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Tonic Electrodermal Activity is a Robust Marker of Psychological and Physiological Changes during Induction of Anesthesia

Bryan Tseng†, *Student Member, IEEE*, Sandya Subramanian†, *Member, IEEE,* Riccardo Barbieri, *Senior Member, IEEE*, and Emery N. Brown, *Fellow, IEEE*

***Abstract*— Electrodermal activity (EDA), which tracks sweat gland activity as a proxy for sympathetic activation, has the potential to be a biomarker of physiological and psychological changes in the clinic. To show this, in this study, we demonstrate that the tonic component of EDA responds consistently and robustly during induction of anesthesia in the operating room in 8 subjects during surgery. This response is seen bilaterally. The response shows a significant increase in EDA in anticipation of induction and then a gradual decrease in response to the administration of medication, which agrees with both the expected psychological effects of stress and anxiety and the physiological effects of anesthetic medication on sweat glands. The results also show a slightly faster response to drug in the arm directly receiving the medication intravenously compared to the opposite, though the magnitude of the effect evens out over time.**

***Clinical Relevance*— EDA can serve as a robust non-invasive biomarker in the clinic to track both psychologically and physiologically induced autonomic changes.**

I. Introduction

Electrodermal activity (EDA), which tracks sympathetically modulated sweat gland responses, has huge potential to be a non-invasive clinical marker of sympathetic activity. [1] This can be highly relevant in cases like pain, stress, or especially during surgery, when patients are not conscious to express how they are feeling themselves. EDA has primarily been used in ambulatory settings, for neuromarketing purposes. [1] However, it is unclear if it can be used as a robust marker of physiological response in a clinical setting.

EDA tracks the build-up of sweat in sweat glands due to firing of the sympathetic nerve that innervates it. As sweat builds up, it changes the electrical conductance of the skin. When it fills the entire length of a sweat gland and reaches the skin surface, it causes a transient burst or increase in conductance measurable as a galvanic skin response or 'pulse' in EDA activity [1]. The gradual change in conductance due to changing baseline volume of sweat in sweat glands is called the tonic component of EDA (tonic EDA), while the faster transient pulses due to filled sweat glands at the skin surface is called phasic component of EDA (phasic EDA).

We have previously shown that phasic EDA has a specific statistical structure that mirrors the physiology of sweat glands [2-3]. We have also developed pre-processing frameworks and instantaneous autonomic markers for EDA based on this statistical structure [4-7]. Finally, we have shown that instantaneous EDA markers, along with other autonomic markers like HRV, can define an autonomic state that tracks with behavioral changes like loss of consciousness in anesthesia. [7-10] In this study, we take this one step further and test whether tonic EDA, which is more visible in real-time, can serve as a robust and instantaneous biomarker of significant psychological and physiological effects on the autonomic nervous system. This would help validate its potential utility in the clinic.

To do this, we examine EDA from 8 subjects during a critical time point of surgery, the induction of anesthesia using propofol, remifentanil, and muscle relaxant. This time period encompasses both psychological effects such as nervousness and anxiety leading up to administration of medication, and physiological effects including the sensation of propofol 'burning' in veins and the actual effects of the drugs themselves.

All of these have known effects on the autonomic nervous system. For example, we know that nervousness, anxiety, pain, or stress increase sympathetic activity, while anesthetic mechanisms dry out sweat glands and decrease sweat gland activity [11]. We show that these effects can be seen robustly in real-time in EDA.

We also show that these effects can be seen bilaterally, regardless of in which arm the subject has the IV in which drugs are being administered. However, we show that there is a tendency towards a time delay between the speed of the drug effects between the arm with the IV and the contralateral arm. The remainder of this paper is organized as follows. In Methods, we describe the dataset used and the analyses performed. In Results and Discussion, we lay out the results and their implications for the potential future use of EDA in the clinic.

†Authors contributed equally

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BT is with the Picower Institute for Learning and Memory, Cambridge, MA 02139 USA (phone: 857-337-4445; e-mail: bryan@ neurostat.mit.edu).

SS is with the Stanford University Department of Bioengineering and the Stanford Division of Pain Medicine, Stanford, CA 94304 USA (phone: 616-406-6087; e-mail: sandyas@stanford.edu).

RB is with the Department of Electronics, Informatics and Engineering, Politecnico di Milano, Milano, Italy. He is also with MGH (barbieri@neurostat.mit.edu).

ENB is with the MGH Department of Anesthesia, Critical Care, and Pain Medicine, MIT Department of Brain and Cognitive Sciences, MIT Institute for Medical Engineering and Science, and Picower Institute for Learning and Memory, Cambridge, MA. (enb@neurostat.mit.edu).

