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Internal State-Dependent Conditioned Stimulus Delivery using Cardiovascular Telemetry in Mice

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ABSTRACT

To further understand mechanisms of neuropsychiatric disease(s) and their impact on physiological systems, improved pre-clinical models and innovative methodology are needed to assess the internal physiological state of the animal in real-time. To address this challenge we developed a customizable software-based program for Ponemah™ that takes into account the animal's diurnal and resting cardiovascular state in a home-cage environment. Using an integrated Pavlovian fear conditioning and cardiovascular telemetry approach in mice, we demonstrate for the first time a novel software application that can remotely trigger a conditioned stimulus (CS) (i.e., audible tone) based on the animal's instantaneous cardiovascular state while in its home-cage environment. This new cardiovascular behavioral tool using cardiovascular telemetry extends the ability to quantify integrated physiological correlates of learned fear and may aid in further understanding mechanisms related to enhanced cardiovascular and autonomic arousal in fear and anxiety-based disorders.

INTRODUCTION

As demand grows for more sophisticated approaches to quantify and analyze integrated multi-modal and internal state-dependent rodent behaviors, new approaches for detection and quantification are needed. Wireless telemetry in freely moving rodents is commonly used to quantify and monitor cardiovascular autonomic responses. This approach allows for *in vivo* monitoring of blood pressure, heart rate, electroencephalography, and nerve activity in conscious rodents. Integrating wireless telemetry approaches with animal behavioral measures (e.g., Pavlovian fear conditioning) provides a unique way to test the impact of pharmacological, behavioral (e.g., exposure therapy/extinction learning), or other non-invasive interventions (e.g., Transcranial Magnetic Stimulation) on cardiovascular autonomic responses to learned threats and emotional regulation.

Using a rodent model, our laboratory has begun to evaluate integrated cardioautonomic and behavioral measures (Swiercz et al., 2020); building upon the pioneering work of Joseph Ledoux, Oliver Stiedl, and others, (Burhans et al., 2010; Iwata & LeDoux, 1988; LeDoux et al., 1988; Schreurs et al., 2005; Stiedl et al., 2009; Stiedl & Spiess, 1997) demonstrating that heart rate, (Tovote et al., 2005) heart rate (HR) variability, (Stiedl et al., 2009) and blood pressure (Hsu et al., 2012) are reliable indicators of fear memory acquisition that can be used to distinguish between nonspecific and associative threat responses. For example, using an adapted conditioned cardiovascular testing paradigm, we recently showed that recall of a consolidated extinction memory reduces the conditioned cardiovascular response, which is influenced by context-dependent differences in blood pressure and HR sensitivity (Swiercz et al., 2018). Subsequent studies from our laboratory used the same conditioned cardiovascular testing paradigm to evaluate the role of an angiotensin receptor blocker, losartan, on conditioned cardiovascular threat responses independent of extinction learning (Swiercz et al., 2020). These studies provide an example of how using other physiological measures of inhibitory learning (conditioned cardiovascular responses) may help with quantifying the efficacy of extinction-based interventions and their physiological effects.

While associated fear-based cardiovascular responses have been shown to be important physiological correlates of the expression of learned fear and threat responses (Gaburro et al., 2011), there is a significant amount of experimental variance implicit in current animal models. Retrieval of the fear conditioned response is often confounded by extraneous environmental factors, which may affect physiological state such as proximity to other animals, foreign scents, noise, or by unrelated

animal behavior like preening or nest building (Janssen et al., 2000; Kurtz et al., 2005). If cardiovascular data is collected during a period of abnormal activity, the potential for variance is unavoidable, as even slight changes in activity can introduce blood pressure and heart rate variation before presentation of a conditioned stimulus (CS) (Stiedl & Spiess, 1997). Moreover, natural circadian fluctuation in blood pressure may significantly alter results if sampled at different time points within the animal's diurnal variation. Fear retrieval has also been shown to peak during the day and is highly dependent on light level (Chaudhury & Colwell, 2002). Additionally, blood pressure response to acute stress is differentially affected by circadian rhythms (Bernatova et al., 2002). These factors can contribute to a longstanding difficulty in establishing an accurate baseline of the internal state of the animals in a home-cage environment.

