Progress in Neuropsychopharmacology & Biological Psychiatry 79 (2017) 136–154

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Impact of juvenile chronic stress on adult cortico-accumbal function: Implications for cognition and addiction

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ARTICLE INFO

Keywords:
Chronic juvenile stress
Adolescence
Drug reward
Executive function
Prefrontal cortex
Nucleus accumbens

ABSTRACT

Repeated exposure to stress during childhood is associated with increased risk for neuropsychiatric illness, substance use disorders and other behavioral problems in adulthood. However, it is not clear how chronic childhood stress can lead to emergence of such a wide range of symptoms and disorders in later life. One possible explanation lies in stress-induced disruption to the development of specific brain regions associated with executive function and reward processing, deficits in which are common to the disorders promoted by childhood stress. Evidence of aberrations in prefrontal cortex and nucleus accumbens function following repeated exposure of juvenile (pre- and adolescent) organisms to a variety of different stressors would account not only for the similarity in symptoms across the wide range of childhood stress-associated mental illnesses, but also their persistence into adulthood in the absence of further stress. Therefore, the goal of this review is to evaluate the current knowledge regarding disruption to executive function and reward processing in adult animals or humans exposed to chronic stress over the juvenile period, and the underlying neurobiology, with particular emphasis on the prefrontal cortex and nucleus accumbens. First, the role of these brain regions in mediating executive function and reward processing is highlighted. Second, the neurobehavioral development of these systems is discussed to illustrate how juvenile stress may exert long-lasting effects on prefrontal cortex-accumbal activity and related behavioral functions. Finally, a critical review of current animal and human findings is presented, which strongly supports the supposition that exposure to chronic stress (particularly social aggression and isolation in animal studies) in the juvenile period produces impairments in executive function in adulthood, especially in working memory and inhibitory control. Chronic juvenile stress also results in aberrations to reward processing and seeking, with increased sensitivity to drugs of abuse particularly noted in animal models, which is in line with greater incidence of substance use disorders seen in clinical studies. These consequences are potentially mediated by monoamine and glutamatergic dysfunction in the prefrontal cortex and nucleus accumbens, providing translatable therapeutic targets. However, the predominant use of male subjects and social-based stressors in preclinical studies points to a clear need for determining how both sex differences and stressor heterogeneity may differentially contribute to stress-induced changes to substrates mediating executive function and reward processing, before the impact of chronic juvenile stress in promoting adult psychopathology can be fully understood.

1. Introduction

More than one in five adults report being exposed to repeated instances of abuse or neglect during childhood (Adverse Childhood Experiences Study, 2013). Individuals that experience such childhood stressors are at greater risk for the later development of behavioral and psychiatric disorders including attention deficit-hyperactivity disorder (ADHD), anxiety disorders, major depressive disorder, psychosis, substance use disorders and schizophrenia (Copeland et al., 2013; Espejo et al., 2006; Gutman and Nemeroff, 2003; Heim et al., 2008; McFarlane

Abbreviations: 5-HIAA, 5-Hydroxyindoleacetic acid; 5-HT, 5-Hydroxytryptamine; ADHD, Attention Deficit-Hyperactivity Disorder; ACC, Anterior Cingulate Cortex; BDNF, Brain-derived Neurotrophic Factor; BLA, Basolateral Amygdala; CB, Cannabinoid; Cg, Cingulate Cortex; CPP, Conditioned Place Preference; CRF, Corticotrophin-Releasing Factor; CTQ, Childhood Trauma Questionnaire; DA, Dopamine; DAT, Dopamine Transporter; dlPFC, Dorsolateral Prefrontal Cortex; DOPAC, 3,4-Dihydroxyphenylacetic acid; fEPSP, Field Excitatory Post-synaptic Potential; GABA, γ-Aminobutyric acid; Glu, Glutamate; GR, Glucocorticoid Receptor; IL, Infralimbic Cortex; LTD, Long-term Depression; LTP, Long-term Potentiation; MAOa, Monoamine Oxidase A; MDMA, 3,4-Methylenedioxymethamphetamine; mOFC, Medial Orbitofrontal Cortex; mPFC, Medial Prefrontal Cortex; MSN, Medium Spiny Neurons; NAA, *N*-acetylaspartate; NAc, Nucleus Accumbens; NAcC, Nucleus Accumbens Core; NAcSh, Nucleus Accumbens Shell; NE, Norepinephrine; NMDA, *N*-methyl-D-aspartate; OFC, Orbitofrontal Cortex; P, Postnatal; PCC, Posterior Cingulate Cortex; PFC, Prefrontal Cortex; PPI, Prepulse Inhibition; PrL, Prelimbic Cortex; SD, Sprague-Dawley; SERT, Serotonin Transporter; VTA, Ventral Tegmental Area

