and functional changes in the brain make the adolescents more susceptible to stressful events, leading to an enhanced risk for psychopathologies later in life (Heim and Nemeroff, 2001; Lupien et al., 2009).

Exposure to stressful events during adolescence, however, does not necessarily predispose individuals to developing stress-related disorders in adulthood. In fact, a growing body of evidence indicates that experiencing adverse events early in life may alter the ability to cope with stress in adulthood such that either susceptibility or resilience to the development of stress-related disorders is enhanced later in life (Champagne et al., 2009; Daskalakis et al., 2013; Krugers et al., 2017; Santarelli et al., 2014). Using the two-hit stress model of psychopathology, numerous studies have investigated whether exposure to different stressors at two different time-points in life increases or decreases the risk of developing stress-related disorders in rodents (Daskalakis et al., 2013; Horovitz et al., 2012). The vast majority of these studies, however, focused on how a stressor experienced during the early postnatal stage (e.g., maternal separation/maternal deprivation) as the first hit affects coping strategies used to respond to a second stressor experienced later in life (Horovitz et al., 2012).

Adolescence, the period of transition between childhood and

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adulthood, represents a sensitive developmental window during which exposure to highly stressful events may induce detrimental programming outcomes. To better understand whether and how stress during adolescence may contribute to the development of stress-related disease, it is essential to investigate whether exposure to stress during adolescence affects the response to a second stress exposure experienced in adulthood. Further, clarifying the neurobiological underpinnings of these effects may pave the way to identifying biomarkers and causative mechanisms of resilience/susceptibility to developing stress-related disorders, and to the development of novel and precision medicine-based prophylactic and/or therapeutic interventions for such diseases (e.g., PTSD) in humans.

Here, we review recent findings from rodent studies on the impact of stressful experiences during adolescence (first hit) on the susceptibility or resilience to developing stress-related disorders when a second stress challenge (second hit) occurs in adulthood. In particular, we describe the programming effects, at both the behavioral and molecular levels, of different types of adolescent stressors (social and nonsocial) and review how experiencing such stress can alter coping strategies in response to an additional stressor later in life. Because sex hormones are known to affect the stress response system and the risk for developing stress-related disorders is twice as high in females compared with males (Balhara et al., 2012; Bangasser and Valentino, 2014), we also discuss sex differences in the response to stress. The paucity of studies of the stress response in females, however, is a major gap that must be addressed in future studies.

We also provide a comprehensive overview of findings from rodent experiments evaluating the potential mechanisms underlying the contribution of stress susceptibility or resilience to developing stress-related psychopathologies as a consequence of the exposure to a combination of different stressors experienced at two different stages in life (adolescence and adulthood). Of note, most of the studies on the two-hit model in rodents (mice and rats) are based on the first hit experienced during early postnatal stage. However, when the first hit occurs during adolescence, the vast majority of the studies have been carried out in rats only. Therefore, the present review is mainly focused on findings obtained from rat models but includes also the few studies present on mice.

2. Adolescence as a critical developmental period

Adolescence is a crucial developmental stage involving profound changes in the structure and function of the brain (Casey et al., 2008; Eiland and Romeo, 2013; Romeo and McEwen, 2006; Spear, 2000); it can be divided in rodents by three stages: early (post-natal day, PND 21–34), mid (PND 34–46), and late adolescence (PND 46–59) (Lupien et al., 2009). Compelling evidence indicates that most adult behavioral features generally result from the continuous development of the brain during adolescence (Eiland and Romeo, 2013). Processes such as synaptogenesis, axonogenesis, myelinogenesis, and the maturation of some brain pathways and regional neurocircuitry occur specifically during adolescence. For example, the frontal lobes and the limbic system, brain regions critically involved in the regulation of specific behaviors and functions (e.g., judgement, spontaneity, impulse control, social interactions, reward, and emotions), develop during this life period both in rodents and humans (Arain et al., 2013; Casey et al., 2008; Gogtay et al., 2004; Konrad et al., 2013).

The prefrontal cortex, amygdala, and hippocampus are key stress-sensitive brain areas that continue to develop throughout adolescence (Eiland and Romeo, 2013; Romeo and McEwen, 2006) and are characterized by a high expression of glucocorticoid receptors (GR), which deeply regulate the stress response system and HPA axis function (Dziedzic et al., 2014; Romeo, 2013; Vázquez, 1998). Stressful experiences stimulate the paraventricular nucleus of the hypothalamus to produce corticotropin-releasing hormone (CRH), which in turn induces the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH then stimulates the final release of glucocorticoids from the adrenal cortex. Glucocorticoids rapidly cross the blood brain barrier and, through genomic and non-genomic mechanisms via binding to their mineralocorticoid receptors (MR) and GR, modulate several brain functions (Campolongo et al., 2009; De Kloet, 2014; de Kloet et al., 2008; Joëls et al., 2013; Paul et al., 2022; Roozendaal et al., 2006). Glucocorticoids can exert genomic actions because GR and MR are intracellular receptors that act as ligand-activated transcription factors (de Kloet et al., 1998; Ulrich-Lai and Herman, 2009). Once glucocorticoids bind to the ligand-binding domain (LBD) of these receptors, the ligand-GR/MR complexes translocate to the cell nucleus where, through their DNA-binding domain (DBD), they bind to glucocorticoid response elements (GREs) at target genes. Although both GR and MR can bind to GREs, there is partial selectivity in the MR/GR DNA-binding which can depend by the nearby binding of other transcription factors. For example, it has been previously demonstrated that NeuroD transcription proteins, which are members of the basic helix-loop-helix protein family, bind to a DNA site close to the GRE inducing specificity for the MR DNA-binding in the adult rat brain (Van Weert et al., 2017). While the genomic effects of glucocorticoids require a prolonged onset of action because they rely on transcription and protein synthesis, the non-genomic effects are fast and seems to be mediated by membrane-associated receptors and signaling cascades (e.g., involvement of the endocannabinoid system) (Di et al., 2003; Groeneweg et al., 2011; Tasker et al., 2006). A large body of evidence demonstrates that GR expression within the adult brain, especially in the hippocampus and central amygdala, can be programmed by stress experienced during early-life and peripubertal periods (Arnett et al., 2015; Enthoven et al., 2010; Papilloud et al., 2019; Santarelli et al., 2017; Sutanto et al., 1996).

