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Inter-relation between autonomic and HPA axis activity in children and adolescents

Sivan Rotenberg, Jennifer J. McGrath*

Concordia University, Canada

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ABSTRACT

Stress research in youth typically considers *either* the autonomic nervous system or HPA axis. However, these systems are highly coordinated and physically interconnected. We examined whether the inter-relation between cardio-autonomic and HPA axis measures was better associated with perceived stress than their singular associations. Children and adolescents ($N = 201$) collected saliva samples to measure cortisol (AUC_{AG}, AUC_I, maximum), wore an electrocardiogram monitor for 24 h to derive heart rate variability (HRV; LF, HF, LF/HF ratio), and completed the Perceived Stress Scale. The interaction between sympathovagal modulation (LF, LF/HF ratio) and cortisol awakening response (AUC_{AG}, AUC_I, maximum) explained significantly greater variance in perceived stress than either stress system alone. Higher sympathovagal modulation combined with higher cortisol awakening response was associated with greater perceived stress. Findings suggest that the inter-relation between cardio-autonomic and HPA axis activity may advance our understanding of how stress impacts health.

1. Introduction

The stress response system is comprised of the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis. Stress and the repeated activation of the stress response system have been associated with adverse health outcomes in children and adolescents. Specifically, using prospective (Adam et al., 2010; Fuligni et al., 2009; Slopen, Kubzansky, McLaughlin, & Koenen, 2013) and cross-sectional designs (Dreger, Kozyrskyj, HayGlass, Becker, MacNeil, 2010; Kazuma, Otsuka, Matsuoka, & Murata, 1997; Nagai, Matsumoto, Kita, & Moritani, 2003; Sen, Aygun, Yilmaz, & Ayar, 2008; Van den Bergh & Van Calster, 2009), dysregulation of the stress response system has been associated with obesity, asthma, inflammation, and depression among children and adolescents. Studies examining the physiological mechanism by which stress "gets under the skin" to affect health outcomes typically consider *either* the autonomic nervous system or the HPA axis (Lovell, Moss, & Wetherell, 2011; Lucini, Di Fede, Parati, & Pagani, 2005; Sloan et al., 1994). Yet, the autonomic nervous system and HPA axis are highly coordinated and physically interconnected. Investigating the inter-relation between the autonomic nervous system and HPA axis may provide a more thorough understanding of the association between stress and health. Among children and adolescents, few studies have considered how stress is related to the inter-relation between the autonomic nervous system and HPA axis.

Activation of the autonomic nervous system and HPA axis in response to a stressor follows a coordinated, temporal sequence. The autonomic nervous system quickly promotes physiological changes through synaptic transmissions by its two branches: the sympathetic and parasympathetic nervous system. The parasympathetic system facilitates the sympathetic response to stress, commonly referred to as the "fight or flight" response, by withdrawing its inhibitory effects (Porges, 1995, 2007). This, in turn, promotes physiological changes including the release of noradrenaline from the locus coeruleus (Curtis, Lechner, Pavcovich, & Valentino, 1997; Jedema & Grace, 2004) and the stimulation of sympathetic preganglionic neurons to increase heart rate (Bengel & Schwaiger, 2004; Engelnad & Arnhold, 2005; Shahar & Palkovits, 2007). Conversely, the HPA axis is a hormonal system; thus, physiological changes associated with its activation occurs minutes after activation. The HPA axis is initiated by the release of the corticotrophin-releasing hormone from the paraventricular nucleus of the hypothalamus, which results in a series of endocrine events that culminates with the release of cortisol from the adrenal cortex (Egliston, McMahon, & Austin, 2007). Cortisol impacts many different physiological systems (e.g., immunity, metabolism) and plays a role in augmenting the activity of the autonomic nervous

* Corresponding author at: Pediatric Public Health Psychology Laboratory, Department of Psychology, Concordia University, 7141 Sherbrooke St. West, Montréal QC H4B 1R6, Canada.
E-mail address: jennifer.mcgrath@concordia.ca (J.J. McGrath).

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system, such as enhancing the sympathetically mediated cardiovascular response to stress (e.g., increased heart rate; Sapolsky, Romero, & Munck, 2000). Together, the autonomic nervous system and HPA axis work in concert to produce a state of biological and behavioral preparedness.

1.1. Interaction between stress systems: animal studies

Animal studies examining the physiological link between the autonomic nervous system and HPA axis provide multiple lines of evidence to support their inter-relation. First, the autonomic nervous system and the HPA axis are reciprocally innervated. Corticotrophin-releasing hormone neuronal afferents from the paraventricular nucleus project to the locus coeruleus (Reyes, Valentino, Xu, & Van Bockstaele, 2005) and noradrenergic neurons from the locus coeruleus project to the paraventricular nucleus (Itoi, Jiang, Iwasaki, & Watson, 2004; Ma & Morilak, 2005). Second, there is a feed forward mechanism between the autonomic nervous system and the HPA axis. Corticotrophin-releasing hormone increases the firing rate of locus coeruleus neurons and stimulates the release of noradrenaline (Jedema & Grace, 2004; Reyes, Valentino, & Van Bockstaele, 2008; Valentino & Van Bockstaele, 2008). In turn, noradrenaline promotes corticotrophin-releasing hormone mRNA expression in the paraventricular nucleus (Itoi et al., 2004; Ma and Morilak, 2005). Moreover, lesions to the locus coeruleus attenuate the HPA axis response to a stressor (Zeigler, Cass, & Herman, 1999). Third, animal studies suggest that the autonomic nervous system and the HPA axis are both under tonic inhibitory control by the Central Autonomic Network, which includes the prefrontal cortex and limbic structures (Benarroch, 1993; Ulrich-Lai and Herman, 2009); these findings have also been observed in adult human studies (Gianaros, Van der Veen, & Jennings, 2004; Herman, Ostrander, Mueller, & Figueriredo, 2005; Radley, Arais, & Sawchenko, 2006). Thus, studies of the structural and functional connectivity between the autonomic nervous system and the HPA axis highlight their interconnection.

