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Review

The impact of adolescent stress experiences on neurobiological development

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ABSTRACT

Adolescence is considered a developmental period of heightened vulnerability to many psychological dysfunctions–primarily due to the high structural neuronal plasticity that accompanies the associated physical and cognitive gains, rendering an individual highly susceptible to environmental stressors during this time.

Recently, interest has been generated in the study of neuronal and behavioral adaptation to adverse experiences during adolescence. This review will provide an overview of the principal neurobehavioral changes that occur during adolescence and describe what happens when the maturation of these functions is altered by stressful environmental stimuli.

Contents

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1. Introduction

The experience of adversities in early life is a predictor of a wide variety of pathological conditions, from psychiatric disorders, such as anxiety, depression, substance use disorders, schizophrenia, and autism spectrum disorders, to pathologies that are influenced by stress, such as cardiovascular disease, diabetes mellitus, and obesity [1–4]. The World Health Organization (WHO) World Mental Health (WMH) Survey Initiative has reported that childhood adversities account for approximately 30% of all instances of first onset of mental disorders in 21 countries [5].

Notably, when disorders are associated with a history of childhood or adolescent trauma, they often present with severe symptomatology and resistance to conventional treatment [6], suggesting different etiological mechanisms. This profile highlights the importance of examining the neurobiological adaptations that lower an individual's threshold to disease susceptibility. What renders the experience of a childhood/adolescent trauma a permanent modifier of individual health is that it acts on the plastic developing brain, which is prone to encoding environmental information into structural and functional modifications.

Throughout postnatal development, the brain undergoes dynamic changes in its epigenetic code, gene expression patterns, neural circuitry, and behavior [7]. These alterations facilitate the completion of stage-specific prerogatives: the formation of mother-attachment bonds in infancy, exploration of the environment, and social interactions with conspecifics during juvenile age.

The developmental framework of the postnatal brain is not genetically determined–rather, it interacts highly with the surrounding environment and is driven plastically by external inputs through gene-environment interplay to finely shape brain connections in their final form, allowing it to cope with similar environments later in life.

Neural and behavioral plasticity is transient and limited to sensitive periods during which various neural systems and behaviors are particularly receptive to several types of experience [8,9]. Thus, a stressful experience during postnatal development–an abrupt variation in the environmental context in which the organism is gradually adapting–causes developmental imbalances that are strictly dependent on the timing in which the stress occurs. In this review, we will focus on adolescence, a developmental period of intense neuroplasticity and thus of heightened vulnerability to many psychological dysfunctions. We will introduce the most relevant behavioral components and the critical neural systems that develop during adolescence and are thus particularly sensitive to environmental stressors.

We will give an overview of the long-term effects that environmental stressors have during this time and can predispose one to or protect one from mental illness through their interaction with individual genetic factors.

2. Adolescence and the maturation of complex behaviors

Adolescence is a unique time for brain development, when, under environmental guidance, important neurobehavioral changes occur that appear to have a significant effect on motivation and emotions. During adolescence (from age 10–18 in humans), several dramatic neurophysiological and hormonal alterations take place, becoming substrates for behavioral changes, such as increases in sociability, impulsivity, and reward sensitivity [10–12]. In this developmental stage, the individual transits from being dependent on caregivers to entering a state of autonomy, during which the peer relationship becomes a relevant component that supports him.

Similarly, adolescent rodents (early adolescence postnatal day, PD, 22–32, mid-adolescence PD 42–46, late adolescence PD46-60; [13]) exhibit increased arousal and search for novelty [14,15], and at the beginning of adolescence, rodents engage in social play and agonistic behavior, and the first primordial social hierarchies can be observed [16,17]. Social play is the first form of non-mother-directed sociability [18], and, as for humans, it is indispensable for the healthy development of social competence and emotional and cognitive processes [12,19].

Because adolescence is associated with high structural neuronal plasticity and the accompanying physical and cognitive gains, it is usually considered a time of heightened vulnerability to several dysfunctions. Disruption of adolescent neurobehavioral development induces permanent alterations in adult biological and behavioral phenotypes, and these changes are linked to the type of stressful stimulus that is experienced, the time at which the stressful event occurs, and the general environmental conditions under which the individual is growing. Further, several psychopathologies, such as psychosis and mood disorders, usually first appear during adolescence (first episode).

3. Modeling the exposure to adverse stressful environments in adolescent rodents

Animal models provide an essential substrate for examining the neurobiological changes that are induced by early-life stressful experiences and tailoring preventive interventions. Reproducing adverse early-life events in rodents, such as losses, maltreatment, and abuse, has evident limits, due to the heterogeneity of experiences, differences in individual perceptions, and the strictly human nature of certain traumatic conditions. Modeling traumatic childhood or adolescence aims to understand how specific perturbations in the developmental environment modify the neurobiology of neural substrates during sensitive periods, disrupting overall homeostasis and ultimately resulting in behavioral dysfunction. Thus, a paradigm of manipulation should assume an ad hoc design to interfere with the development of various behaviors in a time- and substrate-specific manner–ie, the environmental manipulation that is applied during a specific window of postnatal development must be tailored to the brain circuit that is developing and that is highly receptive at that time.

Thus, in recent years, many preclinical rodent studies have been performed to examine the molecular, neurobiological, and behavioral effects of stress interference during adolescence. Most rodent paradigms have applied procedures that interfere with the development of social competence, a highly maturating behavioral function during this age. These protocols can therefore be classified into 2 main categories: 1. those that comprise paradigms in which the animal experiences a considerable decrease in social contacts (absence of stimuli) and 2. those that implement models in which rodents are exposed to social adverse/threatening contexts (aversive stimuli).

In the former, social isolation rearing is one of the most commonly used paradigms [20,21]. During this procedure, animals are reared single-housed for several weeks, frequently starting at weaning, and the effects are evaluated immediately at the end of isolation or after a period of group housing, applied at the end of isolation. In a variation of this paradigm, adolescent rodents are exposed daily to bouts of isolation (repeated social isolation), wherein the short- and long-term effects are usually measured [22].

In paradigms of the second category, adolescent animals are repeatedly exposed to social aversive cues, such as predator odor, or physical interactions with a nonaggressive adult male (exposure to threatening male, [23] or social defeat episodes from an aggressive conspecific [24]. In the social instability protocol, another

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