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Advancing Neuroscience through Wearable Devices

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Faster, more reliable, and comfortably wearable personal devices are producing data from biosensors on an unprecedented scale. Combined with context and analytics, these signals hold great promise to advance neuroscience via real-world data. Here, we discuss wearable technology broadly and provide specific examples of activity patterns from electrodermal sensors found during sleep, stress, and seizures.

Introduction

Wearable technology is booming, rapidly evolving from a niche market to an industry that is estimated to earn USD $54 billion by 2023 (2020 GlobalData Report, https://www.globaldata.com/wearable-tech-set-to-become-a-54bn-industry-by-2023/). Fast, low-power microprocessors laden with sensors enable long-term monitoring of personal biosignals. Continuous streams of quantitative data, often transmitted wirelessly and stored online, are available to consumers, clinicians, and researchers. Combined with advances in machine learning, a unique opportunity has emerged for neuroscience to expand the bridge between the lab and daily life.

Mobile devices and body-worn sensors monitor gait, body temperature, sleep-wake cycles, vocal quality, eye gaze, heart rate, blood oxygen levels, respiration rate, sweat gland activation, and more. Data from wearable devices can be combined with contextual data ranging from location and weather tracking to social media usage to ecological momentary assessments, which sample behaviors and experiences in real time. In human neuroscience, wearable versions of laboratory-based neuroimaging modalities, such as wearable electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS), are prompting ambulatory study designs that more closely mimic everyday experiences. Neuromodulation devices, including implantables, are also changing the landscape of ambulatory perturbation studies; however, this article will focus on the highly accessible, non-invasive measures available from easily body-worn devices.

The rapid growth in adoption of wearables is largely being driven by smartwatches (2020 GlobalData Report). To be truly wearable is to be comfortably wearable, and smartwatches offer convenient, socially acceptable form factors, easy-to-read displays, and a range of customizable features through apps and interconnected devices. For scientists, these small wearable sensors are relatively unobtrusive and accessible to a wide variety of experimental designs. Moreover, they can be used longitudinally, by many people concurrently, and by many of the vulnerable populations that are underrepresented in traditional neuroscience research. They are also orders of magnitude less expensive than most neuroimaging equipment.

In this NeuroView, we illustrate how one particular type of wearable data—electrodermal activity (EDA)—can provide insights into the brain and behavior, and we describe how patterns in this accessible signal are advancing neuroscience and therapeutic interventions.

Electrodermal Activity (EDA)

EDA is a broad term describing changes in the electrical properties of the skin. (Boucsein, 2012 is an excellent comprehensive resource.) Activation of the sympathetic nervous system (SNS) stimulates the sudomotor nerves, inducing sweat secretion. Although direct recordings of sympathetic nerve bundles can be acquired by inserting a thin microelectrode under the skin, comfortable longitudinal recordings call for non-invasive measures. By passing a small external current across two electrodes placed on the surface of the skin (see Figure 1A) and computing the electrical conductance (the reciprocal of resistance), increases in sympathetic nerve activity can be approximated even without observable sweating. Note that there are many other ways to measure electrodermal activity; however, the most thoroughly characterized and wearable form uses this approach. Researchers typically measure and report the skin conductance level (SCL), a slow-moving average of the EDA signal over time, and skin conductance responses (SCRs), representing more rapid fluctuations and phasic changes.

Because sudomotor nerves are innervated by only the sympathetic branch of the autonomic nervous system, EDA provides an ideal means to examine sympathetic control. Unlike pupil diameter or cardio-respiratory measures, EDA does not involve any known parasympathetic driver. Eccrine sweat glands are innervated by the SNS via cholinergic fibers. Notably, the postganglionic fibers for eccrine sweat glands release acetylcholine, differing from all other sympathetic postganglionic fibers that release norepinephrine. Increased EDA has been found to correlate with many kinds of affective and cognitive experiences, including feelings of stress, anxiety, and fear, as well as physical exertion, attention, and high cognitive load. Consequently, EDA provides an accessible, sensitive correlate of sympathetic drive and is well suited as an index of psychophysiological arousal in an awake, healthy person.