The HPA axis is still immature during adolescence, and its activity differs between adolescent and adult subjects (McCormick et al., 2010). Evidence indicates that the paraventricular nucleus of the hypothalamus is more activated in adolescent rats compared with adult rats after exposure to an acute or repeated stressor (Lui et al., 2012; Romeo et al., 2006). Moreover, the release of cortisol (corticosterone in rodents) and ACTH following acute stress is higher and more prolonged in adolescents compared with adults, in both humans and rodents (Andersen, 2003; Goldman et al., 1973; Romeo, 2013, 2010). For example, Romeo and colleagues showed that corticosterone plasma levels in prepubertal male rats exposed to restraint stress for 30 min do not return to baseline until 120 min after stress exposure, while those measured in adults subjected to the same stressor return to baseline levels within 60 min, indicating slower inactivation of the HPA axis response in adolescents compared with adults (Romeo et al., 2004). Similar effects were observed when adolescent and adult rats were exposed to a gas anesthetic (ether) for 3 min or intermittent footshock for 60 s (Goldman et al., 1973; Vázquez and Akil, 1993). Moreover, adolescent rodents have higher corticosterone levels after exposure to repeated stress compared with adults, indicating that adolescents, in contrast to adults, do not habituate to chronic stressors (Lui et al., 2012; Romeo et al., 2006). This effect, however, is strongly dependent on the sex of the animal and the type of the stressor experienced (for review see (McCormick and Mathews, 2010)).

Sex differences in HPA function occur throughout adolescence; for example, adrenal volume increases more in late-adolescent females than in late-adolescent males at basal levels (Green and McCormick, 2016; Heck and Handa, 2019). Notably, stress exposure can also induce different effects on HPA axis function on male vs female adolescent rats. A previous study indicated that the expression patterns of moderators/co-chaperones inhibiting GR translocation is upregulated in chronic stressed female adolescent rats compared to males, and that HPA axis negative feedback is reduced in female, but not male, adolescent rats subjected to an acute stressor (Bourke et al., 2013). Sex differences in the stress response during the adolescence period can be also due to the crosstalk between the HPA and hypothalamic-pituitary–gonadal (HPG) axes, which are reviewed here (Green and McCormick, 2016).

Further, individual differences in the response to a repeated stressor in peripubertal male rats predict the development of an anxiety-like phenotype, altered sociability, and deficits in spatial learning in the long-term (Tzanoulinou et al., 2020; Walker et al., 2017; Walker and Sandi, 2018). Adolescents are also characterized by several behavioral features, including increased social interactions and play behaviors with peers, and novelty-seeking, activities that are necessary to acquire the skills for autonomy and independence from parental caretakers (Spear, 2000). These behavioral characteristics, together with the profound changes in brain structure during this stage, make adolescents more susceptible to stressful life events and to the subsequent development of stress-related disorders compared with adults (Lupien et al., 2009).

3. Adolescence and social stressors

Social interactions and the construction of complex social structures are essential characteristics of humans and many other mammals (Trezza et al., 2011). For adolescents, the quality and quantity of social interactions are critical (Larson et al., 1996). In particular, during adolescence, individuals increase their social interactions with peers while decreasing those with their parents (Buwalda et al., 2011; Spear, 2000). These changes in social behavioral patterns during adolescence are necessary to develop the skills that promote a successful transition from adolescence to adulthood (Gopnik et al., 2017; Tzanoulinou and Sandi, 2016). Exposure to adverse social experiences during adolescence may profoundly affect adult behaviors, resulting in the subsequent development of stress-related disorders. For example, in humans bullying and subordination episodes are social stressors that commonly occur in adolescence, particularly at school (Menesini and Salmivalli, 2017; Rettew and Pawlowski, 2016). Bullying or peer victimization refers to a single individual or a group of individuals (bullies) that exhibit intentional and aggressive behavior against others (victims) viewed as weaker than the bullies and thus unable to defend themselves (Gredler, 2003). Generally, bully-victims are shy, submissive, and introverted individuals, while bullies are generally more aggressive and physically stronger than their victims (Olweus, 1978). The type of bullying depends on the nature of the attack, and includes verbal and physical violence; social aggression such as social exclusion; and cyberbullying, which is currently the most widespread form of bullying associated with the internet, such as via social media and text messaging (Bonanno and Hymel, 2013; Englander et al., 2017; Gredler, 2003; Monks and Smith, 2006). Being bullied is considered a critical factor enhancing suicidality among adolescents (Limbana et al., 2020). Moreover, adolescent bullying not only affects adolescent subjects by increasing the development of health problems, including anxiety, depression, sleeplessness (Arseneault et al., 2010; Hong et al., 2019), but also leads to detrimental effects later in life. In fact, numerous studies suggest that adolescent bully-victims are more likely to develop stress-related disorders later in life, particularly anxiety and PTSD (Gladstone et al., 2006; Mukherjee et al., 2020).

4. Animal models of adolescent stressors

Animal models are useful tools for elucidating the neurobiological underpinnings and potential therapeutic targets of stress-related disorders (Czéh and Simon, 2021; Sarter and Bruno, 2003; Yehuda and LeDoux, 2007). Although the majority of preclinical studies on the long-term effects of stress have been carried out in adult rodents, interest in the long-lasting effects of stress exposure during adolescence has increased over the last few decades (McCormick and Green, 2013). Many different rodent models exist to represent a variety of adverse stressful events experienced by humans during adolescence. Here, we focus on the long-term effects induced in animal models of social and nonsocial adolescent stressors.

4.1. Animal models of social stressors

Sociabilty during adolescence may be disrupted via either lack of social interactions or rather by detrimental social interactions (Gopnik et al., 2017; Tzanoulinou and Sandi, 2016). Animal models of social stressors differ in the type and intensity of the interactions, thus leading to different outcomes. Exposure to social stress can be singular, intermittent, or chronic, and may involve social deprivation (e.g., a social isolation model in which animals are fully deprived of interactions with conspecifics) or social interactions between two or more animals in a dyad, group, or colony (Blanchard et al., 2001). Among experimental models of social stressors, the social defeat paradigm is a highly validated model that mimics, in part, bullying in humans, and generally consists of exposing two rodents to dyadic contests. The resident-intruder paradigm, characterized by social subordination, threat, and physical abuse, is easily implemented in rodents to investigate the main features of human bullying (Björkqvist, 2001; Miczek, 1979). In this paradigm, an experimental rodent (intruder) is placed in the territory of a larger, aggressive conspecific (resident) that attacks the intruder during either a single or repeated encounters (Golden et al., 2011). Although social defeat stress mimics typical features of human bullying, which is particularly common among adolescents (Menesini and Salmivalli, 2017; Rettew and Pawlowski, 2016), for many years preclinical studies were only focused on the effects of this type of social stress experienced in adulthood. These studies demonstrated that exposure to social defeat in adult rats profoundly affects behavior by inducing depression- and anxiety-like profiles, decreased social interactions, cognitive dysfunction, rapid acquisition of psychostimulant self-administration, and hyperlocomotion induced by psychostimulants (Blanchard et al., 2001; Covington and Miczek, 2005, 2001; Haney et al., 1995; Meerlo et al., 1996; Patki et al., 2014, 2013; Riga et al., 2015; Rygula et al., 2005; Tidey and Miczek, 1997).

However, exposure to social defeat stress was reported to produce different effects depending on whether it occurs during adolescence or adulthood (Bingham et al., 2011; Coppens et al., 2011). Studies on the short-term effects of social defeat stress experienced during the adolescent period demonstrated that male rats exhibit enhanced proactive responses in defensive burying and forced swim tests (Bingham et al., 2011), while female rats show increased climbing in the forced swim test compared with their controls (Ver Hoeve et al., 2013). Further, male stressed rats show decreased total water consumption and time spent drinking when placed in the same context in which they were exposed to the social defeat experience, indicating a lack of generalization across different contexts (Vidal et al., 2011a).