In order to eliminate some of the confounds which may result from cardiovascular changes related to stress or other environmental factors, we developed a program for remote application in Ponemah™ (version 6.3) from Data Sciences International (DSI), St. Paul, MN, United States. The software is built as a standalone CS delivery scheduling software which can use any connected computer audio outputs in which conditioned stimuli (i.e., audible tones) can be delivered outside of a dedicated testing chamber in a home-cage environment. This software also has the functionality to receive and store live physiological data from Ponemah™ (version 6.3), allowing it to deliver CS tones dependent on the internal physiological state of the animal. This scheduling system does not require an experimenter to be present and can be used with multiple mice and several speakers of any variety, each with the option of running synchronous or asynchronous schedules for fixed, random, or state-dependent intervals.

METHODS

Animals

All procedures were approved by the Institutional Animal Care and Use Committee at The George Washington University and were in compliance with National Institutes of Health guidelines. An adult male (3–4 months old) C57BL/6J mouse from Jackson Laboratory (Bar Harbor, ME) was used. The animal was individually housed in a temperature and humidity-controlled polyethylene cage on a 12 hour light/dark cycle (lights off at 7 pm) and supplied with food and water *ad libitum*.

Telemetry

HDX-11 transmitters Data Sciences International (DSI; St. Paul, MN) were subcutaneously implanted as previously described (Stiedl et al., 2004). A blood pressure catheter was placed into the left carotid artery and advanced to the aortic arch. Animals recovered for 10 days after surgery before beginning behavioral experiments. During telemetry recording, blood pressure signals were sampled at a rate of 500 Hz. Blood pressure, heart rate, and activity data were continuously collected during memory retrieval and memory testing. Blood pressure data was analyzed using Ponemah software version 6.3 (DSI).

Customized remote connection program integrated with Ponemah (version 6.3)

The telemetry system and data acquisition software used was Ponemah (version 6.3), which has the ability to send telemetry information over Transmission Control Protocol (TCP). The CS delivery program communicates with Ponemah via TCP sockets and sends data packets in real time from Ponemah containing live physiological information on blood pressure, heart rate, and oxygen saturation, among others. The software processes and stores this data in addition to delivering the conditioned stimuli using native USB audio output channels (Figure 1A).

Software parameters and hardware for experimental set-up and testing

The software was configured to deliver six 30-second tones (6 kHz) over a 24-hour period spaced evenly (three daytime and three nighttime). Minimum interval length between the tones was set to 120 minutes to prevent extinction. The software was programmed to deliver the audible tones only at a set resting level state of a mean arterial pressure (MAP) between 85 and 100 mmHg for at least 10 seconds. This was accomplished using TCP packets containing live cardiovascular data sent once per second.

A USB speaker (Powered Stereo Multimedia Speaker, HONKYOB) was wired inside the home-cage of the mouse and connected to the native USB input of the computer. The home-cage was also surrounded by dense polyester soundproofing acoustic panels (SoundAssured; West Lafayette, IN, United States) on five sides, with the front left open to allow in light for the day/night cycle (Figure 1A).

Pavlovian fear conditioning and conditioned cardiovascular reactivity

Auditory fear conditioning was performed as previously described (Stiedl et al., 2004; DSI, n.d.). Mice were individually habituated with the experimenter and conditioning chamber for 20- and 40-minute sessions on days one and two. Fear conditioning consisted of five trials of a conditioned tone (30 s, 6 kHz, 75 dB) co-terminating with an unconditioned stimulus (US) foot

shock (0.5 mA, 0.5 s,) spaced by 3 minute 30 second inter-trial intervals. During fear conditioning, freezing behavior was calculated automatically using Freeze Frame 3.2 (Actimetrics; Wilmette, IL). Conditioned cardiovascular reactivity was assessed 24 hours after fear conditioning in telemeter-equipped animals in their home-cage using the software parameters and experimental set-up as described above and as shown in experimental paradigm (Figure 1B).