Distinguishing Sleep Stages Using a Wrist-Worn Sensor

Yet, EDA is more than a unidimensional measure of arousal. For example, EDA measured on the distal forearm is often high during sleep, when general arousal is low. EDA also exhibits time-varying patterns of behavior across multiple

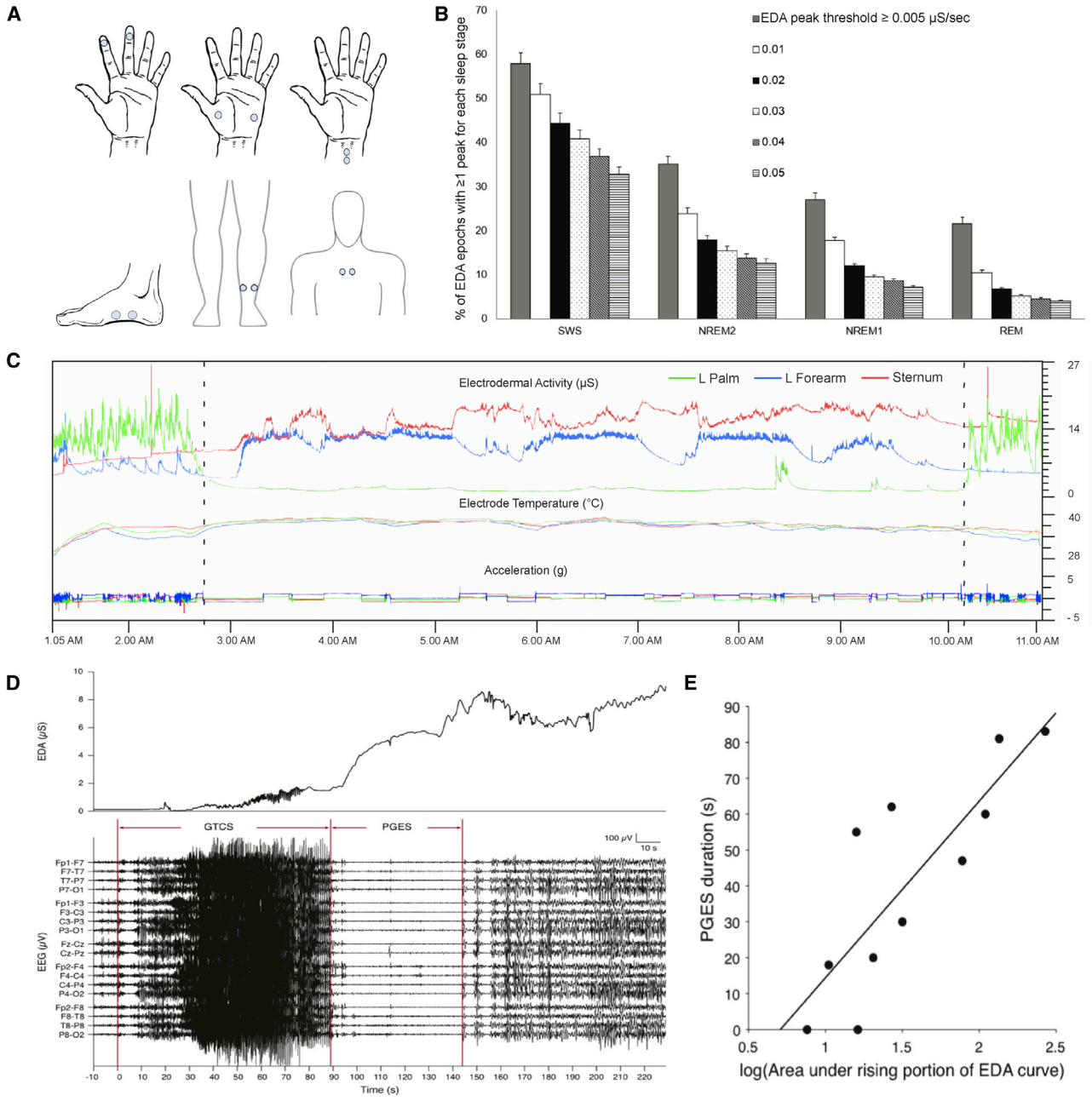

Figure 1. Neurological insights from electrodermal activity using wearable devices

(A) Examples of EDA electrode placements across the body (left to right): palmar surface of the distal phalanges of the index and middle fingers; thenar and hypothenar eminences of the palmar surface; volar surface of the distal forearm; plantar arch; posterior calf; sternum.