Evaluating the long-term outcomes induced by adolescent social defeat is of the utmost importance in view of the risk for the later development of psychopathologies. Different studies showed that adult male rats, that experienced social defeat during adolescence, exhibit increased anxiety (MacKay et al., 2017; Mancini et al., 2021a; Watt et al., 2009), altered fear memory dynamics (Mancini et al., 2021a; Novick et al., 2016), decreased proactive strategies (Bingham et al., 2011), and enhanced social anxiety (Vidal et al., 2011b, 2007); and that the effects are strain-specific (Vidal et al., 2011a). Moreover, adult male rats subjected to social defeat in adolescence exhibit increased locomotion in a novel environment, but reduced amphetamine-induced locomotion compared with controls (Burke et al., 2010). Further, susceptibility to the development of a depressive-like phenotype was more pronounced in adult females compared with adult males exposed to social defeat stress during adolescence (Weathington et al., 2012). However, these findings are at odds with those of another study in which no depressive-like behaviors were observed in adult female rats exposed in adolescence to a social stressor (Ver Hoeve et al., 2013). Taken together this large body of evidence demonstrated that: i) social defeat stress produces different effects if it occurs during the adolescent or adult periods; ii) studies on the effects of social defeat stress experienced in adolescence are less investigated rather than those in adulthood; iii)

adult rats exposed to social defeat stress during adolescence exhibit profound effects on adult behavior.

Beyond the exposure to social defeat stress, other models of social stress are used in rodent studies including predator exposure and alterations in social housing conditions (e.g., social isolation, social crowding and social instability). Predator exposure can be performed either directly, through exposure to a predator (e.g., cat) or indirectly through exposure to a predator scent (e.g., cat collars or 2,3,5-trimethyl-3-thiazoline, TMT, a component of fox feces). Previous studies established that these stressors induce several effects (e.g., fear, anxiety, avoidance, and defensive behaviors in rodents (Adamec et al., 2004; Berardi et al., 2014; Cohen et al., 2012; Dielenberg and McGregor, 2001)), and that such effects are long-lasting, particularly when these stress paradigms occur during adolescence (Post et al., 2014; Tsoory et al., 2007; Wah et al., 2019; Wright et al., 2013, 2008). Male rats exposed to a combination of fox odor (TMT) and an elevated platform for 7 days across the peripubertal period (PND 28–42) exhibit abnormal aggressive behavior, reduced social exploration, increased anxiety-like behavior, and impaired spatial learning in adulthood (Márquez et al., 2013; Papilloud et al., 2019; Tzanoulinou et al., 2020, 2014). Additionally, exposure to a combination of several stressors (e.g., elevated platform, TMT, restrainer, tail suspension test, and forced swim stress) from PND 28 to 42 induces programming brain alterations (e.g., reduced excitability in the nucleus accumbens), and increases adiposity and reduces sociability in adult male, but not female, mice (Morató et al., 2022).

Alterations in social housing conditions can induce detrimental effects in rodents. Social isolation stress for instance consists in housing animals individually depriving them of any form of social interaction with peers, and it is generally conducted for long periods of time (e.g., 4–6 weeks or more) from weaning to adulthood. Post-weaning social isolation represents a highly validated animal model to reproduce in rodents neurochemical and behavioral alterations resembling some of the core symptoms observed in psychiatric disorders (Fone and Porkess, 2008; Heidbreder et al., 2000; Lapiz et al., 2003; Mumtaz et al., 2018). For example, compelling evidence indicates that social isolation stress induces anxious- and depressive-like phenotypes, cognitive deficits, and abnormal aggression in adult rodents (Biro et al., 2017; Butler et al., 2016; Haller et al., 2014; Han et al., 2018; Ieraci et al., 2016; Lukkes et al., 2009; Medendorp et al., 2018). However, these results are inconsistent between male and female rodents (Walker et al., 2019). While social isolation consists in the deprivation of social interactions with conspecifics, social crowding paradigm is exactly the opposite. In fact, in this stress model rodents are housed in groups of generally 4–6 rats or 12 mice in the same sufficiently large area. It has been demonstrated that this housing condition affects many physiological aspects in rodents (Beery and Kaufer, 2015), in a sex-dependent manner (Brown and Grunberg, 1995). However, one study demonstrated that adolescent male mice subjected to social crowding exhibit anxious-like phenotype when tested in adolescence but not in adulthood, indicating that the stress-induced effects are not permanent (Ago et al., 2014). Another social stressor model, highly used in rodents studies, is the social instability stress paradigm which is characterized by changing group composition of group-housed rodents (Buwalda et al., 2011). Interestingly, previous findings suggest that exposure to chronic social instability in adolescent rodents of both sexes induces long-lasting effects in adulthood (McCormick et al., 2020, 2015, 2012; Schmidt et al., 2009; Sterlemann et al., 2010).

Together, these results suggest that exposure to different types of social (direct or indirect) stress paradigms during adolescence may induce profound programming alterations in the response to stress experienced later in life.

4.2. Animal models of nonsocial stressors

Animal models are also useful for investigating the neurobiological mechanisms underlying the effects of adolescent stress exposure on the later development of stress-related disorders (Czéh and Simon, 2021; Sarter and Bruno, 2003; Yehuda and LeDoux, 2007). As previously mentioned, the stress response that is triggered by an acute nonsocial stressor in adolescent rodents differs from that in adults. For example, high plasma corticosterone levels induced by an acute nonsocial stressor (e.g., restraint stress, ether vapor exposure, or footshock exposure) return to baseline more slowly in adolescent rats than in adult rats (Goldman et al., 1973; Romeo et al., 2004; Vázquez and Akil, 1993), which may be a mechanism by which stress experienced in adolescence induces profound effects later in life. In fact, single (PND 28) and repeated (PND 26–28) exposure to an elevated platform in early-adolescence increases the development of anxiety-like behavior in adult male rats (Avital and Richter-Levin, 2005). Different effects can occur when the same stressor is experienced by adolescent rats for longer periods of time. For example, exposure to restraint stress for 28 consecutive days (PND 28–55) induces anxiolytic- and antidepressive-like phenotypes in adult male rats (Suo et al., 2013), indicating that the long-lasting outcomes of exposure to a stressor during adolescence can also depend on the stress duration. In addition to these effects induced later in life by a repeated stressor experienced during adolescence, numerous studies found that the exposure to many different types of repeated nonsocial stressors during adolescence may induce long-term effects. Exposure to variable nonsocial stressors, such as forced swim, elevated platform, and restraint stress, for 3 consecutive days (PND 27–29) induces reduced exploratory behavior (Horovitz et al., 2014; Jacobson-Pick and Richter-Levin, 2010), increased development of anxious- and depressive-like phenotypes (Ilin and Richter-Levin, 2009), and alterations in freezing behavior in male adult rats (Yee et al., 2012). Similar effects were found in female adult rats subjected to the same stress in adolescence (Horovitz et al., 2014; Jacobson-Pick and Richter-Levin, 2010). Additionally, male adult rats exposed to another type of variable nonsocial stressors (e.g., restraint stress, elevated platform and footshock for three nonconsecutive days across PND 27–33) also exhibit increased anxious-like profile (Luo et al., 2014). Further, the exposure to forced swim stress, restraint stress and footshock across PND 25–27 increases the development of anxious-like phenotype in adult rodents, and induces altered cognitive bias and decision making in adult rats of both sexes (Brydges et al., 2014, 2012). A recent study, however, demonstrated that exposure to variable stressors for a more prolonged period of time (e.g., two weeks) and in a different phase of adolescence (e.g., late adolescence) did not induce any alterations in fear memory dynamics in male or female adult rats (Cotella et al., 2022). All together, these results suggest that the use of different repeated nonsocial stress paradigms during adolescence may induce a diversity of programming effects in rats. This could be due to several factors, including the severity, duration, and type of stressor. Additionally, it is important to consider whether the repeated stressor is the same (homonymous) or variable, which is related to controlling and predicting stress, aspects that influence stress-induced behavioral outcomes (Albrecht et al., 2017).