II. Methods

A. Data

In this study, we use EDA data recorded bilaterally from 8 subjects (6 female, 2 male, ages 39-70), collected under protocol approved by the Massachusetts General Hospital (MGH) Human Research Committee. All subjects were undergoing laparoscopic urologic or gynecologic surgery at MGH. The EDA data were recorded from two digits of both arms of each subject at 256 Hz using the Thought Technology Neurofeedback System [12], starting from before induction of anesthesia throughout surgery. We also extracted the anesthesiologists' annotations into the electronic medical record for time annotations. All data were analyzed using Matlab 2020b.

B. Preprocessing and Normalization

For each subject, the artifacts in the EDA data were identified and removed using the methodology described in [4]. Then, the EDA was separated into tonic and phasic components as described in [5]. For this study, we focused only on tonic EDA during the period from before induction to about 20 minutes after. For the remainder of this paper, these are the only segments of EDA included in further analyses.

To be able to compare subjects to each other, we normalized the x and y axes as follows. For each subject, we normalized the EDA data from each arm between 0 and 1 by dividing by the maximum EDA value for that arm. Then, we identified the point in time at which the EDA from the IV-arm began to rise by locating the first local minimum to the left of the peak EDA value of the IV-arm. For each subject, we shifted the x-axis to make that time point 0. While we did have labeled annotations for the time of induction, these annotations were highly noisy since they are entered manually by the anesthesiologist typically several minutes after induction based on memory. Therefore, we chose not to rely on them for time-locking purposes.

We analyzed not only the individual subject trajectories for the 8 subjects, but also the averaged trajectory by IV and non-IV arm with 95% confidence bounds based on standard error. We also computed the difference between both arms.

III. Results

An example of the raw EDA data from one subject during the period of interest is shown in Figure 1. Figure 2 shows the normalized EDA responses to induction by arm and subject with annotated induction marked. A margin of error around induction with 95% confidence bounds is shown to emphasize that the annotations of induction are inexact. Table 1 summarizes the important timepoints in the EDA response of each subject. Finally, Figure 3 shows the average EDA response across all subjects by arm and the difference between the two with 95% confidence bounds. The average of annotated induction time is noted as well.

Based on Figs 1-3, the EDA (both raw and tonic) seems to have a strong visible response around induction consisting of a significant and rapid increase, then followed by a gradual decrease. While there is variability in the precise amplitude and shape of this pattern across subjects (Fig. 2), the overall pattern is highly consistent. This is also supported by Table 1, which shows that the duration of the rising or falling phase of EDA response is variable across subjects. A comparison between Figs 1 and 2 show that analyzing tonic rather than raw EDA does not change the baseline shape of the EDA, but rather removes the higher frequency phasic EDA information while leaving the lower frequency baseline evolution over time.

Based on Fig. 3, the annotation of induction, while noisy, tends to occur right around the beginning of the fall-off in the EDA. It is also worthy of note the confidence bounds of the difference between IV and non-IV arms always include zero after the start of the EDA increase, indicating that the notable changes around induction are observable bilaterally, regardless of which arm receives the drugs. (The period of time before the increase in EDA is highly noisy because the patient is chatting, moving, being positioned, etc.) While the confidence bounds of the difference always include zero, they come the closest to excluding zero around 6.35 minutes after the EDA rise, which is 1.85 minutes after the average time of induction (Fig. 3). This is right around when the fall-off in EDA begins.

TABLE I. Important Timepoints (in minutes) during EDA Response to Induction by Subject

	IV arm					Non-IV arm				
Subj[a]	Time of Rise[b]	Time of Peak	Time of Fall-off[c]	Duration of Rise	Duration of Fall-off	Time of Rise[b]	Time of Peak	Time of Fall-off[c]	Duration of Rise	Duration of Fall-off
1	0	2.90	7.12	2.90	4.22	-0.77	3.58	4.58	4.35	1.00
2	0	0.95	8.19	0.95	7.24	-1.02	5.71	11.22	6.73	5.51
3	0	2.10	6.73	2.10	4.63	0.22	1.58	5.39	1.36	3.81
4	0	3.85	8.72	3.85	4.87	0.08	3.66	8.27	3.58	4.61
5	0	3.61	11.99	3.61	8.38	0.57	2.75	10.23	2.18	7.48
6	0	5.85	0.70	5.85	-5.15	3.99	6.41	18.18	2.42	11.77
7	0	1.65	19.09	1.65	17.44	0.95	8.39	22.90	7.44	14.51
8	0	7.22	15.35	7.22	8.13	1.98	3.47	18.58	1.49	15.11
Avg.[d]	0	3.52	9.74	3.52	6.22	0.75	4.44	12.42	3.69	7.98
Stdev.[d]	0	2.11	5.57	2.11	5.96	1.50	2.19	5.93	2.65	6.32

a. Subj. refers to subject
b. Rise refers to the onset of the rise of EDA
c. Fall-off refers to the end of the rapid decrease in EDA, when it plateaus
d. Avg refers to average, stdev. refers to standard deviation

