The Influence of Puberty on Depression Symptoms and Altered Cortisol Secretion in Adulthood: A Literature Review

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Abstract

This paper was originally written for Dr. Neil Watson and Dr. Marlene Moretti for PSYC 499, *Honours Project*. The assignment asked students to execute a research study and write up the results in a thesis format. For my thesis I explored the association between stress-related cortisol release, puberty, and depression. For the SLC writing contest, the literature review portion of the thesis was revised for submission. The paper uses APA citation style.

Introduction

Depression is a mood state characterized by persistent feelings of sadness and negative thoughts, it subsequently impacts relationships, productivity, sleep, and eating patterns (Rawana, McPhie, & Hassibi, 2016; Riemann, Krone, Wulff, & Nissen, 2020; Sharabi, Delaney, & Knobloch, 2016). Mental health problems such as depression cost the Canadian economy approximately 50 billion dollars a year due to health and social services use and has a high cost to businesses due to absenteeism and turnover (Mental Health Commission of Canada, 2010). Depressed mood has a negative impact on the quality of life at the individual level and societal level. Consequently, it is important to conduct research to understand risk factors for depression.

Depression is associated with dysregulated secretion of the stress hormone cortisol (Knorr, Vinberg, Kessing, & Wetterslev, 2010). Research indicates that adverse childhood experiences, and therefore high cortisol concentrations early in life have a lasting negative impact on physical and mental health (Shonkoff et al., 2012). However, it is also important to study the adolescent period because stress during this time is associated with increased vulnerability to depression (Romeo, 2010). Adolescence is a stage of transition filled with many physiological and psychosocial changes (Holder & Blaustein, 2014). Puberty, on the other hand, is characterized by the development of sexual maturity and takes place during adolescence. Puberty is interesting because of the marked increase of gonadal

hormones; these hormones influence the release of glucocorticoid hormones (such as cortisol) into the blood, and vice versa (Viau, 2002). Seeing as pubertal stressors in mice alters cognitive performance, anxiety, depression, and sexual behaviours in adulthood, high levels of stress-induced cortisol likely impacts the human adult brain (Holder & Blaustein, 2014). This paper serves as an overview of the interrelatedness of stress during pubertal development and depression.

Literature Review

The History of Stress Research

Stress is a broad term with many colloquial and technical connotations. In the biological sciences, stress has been historically understood as a state in which homeostasis is threatened (Meaney, 2000). Stress is evolutionarily adaptive in the short-term; for example, it helped our ancestors flee from predators and to compete for food and mates. Considering this, the word stress (or stressor) in this paper will refer to an experience that is perceived as threatening or adverse. This next section will present important theories and serves to highlight the multifaceted approaches used in the study of stress.

Claude Bernard, Walter Cannon, and Hans Selye are three key pioneers of stress research. Bernard came up with the notion of the *milieu intérieur*, which translates to "the environment within" (Bernard, 1872). This concept states that the body is constantly trying to uphold a balanced internal environment. The *milieu intérieur* is now more popularly known as homeostasis. Cannon elaborated on Bernard's work by researching the mechanisms that maintain the homeostasis. Through his research on animals, Cannon found that adrenaline causes many bodily changes such as increased heart rate and respiration, enhanced visual acuity, and slowed digestion – changes which allow an organism to react to an immediate threat. He named this phenomenon the "fight or flight response". Cannon's work greatly contributed to the understanding of stress as a physiological process, which also laid a general framework for Selye to form his theory (Robinson, 2018).

Recognized as the father of stress research, Hans Selye is perhaps the most well-known theorist out of the three key pioneers. He studied the effects of chronic stress and proposed that the stress response is nonspecific, meaning that many different types of stressors trigger a similar physiological response (Selye, 1976). The General Adaptation Syndrome (GAS) theory outlines that specific chain of events. GAS has three stages: the alarm reaction, stage of resistance, and the stage of exhaustion. The alarm reaction takes place when threat is first perceived, hormones such as adrenaline and cortisol are released which prepare the body for "fight or flight action" (As Walter Cannon would call it). The next stage is resistance, during which the body copes with stress by continuing the release of cortisol. If stress is prolonged, the body enters the exhaustion phase

where its resources are drained and is no longer capable of coping. At this stage, the fatigued body becomes vulnerable to adverse outcomes such as cardiovascular, nervous system, metabolic, and mental diseases (Selye, 1976).