5. Resilience and susceptibility to developing stress-related disorders

Experiencing stressful events can increase the risk for stress-related disorders development (De Kloet et al., 2005; McEwen, 2003), however, it does not affect everyone the same, and not all individuals who are exposed to stressful experiences develop a mental disease. This concept was described for the first time by Hans Selye, the founder of the stress theory summarized by the statement "*it is not stress that kills us, it is our reaction to it*", which suggests that the final consequences of exposure to stress depend on the individual responses (Selye, 1936). Because stress responses cannot be sustained over a long period of time, the organism must develop effective physiological and psychological coping methods (McEwen, 2007). Stressful experiences lead to adaptation, but in some

susceptible individuals this adaption can be either dysfunctional or affected by "mismatched" circumstances, suggesting interindividual differences in the stress response (Champagne et al., 2009; Del Giudice et al., 2011; Ullmann et al., 2019).

The exact mechanisms underlying such differences, however, are not yet well clarified. Interindividual differences in the response to stress may be related to various combinations of numerous factors (McEwen and Stellar, 1993): i) subjective perception of the stressful event (e.g., for some individuals speaking in public is stressful while for others it is not); ii) genetic components, as it has been demonstrated that some genes are more involved than others in the development of stress-related disorders (e.g., serotonin transporter and pituitary adenylate cyclase-activating polypeptide) (Richter-Levin and Sandi, 2021; Smoller, 2016); iii) sex, as it is well known that sex-hormones can affect the stress response system and females have a two-fold greater risk than males for developing stress-related disorders (e.g., PTSD) (Balhara et al., 2012; Bangasser and Valentino, 2014; Kessler et al., 1995); iv) developmental stage during which stress occurs (e.g., adolescence, which is a stress-sensitive period); v) previous life experiences; and vi) rodents strain differences in the responsivity to the same stressor (Anisman and Matheson, 2005; Mineur et al., 2006; Mozhui et al., 2010; Pothion et al., 2004). To elucidate this latter aspect, various theories and hypotheses have been postulated.

Among these theories, the cumulative stress model emphasizes the effects of repeated exposure to stressors throughout life. When the accumulation of stress exceeds a certain threshold, individuals will have an enhanced risk of developing psychiatric disorders (McEwen, 1998). On the one hand, the cumulative stress theory postulates that repeated exposure to stress induces susceptibility to the development of psychiatric disorders, while on the other hand, the match/mismatch hypothesis asserts that resilience or susceptibility to psychopathologies depends on the match or mismatch of the early-life environment with the environment later in life (Champagne et al., 2009; Schmidt, 2011). This theory thus suggests that the environment during early-life itself may promote active coping strategies that allow individuals to better face a similar stressor later in life, which in turn leads to resilience against mental disorders (Tsoory et al., 2007). To test the validity of the match/mismatch hypothesis, an experimental study was performed in which female mice were subjected to an early handling paradigm as a positive condition (early handling is known to increase maternal care) or to a limited bedding and nesting material paradigm as a negative condition. Mice were then housed in a social isolation (negative situation) or group (positive situation) condition during adulthood. Interestingly, female mice exposed to matched (either positive or negative) environmental manipulations during early-life and adult periods exhibited different behaviors compared with animals subjected to a mismatched condition (Santarelli et al., 2014). Even though this study does not investigate stress effects during adolescence it appears relevant for the present review because it highlights how, according to the match/mismatch hypothesis, the two-hit stress model asserts that different types of stress exposure in two different periods of life may affect either the resilience or susceptibility to developing stress-related psychopathologies after the second stress exposure (Daskalakis et al., 2013; Horovitz et al., 2012). For example, male rats experienced a social stressor in adolescence exhibit increased ability to face with a similar stress later in life (resilience) (Buwalda et al., 2013), while an opposite outcome (susceptibility) was found following the exposure to two different stressors (Horovitz et al., 2014). However, these effects do not always occur since several factors are involved.

Although interindividual differences play an important role in the final development of a susceptible or resilient phenotype regarding stress-related disorders, the context and timing of the two stress experiences are key factors involved in this process as well. A recent study evaluated the effects of different manipulations in male mice throughout early postnatal to *peri*-adolescent periods coupled with chronic stress exposure in adulthood (Peña et al., 2019). Specifically, the authors demonstrated that maternal separation paired with reduced bedding material (PND 10–17) increases susceptibility to depression- and anxiety-like phenotypes after adult chronic social defeat stress in adulthood. Predictable chronic mild stress also during *peri*-adolescence (PND 28–56) induced a susceptible phenotype. Conversely, other manipulations throughout the *peri*-adolescent period, such as social isolation (PND 22–60), yoked footshock stress (PND 26–30), and an enriched environment (PND 22–56), produced pro-resilient phenotypes (Peña et al., 2019), indicating that the final development of resilience or susceptibility to developing stress-related disorders is strongly related to the context and timing of the other types of stressors. Therefore, evaluating the biological differences occurring between different life stages is extremely important in terms of translational value.

Most of the studies in rodents have focused on how stress during the early postnatal period (e.g., by subjecting animals to a maternal separation paradigm) affects responsiveness to an additional challenge later in life (Horovitz et al., 2012). Maternal separation is generally performed during the first weeks of life (Marais et al., 2008; Plotsky et al., 2005; Vetulani, 2013), which is a period termed the "hyporesponsive stress period" because the HPA axis is not yet mature, thus leading to a limited secretion of glucocorticoids following stress (Levine, 2001; Sapolsky and Meaney, 1986; Schapiro et al., 1962). Importantly, a previous study demonstrated that the detrimental maternal separation-induced effects strongly depend by the time of the hyporesponsive stress period during which such stressor occurs. In fact, maternal deprivation was only effective when mice were subjected to it between PND 1–12, and not on PND 13 (Enthoven et al., 2008), suggesting that the vulnerability to stress can be different according to the exact moment across the hyporesponsive stress period a stressor is experienced.