RESULTS

Baseline cardiovascular and behavioral measures

Following telemetry surgical recovery, baseline cardiovascular parameters were collected. Mice exhibited normal basal 24 hour blood pressure, heart rate, and diurnal variation. As shown in Figure 1B, following Pavlovian fear conditioning, expected acquisition of learned fear as measured by increased percent freezing over time was displayed. We next assessed the conditioned cardiovascular response in the home-cage environment using our customized software program with multiple modifiable physiological parameters for remote triggering of a conditioned cardiovascular response (Figure 1A-B).

Software application and proof-of-principle methodology

As demonstrated in Figure 2, the software application was pre-programmed to deliver multiple retrieval cues (5x CS/30 s audible tone) set within a cardiovascular threshold state (MAP 85-100 mmHg) across day and night periods. CS onset was pre-programmed to be triggered at all five scheduled CS parameters only when the mouse has a MAP within a preset parameter range (85-100 mmHg). The baseline was defined as the average mean arterial pressure 10 seconds before each CS was presented. On average over the 30-second tone, the mouse demonstrated a distinct response from baseline with an average change in MAP of 6.0 mmHg (SD = 4.7) and heart rate increased from baseline during the tone period by an average of 100 bpm (SD = 29.7) (Figure 3A-B).

The first scheduled tone exhibited a mean negative

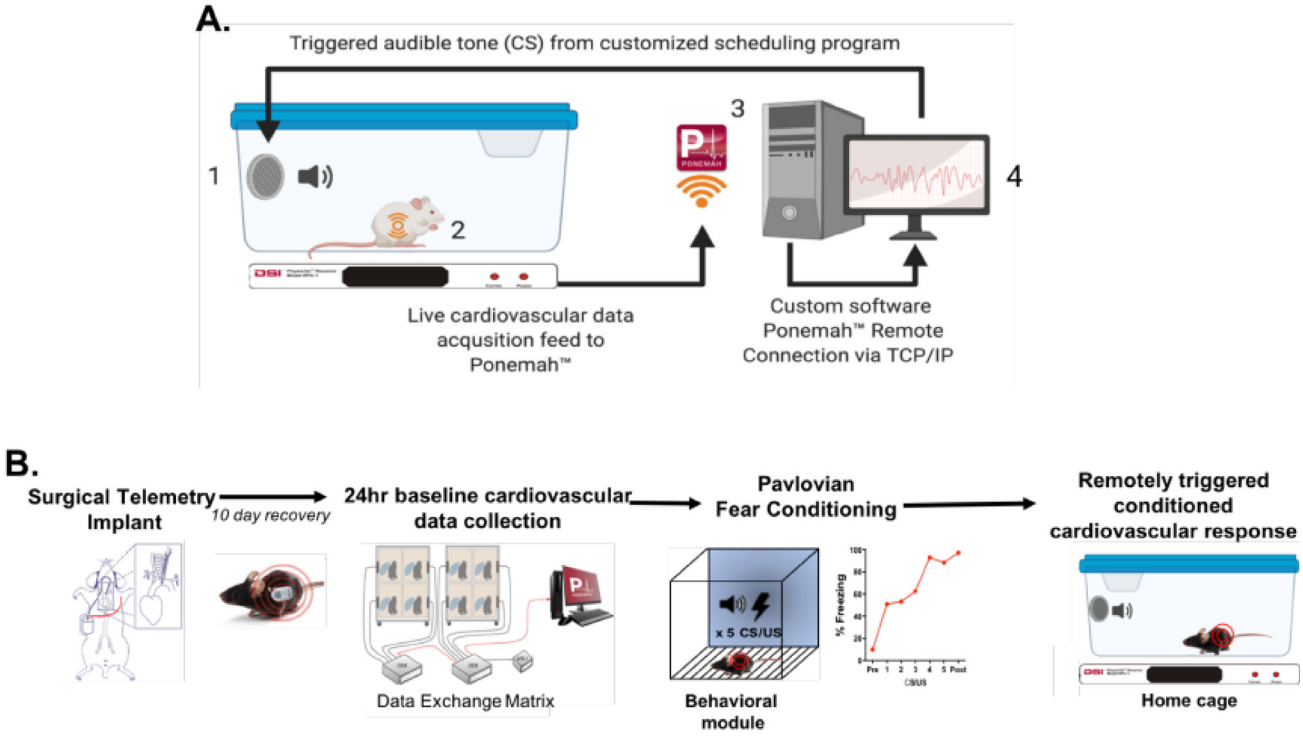


FIGURE 1. ***Integrated behavioral telemetry system and experimental paradigm***
A. *Modified home-cage and communication of audio speaker to TCP connection with Ponemah™. 1. Home-cage with USB speaker setup. 2. Mouse with implanted telemeter 3. Computer running Ponemah™ server. 4. Computer running scheduling software.*
B. *Experimental sequence.*

	Parameter	Unit	Setting
Audio	Tone frequency	hz	6000
	Tone length	seconds	30
Intervals	Start time	time	4:00 PM
	End time	time	4:00 PM
	Number of tones	integer	6
	Minimum interval length	minutes	120
	Fixed interval	boolean	FALSE
	Synchronize tones[1]	boolean	FALSE
Telemetry	MAP trigger range	mmHg	10
	Night time range shift[2]	mmHg	0
	MAP time in range[3]	seconds	10
	Server logging rate	seconds	1
	Wait for telemetry cue[4]	boolean	TRUE

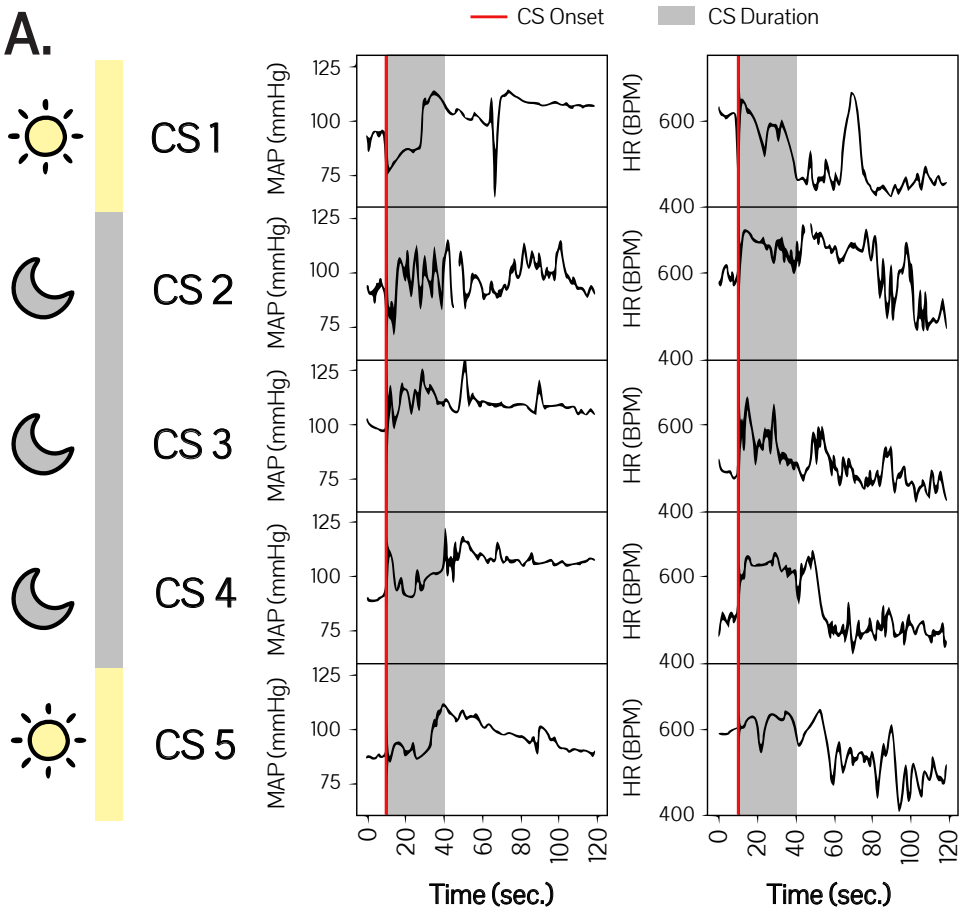
FIGURE 2. ***Customized software with modifiable physiological, time and interval dependent parameters***
1. For multiple speakers, whether the CS schedule is shared or randomized
2. Shifting the parameter range up for the night time to account for diurnal mouse behavior
3. Time MAP must be in parameter range before a CS can be presented
4. Enables state-dependent CS presentation

