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# Biomarkers of post-deployment resilience among military service members

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ABSTRACT

The development of PTSD after military deployment is influenced by a combination of biopsychosocial risk and resilience factors. In particular, physiological factors may mark risk for symptom progression or resiliency. Research in civilian populations suggests elevated catecholamines after trauma are associated with PTSD months following the trauma. However, less is known regarding physiological markers of PTSD resilience among post-deployment service members (SM). We therefore assessed whether catecholamines obtained shortly after deployment were associated with combat-related PTSD symptoms three months later. Eighty-seven SMs completed the Clinician-Administered PTSD Scale for DSM-IV and blood draws within two months after return from deployment to Iraq or Afghanistan ("Time 1" or "T1") and three months later ("Time 2" or "T2"). Linear regression analyses demonstrated that lower norepinephrine at T1 was associated with lower PTSD symptoms at T2. In particular, T1 norepinephrine was positively associated with T2 symptom intensity and avoidance symptoms. The present findings represent a biologically-informed method of assessing PTSD resilience after deployment, which may aid clinicians in providing tailored treatments for those in the greatest need. Further research is needed to validate these findings and incorporate physiological measures within an assessment battery.



## 1. Introduction

Military service members (SM) deployed to wars in Iraq and Afghanistan are more likely to experience posttraumatic stress disorder (PTSD) symptoms related to both warzone and homefront experiences (Smith et al., 2008; Vasterling et al., 2010) than those who did not deploy. Post-deployment PTSD symptoms are associated with reduced quality of life and functional status in SMs (Schnurr et al., 2009; Tsai et al., 2012), even for those whose symptoms fall short of meeting full diagnostic criteria for PTSD (Cukor et al., 2010; Grubaugh et al., 2005; Magruder et al., 2004). The current literature implies a variable risk for PTSD symptom development, attributable to a number of risk (e.g. number of deployments, traumatic brain injury, combat exposure, genetics) and resilience (e.g. unit support, post-deployment social support) factors (Hoge et al., 2008; Pietrzak et al., 2010; Reger et al., 2009; Seal et al., 2009; Skelton et al., 2012). However, less attention has been given to physiological factors that may signal risk for symptom progression, or conversely, the potential for resilience, after deployment, particularly with respect to subthreshold PTSD.

The catecholamines dopamine (DA), epinephrine (EPI), and norepinephrine (NE) are monoamines that are produced both within the central nervous system, where they act as neurotransmitters that are released to facilitate adaptive responses to acute stressors (Cahill and Alkire, 2003; Southwick et al., 2002), as well as in the sympathoadrenal system where they regulate physiologic responses to stressors. While beneficial in acute stress, repeated activation in chronic stress leads to dysregulation of catecholamine release, and increases the risk of PTSD; whereas adaptive catecholamine responses may signal resilience (Krystal and

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Neumeister, 2009). Precipitating events and psychological responses may dictate physiological reactions, but physiological reactions may also lead to psychological effects. Basal catecholamine levels have been associated with PTSD in a community sample (Young and Breslau, 2004), and there is some evidence that neuroendocrine measures (e.g. cortisol and NE) may be linked with trauma-related symptoms in adults within two months after trauma (Delahanty et al., 2000). Findings also indicate that catecholamine elevations can persist longer than 6 months given psychopathology. For example, combat veterans with chronic PTSD have higher baseline cerebral spinal fluid NE concentrations under unstressed conditions than their counterparts without PTSD (Geracioti et al., 2001). Furthermore, recent work suggests that variants of the gene coding for catechol-O-methyl transferase, an enzyme involved in catecholamine metabolism, are associated with PTSD (Kolassa et al., 2010; Norrholm et al., 2013).

Building upon these studies, we hypothesized that basal catecholamine levels obtained shortly after return from deployment could further improve our ability to predict resilience against combat-related PTSD symptoms in the subsequent months. We therefore compared catecholamine levels obtained within two months after return from deployment (T1) with PTSD symptoms three months later (T2). We expected that lower levels of DA, EPI, and NE at T1 would be associated with less severe PTSD symptoms at T2. Given that psychological states can induce changes in catecholamine systems, we also examined the reverse relationship, anticipating that lower T1 PTSD symptoms would be associated with lower catecholamine levels at T2.

## 2. Methods

### 2.1. Participants and procedure

SMs (N = 87) were recruited either through institutional review board-approved advertisements, or via direct contact immediately upon their return to the U.S. during postdeployment demobilization procedures at Fort Dix, NJ. Their current duty stations spanned the United States. They completed a T1 assessment within two months of return from deployment to Iraq or Afghanistan and then again three months later (T2). Inclusion criteria included the ability to complete informed consent, a structured interview, and a morning blood draw. Participants screening positive for probable PTSD (PTSD Checklist score $\geq$ 50), major depression (Patient Health Questionnaire-9 score $\geq$ 10), or post-concussive syndrome at baseline were excluded. Further exclusionary criteria included having a history of head injury resulting in a loss of consciousness for 60 minutes or more, a current Glasgow Coma Scale of less than 14 points, active psychotic symptoms, or active suicidal or homicidal ideation. Participants on alpha blockers or calcium channel blockers were excluded if they were unable to hold these medications for a 24-hour period preceding brain imaging scans. Combat-related PTSD symptoms were assessed by a trained, PhD-level psychologist using the Clinician-Administered PTSD Scale for DSM-IV (CAPS, Blake et al., 1995; Weathers et al., 2001), with traumatic events including improvised explosive devices, firefight, vehicular accidents, and other combat-related traumas. The frequency and intensity of each symptom cluster (e.g. re-experiencing, avoidance, hyperarousal) were combined to create a total score.