It is important to consider that the early postnatal period strongly differs from the adolescent one in several aspects. For example, components of the HPA axis as well as several brain areas (e.g., the hippocampus, prefrontal cortex, and amygdala) are more mature during adolescence than during the early postnatal period. Additionally, rodents during adolescence develop emotional, cognitive, and social skills that are necessary to reach independence from parental caretakers, the same types of characteristics observed in adolescent humans (Spear, 2000). For these reasons, it is critical to evaluate whether stress experienced during early-life, but in a period that more reflects adolescence in humans, can affect the response to an additional stress challenge later in life (Horovitz et al., 2012).

5.1. *The two-hit model: behavioral effects*

5.1.1. *Interaction between adolescent social stress and adult stress*

The two-hit model assumes that exposure to stress during early-life (first hit), such as during the stress-sensitive window of adolescence, induces alterations in brain structure and function, which in turn may affect responsiveness to an additional stressor (second hit) experienced later in life, thus leading to a decreased and/or increased risk of stress-related disorders (Fig. 1). During adolescence, social interactions, including play and novelty seeking-behaviors, represent a fundamental aspect in the development of behavioral features necessary to acquire autonomy and independence (Gopnik et al., 2017; Spear, 2000; Tzanoulinou and Sandi, 2016). Therefore, to understand how early-life social stress affects the responsiveness to a second stressor experienced later in life, we recently investigated whether exposure to the social defeat stress paradigm (first hit) for 7 consecutive days during early-adolescence (PND 28–34) alters the ability to cope with a second hit (single prolonged stress) occurring during adulthood (PND 90) in male rats (Mancini et al., 2021a). Single prolonged stress is a valid model to reproduce in rodents some of the core symptoms of PTSD, and is a multimodal stress protocol consisting in the sequential exposure to three different stressors (restraint stress, forced swim stress and inhalation of gas anesthetic until loss of consciousness) (Lisieski et al., 2018; Souza et al., 2017; Verbitsky et al., 2020; Yamamoto et al., 2009). In our study,

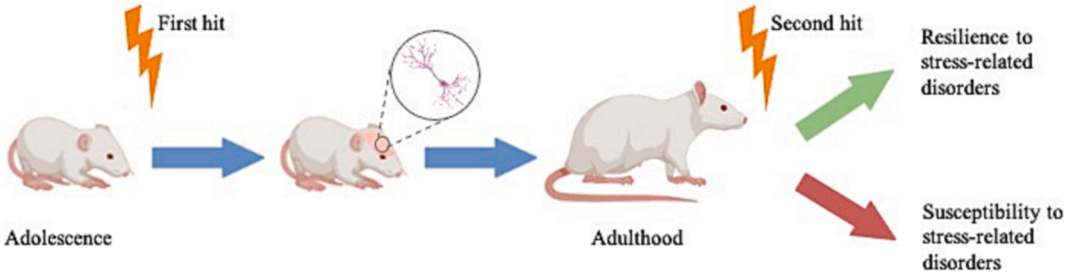

Fig. 1. Schematic representation of the two-hit model. Stress exposure during adolescence (first hit) induces changes in the structure and function of the brain, which in turn can alter the responsiveness to an additional challenge (second hit) experienced later in life, thus increasing and/or decreasing the risk for the development of stress-related disorders.

the final consequences of the exposure to stress were evaluated by testing animals in several behavioral tasks 30 days after the single prolonged stress paradigm, as previously described (Mancini et al., 2021b). We found that exposure to social defeat stress alone during early-adolescence increased the development of anxiety-like behavior and hyperarousal in the open field and acoustic startle response tasks, respectively, in the long-term. The single prolonged stress alone reduced locomotor activity in the open field task, induced hyperarousal in the acoustic startle response task, and altered spatial memory retention long after the trauma. Interestingly, rats exposed to social defeat stress during early adolescence and then to a single prolonged stressor in adulthood exhibited resilience against the development of an anxiety-like phenotype, hyperarousal, and spatial memory retention deficits, but demonstrated susceptibility to dysfunctional fear memory dynamics. It is important to note that these effects seemed to be directional as the effects induced by a single prolonged stressor were not observed in rats exposed only to social defeat stress, and vice versa. Together, these findings suggest that experiencing social stress during early-adolescence affects the ability to cope with additional trauma later in life (Mancini et al., 2021a), in line with the match/mismatch concept. In another study, Buwalda and colleagues (2013) investigated whether exposure to social defeat stress for 3 nonconsecutive days during adolescence (PND 28, 31, and 34) altered the response to the same stressor experienced later in life (PND 89–90), and found that social defeat stress during adolescence did not induce behavioral alterations in the long-term, but rather led to a stronger ability to face the same stressor in adulthood in male rats (Buwalda et al., 2013). These findings demonstrate that exposure to social defeat stress during early-adolescence may promote active coping strategies to positively respond to an additional similar stressor in adulthood.

When a different early-life social stressor occurs, however, such stress-resilient effects are no longer observed. In fact, indirect exposure to a social stressor (predator scent) in juvenile (PND 28) or adult (PND 60) male rats increases anxiety-like behavior in the elevated plus maze and acoustic startle response tasks, and these effects are maintained when the rats experience a combination of these two stressors, indicating that the indirect exposure to a predator (through its scent) during early-life predisposed the rats to developing anxiety-like behavior in response to stress later in life (Tsoory et al., 2007). These findings together suggest that the development of stress vulnerability vs stress resilience is due to differences in the timing and type of the social stressor experienced during early-adolescence. The results described above are summarized in Table 1.

5.1.2. *Interaction between adolescent nonsocial stress and adult stress*

Interest has grown over the last few decades in the effects of nonsocial stress experienced during adolescence on the ability to cope with another stressful event later in life.

Numerous studies in this field were carried out by Richter-Levin's group, who demonstrated that the combined experience of different types of stressors in two different life periods (adolescence and adulthood) increased susceptibility to stress-related disorders later in life in rats (most such studies were reviewed here (Horovitz et al., 2012)). The early-life stress model used in these studies is applied in the juvenile stage (PND 26–28 or PND 27–29) and therefore referred to as juvenile stress and consists of exposure to variable nonsocial stressors for 3 consecutive days (one stressor per day). To determine whether such stress affects the ability to cope with additional stress later in life, the two-way shuttle avoidance task has been used as the adult stressor. Briefly, rats were exposed to several conditioning trials (tones) paired with footshock and learning abilities were measured by evaluating how animals respond to each stimulus (e.g., avoidance behavior).