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http://dx.doi.org/10.1016/j.pnpbp.2017.06.015
Received 2 January 2017; Received in revised form 16 June 2017; Accepted 18 June 2017
Available online 19 June 2017
0278-5846/

et al., 2005; Merrick et al., 2017; Niemela et al., 2011; Rossow and Lauritzen, 2001; Schilling and Christian, 2014; Seidenfaden et al., 2017; Sigurdson et al., 2014; Trotta et al., 2015; van Dam et al., 2012). The vulnerability to later psychopathology is positively related to the number of abusive/stressful events experienced during childhood, and is further increased by exposure to more than one type of abuse, e.g., emotional combined with physical or sexual abuse (Davis et al., 2001; Merrick et al., 2017; Rehan et al., 2016; Teicher et al., 2006). A central question is how exposure to repeated stressors during childhood translates into such a wide range of symptoms and disorders later in life. We hypothesize that this may be explained by stress-induced changes to brain regions associated with executive function and reward processing, deficits in which are common features of disorders associated with childhood stress.

Here, we sought to test our hypothesis by systematically evaluating published findings regarding the longer-term effects of chronic juvenile stress in both animal models and humans. The term chronic used throughout the review refers to repeated stress exposure (either multiple occurrences of the same stressor or experience of more than one stressor type), and our evaluation of pertinent literature is restricted to studies examining the effect of chronic stress. Juvenile is used here to encompass the pre-adolescent and adolescent stages, often considered within the stress literature as the post-weaning to adulthood period in rodents and ages under 18 years old in humans. Models of pre-weaning stress in rodents, such as maternal separation, were not included in this review. The pre-weaning period of rodents is a unique developmental period, with offspring exhibiting neural development during the first days of life equivalent to that seen in the human third trimester (Dwyer et al., 2009). The pre-weaning period thus represents a time of rapidly changing developmental processes in the rodent brain, which is accompanied by altered hypothalamic-pituitary-adrenal axis sensitivity to stressors (Levine, 2001; Dwyer et al., 2009). Combined with the complexity of the different maternal separation models (Nylander and Roman, 2013; Tractenberg et al., 2016), this means that the consideration of pre-weaning rodent stress models and their findings requires more detailed consideration than can be given here. For further information in this field, see recent reviews such as Kosten et al. (2012), Nylander and Roman (2013), and Tractenberg et al. (2016).

The goal of this review is to provide an overview of the neural circuitry involved in top-down (executive) control of motivated behavior, along with examples of how aberrations in this functional circuitry as elicited by chronic juvenile stress may contribute to adult psychiatric disorders. To achieve this, we first introduce the concept that symptoms and disorders associated with chronic juvenile stress such as substance use disorders, major depressive disorder, and schizophrenia are typified by profound deficits in executive function and reward behavior. We then introduce brain regions and neurotransmitters associated with executive function and reward behavior, in order to highlight the complexity of the neural mechanisms underlying these behavioral processes, before summarizing the major developmental transitions in brain function and motivated behavior occurring from the juvenile to adult state that could provide targets for stress-induced insult. Finally, we critically evaluate findings from animal models and human studies investigating the impact of chronic juvenile stress on executive function and reward processing and their neurobiological substrates, to provide empirically-derived insight into how early-life stress increases the risk for neuropsychiatric illness in adulthood and to identify gaps in current knowledge that should be addressed by future research.