1.2. Stress systems in humans: measurement of autonomic nervous system and HPA axis

Autonomic nervous system activity can be measured in humans using heart rate variability (HRV), an indicator of cardio-autonomic control (Pumprla, Howorka, Grove, Chester, & Nolan, 2002). Both the parasympathetic and sympathetic nervous systems innervate the sinoatrial node, the pacemaker of the heart (Berntson et al., 1997; Task Force, 1996), and modulate heart rate. Noradrenaline from sympathetic postganglionic receptors increases heart rate, while acetylcholine from parasympathetic postganglionic receptors decreases heart rate (Berntson et al., 1997). HRV is commonly quantified by frequency domain measures, which describe how power is distributed as a function of frequency. Two frequencies are predominantly considered: low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.40 Hz; Task Force, 1996). Pharmacological blockade studies indicate that HF is strongly associated with parasympathetic modulation, and LF is associated with both sympathetic and parasympathetic modulation (Cacioppo et al., 1994; Polanczyk et al., 1998). Some suggest that the LF/HF ratio reflects the balance of sympathetic and parasympathetic nervous systems, and is an indicator of sympathovagal modulation (Lahiri, Kannankeril, & Goldberger, 2008; Malliani, 2005; Sztajzel, 2004; Task Force, 1996); however, the physiological underpinning of LF remains debated in the literature (de Geus, Montano, Sloan, & Thayer, 2014). For instance, the LF/HF ratio has been associated with some measures of sympathetic modulation, such as orthostatic changes (Malliani, 2005), but not others (Heathers, 2014). Nevertheless, Heathers (2014, p. 3) notes that "a metric [such as LF/HF ratio] may be useful before it appears meaningful".

HPA axis activity can be assessed using salivary cortisol sampling. Cortisol is released in a circadian fashion characterized by cortisol levels that peak within the first hour post-awakening and gradually decline throughout the day (Fries, Dettenborn, & Kirschbaum, 2009). The collection of multiple samples across the day are used to derive aggregate measures that describe the diurnal cortisol profile, including the awakening response and diurnal slope (Rotenberg, McGrath, Roy-Gagnon, & Thanh Tu, 2012). The awakening response refers to the rise in cortisol by 50–75% (approximately 4–15 nmol/L) during the first hour post-awakening, and is measured by total amount of cortisol released during the awakening response (AUC_{AG}; area under the awakening response relative to ground or zero) and dynamic increase in the amount of cortisol secreted following awakening (AUC_I; area under the curve relative to increase; Clow, Thorn, Evans, & Hucklebridge, 2004; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Diurnal slope is characterized as the decline in cortisol over the day. Single sample cortisol measures are commonly reported as well, including the maximum or specific time of day (e.g., morning, afternoon, bedtime; cf., Blair, Peters, & Granger, 2004; Cohen et al., 2006; El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008; Lupien, King, Meaney, & McEwen, 2001).

1.3. Interaction between stress systems: human studies

Human studies examining the concurrent functioning of cardio-autonomic and HPA axis activity provide further evidence in support of their inter-relation. Specifically, higher morning and afternoon cortisol levels have been associated with low HF among adolescents in ambulatory settings (El-Sheikh, Arsiwalla, Hinnant, & Erath, 2011); although, no association has been reported as well (Oldehinkel et al., 2010). Additionally, elevated cortisol awakening response (AUC_I) has been associated with reduced LF and HF among young adults (Stadler, Evans, Hucklebridge, & Clow, 2011). These findings, taken together with those from the animal literature, converge to suggest that autonomic and HPA axis activity are coordinated and work together to respond to stress across the lifespan.

1.4. Theoretical rationale for considering the inter-relation

Extant psychophysiology theories highlight the importance of considering the role of the inter-relation between the autonomic nervous system and HPA axis. Bauer, Quas, and Boyce (2002) hypothesized that the coordination of the autonomic and HPA axis response to stress is related to an individual's risk for adverse outcomes. Bauer et al. proposed two competing inter-relation models: Additive or Interactive. The Additive model contends that symmetrical activation of both systems (hyper-arousal: high autonomic and HPA axis activity; or hypo-arousal: low autonomic and HPA axis activity) increases risk. In contrast, the Interactive model contends that asymmetric activation increases risk, as the most adaptive physiological response may be when there is a balance between autonomic and HPA axis activity. Del Giudice, Ellis, and Shirtcliff (2010) extended Bauer et al.'s model by suggesting that distinct response patterns between the autonomic nervous system and HPA axis emerge due to early life experiences (e.g., exposure to chronic stress) and that the match or mismatch between environmental context and stress response patterns is vital for determining risk.

The Polyvagal Theory (Porges, 1995, 2007) and Neurovisceral Integration Model (Thayer & Lane, 2000 Thayer & Sternberg, 2006) also support examining the inter-relation and provide greater insight into how the autonomic nervous system and HPA axis may be inter-related. Grounded in Porges' work on emotion