Selye also emphasized that not all stress is bad. A moderate amount is beneficial and needed to function properly – this optimal amount of stress is called 'eustress' (Selye, 1974). 'Distress' on the other hand consists of too much or too little stress; distress compromises health. A sedentary lifestyle is an example of too little stress and has many well-known health risks such as obesity. An overactive lifestyle is not good either, for example, an athlete that over trains may develop overuse injuries in their muscles and joints.

Selye's theory laid the groundwork for studying the long-term effects of stress and a large body of research has since built upon his model (Robinson, 2018). Notably, McEwen's Theory of Allostatic Load elaborates on Selye's stage of exhaustion and states that consequences of chronic stress arise due to disruption of physiological systems rather than by exhaustion of the body's energy (McEwen, 1998, 2005). Essentially, long term stress causes a "wear and tear" effect on the body due to repeated activation of the fight or flight response (McEwen, 1998). Specifically, living organisms have adapted to initiate certain neural, endocrine, and immune system responses to get out of stressful situations and return to homeostasis, which McEwen refers to as "allostatic processes" or "allostasis". Allostasis is beneficial for infrequent life-threatening encounters. However, repeated activation of allostatic processes increases the risk of negative outcomes such as disease, dysregulated emotional function, and premature death (McEwen, 1998).

The frameworks by Cannon, Selye, and McEwen focus on the physiological aspect of the stress response, however, they lack consideration of how individual differences may impact the experience of stress. The models by Richard Lazarus and The National Scientific Council on the Developing Child (NSCDC) fill this gap. Lazarus theorized that there are individual differences in evaluation and coping with stress. Firstly, similar stressors can be perceived as more or less threatening by different people. Additionally, chosen coping methods vary between people depending on individual motivation and past experiences (Lazarus, 1966).

Moreover, the toxic stress model by the NSCDC postulates that chronic activation of the stress response without adequate social support from a parent or caregiver has consequences on the developing brain. This model was developed based on research showing that children who have experienced stressors such as abuse, neglect, parental substance abuse, and maternal depression have altered brain morphology. Specifically, these children have altered volume and structure of the amygdala, hippocampus, and prefrontal cortex (Chen & Baram, 2016; Shonkoff et al., 2012).

The Biology of Stress

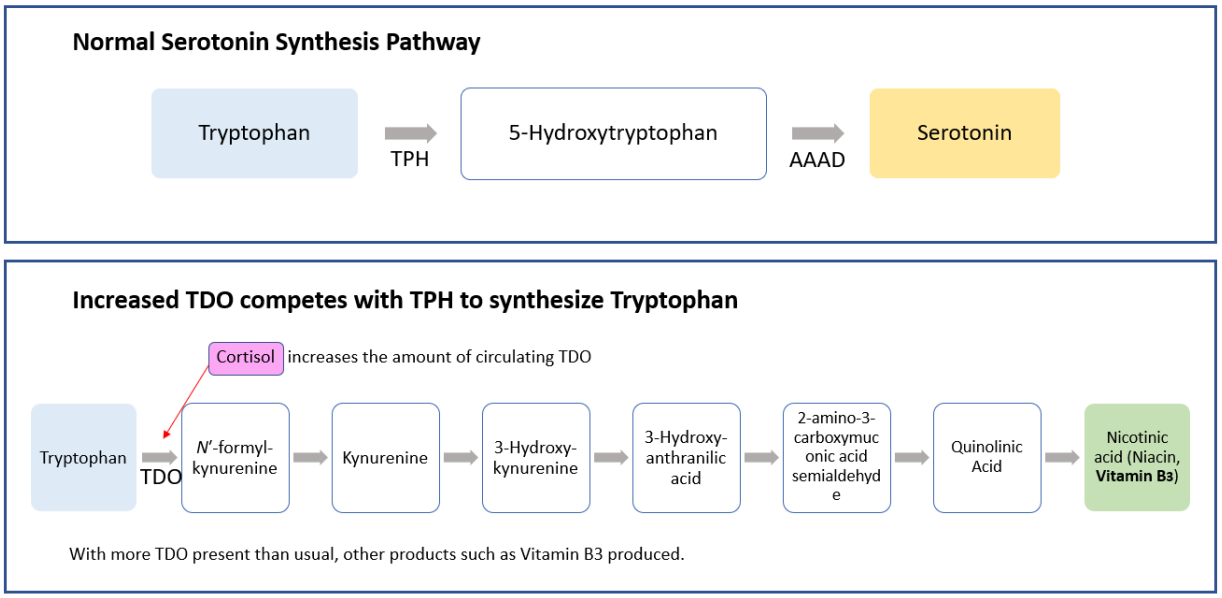
A wealth of research has previously described the biology of stress. The systems receiving the most attention are the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. They release hormones such as adrenaline, norepinephrine, and cortisol which are beneficial for survival because they promote adaptive behavioural and metabolic responses to threat (De Kloet, Joëls, & Holsboer, 2005).

