



Only time will tell: Acute stress response patterns with time series analysis

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ABSTRACT

Stress has long attracted attention in psychophysiological research, due to its effects on physiology that are measurable and well documented. Acute stress is often conceptualized as a response pattern that activates the fight-or-flight response via the sympathetic nervous system (SNS). However, other stress response patterns can manifest as well, such as parasympathetic nervous system (PNS) shutdown, and SNS-PNS coactive hypervigilance. Each response pattern engages many dimensions, including physiological, emotional, and behavioral. Additionally, as stress unfolds over time, these patterns can change to adjust to the changing nature of the stressor. This proof of concept study introduces novel methodology to track the patterns and multidimensional manifestations of stress. Virtual reality (VR) was used to induce a dynamic range of stress responses. The defense cascade provides a model with which to understand and predict response patterns over the time course of an acute stressor.

1. Introduction

Stress can have detrimental effects on both physical and emotional well-being, with outcomes as wide-ranging as cardiac disease, digestive disorders, anxiety, depression, and posttraumatic stress disorder (PTSD; e.g. Steptoe and Kivimäki, 2012; Mayer, 2000; Roza et al., 2003; Holsboer, 2001; Yehuda, 2002). Accordingly, stress is a well-researched construct across many disciplines including psychophysiology. Although there is still debate about the precise definition of stress, it is generally understood as an organism's response to a threat, in which threats can include a potential predator, competitor, or other environmental danger (see DelGuidice et al., 2018, for a nuanced review of the definition of stress). These threats are typically referred to as “stressors” in stress literature.

Acute stress is experienced over a short-term time course that can last seconds to minutes and typically engages the sympathetic-adrenal-medullary axis (SAM; Lovallo, 2015). In acute stress, catecholamines are released in combinations needed to effect changes in the autonomic nervous system (ANS; Hermans et al., 2014). Recovery from acute stress engages the hypothalamic-pituitary-adrenal (HPA) axis, releasing hormones such as cortisol to restore homeostasis or allostasis after the stressor. Chronic stress involves exposure to acute stressors that recur over the course of hours, days and/or years and can alter the way in which the HPA axis operates (Wadsworth et al., 2019). Because of its deleterious health effects, chronic stress is the more commonly re-

searched construct in recent literature. However, the way in which acute stress is experienced and psychologically metabolized can determine whether it is even processed as the type of stress that accrues long-term harm to physical and emotional health. This study uses the defense cascade to model acute stress, highlighting the patterns of physiological and psychological responses to an acute stressor.

1.1. Defense cascade

The defense cascade is an empirically supported sequence of the defensive strategies employed in response to a perceived threat (Lang et al., 1997). This model suggests that the threat response invokes “the 6 F's” in the following order: *freeze, flight, fight, fright, flag, and faint*. Each stage activates the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and behavioral responses in different combinations to address increasing danger and emotional distress.

The defense cascade is activated when a person first detects the potential of threat, engaging the freeze response (Blanchard & Blanchard, 1990). This *attentive immobility* and hypervigilance minimizes predator detection while orienting to the potential danger (Schauer and Elbert, 2010), and is supported by co-activation of the SNS and PNS (Lang et al., 1997). If a threat is confirmed and approaching, the person will switch into flight, engaging reciprocal SNS activation (Berntson et al.,

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1991). If flight fails, the person will switch to fight; reciprocal SNS activation continues, now supporting direct engagement with the threat.

If flight and fight fail and damaging contact is made, fright will be invoked (Bracha, 2004). This *tonic immobility*, supported by SNS/PNS coactivation, dampens predatory aggression and minimizes blood loss or potential injuries from struggle. If escape is not possible, the fifth stage, flag will be triggered (Schauer and Elbert, 2010). Sympathetic tone is withdrawn, leaving unbridled PNS activation to cause a precipitous drop in heart rate, and consciousness flags. The sixth and final stage, faint follows quickly from flag. This *flaccid immobility*, supported by reciprocal PNS activity, dampens predatory appetite by appearing to be already dead before the kill. During this physiological shut-down, remaining energy is conserved for the possibility of a later escape.

1.2. Acute stress responses

The defense cascade illustrates the multifaceted nature of acute stress; “the acute stress response” is better conceptualized as “acute stress responses”. Further, the multidimensional nature of these stress responses is better conceived as response patterns, rather than a unidimensional response. Even the “stressor” itself is best viewed as dynamic, rather than as static.