blood pressure response for the 30-second presentation of the CS. However, as shown in Figure 3A, a sharp incline in blood pressure was recorded during the last 10 seconds of the CS, followed by a sustained elevation in blood pressure persisting over a minute following the cessation of the tone. A similar delay in response by ~20 seconds was found for CS 5. Both of these tones were scheduled during the animal's resting period during the day, which may have affected the immediacy in response. Interestingly, for conditioned stimuli presented during the animal's active period (CS 2, 3, 4), the response was immediate. To further illustrate the software's threshold-dependent component and triggered CS onset and MAP response, Figure 4A-B provides a representative trace of a longer duration (> 10 minutes) highlighting this period. We also include a real-time recording of this software-initiated, CS-dependent MAP and HR response. Overall, this data demonstrates novel application of a programmable software that can be used to remotely deliver conditioned stimuli (i.e., audible tone) within a preset cardiovascular parameter range (e.g., MAP 85-100 mmHg) and takes into account a cardiovascular state-dependence for quantification of a conditioned cardiovascular response.

DISCUSSION

Using an integrated Pavlovian fear conditioning and cardiovascular telemetry approach in mice, we demonstrate for the first time a novel software application that can remotely trigger a CS based on the animal's instantaneous cardiovascular internal state while in its home-cage environment. This is the first study to our knowledge to demonstrate that a conditioned stimulus can be triggered based on the cardiovascular state of an animal. We show that this program accurately delivers a conditioned stimulus at a pre-scheduled time within a preset blood pressure parameter range. The data logging functionality of the program also revealed changes in mouse behavior related to its diurnal cycle and subsequent response to the CS. By taking into account environmental and cardiovascular states, the novel software application and experimental approach described here represent a new tool for quantifying the physiological effects of learned fear and/or time-dependent physiological responses to threat.

Adaptations to fear are most commonly assessed by changes in behavior, which are rapid, robust, and relatively easy to observe and quantify (Mahan & Ressler, 2012). Freezing behavior, for example, is the cessation of all movement aside from that caused by respiration.



B.

Day/Night	Time Scheduled	Time Delivered	MAP Baseline (mmHg)	Δ MAP (mmHg)	HR Baseline (BPM)	Δ HR
CS 1	18:00:00	18:00:40	92.9	-0.72	616	58
CS 2	21:40:00	21:48:50	92.8	3.13	585	137
CS 3	1:20:00	1:20:00	100.0	11.64	509	97
CS 4	5:00:00	5:05:00	89.0	7.87	496	89
CS 5	8:40:00	8:49:50	89.2	7.86	608	114

* The mouse never arrived in range at the time CS 6 was scheduled and the experiment ended before the CS could be delivered

FIGURE 3. ***Remotely scheduled experimental conditioned cue and cardiovascular response*** *CS 1-5 with corresponding CS onset (red line) and CS duration (grey shading) for both mean arterial pressure (MAP) and heart rate (HR) over 120 second period.*