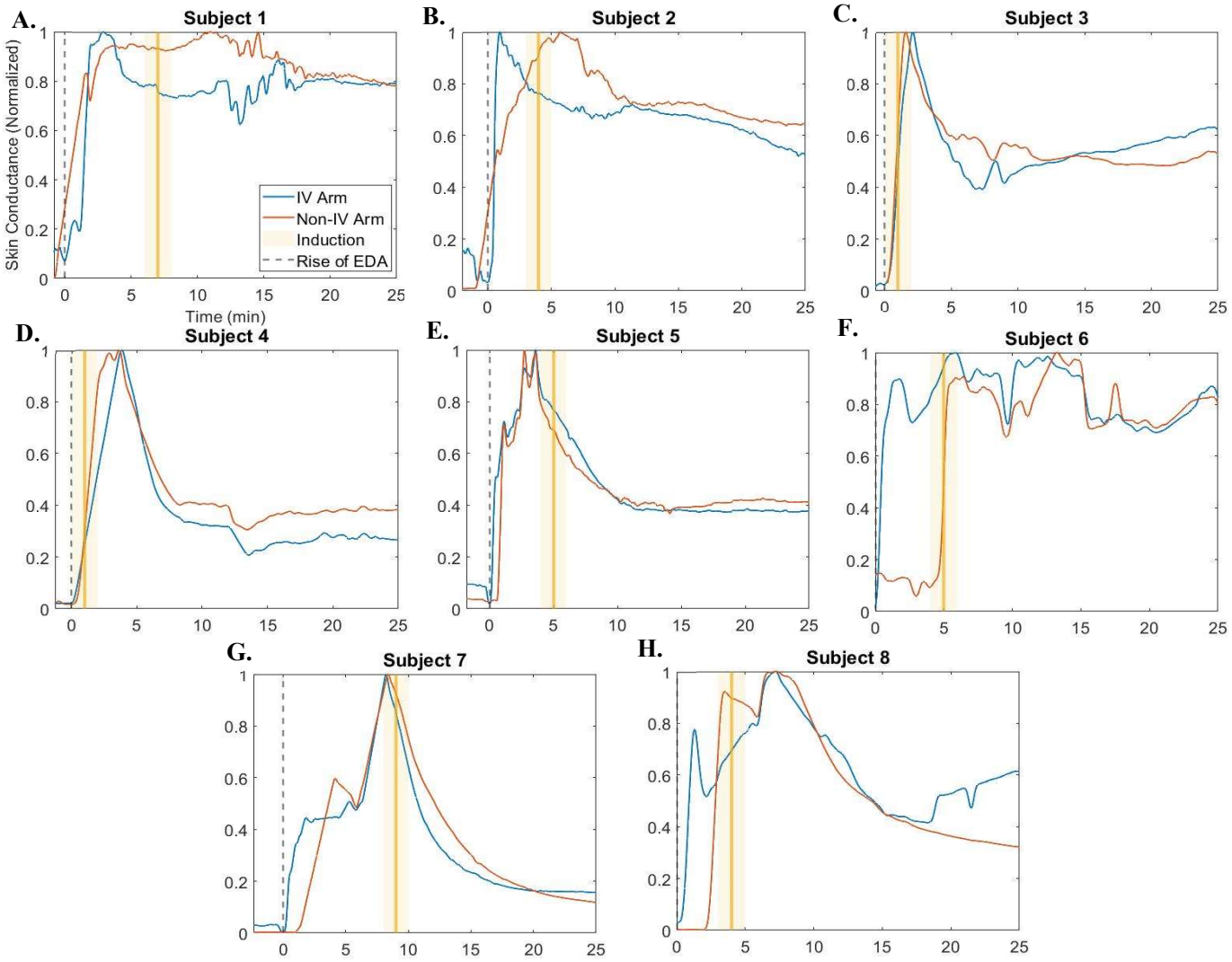

Figure 2. Tonic EDA data around induction for all 8 subjects. Time axis is locked at zero for the rise in EDA from the IV-arm.