In order to investigate these acute stress response patterns, we developed a novel virtual reality (VR) stressor to provide a dynamic sequence of threats. We then measured multiple dimensions of acute stress responses, including SNS, PNS, and emotional responses. Time series analysis helped identify when the VR stimulus effected a change in acute stress response patterns. The aim of the current study was to provide a proof of concept (Schmidt, 2006) for time series measurements of multiple dimensions of acute stress. In accordance with the defense cascade, we hypothesized that ANS coactivation and small increases in self-reported distress would present during initial threat detection. We further hypothesized that reciprocal sympathetic activation and increased distress would be seen during the increasing threat intensities suggested by the flight or fight stages. Out of ethical concerns, our stimulus did not target the extreme danger stages of fright, flag, and faint.

2. Materials and methods

2.1. Subjects

Virginia Tech undergraduate psychology students from were recruited using an electronic experiment management system. Two hundred fifty-two subjects completed an online screening to ensure they met inclusion criteria, which included being 18 years or older, no history of heart conditions, high blood pressure, neurological disorders or seizures, no medications affecting the cardiovascular system and no heavy smokers as defined by using tobacco products less than six days a week. One hundred sixty-six subjects met these inclusion criteria, of which 86 were invited to the lab for the study.

A final sample size of 85 was sought to obtain a target correlation of 0.3, with $\alpha = 0.05$ and $\beta = 0.20$ based on a power analysis from the G*Power applet (Faul et al., 2007). However, this number was not attained due to research restrictions imposed in response to the COVID-19 pandemic. Nineteen completed the study before COVID restrictions halted the research. The study was approved by the Virginia Tech Institutional Review Board, and all subjects gave informed consent for their participation. The sample consisted of 5 male and 14 female subjects, with a mean of 19.4 years (range: 18–22 years). Seventy-four percent were White, 11% Asian, 5% African-American, and 5% multi-racial. Five percent identified as Hispanic/Latino.

2.2. Stimulus

A novel virtual reality (VR) stimulus was developed for this study using Unity version 2019.1.4f1. The VR experience was downloaded to and presented on an Oculus Go, which provided 1280 × 1440 resolution, a 60 Hz refresh rate, and field of view specifications of 89° horizontal, 90° vertical, 127° diagonal. After initial download of the VR stimulus, the Oculus Go presented the experience without connection to a computer. The VR stimulus is available upon request.

The VR experience consisted of a 6.5-min baseline period, immediately followed by a 6.5-min stress stimulus period. Recovery began with removal of the VR headset and varied from 3.5 to 8 min, depending on how quickly subjects moved through the recovery procedures.

The VR experience began with subjects appearing to be seated in a hard-backed wooden chair in a basement-like room reminiscent of a physiological lab from the 1960s. Old-fashioned physiological equipment sat on countertops on both sides of the subject, and a medical cart sat at a one o'clock angle. Overhead was a movie projector and straight in front was a large movie screen, partially obscured by the medical cart. The baseline began with a 3-min tutorial video, shown within VR on the virtual movie projector. This video introduced the Subjective Units of Distress Scale (SUDS; Wolpe & Wolpe and Lazarus, 1966) and provided instructions for subjects to announce aloud their SUDS ratings throughout the remaining experience when prompted. Following the SUDS video, subjects were prompted on the virtual projection screen for their first SUDS rating while the virtual projection screen was otherwise black and silent for 10 s. The remaining VR experience included SUDS prompts at one-minute intervals. Next, the virtual projection screen presented a 3.5 min “vanilla baseline” video illustrating marine life, as suggested by Piferi et al. (2000), accompanied by relaxing music.

As the marine life video faded to black, the lights in the VR “room” flickered and went out, accompanied by a sudden loud electrical buzzing sound. This marked the end of the baseline period and the simultaneous beginning of the stimulus period. The VR space during this time remained dark to simulate the lights out in a room with only faint ambient lighting to keep the subjects present within the VR experience.

After 90 s of darkened room, a stimulus video began to play on the virtual projection screen. This five-minute video portrayed threatening images, accompanied by a cinematic sound score that included vague echoing voices and sound effects that increased in intensity and tempo. Just over two minutes into this video, a monster suddenly materialized directly in front of the subject, obscuring their view of the projector screen. This image remained in the virtual space for only one second before disappearing. The threat video continued for another three minutes until the same monster appears to climb out of the virtual projector screen, directly approaching and then lunging at the subject. This sequence is illustrated in Fig. 1.