(B) The number of EDA peaks, measured from electrodes on the forearm, varies consistently across stages of sleep (Sano et al., 2014).

(C) EDA measured across several sites using synchronized wearable sensors during a night of sleep for a healthy adult. Dashed lines denote sleep onset and cessation. Electrode temperature and acceleration were collected from the same sensors and suggest that the observed EDA phenomena are not fully explained by thermoregulatory sweating or movement activity.

(D) Time-synchronized EDA (top) and EEG (bottom) from a single pediatric epilepsy patient. Both signals show three phases: a generalized tonic-clonic seizure (GTCS), followed by postictal generalized EEG suppression (PGES), followed by recovery of normal EEG behavior (Poh et al., 2012).

(E) Log-transformed area under the rising portion of the EDA response is correlated with the duration of PGES for a pediatric cohort of epilepsy patients ($r = 0.83$, $p = 0.002$; $n = 11$ GTCSs; Poh et al., 2012) and was replicated ($\beta = 0.67$, $p = 0.034$; $n = 30$ GTCSs; Sarkis et al., 2015).

measurement sites during sleep, reflecting more nuanced manifestations of arousal than a single dimension conveys.

As an illustrative example, Figure 1C shows EDA measured concurrently across several body locations using wearable sensors during a single night of sleep. Prior to sleep onset, the palmar EDA (measured from electrodes on the hypothenar eminence; see Figure 1A) exhibits both high SCL and SCRs. After sleep onset, the palmar signal decreases exponentially and remains low throughout the night. Conversely, the distal forearm (i.e., the "inner wrist") and sternum recordings show segments of elevated SCRs, followed by short periods of decay. These segments of rapid SCRs, called "sleep storms," usually start in the middle of non-REM (NREM) sleep and end at the transition to REM for palmar and distal forearm recordings (Boucsein, 2012; Sano et al., 2014).

Counts of SCR peaks during each 30 s epoch of sleep are regularly and reliably found to be highest during slow-wave sleep (SWS) and lowest during REM (Sano et al., 2014). Figure 1B displays summary statistics showing that, independent of peak-amplitude threshold, the percentage of 30 s sleep epochs containing EDA peaks within each sleep stage was greatest during SWS. This value monotonically decreased across stages of sleep from SWS to REM. In addition, this study and others have found significantly larger median EDA SCLs on the forearm during SWS than in other sleep stages, providing multiple robust properties that are informative to sleep stages using a wrist-worn sensor. While many wearable sleep trackers monitor sleep-wake cycles using accelerometer and gyroscope sensors, wearable EDA signals could expand studies of sleep phenomena in ecologically valid home environments, over long-term experiments, and with underrepresented participant groups.

Factors such as measurement location, sweat gland distribution, skin hydration, handedness, thermoregulation, or movement can influence EDA, but these can often be controlled or accounted for. For example, wearables that capture temperature and motion alongside skin conductance reveal that, while SCLs and storm patterns are usually more pronounced on the distal forearm than on palmar sites during sleep, the patterns are not simply attributable to movement or thermoregulatory sweating (Sano et al., 2014; see example in Figure 1C). Sweat-gland distribution, which is lower on the forearm and static in adulthood, does not explain the sleep storming patterns from the forearm, nor does skin hydration, which should be relatively uniform on short timescales across body sites.

These signals provide potential metrics for accessible, longitudinal sleep studies and are an example of how data acquired from wearable sensors could elicit new science questions. For instance, bilateral EDA (i.e., EDA acquired concurrently on both sides of the body) regularly exhibits asymmetric measurements during sleep (Boucsein, 2012). The dominant EDA signal oscillates repeatedly between being higher on the left and higher on the right. This switching does not appear to depend on participant or night of measurement, but the asymmetric signals have been observed to most frequently switch around the sleep-stage boundaries. Open questions include: what is driving the switching, and are the spatiotemporal EDA peak patterns associated with cross-hemispheric communication or neural network synchronization during sleep? Wearable devices synchronized with neuroimaging may provide clues, with wearables allowing for much broader sets of population data than traditional forms of neuroimaging.