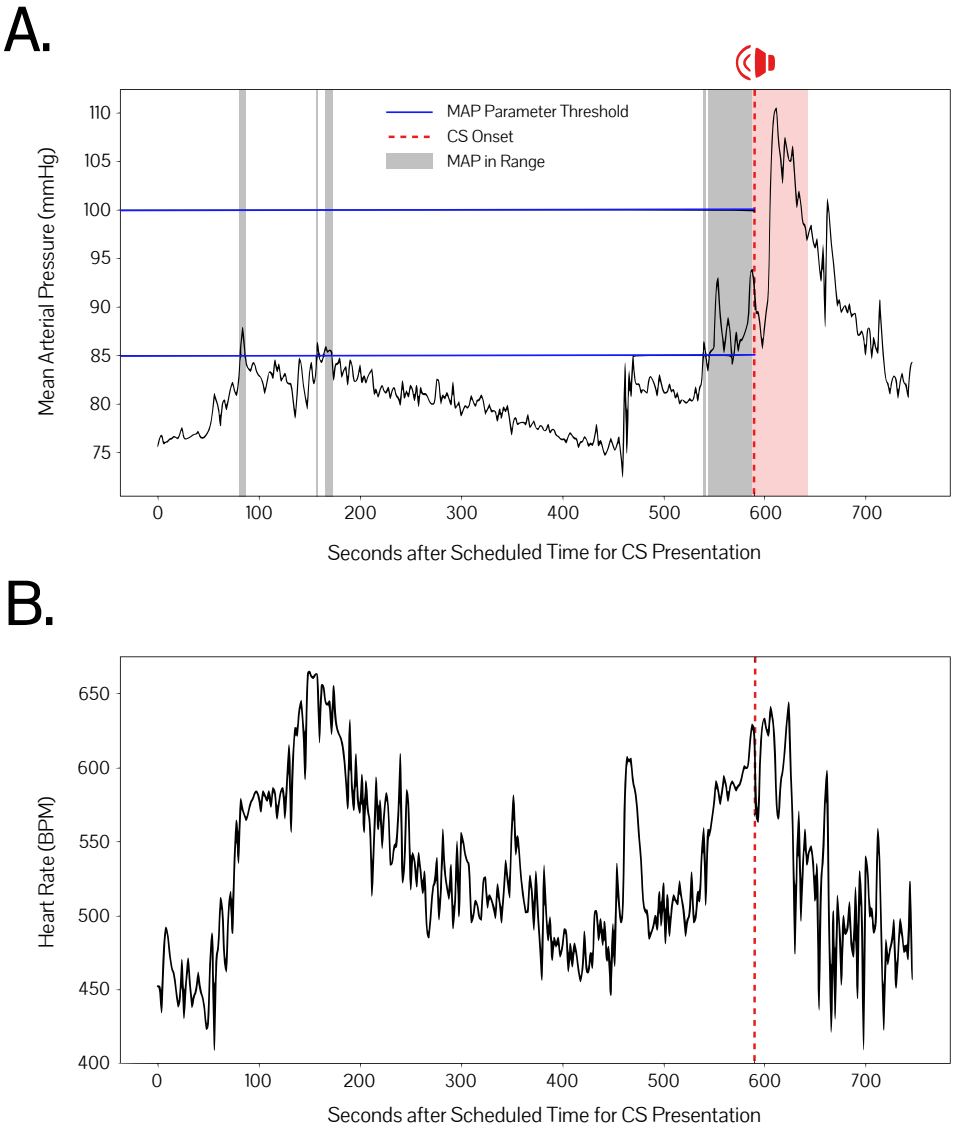


FIGURE 4. ***Example of triggered CS and conditioned cardiovascular MAP and HR tracing***
Pre-programmed MAP threshold (hashed blue line). MAP within pre-programmed range (grey shade) and triggered CS onset (red) with corresponding conditioned MAP/HR reactivity (red shade).

This behavior is used to operationally define fear in Pavlovian models of fear conditioning. Freezing is centrally controlled and represents a complex defensive response that is accompanied by significant physiological adjustments. Although they are easily observed and well-characterized, purely behavioral readouts of fear responses provide little information about the internal changes taking place within an organism. This presents a compelling need for additional measures that reliably indicate the emotional state of animals (Lee et al., 2001; Stiedl et al., 2004). One way to address this is by either directly or indirectly monitoring alterations in cardiovascular and autonomic activity, which reflect physiological adjustments to changes in emotional state. This software achieves this by using a parameter range to ensure physiological state is within acceptable limits any time a conditioned stimulus is presented.

