Psychoneuroendocrinology 94 (2018) 63–71

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Association between changes in heart rate variability during the anticipation of a stressful situation and the stress-induced cortisol response

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ARTICLE INFO

Keywords:
Heart rate variability
HRV
Cortisol
Stress
Anticipation
HPA axis

ABSTRACT

Vagal activity – reflecting the activation of stress regulatory mechanisms and prefrontal cortex activation – is thought to play an inhibitory role in the regulation of the hypothalamus–pituitary–adrenal axis. However, most studies investigating the association between stress-induced changes in heart rate variability (HRV, an index of cardiac vagal tone) and cortisol have shown a non-significant relationship. It has been proposed that physiological changes observed during anticipation of a stressor allow individuals to make behavioral, cognitive, and physiological adjustments that are necessary to deal with the upcoming actual stressor. In this study, in a large sample of 171 healthy adults (96 men and 75 women; mean age = 29.98, *SD* = 11.07), we investigated whether the cortisol response to a laboratory-based stress task was related to anticipation-induced or stress task-induced changes in HRV. As expected, regression analyses showed that a larger decrease in HRV during the anticipation of a stress task was related to higher stress task-induced cortisol increase, but not cortisol recovery. In line with prior research, the stress task-induced change in HRV was not significantly related to cortisol increase or recovery. Our results show for the first time that anticipatory HRV (reflecting differences in stress regulation and prefrontal activity before the encounter with the stressor) is important to understand the stress-induced cortisol increase.

1. Introduction

An excessive and/or prolonged cortisol response to stress has been related to physical and psychological disorders (McEwen, 2008). Understanding the factors that contribute to differences in the stress-induced cortisol response is crucial to prevent and treat stress-related disorders. The vagus nerve, the main component of the parasympathetic division of the autonomic nervous system, is assumed to play an inhibitory role in the regulation of the hypothalamus–pituitary–adrenal (HPA) axis (Thayer and Sternberg, 2006). Considering its link with the HPA axis, vagal activity may provide relevant information to understand the inter-individual differences in stress-induced cortisol response to stressors.

High vagal activity is considered a marker of successful emotion regulation and stress adaptability (Park et al., 2014; Thayer et al., 2012; Vanderhasselt et al., 2015). Recent meta-analyses demonstrated that high vagal function is associated with prefrontal cortex activity (Makovac et al., 2017; Thayer et al., 2012), a brain region that has inhibitory connections with the amygdala (Baeken et al., 2010). Under stress, the amygdala is activated and initiates the HPA axis response to stress (Herman et al., 2005); however, an increase in prefrontal cortex activity would inhibit the activation of the amygdala and reduce the HPA axis response to stress (Baeken et al., 2010, 2014). Thus, given that the activity of the vagus nerve reflects the inhibitory control of the prefrontal cortex on the amygdala, better emotion regulation and stress adaptability are expected in individuals showing higher vagal activity (Thayer et al., 2012; Vanderhasselt et al., 2015). Moreover, it has been proposed that there are bidirectional connections between vagal nuclei in the medulla oblongata and the hypothalamus, supporting the idea of a connection between the two systems (Benarroch, 1997; La Marca et al., 2011; Palkovits, 1999). Taken together, given that vagal activity reflects stress/emotion regulation and have bidirectional connections with the HPA axis, an association with cortisol in stressful events could be expected.

Vagal activity can be indexed by heart rate variability (HRV; variation in inter-beat intervals; Task Force, 1996). Under stressful situations, a decrease in HRV and an increase in cortisol levels is observed (e.g., La Marca et al., 2011; Zandara et al., 2016, 2017), and resting HRV has been related to cortisol increase and recovery during stress, and during cognitive challenge (Gunnar et al., 1995; Johnsen et al.,

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https://doi.org/10.1016/j.psyneuen.2018.05.004
Received 22 September 2017; Received in revised form 2 May 2018; Accepted 2 May 2018

2012; Smeets, 2010; Weber et al., 2010). Although these results suggest a relationship between HRV and cortisol under stress, most of the studies that investigated the association between changes in HRV and cortisol in stressful situations have found non-significant results (Altemus et al., 2001; Bosch et al., 2009; Cacioppo et al., 1995; Gunnar et al., 1995; Heilman et al., 2008; Looser et al., 2010; La Marca et al., 2011; but see Doussard-Roosevelt et al., 2003). For instance, Looser et al. (2010) showed an association between cortisol values and changes in HRV during high levels of stress, but they did not observe a significant relationship between changes in HRV and changes in cortisol. Moreover, La Marca et al., 2011 showed a negative relationship between stress-induced changes in HRV and cortisol, but the association was not statistically significant. Therefore, although a link between vagal activity and the HPA axis is assumed (Thayer and Sternberg, 2006), most studies have shown weak and non-significant relationships between changes in both HRV and cortisol levels in response to stress (Altemus et al., 2001; Bosch et al., 2009; Cacioppo et al., 1995; Gunnar et al., 1995; Heilman et al., 2008; La Marca et al., 2011; Looser et al., 2010).