2.3. Procedure

Subjects completed an online pre-screen of health history to assess for alignment with the inclusion criteria described above. Additional online questionnaires were also completed that assessed for previous experiences with trauma, worry, panic, anxiety, and mindfulness. Subjects who passed the pre-screen were invited to participate in the lab study and instructed to abstain from the following: alcohol for 12 h prior to the study, caffeine and other non-prescription drugs for 6 h, and eating and exercise for 2 h.

The day of the study, after subjects arrived and provided their informed consent, they completed a short survey assessing their compliance with the abstention requirements. All subjects reported compliance. They were then connected to the physiological equipment as described below.



Fig. 1. Monster approach and “attack”.

Once connected to the physiological equipment, subjects were given time to acclimate to the equipment while they completed an additional series of questionnaires to assess for phobias, anxieties, PTSD, and interoceptive awareness. These questionnaires took an average of 20 min to complete. Subjects were then briefly instructed on the use of the SUDS.

Next, the VR headset was placed on the subject and adjusted to ensure optimal viewing. When ready, the subjects began the 13-min baseline and stimulus VR experience previously described. Following the VR experience, the recovery period began with subjects being assisted in removing the headset and asked for another SUDS rating. After completing the interoceptive questionnaire a second time, a second recovery SUDS was given. Subjects were asked to give 0 to 10 ratings of how fearful the experience was for them overall and prompted to offer qualitative commentary:

“How difficult was it to stay engaged with this experience?”
 “If you had difficulty, can you explain why?”

“Do you have any other comments or suggestions about the experience you’d like to add?”

After a third and final recovery SUDS rating, the physiological equipment was removed, subjects debriefed, and released from the study.

2.4. Measures

Physiological measures included pre-ejection period (PEP) to index SNS responses and respiratory sinus arrhythmia (RSA) to index PNS responses. Raw physiological signals were gathered using the Biopac MP150 Data Acquisition System (Biopac Systems, Inc., Goleta, CA). Electrocardiography (ECG) was acquired at 2000 samples per second using the Biopac ECG100C and using an ECG Lead II configuration. Impedance cardiography (ICG) was collected at 2000 samples per second using the BioNomadix wireless Noninvasive Cardiac Output System (BN-NICO) and an additional channel was calculated in real-time of the first derivative (dZ/dt) of the raw ICG channel. Respiration was gathered using the Biopac RSP100C and the Biopac TSD-201 respiration belt.

After data collection, Biopac AcqKnowledge 4.4.3 software was used for data reduction and analysis. A bandpass filter from 0.5 Hz to 35 Hz was applied to the raw ECG signal following guidelines set forth in “Biopac Application Note 233: Heart Rate Variability” (2016). The resulting waveform was visually inspected and cleaned of aberrant cardiac cycles. ECG waves and complexes were then classified and a time series of the inter-beat interval (IBI) was created. A time series of RSA was calculated from the respiration and IBI signals, using the peak-to-trough method (Grossman & Grossman and Wientjes, 1986; Grossman et al., 1990). The ICG’s dZ/dt channel was classified using the R-to-C polynomial method outlined in Lozano et al. (2007). PEP was calculated from the classified dZ/dt and the cleaned ECG, following methodology from Sherwood et al. (1990). PEP was then visually inspected

and outlier values were removed. Finally, a moving average was applied to both PEP and RSA to smooth variability and to better visualize underlying data trends. A centered moving average was used, consisting of 37 cardiac cycles.

The SUDS measured emotional stress responses. Repeated SUDS requests were used over the course of the baseline, stimulus, and recovery to develop a moving picture of emotional responding. In all, 14 SUDS reports were gathered per subject, sampled at roughly one SUDS rating per minute.

3. Results

3.1. Aggregation analysis

Change in physiological and emotional variables were aggregated across subjects, between conditions. SUDS represented emotional response, RSA indexed PNS response, and PEP indexed SNS response. Throughout the analysis, PEP values and directionality were inverted to reflect its inverse relationship with SNS, and to better visualize SNS directionality.