Exposure to forced swim stress (PND 27), an elevated platform (PND 28), and footshock or restraint stress (PND 29) induced low exploratory activity and poor avoidance learning in the two-way shuttle avoidance task in male rats at adulthood (Tsoory et al., 2008, 2007). The same effect was observed in another study in which the combination of these juvenile and adult stressors induced susceptibility to developing depressive-like behavior, as demonstrated by reduced consumption of saccharine in a saccharine preference test, in both male and female adult rats (Horovitz et al., 2014). Further, male adult rats exposed to both stressors exhibited reduced exploratory activity and a stronger anxiety-like phenotype in the open field task (Gruber et al., 2015) and in the elevated zero maze (Horovitz et al., 2020). In another study, male rats were subjected to an elevated platform (day 1), forced swim stress (day 2), and footshock (day 3) during the juvenile (PND 27–29) or adolescent

Table 1
Two-hit studies: social adolescent stress (first hit) + adult stress (second hit).

Sex and strain	First hit (PND)	First hit (type)	Second hit (PND)	Second hit (type)	Behavioral effects (two-hit)
Male rats (Mancini et al., 2021a)	PND 28–34	Social defeat stress	PND 90	Single prolonged stress (2 h restraint stress, 15 min forced swim stress and, after 15 min, isoflurane exposure until loss of consciousness)	Reduced alterations on emotionality and spatial memory, and increased cued fear memory dysfunction
Male rats (Buwalda et al., 2013)	PND 28, 31, 34	Social defeat stress	PND 89–90	Social defeat stress	Increased ability to face towards social defeat stress in adulthood
Male rats (Tsoory et al., 2007)	PND 28	Predator scent	PND 60	Predator scent	Increased anxious-like behavior

(PND 33–35) periods, and then to a different stressor (two-way shuttle avoidance task) in adulthood (Tsoory and Richter-Levin, 2006). Exposure to variable stressors during the juvenile or adolescent periods reduced exploratory activity in the open field task in the long-term, and this effect was maintained when rats were exposed to additional stress later in adulthood. Moreover, alterations in learning performances during the two-way shuttle avoidance paradigm were found. When adult rats previously exposed to stress in either the juvenile or adolescent periods exhibited poor avoidance learning in the two-way shuttle avoidance task, those stressed in the juvenile stage also demonstrated a high frequency of no-response trials ("learned helplessness-like behavior"), while adult animals subjected to stress during the adolescent stage demonstrated a low frequency of no-response trials ("bad learners"), suggesting a difference in learning abilities based specifically on when the early-life stress occurs (Tsoory and Richter-Levin, 2006).

Avital and colleagues (2005) used a different two-hit model than the previous models already described. They subjected male rats to an elevated platform for a single day at PND 28 (experiment 1) or for 3 consecutive days at PND 26–28 (experiment 2), and then, to determine whether this stressor alters the ability to cope with another stressor later in life, rats were exposed to acute swim stress for 15 min in adulthood. In experiment 1, they found that a single exposure to an elevated platform at PND 28 reduced exploratory activity in the open field task, and ameliorated reversal learning abilities during day 1 of the reversal learning session in the Morris water maze task in the long-term. Acute swim stress in adulthood reduced exploratory activity in the open field, increased anxiety-like behavior in both the open field and acoustic startle response tasks, and induced faster reversal learning during day 1 of reversal learning in the Morris water maze task compared with controls. Interestingly, exposure to both stressors exacerbated the development of impaired exploratory activity, increased anxiety-like effects, and altered spatial memory performances. The same effects were found in experiment 2, in which increased anxiety-like behavior in both open field and acoustic startle response tasks was observed in adult rats previously exposed to juvenile stress (Avital and Richter-Levin, 2005). Together, these studies demonstrate that experiencing a first hit during early-life exacerbates behavioral alterations induced by exposure to a second stress challenge later in life. It is important to note, however, that resilience effects may also occur after exposure to both stressors at two different life periods. For example, Suo and colleagues (2013) found that repeated predictable chronic mild stress during adolescence (PND 28–55) induced anxiolytic- and antidepressive-like behaviors in adult male rats compared with their controls in the long-term, while exposure to chronic unpredictable stress in adulthood (PND 63–83) increased the development of anxiety- and depression-like behaviors. Interestingly, they found that when rats were exposed to both types of stress, they exhibited resilience against the development of such phenotypes, indicating that, in this case, stress during adolescence helped rats to cope with another stressful event later in life (Suo et al., 2013). Similar resiliency-inducing effects were found in a more recent study in which late-adolescent male and female rats were subjected to chronic variable stress for 2 weeks (starting at PND 45 ± 2) and then to single prolonged stress in adulthood (PND 85). Specifically, they found that exposure to stress in adolescence did not induce later alterations in fear memory dynamics in either sex, but that the adult stressor reduced extinction only in males and enhanced reinstatement in both sexes in an auditory-cued fear conditioning paradigm. Further, they demonstrated that the combination of these two stressors induced the development of resilience against such alterations in fear memory (Cotella et al., 2022). These results indicate that the final consequences of susceptibility or resilience to stress depend on several factors, such as the duration and type of the stressors. Another possible explanation for such different outcomes could be the interindividual variability in the stress response, which was not considered in the studies described above. Generally, in animal studies, the data are interpreted by considering the whole population of the stress-exposed subjects homogeneously, i.e., as having the same phenotype (vulnerable or resilient) (Cohen et al., 2004). Evaluating individual values instead of the average of a certain behavioral parameter in stress-exposed animals could be helpful, however, to better understand interindividual variability in the stress response and enhance the translational value of the study. All the results described above are summarized in Table 2.

5.2. *Neurobiological mechanisms underlying the effects of combined adolescent social/nonsocial and adult stress*

Clarification of the neurobiological mechanisms underlying the effects induced by early-life adverse events on the individual's responsiveness to an additional stressor experienced later in life in animal models has high translational value. This understanding will provide the basis to unravel biomarkers and causative mechanisms of resilience/susceptibility to developing stress-related disorders, which in turn will open the way for the development of new pharmacological tools to treat and prevent the development of such diseases following an additional stress exposure in adulthood. Evidence suggests that epigenetic regulation of gene expression (histone modification, DNA methylation and microRNAs) is responsible for the permanent effects of stress (Klengel and Binder, 2015). In fact, it is hypothesized that stress affects the expression of genes related to the HPA axis or to important processes within the brain. These alterations may change stress-induced adaptive (allostasis) or maladaptive (allostatic load) mechanisms, which can result in the adoption of either successful coping strategies (health) or dysfunctional coping strategies (stress-related disorders) (Gray et al., 2017). Although it is clear that adolescent (social and nonsocial) stressors may affect the ability to cope with an additional stressful event experienced later in life (see behavioral results described in the above two paragraphs), the precise brain areas and signaling involved in such effects are not yet well elucidated.

