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Use of electric field sensors for recording respiration, heart rate, and stereotyped motor behaviors in the rodent home cage

Donald J. Noble[a], Camden J. MacDowell[a], Michael L. McKinnon[a], Tamra I. Neblett[a], William N. Goolsby[b], Shawn Hochman[a,*]

[a] Department of Physiology, Emory University School of Medicine, 30322 Atlanta, GA, United States
[b] Department of Cell Biology, Emory University School of Medicine, 30322 Atlanta, GA, United States

HIGHLIGHTS

- A novel method to continuously monitor animal physiology and behavior is proposed.
- Plessey EPIC sensors offer a cheap, noninvasive alternative to traditional methods.
- Sensors accurately detect respiratory and heart rate when appropriately positioned.
- Sensors detect stereotyped rodent behavior and activity in a home cage environment.
- Widespread applicability for high-throughput home cage studies is envisioned.

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ABSTRACT

Background: Numerous environmental and genetic factors can contribute significantly to behavioral and cardiorespiratory variability observed experimentally. Affordable technologies that allow for noninvasive home cage capture of physio-behavioral variables should enhance understanding of inter-animal variability including after experimental interventions.
New method: We assessed whether EPIC electric field sensors (Plessey Semiconductors) embedded within or attached externally to a rodent's home cage could accurately record respiration, heart rate, and motor behaviors.
Comparison with existing methods: Current systems for quantification of behavioral variables require expensive specialty equipment, while measures of respiratory and heart rate are often provided by surgically implanted or chronically affixed devices.
Results: Sensors accurately encoded imposed sinusoidal changes in electric field tested at frequencies ranging from 0.5–100 Hz. Mini-metronome arm movements were easily detected, but response magnitude was highly distance dependent. Sensors accurately reported respiration during whole-body plethysmography. In anesthetized rodents, PVC tube-embedded sensors provided accurate mechanical detection of both respiratory and heart rate. Comparable success was seen in naturally behaving animals at rest or sleeping when sensors were attached externally. Video-verified motor behaviors (sniffing, grooming, chewing, and rearing) were detectable and largely separable by their characteristic voltage fluctuations. Larger movement-related events had comparably larger voltage dynamics that easily allowed for a broad approximation of overall motor activity. Spectrograms were used to quickly depict characteristic frequencies in long-lasting recordings, while filtering and thresholding software allowed for detection and quantification of movement-related physio-behavioral events.
Conclusions: EPIC electric field sensors provide a means for affordable non-contact home cage detection of physio-behavioral variables.

1. Introduction

Continuous capture of the physiological and behavioral variables of naturally behaving animals provides an important platform for understanding the origins of observed inter-individual vari-

* Corresponding author at: Department of Physiology, Emory University School of Medicine, 615 Michael Street, Suite 641, Atlanta, GA 30322, United States.
E-mail addresses: shochm2@emory.edu, shawn.hochman@gmail.com (S. Hochman).

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ability. Here, we briefly summarize current approaches to the measurement of these variables prior to the introduction of EPIC electric field sensors as a viable, affordable alternative.

1.1. Non-contact monitoring of cardiorespiratory variables

Respiratory and heart rate are reliable markers of autonomic drive, both known to be elevated during stress. Elevated respiratory rate is a key predictor of adverse clinical events (Cretikos et al., 2008; Fieselmann et al., 1993; Grossman, 1983) and elevated heart rate is an important indicator of subsequent mortality in cardiovascular disease (Fox et al., 2007; Jensen et al., 2012; Palatini, 2007; Woodward et al., 2014). To this end, there is demand for increasingly versatile and economical methods for tracking cardiorespiratory parameters. This demand has led to the development of novel technologies for monitoring rodent physiology (Hegoburu et al., 2011; Zehendner et al., 2013). Whole-body plethysmography (Aaron and Powell, 1993; Jacky, 1978; Wilkinson et al., 2010) and arterial transducer-coupled radiotelemetry (Huetteman and Bogie, 2009; Kuwahara, 2011) remain the "gold standards" for monitoring respiratory and cardiovascular variables (respiratory rate, heart rate, and blood pressure). However, these methodologies are expensive and have additional limitations. Plethysmography requires moving animals to airtight chamber environments that are separate from home cages, and cardiorespiratory monitoring requires use of expensive and surgically invasive approaches. These limitations restrain experimental design, increase cost, and decrease throughput.