2. Childhood stress and later psychiatric illness – a function of disruption to executive function and reward processing?

Repeated exposure to stress during childhood may increase risk for a wide range of symptoms and disorders later in life due to disruption in the interplay between executive function and reward sensitivity. Executive function encompasses the higher order cognitive processes largely mediated by the prefrontal cortex (PFC), which are critical for maintaining a balance of behavioral focus and flexibility necessary to meet the demands of the current situation, and include working memory, attention, impulse control, and decision-making (Holmes and Wellman, 2009; Logue and Gould, 2014; Testa and Pantelis, 2009). Executive function is also essential for reward processing, allowing pursuit of reward when availability is indicated, but inhibiting goal-seeking behavior when reward contingencies change, such as when previously learned cues are either no longer predictive or value decreases in relation to the effort required to obtain the reward (Perry et al., 2011; Arnsten and Rubia, 2012; see Section 3.2). Notably, varying degrees of impairment in both executive function and reward processing are a common feature of the psychiatric disorders associated with childhood stress (e.g., Brown, 2008; Etkin et al., 2013; Green, 2006; Lewandowski et al., 2016; Whitton et al., 2015). As an example, working memory and other executive function deficits are seen in ADHD, substance abuse and other addictive disorders, bipolar disorder, major depressive disorder, and schizophrenia (Brown, 2008; Craig et al., 2016; Crews and Boettiger, 2009; Cullen et al., 2016; Etkin et al., 2013; Grant and Chamberlain, 2014; Kuswanto et al., 2016; Leeman et al., 2014). Furthermore, disrupted reward processing as a function of diminished executive processes is demonstrated in individuals with major depressive disorder (Whitton et al., 2015), who show deficits in working memory, sustained attention, and task switching (Etkin et al., 2013). These factors combine to cause difficulty in the ability to change behavior in response to altered reward contingencies, resulting in a reduced reward anticipation and unwillingness to engage in effortful goal pursuit that is thought to promote the anhedonic state associated with depression (Whitton et al., 2015).

Schizophrenia, on the other hand, appears not to encompass a dichotomous extreme of reward hypo/hypersensitivity, but rather represents impairments in the ability to assign salience to relevant reward cues (Whitton et al., 2015). Thus, schizophrenic patients show difficulty in learning relevant cues and instead allocate greater attention to irrelevant stimuli, which one study found to be directly correlated with the degree of positive (psychotic, e.g., delusions, hallucinations) symptoms (Morris et al., 2012). Impairments in predicting the effort required to achieve goals of varying magnitude are also seen in schizophrenia, particularly in patients presenting with negative symptoms (e.g., flat affect, lack of motivation) (Fervaha et al., 2013; Gard et al., 2014; Gold et al., 2013). Diminished executive function (attention, working memory, flexibility etc.) in schizophrenics is also correlated with deficits in reward discrimination (Lewandowski et al., 2016). Combined, this lends support to the hypothesis that failure to update information about changes in reward cue salience in schizophrenia results from ineffective top-down modulation by the PFC of subcortical reward pathways.

Finally, disrupted cortical control of reward behavior appears to be fundamental to substance use disorders, which are characterized by a preference for impulsive choices in favor of an immediate or strongly reinforced reward, along with an inability to inhibit impulsive pre-potent conditioned motoric responses despite changes in reward contingency (Crews and Boettiger, 2009; Grant and Chamberlain, 2014; Perry et al., 2011). Interestingly, such increased impulsive choice and decreased response inhibition is characteristic across not only substance use disorders (MacKillop et al., 2011) but also appears to be a core feature of behavioral addictions such as pathological gambling (Grant and Chamberlain, 2014).

3. Nucleus accumbens and prefrontal cortex - modulation of executive function and reward behavior

The learning of and response to reward-associated stimuli is largely mediated by the mesolimbic system, with dopamine activity in the ventral striatum/nucleus accumbens (NAc) playing a pivotal role in the evaluation of stimulus salience (Berridge and Kringelbach, 2013;