In spite of the relatively small sample size, several results were robust enough to be statistically significant, including SUDS changes across both conditions and RSA change from stimulus to recovery. SUDS is reported as raw change because values of zeroes precluded the calculation of percentage changes. Change in PEP from baseline to stimulus approached, but did not reach significance. All changes were in the expected direction. The group-averaged responses are shown in Table 1.

3.2. Correlation analysis

Subject-specific data was analyzed with respect to correlations among the two physiological variables: PEP on reverse scale as an index of SNS and RSA as an index of PNS. The correlations between these SNS and PNS indices was dynamic across conditions. Further, average correlations for the entire experiment often varied significantly from condition average correlations. For example, one subject’s overall SNS-PNS Pearson’s correlation was $r(1233) = -0.18, p < 0.001$. By condition, these correlations varied markedly: Baseline: $r(444) = -0.23, p < 0.001$; Stimulus: $r(447) = 0.16, p < 0.001$; Recovery: r

Table 1
 Change in conditions across all subjects.

| | Average Change across All Participants (df = 18) | | | | | |
|------|--|-------|-------|----------------------|-------|-------|
| | Baseline-to-stimulus | | | Stimulus-to-recovery | | |
| | M | SD | p | M | SD | p |
| PEP | 1.1% | 2.9% | 0.062 | -1.6% | 5.3% | 0.129 |
| RSA | -1.4% | 31.4% | 0.141 | 38.1% | 63.8% | 0.005 |
| SUDS | 1.8 | 1.2 | 1.2 | -1.4 | 1.1 | 0.000 |

(336) = -0.26 , $p < 0.001$. Overall averages and even condition averages therefore only provided a partial understanding of the SNS-PNS interrelationship during the acute stressor.

3.3. Time series analysis

Results were expanded to be viewed as time series across all conditions. Where feasible, group-averaged time series were analyzed alongside individual subject time series. The study's smaller sample size allowed for more detailed analysis of each time series by subject.

3.3.1. Emotion

Subject ratings for SUDS were analyzed as both a group-averaged time series and on a subject-by-subject basis. These SUDS data indicate that the VR stimulus was effective at inducing a sense of threat for most subjects. Group mean SUDS rating for the baseline period was 0.5 out of 10, (SD = 0.92, range = 0 to 5), mean SUDS rating for the stimulus was 2.3 (SD = 1.72, range 0 to 8), and mean SUDS rating for recovery was 0.0 (SD = 1.38, range 0 to 6). Fig. 2 shows a time series of SUDS ratings for all subjects and for the mean SUDS rating.

Eight out of the 19 subjects indicated that they had difficulty staying engaged with the baseline SUDS and/or the marine life video, but none of the subjects reported difficulty staying engaged with the stimulus. Several other subjects indicated feeling worried that the marine life video would produce a fearful stimulus. The advertised title of the study was, "Virtual Reality: Physiology and Subjective Experience under Stress or Threat" and featured two images of frightened-looking people with VR headsets on. Qualitative color was added using the open-ended questions. A sample of subject responses include:

"Whoever made that should be checked on!"

"It was more disturbing than it was stressful."

"Do the eyes go away? I don't like the eyes."

When the lights suddenly flickered, one subject simply exclaimed, "Oh s***!"

3.3.2. Physiology

Physiological responses were analyzed on a subject-by-subject basis, which allowed for the examination of subject-specific trends in the time series. Because of the extreme lability of RSA and PEP, a centered moving average was constructed spanning 37 cardiac cycles to smooth the values and visualize underlying trends. PEP and RSA were originally plotted together using their raw scales. These graphs suggested a dynamic relationship between SNS and PNS. Some moments of the experience showed reciprocal SNS activation, while other moments showed SNS - PNS coactivation.

To examine these changing correlations, we made several calculations following the recommendations of [Berntson et al. \(2008\)](#), to better visualize autonomic space. First, we calculated Z-scores for both au-

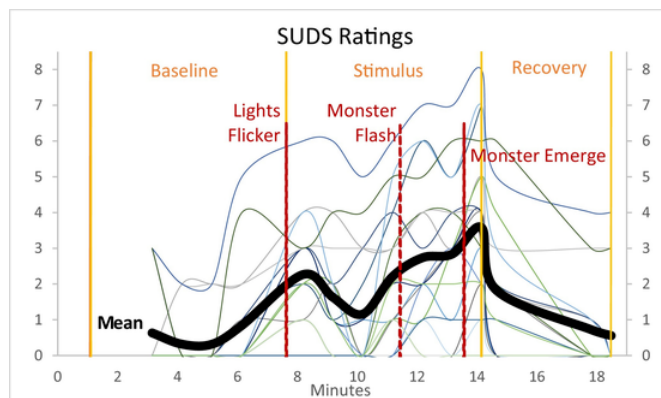


Fig. 2. SUDS ratings of all subjects (thin lines) and mean SUDS (bold line).