The system of interest to this paper is the HPA axis, which refers to the interaction of the hypothalamus and pituitary gland (brain structures), and the adrenals (small glands that sit on top of the kidneys). The HPA axis releases various hormones which contribute to cortisol production (Tsigos & Chrousos, 2002). Cortisol triggers glucose (sugar) release which provides energy to the muscles, thus facilitating physical activity to fight, flee, or freeze (De Kloet et al., 2005). When no longer in the face of threat, the brain then decreases further hormone production (Acevedo-Rodriguez et al., 2018). If stress is prolonged, this prompts the HPA axis to continue producing cortisol, and chronically elevated cortisol is considered a risk factor for cognitive deficits, obesity, behavioural disorders, and mood disorders such as depression (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Pervanidou & Chrousos, 2011).

Cortisol and Depression

Depression is an umbrella term often used to refer to mood disorders such as major depressive disorder or dysthymia. Depressive disorders share a set of common characteristics such as low mood, feelings of worthlessness, and fatigue (American Psychiatric Association, 2013). However, depression itself is an emotional state anyone can experience, it ranges from transient feelings of sadness to severe, persistent, and debilitating feelings of sadness (Dozois, 2019).

Research has consistently found that stressors such as adversity and traumatic events are associated with depression. This connection exists because high cortisol levels decrease serotonin in the brain (van Praag, de Kloet, & van Os, 2004). Serotonin is a well-studied neurotransmitter implicated in mood regulation, and individuals with major depression often have lower levels of serotonin compared to their healthy counterparts (Cowen, 2002). Serotonin is produced from the amino acid tryptophan via the enzymes tryptophan hydroxylase (TPH) and aromatic L-amino acid decarboxylase (AAAD). Prolonged HPA axis activation increases cortisol, which therefore decreases serotonin synthesis. Specifically, cortisol increases the availability of Tryptophan 2,3-dioxygenase (TDO), an enzyme that catalyzes tryptophan into other substances, for example, vitamin B_3 (Badawy, 2017; Cowen, 2002; Sorgdrager, 2014). This process leaves less tryptophan available to be synthesized into serotonin. See below for an infographic.



Note: Gray arrows represent enzymes
Acronyms = AAAD: aromatic L-amino acid decarboxylase, TDO: tryptophan 2,3-dioxygenase, TPH: tryptophan hydroxylase.
Credit: Badawy, 2017, Sorgdrager, 2014, & Tryptophan metabolism (Homo sapiens) www.wikipathways.org/index.php/Pathway:WP465

Furthermore, cortisol itself can cross the blood-brain barrier and cause changes to brain structure. In mice, long term exposure to corticosterone (this hormone is the equivalent to human cortisol) reduces the length and number of hippocampal CA3 neurons, which are involved in cognition and mood (De Kloet et al., 2005; McEwen, 2016). High stress and cortisol likely have a similar effect in humans. For instance, adults with a history of childhood abuse have been found to have reduced hippocampal volume (Marrocco et al., 2019).