Side-Specific EDA during Affective Experiences

While the neural mechanisms involved in mediating EDA are numerous, complex, and in need of more research, a seminal study by Mangina and Beuzeron-Mangina (1996) showed correlations between human limbic structure activation and specific, lateralized EDA responses. These researchers electrically stimulated eight limbic and four cortical regions of the human brain via intracerebral electrodes while simultaneously recording bilateral skin conductance in five adult epilepsy patients. EDA responses to direct stimulation of the eight limbic regions were strongly ipsilateral (i.e., same side of the body), with the left and right amygdalae producing the strongest EDA responses for their respective sides. Conversely, stimulation of the four cortical regions elicited small, nearly symmetric left and right EDA responses.

Based on these findings, it was hypothesized that EDA on the right forearm would be higher than on the left in a stress task involving mild social threat, which would be expected to more greatly activate the right amygdala. Adult participants (n = 25) were asked to count backward from 4,000 by sevens while an experimenter sat behind the participant listening and judging them, sounding a loud buzzer with every mistake and requiring that the participant correct mistakes out loud before continuing (Picard et al., 2016). Skin conductance was measured on bilateral distal forearms, and all but one participant reported being right-handed. Significantly higher median values of right-forearm SCLs were observed than median left-forearm SCLs, with 19 of the 25 participants having higher right- than left-forearm median SCLs across the experiment. This result supports the hypothesis for asymmetric EDA during certain affective experiences and suggests that EDA measured across body sites could provide more nuanced information than a single measurement location.

Similar work comparing bilateral measurements of both the lower and upper limbs has shown that the direction of asymmetry in the lower limbs can differ from the upper (Picard et al., 2016). Hence, a person exhibiting larger right than left palmar EDA may simultaneously show an opposite laterality (i.e., greater left than right EDA) measured near the calf. These results highlight the need and opportunity to examine the evolving spatiotemporal patterns of EDA within and across participants.

Seizure Characterization and Detection Using EDA

Dynamic and informative patterns of EDA can be observed via synchronous EEG and EDA recordings during seizure events—particularly generalized tonic-clonic seizures (GTCSs). A GTCS consists of unusual electrical activity that generalizes across all EEG channels, occurring with convulsive movements and loss of consciousness. Figure 1D shows concurrent EEG and EDA data for a patient having a GTCS. Notably, while the EEG signals are flattening during the postictal

generalized EEG suppression (PGES) phase, the EDA is surging.

This pattern of suppressed post-seizure EEG signals concurrent with large EDA responses has been repeatedly observed, characterized, and replicated in both pediatric and adult epilepsy patient groups (Poh et al., 2012; Sarkis et al., 2015; see Figure 1E). In these studies, measures of EDA were correlated with the duration of PGES and not associated with other aspects of the seizure, such as its duration or the duration of its motor-convulsive component. This correlation between a peripheral physiological measure and seizure-related EEG activity enables powerful new advances for real-world diagnostics and interventions.

As an example, generalized EEG suppression has been observed in *all* EEG-monitored cases of sudden unexpected death in epilepsy (SUDEP) (Ryvlin et al., 2013). SUDEP is the second leading cause of years of potential life lost out of all neurological disorders, and while its exact mechanisms are undergoing active research, SUDEP likelihood is highest with frequent GTCSs and with being alone at the time of a seizure. When observed in epilepsy monitoring units, the progression toward death has always started with generalized EEG suppression and apnea, prior to asystole.

By applying machine learning to wearable EDA and movement (accelerometry) data, it is now possible to detect convulsive seizures in real time with ~95% sensitivity and a false alarm rate of 0.2 events/day (Onorati et al., 2017). Importantly, these detections are rendered, on average, before the seizures have ended, enabling caregivers and friends to be alerted to attend the person seizing and to provide assistance if necessary. EDA is also being combined with other kinds of data to more specifically characterize seizure types beyond GTCS (e.g., Sarkis et al., 2015, among many others) and to learn more about the causes of seizures.