tonomic variables to allow PEP and RSA to be placed on the same scale. Next, we calculated Cardiac Autonomic Regulatory Capacity (CAR) by adding the Z-score for PEP to the Z-score for RSA. CAR reflects the combined autonomic "power" stemming from both SNS and PNS. We also examined Cardiac Autonomic Balance (CAB), which reflects relative activation of SNS and PNS. CAB can be calculated by subtracting a normalized SNS index from a normalized PNS index.

We developed two novel features for measuring autonomic space: (1) we combined CAB and CAR into one graph, and (2) we plotted this combination as a stacked time series graph to visualize both concepts simultaneously and dynamically over time. These time series graphs of autonomic space revealed that moments of greatest CAR involved strong autonomic coactivation. This coactivation and relatively high CAR were most prominent in response to the most potent stressors, including the startling flickering and buzzing of the lights that marked the beginning of the VR stimulus period.

3.3.3. Multidimensional responses

Combining physiological and emotional stress responses provided a holistic understanding of how these dimensions interact. We therefore developed a method for superimposing the SUDS emotional ratings onto the physiological metrics, in Fig. 3.

Lts Flkr = Lights flickered and buzzed loudly in the VR experience.
M Flash = VR monster momentarily flashed in front of the subject.
M Emg = VR monster emerged from the projector screen and approached the subject.

CAR can be visualized as the overall shape of the peaks and valleys in Fig. 3. CAB is visualized as the relative contribution of the PEP-colored time series to the RSA-colored series. The most potent aspects of the VR stimulus can be seen by combining the CAR time series with the SUDS ratings. For example, when the lights flickered and loudly buzzed in the VR space, a large increase in CAR resulted, supported by coactive increases in both SNS and PNS indices. The SUDS ratings provided self-report subjective color to these physiological data, jumping from 0 to 3. The ANS coactivation coupled with minor distress suggests the freeze response. A nearly identical physiological profile appeared just before the stimulus period, but the emotional profile did not match, with SUDS still zero.

After the subject's freeze response, the data do not suggest a progression to flight. Instead of the predicted SNS dominance, the data instead showed more pronounced PNS movements that appeared to be uncoupled from the SNS response. This primarily PNS response was combined

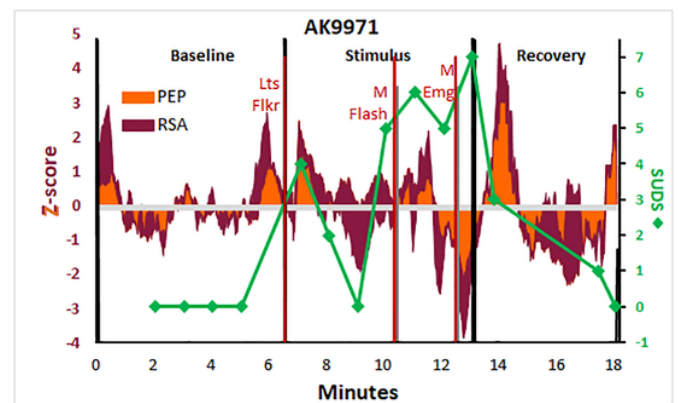


Fig. 3. Cardiac Autonomic Balance (CAB) and Cardiac Autonomic Regulatory Capacity (CAR) are shown with SNS (PEP Z-score: orange), PNS (RSA Z-score: maroon). These physiological stress response measures are combined with a measure of emotional stress response (SUDS: green) for subject "AK9971". (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with a drop in SUDS back to zero. This may be related to the VR experience during this subsequent 90 s; the virtual projector screen was dark and there were no auditory cues. The VR therefore may not have provided the evolutionarily-expected escalation of threat.

Several minutes later, a second multidimensional stress response pattern is seen in Fig. 3 just after the monster briefly flashed in the VR space (“M Flash”). Both CAR and SUDS jumped again in tandem. This simultaneous increase in both ANS coactivation and emotional responses suggest advancing in the defense cascade perhaps towards fright.