Gamma-aminobutyric acid (GABA) and opioid neurotransmission play important roles in the pathophysiology of stress-related disorders, and altered modulation of $GABA_A$ receptors ($GABA_AR$) and κ opioid receptors (KOR) may be involved in the development of anxiety (Horovitz et al., 2012; Nuss, 2015; Van'T Veer and Carlezon, 2013). Horovitz and colleagues (2020) showed that exposure to stressors in both the juvenile and adult stages induces susceptibility to anxiety-like behavior in adult male rats (Horovitz et al., 2020). To investigate the neurobiological mechanisms underlying such effects, they analyzed protein expression levels of α_1 and α_2 subunits of the $GABA_AR$ ($GABA_AR$ α_1 and α_2) and KOR in different stress-related brain areas, such as medial prefrontal cortex, nucleus accumbens, amygdala, and periaqueductal gray. By using an integrated receptor expression network profile (useful approach since the stress response involves the activity of multiple brain areas at the same time), they found that exposure to variable stressors in juveniles and to a two-way shuttle avoidance task in adulthood affects the expression of $GABA_AR$ α_1 and α_2 and KOR within the brain and that these alterations occur in parallel. These findings suggest that the enhanced anxiety-like phenotype induced by both stressors could be explained by alterations in neurotransmission involved in this brain network (Horovitz et al., 2020).

Compelling evidence, however, indicates that the development of anxiety-like symptoms can be related to several pathways, including the serotonergic (5-HT) system (Akimova et al., 2009; Baldwin and Rudge, 1995). Further, it is established that cross-talk between the 5-HT and GABA systems occurs within the brain, particularly in the hippocampus, as GABAergic neurons express various 5-HT receptor types (Dale et al., 2016). According to these findings, Gruber and colleagues (2015) investigated the contribution of 5-HT–induced GABAergic inhibition in the ventral dentate gyrus of the hippocampus to the susceptibility of developing anxiety-like behavior in adult male rats subjected to a combination of two stressors experienced in adolescence and adulthood (Gruber et al., 2015). Their findings indicated that rats singularly exposed to juvenile or adult stress exhibited altered modulation of 5-

Table 2
Two-hit studies: nonsocial adolescent stress (first hit) + adult stress (second hit).

Sex and strain	First hit (PND)	First hit (type)	Second hit (PND)	Second hit (type)	Behavioral effects (two-hit)
Male rats (Tsoory et al., 2007)	PND 27–29	Forced swim stress (PND 27) + elevated platform (PND 28) + footshock (PND 29)	PND 60	Two-way shuttle avoidance task	Reduced exploration and avoidance learning
Male rats (Tsoory et al., 2008)	PND 27–29	Forced swim stress (PND 27) + elevated platform (PND 28) + footshock/restraint (PND 29)	PND ~ 60	Two-way shuttle avoidance task	Reduced avoidance learning
Male rats (Horovitz et al., 2014)	PND 27–29	Forced swim stress (PND 27) + elevated platform (PND 28) + restraint (PND 29)	PND 60	Two-way shuttle avoidance task	Reduced exploration and avoidance learning, and increased depressive-like behavior
Female rats (Horovitz et al., 2014)	PND 27–29	Forced swim stress (PND 27) + elevated platform (PND 28) + restraint (PND 29)	PND 60	Two-way shuttle avoidance task	Reduced avoidance learning, and increased depressive-like behavior
Male rats (Gruber et al., 2015)	PND 27–29	Forced swim stress (PND 27) + elevated platform (PND 28) + restraint (PND 29)	PND 60–69	Two-way shuttle avoidance task (one single exposure)	Reduced exploration, and increased anxious-like behavior
Male rats (Horovitz et al., 2020)	PND 27–29	Forced swim stress (PND 27) + elevated platform (PND 28) + restraint (PND 29)	PND ~ 60	Two-way shuttle avoidance task	Increased anxious-like behavior
Male rats (Tsoory and Richter-Levin, 2006)	PND 27–29	Elevated platform (PND 27) + forced swim stress (PND 28) + footshock (PND 29)	PND 59–60	Two-way shuttle avoidance task (one single exposure)	Reduced exploration and avoidance learning with high frequency of no-response trials ('learned helplessness-like behavior)
Male rats (Tsoory and Richter-Levin, 2006)	PND 33–35	Elevated platform (PND 33) + forced swim stress (PND 34) + footshock (PND 35)	PND 59–60	Two-way shuttle avoidance task (one single exposure)	Reduced exploration, and avoidance learning with low frequency of no-response trials ('bad learners')
Male rats (Avital et al., 2005)	PND 28	Elevated platform	PND 86	Acute swim stress	Reduced exploration, increased anxious-like behavior, and ameliorated spatial memory performances
Male rats (Avital et al., 2005)	PND 26–28	Elevated platform	PND 60/ 90	Acute swim stress	Reduced exploration, increased anxious-like behavior, and ameliorated spatial learning
Male rats (Suo et al., 2013)	PND 28–55	Predictable chronic mild stress	PND 63–83	Chronic unpredictable stress	Reduced anxious- and depressive-like behaviors
Male rats (Cotella et al., 2022)	PND 45 ± 2; two weeks	Chronic variable stress	PND 85	Single prolonged stress (2 h restraint stress, 20 min forced swim stress and, after 15 min, ether anesthesia until loss of consciousness)	Reduced fear memory dynamics alterations (e.g., impaired extinction and increased reinstatement)
Female rats (Cotella et al., 2022)	PND 45 ± 2; two weeks	Chronic variable stress	PND 85	Single prolonged stress (2 h restraint stress, 20 min forced swim stress and, after 15 min, ether anesthesia until loss of consciousness)	Reduced fear memory dynamics alterations (e.g., increased reinstatement)

HT–induced granule cell inhibition, and that some of these effects remained when rats were subjected to both stressors, while other effects at the synaptic level disappeared. This suggests that alterations of 5-HT-induced GABAergic inhibition in the ventral dentate gyrus of the hippocampus may be related to the enhanced anxiety-like state in animals exposed to both stressors (Gruber et al., 2015).

Although published data indicate that early-life stress alters synaptic plasticity in the long-term (Akers et al., 2006; Gruss et al., 2008), how stress exposure at two different life periods affects synaptic plasticity is not well investigated. Maggio and Segal (2011) evaluated whether exposure to variable stressors during adolescence and to forced swim stress in adulthood changes the ability to produce long-term potentiation and depression in the CA1 region of both the ventral and dorsal hippocampus in male rats. Their findings demonstrated that stress in adolescence profoundly affects brain plasticity by enhancing long-term potentiation in the dorsal hippocampus and reducing long-term depression in the ventral hippocampus, but these effects are no longer observed 1 week after stress exposure. Additional exposure to adult stress strengthens the effects induced by adolescent stress, indicating that stress in adolescence can permanently alter neuronal plasticity when a second stress event occurs later in life (Maggio and Segal, 2011).

Beyond the effects of glucocorticoids to alter synaptic plasticity within the hippocampus, it is important to note that this mechanism can be also regulated in an opposite way by brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, whose signaling and expression are affected by stress hormones (Jeanneteau and Chao, 2013). A recent study investigated the interplay between glucocorticoids and BDNF to elucidate the neurobiological mechanisms of resilience in male rats that experienced social defeat stress during adolescence and single prolonged stress in adulthood (Mancini et al., 2021a). In parallel with the behavioral results, early-life social stress increased hippocampal BDNF protein expression levels and reduced plasma corticosterone levels in the long-term, and such effects disappeared when rats were exposed to additional trauma later in life. These results suggest the BDNF pathway as a possible mechanism underlying the long-lasting effects of adolescent social defeat stress and that the combination of two stressors, which is responsible for resilience toward emotional and cognitive behavioral alterations, could be explained by the altered hippocampal BDNF protein expression levels that are completely normalized following a single prolonged stress exposure in adulthood (Mancini et al., 2021a).