Our customizable program works with Ponemah™ and possesses several advantages in that it receives physiological input (i.e., blood pressure) for use in a conditioning schedule, as demonstrated here. Moreover, due to the flexibility and pervasiveness of the JavaScript/TCP framework the software was built on, there are several ways it can be expanded for various other uses. The experiment conducted used mean arterial pressure to determine the parameter range in which the CS would be delivered, but because the data packet sent by Ponemah™ also contains information on heart rate, separate systolic and diastolic blood pressure values, oxygen saturation (SpO_2), and movement behavior, basic modification of the

software could enable CS delivery based on several other physiological measures, including multiple indices at once. Use of the HDX-11 transmitters has also been listed by Ponemah™ for use in other biopotential applications such as electroencephalography (EEG), use of which would allow real-time neurofeedback dependent only on packet rate (*DSI Guidelines for Biopotential Applications*, n.d.). Additionally, modification of the software could allow communication with other hardware beyond the built-in speaker array for delivery of other conditioned or unconditioned stimuli, such as a programmable drug delivery apparatus.

This study was conducted under several limitations. Use of one animal increases the potential for variability in the conditioned cardiovascular fear response, however the CS-dependent cardiovascular reactivity data here are consistent with our previous work and others (Swiercz, 2018). Moreover, the focus of this paper is on the novel methodology and application for cardiovascular behavioral studies. The experimental design included multiple CS delivered tones, which increases the possibility that the conditioned response of the mouse may undergo some level of extinction over time, especially considering this new methodology delivers the CS in the home-cage and only when MAP is constrained within a normalized range. This may increase association of the CS with an inherently lower stress physiological state. However, fear response was not found to show any signs of extinction over the course of the experiment. Data from the Ponemah™ telemetry system would also occasionally experience packet loss with unknown cause, sometimes for five or more minutes. This connection problem did not happen often and never when a CS was scheduled to be delivered and so was not considered detrimental to the data collection. If this issue were to occur during live analysis of blood pressures, the software automatically considers data not received to be out of parameter range. Finally, this software application also incurs the inherent possibility that a scheduled CS may not be delivered because of parameter range constraints, as demonstrated by the sixth scheduled CS during this proof-of-concept. This represents a useful aspect of the software, as identification that the baseline variability of the vital sign in question was beyond what could be useful to experimenters allowed the CS to be rejected automatically, increasing confidence in the resultant data.

There are many future applications for this software application approach to aid in further investigating the cardiovascular physiological responses to fear and threat stimuli. Although mean arterial blood pressure was used in the current study, basic modification of Ponemah™ software could enable CS delivery based on several other physiological measures (alone or simultaneous) as described above and including oxygen saturation (SpO_2), movement behavior, and heart rate. Furthermore, in response to threat or acute stress, as observed during the fight-or-flight response, animals exhibit a sharp rise in blood pressure and heart rate (Kayaba et al., 2003). This application enables such a response to be more acutely studied using set physiological parameter ranges. For example, one can measure the degree to which an out-of-range blood pressure or heart rate modifies fear response. Conversely, it could also allow for CS presentation during low blood pressure for extended periods when the animal is in its non-active, non-threat, resting or sleep state. Understanding the impact of conditioned threat stimuli on the cardiovascular system at different stages of physiological and non-physiological arousal and day/night variations could also be studied, which has translational applications for further understanding mechanisms related to physiological co-morbidities (e.g., cardiovascular disease and sleep disorders) associated with post-traumatic stress disorder (PTSD). Overall, these future applications are grounded in the basis for expanding the current understanding and quantification of monitoring real-time physiological effects of fear or threat learning (Seligowski et al., 2020) and the impact and role of cardiovascular arousal.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Mentor Details

Dr. Paul Marvar is an Assistant Professor at the GW School of Medicine & Health Sciences. His research is focused on understanding the link between stress and anxiety disorders (i.e., Posttraumatic Stress Disorder - PTSD) and increased cardiovascular disease (CVD) risk. The laboratory specializes in utilizing multi-disciplinary approaches that combine integrated physiological, molecular, analytical and behavioral neuroscience tools to examine neuroendocrine (i.e., renin angiotensin system), autonomic nervous system and inflammatory pathways in PTSD-related CVD. The basic science pre-clinical research funding is complemented by translational clinical research funding focused on identifying new therapeutic targets and opportunities for treatment for PTSD and co-morbid CVD.