A third multidimensional stress response pattern emerged in Fig. 3 when SUDS reached its crescendo of 7, as the VR monster emerged from the virtual projection screen and lunged at the subject. During these final moments of the stimulus period, when SUDS was peaking, CAR moved in the opposite direction, reflecting pronounced ANS *coinhibition*. This sudden divergence of physiological variables (SNS and PNS via CAR) from the emotional variable is intriguing, perhaps indicative of a shut-down related stress response pattern, such as in flag.

4. Discussion

Our results provided support for the freeze acute stress response pattern predicted in the defense cascade, showing coactive SNS-PNS combined with increasing SUDS in response to a startling stimulus. We did not find a shift to reciprocal SNS activation predicted by the defense cascade’s flight and fight, although SUDS reports suggest that our VR stimulus may not have been sufficiently threatening to invoke these defensive stages. The most extreme threat invoked a robust surge in SUDS combined with considerable SNS-PNS coactivation at the end of the stimulus period. This specific acute stress response pattern has not been previously reported in the defense cascade literature.

Our proof of concept study used the defense cascade to model and predict acute stress response patterns. Our novel VR stress stimulus provided an advance in the ecological validity of an acute stressor, making it possible to engage multiple response patterns, as modeled in the defense cascade. We introduced a new approach to measuring acute stress response patterns that combines time series analysis with advances in measuring autonomic space. To our knowledge, this is the first study to analyze pre-ejection period, respiratory sinus arrhythmia, and cardiac autonomic space as time series. This analysis revealed marked variability in SNS and PNS activation that was masked when looking at condition averages. Combining these autonomic variables with SUDS provided a multidimensional map of acute stress response patterns by subject. Graphical markers of salient threat events during the stimulus period allowed us to identify when the intervention induced a change in acute stress defensive strategies.

These advances in mapping multidimensional stress response patterns introduce a new level of precision in stimulus-response measurements. Our time series analysis may hold promise for investigating mechanisms of change. Etiological studies examining disordered response patterns may benefit, as well as translational and clinical research investigating when therapy produces a response.

The multidimensional nature of this study helped to identify the study’s limitations. First, the VR experience may not have fully represented an evolutionary threat. The startling nature of the lights flickering appeared to successfully induce freeze and orienting in many participants, but it was not quickly followed by an increasing sense of danger. Further, the experience of threat appeared to ebb and flow for most participants, rather than escalating at the steadier rate of an actual life threat.

In addition, as previously mentioned, the advertised title of the study was “Virtual Reality: Physiology and Subjective Experience under Stress or Threat”. This may have predisposed the subjects to anticipate threat responses even before the VR experience provided sufficiently threatening stimuli. This bias could cause one of two effects:

some subjects may have shown heightened threat responses either via demand characteristics and/or emotional priming. Others may have experienced the reverse, finding that the actual experience did not live up to its “hype”. Another limitation is that the prompts for SUDS ratings may have detracted from the ecological validity of the VR experience. Finally, the relatively small sample size did not provide the statistical power to assess averages across groups.

Future directions examining acute stress response patterns could develop improved VR as a lab threat experience. The aim would be to more closely simulate an evolutionary threat to further explore the defense cascade empirically. Future studies might also provide an enhanced sampling rate for SUDS. Our experience suggests that SUDS could be polled every 30 s, rather 60 s, without significant interruption in the VR experience. The methodology outlined here could ultimately be used to track therapeutic interventions over the course of the entire session, perhaps pinpointing elements effecting change.

“The acute stress response” is better conceptualized as “acute stress responses”. This reconceptualization underscores the diversity of acute stress response patterns that are reflected in the “6 Fs” of the defense cascade. Acute stress research that focuses on markers of sympathetic activation captures only the flight and fight stress responses. Future research may target the hypervigilance of the freeze response, tonic immobility in the fright response, and the shutdown of the flag and faint response. These under-researched patterns demand a robust methodological repertoire to capture the dynamic, multidimensional, and sequential nature of acute stress response patterns. If acute stress responses are conceived as a roller coaster, time series analysis is best positioned to capture the human experience of stress.

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Declaration of competing interest

The authors have no conflict of interest, nor any financial or personal relationships that could inappropriately influence their work.

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