IV. Discussion

In this study, we analyzed bilateral EDA data from 8 subjects as they were given drugs to induce anesthesia at the start of surgery. We specifically examined the tonic component of EDA, which reflects baseline filling of sweat glands, and showed that across the 8 subjects, there was a robust response of initial increase and then exponential-like fall-off around induction. Specifically, the annotated marking of induction of anesthesia was typically around the start of the fall-off. In addition, this effect could be seen bilaterally, though there was a slight tendency for the fall-off to be steeper in the arm into which the drug was administered compared to the opposite arm.

The robustness of the response across subjects indicates strong psychological and physiological factors at play. The fall-off in the EDA is an expected response to the administration of most anesthetics, especially propofol, which has been shown to reduce spontaneous sweat production and 'dry out' sweat glands.

We hypothesize that the strong increase in tonic EDA prior to this fall-off reflects a combination of psychological and physiological factors, including acute nervousness and anxiety as the anesthesiologist administers drugs standing at the side of the operating table, as well as the pain response to the known feeling of "burning" in the veins caused by propofol administration. These hypotheses are corroborated by our observations of the patient in the operating room when collecting the data.

The average timing of the annotation for induction, right around the start of the EDA fall-off, supports this hypothesis as well. The patient experiences the most nervousness and anxiety in anticipation of anesthesia just before the actual administration of the drug when the anesthesiologist is standing at the side of the operating table with syringes full of medication. This is reflected in the sharp rise in EDA just before marked induction on average, sometimes increasing further with the sensation of 'burning' in the veins as the drug

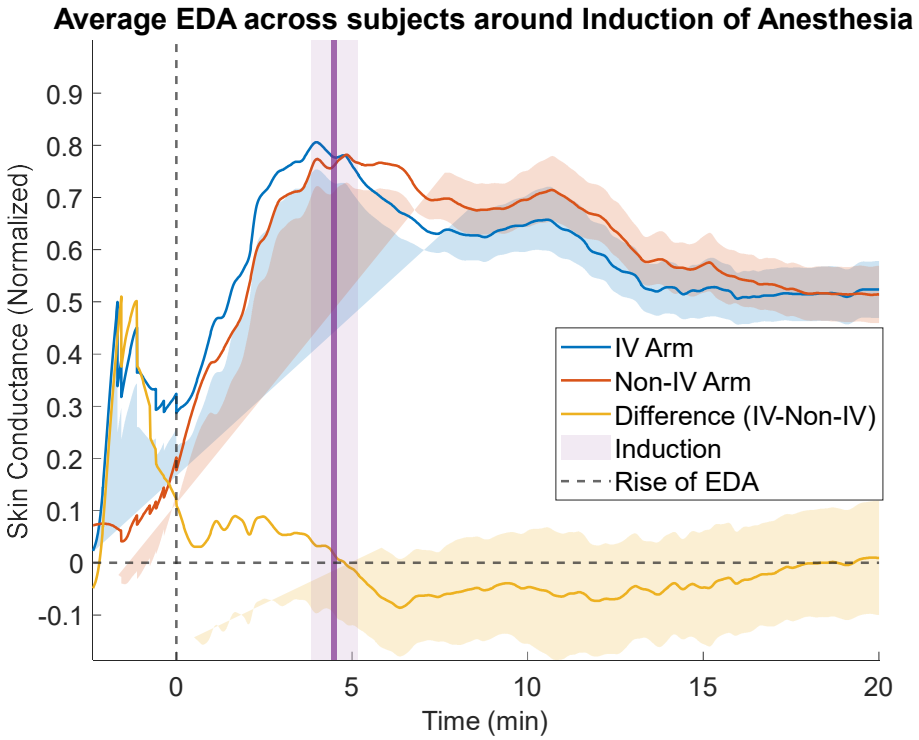

Figure 3. Average tonic EDA and bilateral difference across subjects around Induction of Anesthesia. Confidence bounds ($\alpha = 0.05$) are marked by the shaded regions for both average EDA and induction time.

goes in. Then within a minute or so of drug administration through the IV, the EDA starts to fall, which reflects the strong effects of the drug.

These results demonstrate the potential value of EDA as a non-invasive biomarker of both psychological and physiological stressors in the clinic. Specifically, in the case of the operating room, several of the drugs administered during anesthesia are intended specifically to alter hemodynamics (e.g. pressors, beta-blockers, etc.), rendering autonomic markers such as heart rate or heart rate variability noisy and possibly incomplete measures of other stressors as they occur. In our future work, we will validate these results with larger cohorts and combine our phasic EDA measures with tonic EDA signatures for a more complete autonomic picture.

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