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Salivary biomarkers of neural hypervigilance in trauma-exposed women

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ABSTRACT

Objectives: More than half of all adults will be exposed to a traumatic event at some point in their lives, yet we do not yet have reliable biomarkers to help predict who experiences trauma-related symptoms in response to exposure. We tested the utility of salivary cortisol and salivary alpha amylase as markers of (1) neural reactivity to negative affective information and (2) neural hypervigilance in the absence of threat.
Participants: 20 women (mean age 23.6 +/− 5.8 years) with a history of trauma exposure.
Measures: Salivary cortisol and alpha amylase reactivity were measured in response to a trauma reminder during a clinical interview. Neural reactivity to novel and familiar affective scenes was measured in a later session using functional magnetic resonance imaging.
Results: Salivary alpha amylase, but not cortisol, increased in response to the trauma reminder. Salivary alpha amylase reactivity was associated with neural reactivity in the salience network in response to novel negative scenes and neural hypervigilance as indexed by reactivity to novel neutral scenes.
Conclusions: Salivary alpha amylase might serve as a more reliable marker of trauma-related reactivity to negative affective information, and also as a marker of hypervigilance in the absence of threatening information.

1. Introduction

More than half of all people will experience a traumatic event at some point in their lives (Kessler et al., 2005). Trauma exposure can lead not only to exaggerated physiological reactivity to trauma reminders (e.g., McTeague et al., 2010), but also to chronic elevation of basal autonomic arousal (e.g., Pole, 2007), and maladaptive and distressing hypervigilance for potential threat even in a safe environment (e.g., Dalgleish et al., 2001). Heightened reactivity to threat-relevant cues combined with generalized hypervigilance can be distracting and exhausting, as the person is constantly on alert physiologically and cognitively for potential threat. Although the identification of reliable biomarkers for trauma-related symptoms will help enhance precision of assessment and diagnosis, and non-invasive and relatively inexpensive salivary biomarkers hold particular appeal, the field has not yet identified a reliable biomarker for tonic trauma-related symptoms such as hypervigilance.

In the brain, both reactivity to threat and hypervigilance for threat are associated with heightened neural activity in the salience network: the amygdala, the dorsal anterior cingulate cortex (dACC), and the rostral middle frontal gyrus (i.e., the core areas of dorsolateral PFC and dorsomedial PFC; e.g., Bryant et al., 2005; Straube et al., 2009). The salience network is implicated in vigilance, orienting of attention, and processing of affective information (e.g., Van Marle et al., 2010). Following trauma exposure, reactivity as indexed by amygdala and dACC response is heightened to both trauma-related stimuli (e.g., Protopopescu et al., 2005; Shin et al., 2007) and trauma-unrelated, negatively-valenced stimuli (e.g., Williams et al., 2006). The neuroimaging literature on stress-related states also highlights neural reactivity to threat information in high arousal states. For example, state anxiety is associated with threat-related amygdala hyperreactivity (e.g., Bishop et al., 2004) and heightened activity in dorsal ACC and rostral middle frontal gyrus (e.g., Milad et al., 2007; Simmons et al., 2008).

In addition to reactivity to actual threat as measured by trauma-relevant or negative information, people in stress-related states show neural hypervigilance for potential threat in the salience

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network even in the absence of threat information. For example, people with PTSD show increased amygdala and dorsal ACC response to salient non-affective stimuli (Bryant et al., 2005), and PTSD symptoms and state anxiety also are associated with heightened amygdala response to affectively ambiguous (i.e., neutral) faces (Brunetti et al., 2010; Somerville et al., 2004). In addition, the amygdala response to novel faces is greater in people with inhibited temperament in childhood (Schwartz et al., 2003), which is linked to stress-system hyperactivity (Tyrka et al., 2006), potentially due to the additive influence of novelty beyond arousal and valence in neural responding to affective information (e.g., Weierich et al., 2010).

Trauma-related reactivity and hypervigilance are examples of overactive stress system responses, and trauma exposure is associated with alterations in the neuroendocrine response to stress, as indexed by hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) responses. Results from investigations of HPA axis reactivity via salivary cortisol have been inconsistent, with some evidence for blunted cortisol reactivity (e.g., Elzinga et al., 2008) and some evidence for heightened cortisol reactivity (e.g., Bremner et al., 2003) in trauma-exposed people. Other studies show no relation between trauma exposure and cortisol reactivity (e.g., Simeon et al., 2007). These inconsistencies have been attributed in part to the effects of stress history profiles that reflect complex interactions between chronic stress, early life stress, and acute stressors on basal (e.g., Meewisse et al., 2007) and reactive cortisol (e.g., Suzuki et al., 2014).