Blood draws occurred prior to 0900. Plasma samples were isolated from whole blood in sodium heparin preserved collection tubes with centrifugation for 10 minutes at room temperature. Samples were stored at −70 °C and run in a single batch. A commercially available Enzyme Immunoassay measured plasma catecholamine (EPI, NE, DA) levels, using Alpco Diagnostics (Salem, NH) Tri-Cat assay (17-TCTHUE03-RES).

### 2.2. Data analysis

First, step-wise linear regressions assessed whether T1 catecholamine levels were associated with T2 CAPS scores. Age, gender, and T1 CAPS score served as control variables. Catecholamine levels (DA, EPI, and NE) were entered as independent predictors. Both controls and predictors were entered in a step-wise fashion. The corresponding T2 CAPS score was analyzed as the dependent variable. T2 analyses modeled CAPS frequency and intensity, and CAPS symptom clusters, separately. Additional analyses were conducted to determine whether the reverse relationship was supported, such that T1 CAPS scores were associated with catecholamine levels at T2 when controlling for T1 catecholamine levels.

## 3. Results

Reflecting the overall deployed population, study participants were predominantly male (85%), single (53%), Caucasian (73%), and employed (71%). On average, participants were 30.0 (SD = 8.0) years old, had served 9.4 (5.9) years in the military, and had been deployed 1.7 (SD = 1.0) times since 2001. Total CAPS scores decreased from T1 to T2. In particular, symptom frequency and re-experiencing symptoms showed significant decreases between time points. Catecholamine levels and CAPS scores are shown in Table 1. There were no significant correlations between T1 catecholamine levels and T1 CAPS scores. The correlations between T1 variables, as well the correlations among T1 and T2 variables, are shown in Table 2.

In order to examine the relationship between T1 catecholamines and PTSD symptomatology at T2, we completed step-wise linear regressions, while adjusting for T1 PTSD symptomatology. When controlling for T1 CAPS scores, step-wise linear regressions demonstrated that T1 NE was predictive of PTSD symptomatology at T2, in as much as T1 NE ($\beta$ = .28, SE = .01, p = .03) was positively associated with T2 total CAPS scores (see Fig. 1). T2 step-wise linear regressions examined whether this association was due to symptom frequency or intensity. T1 NE levels ($\beta$ = .32, SE = .004, p = .02) were associated with T2 CAPS intensity but not CAPS frequency. For these regressions, age, gender, and other catecholamines were not included in the final models as they were not significantly associated with T2 CAPS scores.

Next, step-wise linear regressions examined whether T1 catecholamine levels were associated with particular CAPS symptom clusters. T1 catecholamines were not associated with re-experiencing or hyperarousal at T2. However, T1 NE was positively associated with T2 avoidance scores ($\beta$ = .38, SE = .004, p = .01). In particular, NE was positively associated with T2 avoidance frequency ($\beta$ = .36, SE = .002, p = .006) and intensity ($\beta$ = .38, SE = .002, p = .007). As noted in the previous step-wise regressions, age, gender, and other catecholamines were not retained in any of the final models.

**Table 1**
Total, intensity, frequency, and cluster CAPS scores across time points.

| | T1 mean (SD) | T2 mean (SD) | *t* (*p*) |
|---|---|---|---|
| Dopamine | 28.64 (16.05) | 28.67 (16.03) | .26 (.79) |
| Epinephrine | 51.20 (25.57) | 61.01 (36.43) | 1.44 (.16) |
| Norepinephrine | 274.77 (173.50) | 309.67 (215.32) | 1.18 (.25) |
| Total CAPS | 19.6 (12.8) | 15.4 (15.1) | 2.32 (.02) |
| CAPS – intensity | 7.7 (5.4) | 6.1 (6.04) | 1.99 (.05) |
| CAPS – frequency | 12.0 (7.6) | 9.1 (9.0) | 2.56 (.01) |
| CAPS – re-experiencing | 4.3 (4.3) | 2.02 (3.7) | 3.65 (.001) |
| CAPS – avoidance | 4.9 (4.94) | 4.4 (6.5) | .62 (.54) |
| CAPS – hyperarousal | 10.5 (6.4) | 8.9 (7.5) | 1.65 (.11) |

Note: CAPS: Clinician Administered PTSD Scale.