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Mapping the developmental trajectory of stress effects: Pubescence as the risk window

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Summary The exposure to stress at different developmental time points has long been postulated to have a crucial impact on various brain structures involved in mental disorders. The long-term specific effects seem to emerge as a function of timing and duration of the exposure to stress, as well as the characteristics of the stressor. Previous studies have addressed this issue with an effort to describe a single ''hyper-sensitive'' time point, and have led to disagreement on a particular sensitive period for stress exposure. The primary aim of our study was to investigate the hypothesis that indeed there is a developmental stress risk window in male Wistar rats.

We conducted a systematic mapping of the long-term effects of an acute stress protocol, applied both prenatal (gestational days 14—16) and postnatal (days 9—151), overall at 11 different time-points during development. Stress protocol consists of 3 days of either maternal separation (for rats at postnatal days 9—19) or exposure to the stressors forced swim, elevated plus maze and restraint (for both dams and males at postnatal days 24—151). Consequences in adulthood were measured by investigating the animals' behavior in both the open field and startle box, together with the physiological measure of corticosterone.

We found both behaviorally and physiologically that the pubescence time points are the most vulnerable to stress compared to all other tested time points along the developmental trajectory. Carefully considering the comparison between rat and human age, our findings may imply the importance of childhood-to-adulthood transition, as a sensitive time-point which may exacerbate a predisposition for the development of stress-induced psychopathologies.

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1. Introduction

The term ''stress'' was coined in 1940s by Hans Selye as ''a nonspecific response of the body to any demand made on it'' (Selye, 1998). Currently, ''stress response'' is understood as an adaptive response (caused by internal mechanisms developed through evolution), that allows the individual to maximize the chance of survival when confronted with stress'' (Kalueff and LaPorte, 2008). Stress is not necessarily a harmful or pathological factor to be avoided. Only when the adaptive mechanisms cannot be recruited, stress will result in a number of deleterious effects and health may be endangered. Nevertheless, stress seems to be an integral part of any species life. Thus, the desire to better understand its effects and underlying mechanisms turn the field of stress to be extensively researched.

There is a long history attempting to evaluate the developmental trajectory of stress in humans (Hildyard and Wolfe, 2002; Ethier et al., 2004), but these studies are limited by their retrospective nature. Thus, an animal model is ideal for studying developmental and longitudinal processes, or the developmental programming of the stress system, such as the hypothalamic—pituitary—adrenal (HPA) axis which is activated in response to a stressor (de Kloet et al., 2005). Many animal models evolved for this purpose, in an effort to investigate the existence of a possible hyper-sensitive developmental period for applying a stressor. Some models applied a physical stressor whereas others applied a psychological one, either in acute or chronic paradigms. Moreover, stressors were applied at different time points during development, together with various time points of evaluation of the either short- or long-term effects of the original stress paradigm (see rev. Bhatia et al., 2011; Holder and Blaustein, 2014). In support of this idea, long-term changes have been previously reported following stress in early stages of life. Increased anxiety-like behaviors were observed in adult rats following juvenile stress (Tsoory et al., 2007; Jacobson-Pick and Richter-Levin, 2012) as well as decreased locomotion in an open field (Avital and Richter-Levin, 2005), elevated plus-maze (Jacobson-Pick and Richter-Levin, 2012) or a novel environment (Tsoory et al., 2007). Increased startle response in adulthood has also been described (Avital et al., 2006; Tsoory et al., 2007). Moreover, a single maternal deprivation was reported to produce long-term changes when applied within the stress hypo-responsive period between postnatal days 1—12 (Enthoven et al., 2008). Other studies, which applied stressors in early adolescence, have observed no specific effect on adulthood behavior (Kubala et al., 2012; Saul et al., 2012).

Since the accumulated data suggest the outcome of early life experiences largely depends on the timing, frequency, and duration of the particular environmental experience (Meaney and Aitken, 1985; Enthoven et al., 2008; Champagne et al., 2009) and although stress is highly investigated, the current literature cannot offer a consistent behavioral overview of a suggested stress-sensitive period with relation to its long-term effects in adulthood.

When exploring the underlying physiological explanations of the behavioral effects, the broad spectrum of corticosteroids activity is well recognized, suggesting their short- or long-term effects, when mediating a stress response through many expression and regulation processes in various brain regions. A breakthrough in the field of developmental programming came with the discovery of epigenetic modifications in the promoter area of the glucocorticoid receptor gene, revealing a mechanism underlying the environmentally driven effects on later life stress phenotype. Specifically, it has been shown that prenatal stress resulted in decreased hippocampal glucocorticoid receptor expression in the adult offspring together with maladaptive behavioral stress responsivity (McCormick et al., 1995). However, the impact of the prenatal factors is strongly influenced by postnatal experiences (Meaney et al., 2007). Recently, it has also been shown that stress during adolescence induces epigenetic control of dopaminergic neurons via glucocorticoids (Niwa et al., 2013).

Thus, the current literature suggests that stress has enduring effects on the brain, with a heightened impact on developing structures. Moreover, it has been implied that the HPA axis response to acute stress depends on the animal's developmental stage (Romeo et al., 2006). These observations are supported by human studies, demonstrating the 'programming' effects of stress in early life on the HPA axis and the brain (Barker, 1991), and further presented in adult patients suffering from major depressive disorders who had experienced early life stress, and show persistent hyper activity of the HPA axis and of the autonomous nervous system, as well as increased sensitivity of these systems to stress (Heim et al., 2000a,b).

Carefully considering the complex translation of rat to human lifespan (Quinn, 2005), together with the vigorous maturation which the brain undergoes during the transition period between childhood to adulthood (Sowell et al., 1999; Rubinow and Juraska, 2009; Avital et al., 2011), it seems that the available data supports the hypothesis that adolescence is a 'stress-sensitive' period (Andersen and Teicher, 2008; Leussis and Andersen, 2008). However, it has been also suggested that the development of emotionality and its underlying neural systems, remain highly plastic during the juvenile and pubescence periods (Holmes et al., 2005; Holder and Blaustein, 2014).

Again, since previous studies have applied diverse stressors in distinctive developmental time points, while observing different short- or long-term physiological and behavioral changes (Cadet et al., 1986; Koehl et al., 1999; Avital and Richter-Levin, 2005; Saul et al., 2012), the long-term effects of the possibly hypersensitive-stress time point during the rats' developmental trajectory remains unclear.

In the current study we conducted a systematic research, aimed to map the long-term effects of an exposure to an acute stress applied at different developmental time-points. In order to allow an overall comparison between the various time points, we applied an equivalent three days acute stress protocol for all 11 groups (starting prenatally until PND 150), and tested its long-term consequences in adulthood (postnatal days 127 or 180) on behavior as well as corticosterone serum level.

Unfortunately, the stress protocol we chose may not be applied on rats before weaning (postnatal day 21), therefore we had to apply maternal separation. Nevertheless, we utilized a protocol (5 h separation on 3 consecutive days) that meets the criteria for a stressor: a set of physical events that together create an aversive, uncontrollable and unpredictable experience (Kim and Diamond, 2002; Koolhaas