It is worth noticing that the physiological response to stress does not occur only when confronted with the stressful situation (Engert et al., 2013). Instead, before the actual encounter with the stressor, the anticipation of a threat to well-being or disruption of homeostasis may also trigger the HRV response (e.g., Zandara et al., 2017). This rapid response suggests that differences in stress regulation might be observed before the actual encounter with the stressful event and that the regulatory role of the vagal tone in the HPA axis response to stress might start during the anticipation of the stressor. Importantly, the physiological changes observed during anticipation are considered an adaptive response that allows individuals to make behavioral, cognitive, and physiological adjustments that are necessary to deal with the upcoming actual stressor (Schulkin, 2011; Schulkin et al., 1994; Turan, 2015; Turan et al., 2015), and previous studies have shown that stress anticipation is crucial to understand the differences in the physiological response to stress (Engert et al., 2013; Gaab et al., 2003, 2005). For instance, the anticipatory stress appraisal (i.e., the evaluation of the stressor as a threat or challenge and the evaluation of the own abilities to deal with the stressor) is associated with lower cortisol response to a stress task (Gaab et al., 2003, 2005). Moreover, in their Neurocognitive Framework for Regulation Expectation, De Raedt and Hooley (2016) have proposed that proactively anticipating a stressful event is associated with sustained prefrontal activation, which would decrease amygdala activation and improve stress regulation. Together, it is possible that changes in HRV during stress anticipation reflect the ability of the individuals to anticipate the stressful event successfully. Following this idea, one could expect that larger decreases in HRV during anticipation (reflecting poorer stress/emotion regulation associated with reduced prefrontal activity) might be associated with higher HPA axis responses to stress (reflected in higher increases in cortisol).

To test this idea, we investigated the relationship between changes in HRV provoked by the anticipation of a stressful task and the changes in cortisol levels in response to a laboratory-based stress task in 171 healthy adults. We expected a larger decrease in HRV during the anticipation of the stress task to be related to higher stress-induced cortisol increase. To compare our results with previous studies, we also investigated the relationship between changes in HRV due to the stress task and cortisol indexes. In accordance with previous studies, we expected no significant relationship in these analyses.

2. Methods

2.1. Participants

The sample of this study was recruited for the Pittsburgh Cold Study 3, a prospective viral challenge study with data collected from 2007 to 2011 among 213 healthy volunteers ages 18–55 from the Pittsburgh, Pennsylvania metropolitan area. The data were collected by the Laboratory for the Study of Stress, Immunity, and Disease at Carnegie Mellon University under the directorship of Sheldon Cohen, Ph.D.; and were accessed via the Common Cold Project website (www.commoncoldproject.com; grant number NCCIH AT006694). The exclusion criteria for the whole project were: regular medication regimen (including but not limited to use of antidepressants, sleeping pills, or tranquilizers), previous nasal/otologic surgery, psychiatric hospitalization within the last 5 years, history of chronic illness or any psychiatric disorder treated within one year or before study enrollment, abnormal clinical profile (discovered via urinalysis, complete blood count, or analysis of blood chemistry), human immunodeficiency virus seropositivity, current pregnancy or lactating, use of steroids or immunosuppressants within three months of the trial, participation in another study involving psychological questionnaires and/or investigational products within the last 30 days or plans to participate in such research while enrolled in the current study, cold or flu-like illness within 30 days prior the infection with a virus as part of the project, living with someone who has chronic obstructive pulmonary disease or an immunodeficiency, previous hospitalization as a consequence of a flu-like illness and allergies to eggs or eggs products.

The final sample included in this study was 171 (96 men and 75 women). Table 1 shows the characteristics of the study sample.

Table 1
Characteristics of the sample, positive and negative affect during the session and, HRV and cortisol indexes.

	Mean/n	SD
Age (years)	29.98	11.07
Sex and hormonal status	Men = 96 Women = 75 Premenopausal: • -Free cycling = 52 • -H. contraceptives = 13 Postmenopausal = 10	
Subjective Socioeconomic Status	6.01	1.64
Body Mass Index (kg/cm^2)	27.01	6.24
Smoking	No = 118 Yes = 53	
Alcohol (drinks consumed per week)	3.54	7.26
Time beginning session	16:58	01:07
Mean respiration rate	12.91	2.97
Positive Affect baseline	1.96	0.82
Positive Affect 10 min Post-stress	1.34	0.90
Positive Affect 45 min Post-stress	1.79	0.89
Negative Affect baseline	0.29	0.43
Negative Affect 10 min Post-stress	0.88	0.78
Negative Affect 45 min Post-stress	0.37	0.50
$HRV_{Anticipation}$	−9.13	22.42
HRV_{Stress}	−8.80	19.68
Cortisol reactivity	2.31	5.50
Cortisol recovery	3.57	4.09
Cortisol AUCi	7.65	250.76
Cortisol AUCg	465.31	308.79

Note: n = 171 for all the variables except for HRV_{Stress} (n = 159), Positive affect baseline (n = 170), Positive affect 10 min post-stress (n = 169), and Negative affect 10 min post-stress (n = 170). $HRV_{Anticipation}$ was calculated as the change in HRV from baseline to the anticipatory phase. HRV_{Stress} was calculated as the change in HRV from baseline to the stress task. Cortisol reactivity was computed as the change in cortisol from baseline to the maximum cortisol levels after the stress task was computed as the change in cortisol from baseline to the maximum cortisol levels after the stress task. Cortisol recovery was computed as the decrease in cortisol from the maximum cortisol levels after the stress task to the last cortisol sample. Cortisol AUCi and AUCg were calculated, using the seven cortisol samples, as a measure of dynamic of the cortisol change after the stress task and total cortisol secretion, respectively (see Pruessner et al., 2003 for the specific formulas). H. contraceptives = Hormonal contraceptives