1.2. Non-contact, continuous behavioral monitoring

Characterization of variability in motor behaviors also provides important predictive and diagnostic information. For example, analysis of grooming behavior may be able to discriminate between highly stereotyped chain movements and different levels of anxiety in the rat (Fentress, 1988; Kalueff and Tuohimaa, 2005). Healthy rodents spend a large portion of their waking time grooming, which aids in thermoregulation (Gaskill et al., 2013). Decreases in grooming are also particularly common in animal models of disease (Paumier et al., 2013; van Loo et al., 1997; Weary et al., 2009). In recent years there has been an increased focus on generalizing the behavioral changes that occur in a variety of disease states (Weary et al., 2009). For instance, mice with cancer (developing SL2 lymphoma) spend less time rearing as the disease progresses, reflecting common changes in activity and exploratory behaviors (van Loo et al., 1997). While several technologies have been developed for detection of animal behavior and its alteration in models of stress and disease (Richardson, 2015; Spruijt and DeVisser, 2006), these technologies are expensive and typically require additional equipment and concomitant video monitoring, making their use impractical for large-scale studies. Partly for this reason, and despite what is known about changes in behavior that accompany disease, behavioral phenotyping of rodent models of disease is relatively rare (Richardson, 2015). Most disease studies with behavioral phenotyping make use of existing technologies such as Phenotyper® (Noldus), LABORAS (Metris), or the Intellicage (NewBehavior) (de Visser et al., 2006; Krackow et al., 2010; Pham et al., 2009; Quinn et al., 2003; Van de Weerd et al., 2001). More recent studies have employed high-throughput systems such as the Behavioral Spectrometer and automated behavior recognition (ABV) (Brodkin et al., 2014; van Dam et al., 2013).

1.3. EPIC electric field sensors

Proposed here is the use of inexpensive EPIC electric field sensors as a multipurpose alternative to the aforementioned technologies for use in existing animal home cages. We sought to determine whether EPIC sensors accurately record respiration, heart rate, general activity levels, and stereotyped rodent behavior in a conventional home cage environment. To achieve this, we first compared sensor recordings to the conventional methodology for monitoring respiration (using whole body plethysmography) and heart rate (using ECG in anesthetized rodents). We then extended testing of sensor applications to a home cage environment to monitor stereotyped animal behaviors and activity levels, as well as the physiological response to experimental stressors.

We demonstrate that EPIC electric field sensors embedded within or attached to the exterior of a home cage environment provide a novel, affordable non-contact means to detect movement-related events including respiratory and heart rate as well as various motor behaviors.

2. Materials and methods

2.1. Experimental animals

Male Sprague-Dawley rats (300–550 g) and C57BL/6J mice (20–30 g) were housed in standard cages in a vivarium with a 12:12-h light-dark cycle and were fed *ad libitum* standard rodent diets. All experiments were approved by the Animal Care and Use Committee of Emory University. The experiments conformed to national standards for the care and use of experimental animals and the American Physiological Society's "Guiding Principles in the Care and Use of Animals."

2.2. Plessey Semiconductors EPIC sensors

Plessey Semiconductors manufacture a series of ultra-high impedance, dry-contact capacitive coupling electric field sensors. These high sensitivity sensors are advertised as capable of use for contact or non-contact based detection of proximity to sensor, movement or specific gestures, and electrocardiographic (ECG) activity in humans (http://www.plesseysemiconductors.com/epic-plessey-semiconductors.php). We tested Electric Potential Integrated Circuit (EPIC) PS25251 sensors. Each Plessey PS25251 sensor is 1 cm^2 in size with four pins: Vdd (the positive power supply = +5 V), Vss (the negative power supply = −5 V), Gnd (ground), and output. To interface with an A/D converter (Digidata 1321A: Axon Instruments, or PCI-6221 multifunction DAQ board: National Instruments), each of these pins was soldered to one of four pins on a 9-pin DB rectangular connector (DB-9). A dab of Epoxy was applied to each soldered joint on the sensors to provide additional strength and protection. Standard electrostatic discharge precautions were followed throughout the construction and handling process, which was an essential step. A Hammond 1598BBK enclosure housed the DC power supply which provided ± 5 V and ground to the Vdd, Vss, and Gnd DB-9 pins, respectively (Fig. 1). The output and Gnd pins of the DB-9 were soldered to a BNC adapter, which allowed them to be connected to the A/D converter. Total cost for two EPIC sensors was $43 (Mouser.com) and the remaining supplies totaled $32 (Digikey.com). The analog signal was digitized at unity gain at a sample rate of 1–10 kHz. The digitized data was continuously output to a Windows computer running pCLAMP data acquisition and analysis software (Molecular Devices) or LabVIEW (National Instruments). Sensors were either embedded in PVC tubing shelters or taped externally to the chamber, with their wires running along the length of the cage and connected to a power supply box. This box also adapted connections to BNC outputs for subsequent signal digitization and data collection as described above.