Regarding stress resilience mechanisms, another study demonstrated that adult male rats singularly exposed to chronic unpredictable stress in adulthood, but not predictable chronic mild stress during adolescence, exhibited anxiety- and depression-like behaviors, and that these effects were attenuated following exposure to both stressors (Suo et al., 2013). Because the rapamycin (mTOR) pathway may be involved in the development of depression (Abelaira et al., 2014; Ignácio et al., 2016),

Suo et al. (Suo et al., 2013) evaluated the role of this pathway in resilience against anxiety- and depression-like behaviors. They demonstrated that chronic unpredictable stress in adulthood led to decreased expression of phospho-mTOR protein in the prefrontal cortex and yet when rats were subjected to the combination of both stressors these decreased phospho-mTOR levels were no longer observed, suggesting that mTOR signaling represents a possible mechanism underlying resilience against the later development of stress-related psychopathologies when separate stressors occur in different life stages (Suo et al., 2013).

The important role of the prefrontal cortex in regulating the development of resilience was also suggested by the results of another study in which exposure to chronic variable stress during late-adolescence prevented fear memory alterations induced by single prolonged stress in adulthood (Cotella et al., 2022). Cotella and colleagues (2022) found reduced neural activation (fos expression) in the infralimbic region of the medial prefrontal cortex after the reinstatement session of a fear conditioning paradigm in male adult rats, but not female adult rats, exposed to single prolonged stress. This effect was abolished when animals were exposed to both stressors. These authors then used whole-cell patch clamp recordings to demonstrate that the previous exposure to stress in adolescence prevented the reduced infralimbic pyramidal cell excitability induced by stress in adulthood. Together, their findings indicate the involvement of the medial prefrontal cortex in the development of stress-resilience after exposure to different stressors in adolescence and in adulthood, but the exact mechanism by which resilience develops requires further investigation.

Results described above including both behavioral data and neurobiological mechanisms are summarized in Table 3.

6. Conclusion

The present review summarizes recent findings on the programming effects induced by social and nonsocial stress during adolescence as a first hit, and how they can affect the resilience and susceptibility to the development of stress-related disorders when a second stressor (second hit) is experienced later in life. Further, we described the potential neurobiological underpinnings responsible for the stress response differences to the combined experience of different stressors at two different time-points in life (adolescence and adulthood).

Interestingly, not all individuals experiencing adverse stressful events will eventually develop a mental disorder. To elucidate this aspect, several hypotheses have been postulated, such as the two-hit model, which describes that stress during early-life (first hit) can produce some alterations within the brain that in turn modify the ability to cope with an additional challenge (second hit) later in life, and thereby lead to an increased or decreased risk for stress-related disorders. The majority of these preclinical studies used an early postnatal stressor as the first hit (e.g., maternal separation paradigm). A previous review, however, highlighted the fact that subjecting rats to a stress in a period that reflects some of the characteristics observed during adolescence in humans provides these studies a high translational value (Horovitz et al., 2014). What we found is that following the exposure to different stressors in two different life periods (adolescence and adulthood), adult rats exhibit either susceptibility or resilience depending on the type, duration, and intensity of the stressor (e.g., social or nonsocial, repeated homonymous or repeated variable, and different phases of adolescence), indicating that the final development of susceptibility or resilience to developing stress-related disorders is strongly related to the context and timing of both stressors. Beyond these two aspects, interindividual variability in the stress response also plays an important role in these effects and depends on a combination of factors. In fact, people can react differentially to stress for several reasons, including subjective interpretation of the stressful event, genetic components, as well as sex (e.g., females are twice as likely as males to develop stress-related disorders). Another important aspect that remains to be clarified is the exact neurobiological mechanisms underlying susceptibility and resilience. We described the literature evidence on possible pathways and brain areas involved in such processes, but further studies are needed to better clarify the precise neurobiological underpinnings of these effects.

Unravelling stress susceptibility/resilience mechanisms could be helpful toward identifying biomarkers and causative mechanisms of susceptibility and/or resilience to developing stress-related disorders, as well as for developing new potential pharmacological tools for treating and preventing these disorders in humans when an additional stressor is experienced later in life.

In conclusion, the data discussed in our review suggest that exposure to social or nonsocial stressors during adolescence, a critical window for brain development and a stress-sensitive period, can affect responsiveness towards an additional stressor experienced later in life, which in turn can lead to an increased or decreased risk for the development of stress-related disorders.

Table 3
Two-hit studies: neurobiological underpinnings of susceptibility/resilience.

Sex and strain	First hit (PND and type)	Second hit (PND and type)	Behavioral effects (two-hit)	Neurobiological underpinings (two hit)
Male rats (Horovitz et al., 2020)	Forced swim stress (PND 27) + elevated platform (PND 28) + restraint (PND 29)	Two-way shuttle avoidance task (PND ~ 60)	Increased anxious-like behavior	Altered expression of $GABA_AR$ α1 and α2 and KOR within the brain (e.g., medial prefrontal cortex, nucleus accumbens, amygdala, and periaqueductal gray)
Male rats (Gruber et al., 2015)	Forced swim stress (PND 27) + elevated platform (PND 28) + restraint (PND 29)	Two-way shuttle avoidance task (one single exposure; PND 60–69)	Reduced exploration, and increased anxious-like behavior	Altered 5-HT-induced GABAergic inhibition in the ventral dentate gyrus of the hippocampus
Male rats (Mancini et al., 2021a)	Social defeat stress (PND 28–34)	Single prolonged stress (2 h restraint stress, 15 min forced swim stress and, after 15 min, isoflurane exposure until loss of consciousness; PND 90)	Reduced alterations on emotionality and spatial memory, and increased cued fear memory dysfunction	Altered BDNF protein expression levels within the hippocampus
Male rats (Suo et al., 2013)	Predictable chronic mild stress (PND 28–55)	Chronic unpredictable stress (PND 63–83)	Reduced anxious- and depressive-like behaviors	Altered expression of phospho-mTOR protein in the prefrontal cortex
Male rats (Cotella et al., 2022)	Chronic variable stress (PND 45 ± 2; two weeks)	Single prolonged stress (2 h restraint stress, 20 min forced swim stress and, after 15 min, ether anesthesia until loss of consciousness; PND 85)	Reduced fear memory dynamics alterations (e.g., impaired extinction and increased reinstatement)	Altered activation of the infralimbic region of the medial prefrontal cortex
Female rats (Cotella et al., 2022)	Chronic variable stress (PND 45 ± 2; two weeks)	Single prolonged stress (2 h restraint stress, 20 min forced swim stress and, after 15 min, ether anesthesia until loss of consciousness; PND 85)	Reduced fear memory dynamics alterations (e.g., increased reinstatement)	Altered activation of the central lateral region of the central amygdala

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Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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