Although previous research has shown links between cortisol and depression, the apparent connections seem to change over the lifespan. Research supports the notion that depressed patients have higher resting levels of cortisol compared to controls, as seen in the meta-analysis by (Knorr et al., 2010). However, other evidence shows that lower basal cortisol concentrations are also involved in depression, specifically in elderly patients (Penninx et al., 2007). Further research is needed to understand how elevated and diminished cortisol is involved in predicting depression in different stages of life.

The Role of Puberty in the Cortisol – Depression link

To further understand the link between stress and depression, puberty will be examined as an additional variable. Puberty usually occurs between the ages of 9 and 14 and is a period in which steroid hormones have an 'organizational effect'

on the nervous system (Phoenix, Goy, Gerall, & Young, 1959). That is to say, hormones induce permanent changes throughout the body, such as dictating neuronal circuitry, and shape future behaviours. Organizational effects only take place during critical developmental periods such as the neonatal and pubertal periods. Following a critical period, hormones have an activational effect on behaviour, meaning that hormones released later in life act on the neural circuitry that was previously constructed (Phoenix et al., 1959) and temporarily activates certain physiological functions and behaviours. Given that the brain undergoes complex neuronal reconstruction and reorganization following the emergence of gonadal hormones at puberty, it follows that this period should lack disturbance to successfully develop. Therefore, it's plausible that stress-induced increases of blood cortisol levels negatively impact typical brain development.

How does this happen? To explain this, the mechanisms underlying puberty will be described in relation to how cortisol is implicated in brain development. Puberty is marked by many changes, such as the development of pubic hair, body odor, and acne. These processes are led by the release of sex hormones such as testosterone and estradiol, which are a part of the androgen and estrogen hormone classes, respectively. These hormones guide the development of a typical male or female nervous system, as well as overseeing the development of reproductive organs, physical characteristics, and behaviour (Kanwal, Jung, & Zhang, 2016). In females, estrogens promote breast growth, menstruation, and ovulation – in males, androgens prompt testicular growth, deepen the voice, and are associated with increased aggression (Vijayakumar et al., 2018).

Sex hormones and stress hormones are active in puberty and there is evidence that they influence each other. Specifically, the presence of cortisol suppresses androgen and estrogen production (Acevedo-Rodriguez et al., 2018; Whirledge & Cidlowski, 2010). In other words, increased cortisol during puberty can disrupt normal development by decreasing gonadal hormone release (Acevedo-Rodriguez et al., 2018; Whirledge & Cidlowski, 2010). This would impact neural organization, consequently leading to enduring changes on the brain and behaviour. Research on mice supports this line of thought. As seen in the review by Holder & Blaustein (2014), pubertal mice exposed to stressors such as the foot shock paradigm show higher than normal resting state cortisol levels and increased depression-like behaviour in adulthood.

Human Research

Many studies examine how early childhood stressors lead to negative health outcomes such as depression and altered cortisol release, and an increasing amount of research is now investigating the adolescent period (Romeo, 2010; Holder & Blaustein, 2014). However, human studies are largely focused on depression symptoms during puberty, rather than the long-term effects after

puberty ends. Moreover, longitudinal studies that investigate adolescent stress and depression often do not incorporate cortisol as a variable. For example, one study followed teenagers who experienced a stressful life event in grade seven and took annual measurements for depression. The researchers found that depressive symptoms steadily increased over the 5 year follow up period (Ge, Conger, & Elder, 2001). To date, only a couple of prospective studies investigate pubertal stressors and assess both cortisol and depression in adulthood (see Negriff et al., 2019; Trickett, Noll, & Putnam, 2011).

Conclusion

Researching stress during pubertal maturation would help clarify conflicting associations between cortisol and depression and increase understanding of how depression symptoms manifest (Fiksdal et al., 2019). Moving forward, future studies should aim to address lingering questions related to the developmental trajectory of depression symptoms and HPA axis function in later stages of adulthood. How do these outcomes change in young adulthood? Or mid-adulthood? What about late adulthood? Researching how these evolve over the lifespan would be important for personalizing psychotherapy or pharmacological treatments for adolescents and adults alike (Klimes-Dougan et al., 2019).

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