More recent investigations of sympathetic reactivity using salivary alpha amylase (sAA) have been more consistent and suggest that sAA is promising as a convenient and non-invasive biomarker for SNS activity (e.g., Granger et al., 2007; Nater and Rohleder, 2009). People who have been exposed to trauma show sustained elevation of basal SNS activity (e.g.,Vigil et al., 2010), and also exaggerated SNS reactivity to trauma reminders and more generally aversive stimuli (e.g., Bedi and Arora, 2007; McTeague et al., 2010). SAA is an enzyme that is synthesized and secreted from the acinar cells of the salivary glands (e.g., Baum, 1993). Under normal conditions, the acinar cells are innervated by both the sympathetic and parasympathetic branches of the autonomic nervous system. Parasympathetic impulses stimulate fluid secretion, sympathetic impulses modulate saliva composition by increasing exocytosis from the acinar cells, and in combination both branches influence the level of amylase in saliva (e.g., Proctor & Carpenter, 2007). However, during physical or psychological stress, sAA level is predominantly influenced by SNS activity in the cervical sympathetic pathway (e.g., Bosch et al., 2003; Nater et al., 2007), and sAA levels rise immediately in response to stress (e.g., Nater et al., 2007).

Further supporting the potential utility of sAA as a potential biomarker for stress-related symptoms such as hypervigilance, the salience network is extensively interconnected anatomically to the central sympathetic network, which includes the thalamus, hypothalamus, brainstem, and adrenal medulla (e.g., Westerhaus and Loewy, 2001). Through these multi-synaptic connections, amgydala-PFC circuitry modulates the downstream SNS response to stress. For example, greater amygdala and dorsal medial PFC response to affective information is associated with concurrent physiological indices of SNS activity in healthy participants (e.g., Wager et al., 2009; Yang et al., 2007).

Given the inconsistencies in cortisol reactivity data in trauma-exposed people, and the strong interconnections between the salience network and the sympathetic system, sAA reactivity might be a more reliable neuroendocrine marker for exaggerated threat sensitivity or vigilance. Our overarching aim was to test and compare two candidate analytes as potential biomarkers of excessive neural reactivity to *actual* threat information and vigilance for *potential* threat information. We assessed HPA (cortisol) and SNS (alpha amylase) reactivity to a naturalistic trauma reminder as predictive markers of hypervigilant activation patterns in the salience network (i.e., amygdala, dorsal ACC, and rostral middle frontal gyrus). We tested two specific sets of hypotheses. First, if HPA and/or SNS reactivity to trauma reminders predict neural reactivity to *actual* threat, we hypothesized that reactivity would be associated with activation to negatively-valenced information. Second, if HPA and/or SNS reactivity to trauma reminders predict neural hypervigilance for *potential* threat, we hypothesized that reactivity would be associated with activation to novel and/or neutral information.

Table 1
Participant characteristics ($N = 20$).

Variable	Statistic
Age in years, *M* (*SD*)	23.6 (5.8)
Race/ethnicity, n (%)	
White, non-Hispanic	3 (15.0)
Black, non-Hispanic	4 (20.0)
Asian/Pacific Islander	7 (35.0)
Hispanic	1 (5.0)
Multiple	2 (10.0)
Other	3 (15.0)
Number of trauma types, *M* (*SD*)	2.5 (0.9)
Trauma type, *n* (%)	
Natural disaster	1 (2)
Fire/explosion	3 (6)
Motor vehicle accident	5 (10)
Other serious accident	5 (10)
Physical assault	10 (20)
Sexual assault	5 (10)
Other unwanted sexual experience	1 (2)
Life-threatening injury/illness	3 (6)
Severe human suffering	1 (2)
Witness violent death	2 (4)
Sudden, unexpected death of loved one	6 (12)
Caused serious injury/death of another	1 (2)
Other very stressful event	7 (14)
Total number of PTSD symptoms, *M* (*SD*), Range	7.3 (5.1), 0–15
Re-experiencing symptoms	2.5 (1.7), 0–5
Avoidance symptoms	2.6 (1.9), 0–6
Hyperarousal symptoms	1.8 (1.8), 0–5
Perceived Stress Scale, *M* (*SD*), Range	23.5 (7.2), 11–38
STAI-S, *M* (*SD*), Range	
Session 1	46.5 (13.3), 25–64
Session 2	41.9 (9.7), 26–61
BDI II, *M* (*SD*), Range	
Session 1	17.1 (7.1), 5–32
Session 2	12.3 (8.2), 1–31

2. Method

2.1. Participants

We recruited 20 adult women who reported exposure to potentially traumatic events in an online screening measure. Potential participants were recruited from introductory psychology subject pool at a large urban university in the northeast US and by responses to an anonymous online screen advertised on flyers. In the current analyses, we included 20 women (age $M = 23.6$, $SD = 5.8$, range 18–37 years; see Table 1) who met the trauma exposure criterion (Criterion A) of the posttraumatic stress disorder (PTSD) module of the Diagnostic and Statistical Manual of Mental Disorders IV. Additional inclusion criteria included right-handedness and eligibility for an MRI scan via a standard MRI safety screen (e.g., no metal in the body, no history of claustrophobia).