EDA Biofeedback Therapy

Research teams have deployed and tested biofeedback systems that teach patients to control their EDA in order to reduce seizure frequency. For example, Nagai et al. (2018) recruited 38 drug-resistant temporal lobe epilepsy patients into control (treatment as usual, n = 18) and biofeedback (n = 20) groups. During 12 in-lab 30-min sessions across 4 weeks, the biofeedback patients learned how to recognize and control their sympathetic arousal by modulating their skin conductance levels. During the biofeedback training, patients moved a digital animation forward by increasing their SCL and moved it backward by decreasing their SCL. After a month of training, a significant reduction in mean seizure frequency (43%) was obtained for the biofeedback group, while a mean seizure frequency *increase* (31%) was found in the control group.

Resting-state functional and structural MRI data were acquired pre- and post-therapy. Enhanced functional connectivity between the right amygdala and both the orbitofrontal cortex and frontal pole was found to linearly correlate with post-therapy seizure reduction, while no significant functional connectivity changes were found in the control group. These results add compelling data supporting the use of electrical changes in the skin not only to reflect but also to influence changes in the brain. EDA biofeedback is offered today as therapy in some research clinics to reduce seizure frequency in patients with drug-resistant epilepsy.

Conclusion and Outlook

Although the science of EDA has been studied since the 19th century, it is the advent of wearable technology almost 150 years later that enables a deep exploration of autonomic and affective processes in everyday life. These wearable devices have revealed distinct spatiotemporal patterns, asymmetric responses, and differences across body sites during neurophysiological situations such as stress, sleep, and seizures. Manipulation of EDA through biofeedback has been shown to potentially influence neural function. Together, these bursts of insights are sharpening EDA as a tool for human neuroscience, psychology, and medicine—and the promise extends to other wearables.

Importantly, for many vulnerable and underserved populations, including the very young, old, sick, or differently abled, typical neuroimaging techniques are not widely available, but wearable technology is. For example, preterm infants who have increased exposure to stressors in the neonatal intensive care unit (NICU) have shown altered brain microstructure and functional connectivity within the temporal lobes and decreased brain size in the frontal and parietal lobes, even after adjusting for confounders (Smith et al., 2011). Physiological synchrony between a mother and her child, as indexed by an increase in respiratory sinus arrhythmia (RSA) and a decrease in skin conductance levels, has been shown to calm the child (Ham and Tronick, 2009). Thus, wearable sensors could potentially monitor and prompt caregivers to physiologically synchronize with the baby—not only calming the child but also possibly improving the child's brain development.

Similarly, data from wearable devices could provide personalized insights that influence drug delivery and therapeutics. Forty years ago, it was widely believed that a hyperactive child was over-aroused. However, the SCLs of children with attention-deficit/hyperactivity disorder (ADHD) were often found to be *lower* than those of matched normal controls. Stimulant medication, or even optimal reinforcement or physical activity, often upregulated or normalized the general state of arousal for ADHD children, improving cognition and attention (Bellato et al., 2020). While individuals and their physiological responses are heterogeneous, wearable devices offer the opportunity to personalize a treatment, indicating real-time arousal-boosting or arousal-diminishing activities for an individual and targeting specific attentional and cognitive outcomes. Researchers are actively searching for similar wearable-based personalized biomarkers within heterogeneous populations such as those with autism spectrum disorder (ASD), depression, and anxiety.

Even with the potential for profound new insights, wearable technology is not without its limits. Many of the wearables on the market today have their own proprietary algorithms and no access to the raw data. Without the original data, claims cannot be validated, research questions are limited to the available aggregate data, and intriguing new behavior is difficult to discern from artifacts. Likewise, it is the combination of *both* the raw data and the analytics of these data that lead to breakthroughs, requiring interdisciplinary pursuits between neuroscientists,

clinicians, engineers, and computer scientists. Issues surrounding the privacy, transparency, and ethical use of these data are also still unresolved. Moreover, despite decreasing costs, these devices are added expenses—in both time and money—for labs and clinics.

Yet, wearable technology is already changing health care and consumer electronics. Its integration into research toolkits has the potential to transform behavioral neuroscience as well. By combining modern neuroimaging techniques with concurrent peripheral physiological measurements—and then extending those measurements to real-world long-term wearable devices—we have the ability to create a pipeline of science from the lab to everyday life. This effective translation could expand basic science understandings of the brain and behavior; lead to new therapies, drug delivery, and personalized medicine; and help improve well-being for all.

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