On-body Sensing of Cocaine Craving, Euphoria and Drug-Seeking Behavior using Cardiac and Respiratory Signals

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Drug addiction is a chronic brain-based disorder that affects a person's behavior and leads to an inability to control drug usage. Ubiquitous physiological sensing technologies to detect illicit drug use have been well studied and understood for different types of drugs. However, we currently lack the ability to continuously and passively measure the user state in ways that might shed light on the complex relationships between cocaine-induced subjective states (e.g., craving and euphoria) and compulsive drug-seeking behavior. More specifically, the applicability of wearable sensors to detect drug-related states is underexplored. In the current work, we take an initial step in the modeling of cocaine craving, euphoria and drug-seeking behavior using electrocardiographic (ECG) and respiratory signals unobtrusively collected from a wearable chest band. Ten experienced cocaine users were studied using a human laboratory paradigm of self-regulated (i.e., "binge") cocaine administration, during which self-reported visual analog scale (VAS) ratings of cocaine-induced subjective effects (i.e., craving and euphoria) and behavioral measures of drug-seeking behavior (i.e., button clicks for drug infusions) are collected. Our results are encouraging and show that self-reported VAS Craving scores are predicted with a normalized root-mean-squared error (NRMSE) of 17.6% and a Pearson correlation coefficient of 0.49. Similarly, for VAS Euphoria prediction, an NRMSE of 16.7% and a Pearson correlation coefficient of 0.73 were achieved. We further analyze the relative importance of different morphology-related ECG and respiratory features for craving and euphoria prediction. A demographic factor analysis reveals how one single factor (i.e., average dollar ($) per cocaine use) can help to further boost the performance of our craving and euphoria models. Lastly, we model drug-seeking behavior using cardiac and respiratory signals. Specifically, we demonstrate that the latter signals can predict participant button clicks with an F1 score of 0.80 and estimate different levels of click density with a correlation coefficient of 0.85 and an NRMSE of 17.9%.

CCS Concepts: • **Applied computing → Life and medical sciences**;

Additional Key Words and Phrases: Craving, Euphoria, Drug-seeking behavior, On-body sensing, Cardiac, and Respiratory signal

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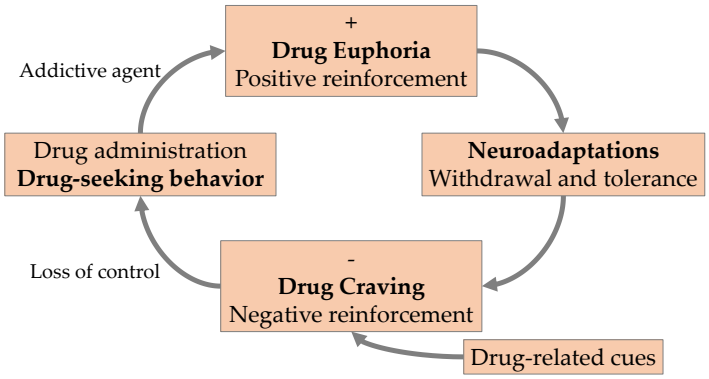


Fig. 1. The addiction loop [16].

1 INTRODUCTION

Abuse of illicit drugs such as cocaine costs the US healthcare system more than $600 billion annually [23], and there is substantial interest in finding better drug addiction treatments. Beyond reducing health care costs, improved treatments are desperately needed to reduce drug-related morbidity, mortality (e.g., drug overdose) and lost productivity in those who suffer from the disorder. One of the greatest challenges in treating drug addiction is understanding the real-world antecedents of recurrent drug use, including the relationship between drug craving, drug-seeking behavior and drug-induced euphoria (i.e., "high"). Current clinical approaches, including brief in-person appointments, insufficiently capture the dynamic nature of drug craving, use, and euphoria. For example, retrospective self-reports during such visits are inevitably subject to recall bias, prone to misrepresentation, and fail to capture unconscious aspects of addictive behaviors that may be genuinely beyond the subject's awareness. If ubiquitous and mobile health sensing technologies were able to automatically and reliably measure physiological predictors of drug use, including on an individualized (i.e., personalized) basis, such methods might dramatically and positively impact current approaches to addiction treatment.

While there have been several recent efforts to use mobile health sensing technologies such as smartwatches, chestbands, and smartphones in the context of understanding drug-use behavior [11, 21, 40], crucial gaps exist in our ability to model the other integral components in the positive and negative reinforcement loop that characterizes addiction (Figure 1). With the exception of neuroadaptations which would require neuroimaging [24], other components in this cycle, including drug craving, drug-seeking behavior, and drug-induced euphoria are amenable to continuous sensing by mobile health technologies. Although some recent studies have proposed mobile and wearable sensor-based solutions to detect drug use [21, 40], psychological stress [22, 30] and other contextual variables [28], the potential to continuously infer *subjective effects* variables that occur in anticipation of (i.e., "before") and during (i.e., "after") drug use from physiological signals detected by wearable sensors is underexplored. In this paper, we aim to bridge this important gap by demonstrating that passively captured cardiac and respiratory signals from a wearable chest band can be used to predict cocaine craving and euphoria, as well as drug-seeking behavior.

Our paper deals with three variables – drug craving, euphoria, and drug-seeking behavior which are key components of the addiction loop model (as can be seen in Figure 1) [25, 37, 57]. Craving constitutes a state of drug-wanting, one thought to precede recurrent and/or repeated drug use. Conversely, cocaine euphoria most commonly connotes a positive affective state or subject "high" that a user experiences upon consumption of the drug. Drug-seeking behavior may include real-world compulsive behaviors such as visiting locations where the

drug can be obtained, or in the case of our human laboratory study, repeated button pressing in an effort to acquire additional doses of the drug. The positive reinforcement model suggests that a drug's euphoric effects and associated development of memory traces for the drug experience lead to drug craving and compulsive drug seeking. The negative reinforcement model suggests that withdrawal symptoms can increase craving and compulsion to use substances. Frequent craving and the lack of self-control can be associated with different addictive disorders and relapse [48]. Figure 1 shows how these two models interact within the cycle of addiction to predispose to relapse/recurrent drug use, including by conditioned, drug-related cues and by psychological stress.

We seek to address these gaps by developing a prediction model for drug craving, euphoria, and drug-seeking behavior using physiological (i.e., cardiac and respiratory) signals obtained from wearable technology. We accomplish this using a wearable chest band that continuously measures the electrical activity of the heart and the periodic expansion/compression of our chest by using electrocardiographic (ECG) and respiratory inductance plethysmography (RIP). With the help of systematic feature engineering, we identify a set of craving and euphoria correlates by extracting the morphological information from ECG and breathing signals and then by capturing the temporal changes of their distribution.

We obtained promising results on two fronts. First, we show that we can accurately predict self-reported craving and euphoria. From a Leave-One-Subject-Out Cross-Validation (LOSOXV) experiment with a linear regression model trained on a set of highly informative, morphology-related ECG and breathing features, we show that we can predict the self-reported visual analog scale (VAS) craving scores which were reported on a scale 0-10 with a Pearson correlation coefficient (ρ) of 0.49 and a root-mean-square error (*RMSE*) of 1.76. Similarly, with another LOSOXV experiment using a linear regression model trained on a different set of highly informative ECG and breathing features, we show that we can predict the self-reported VAS euphoria scores which also were reported on a scale 0-10 with ρ of 0.73 and *RMSE* of 1.67. We demonstrate that ECG features contain more information about cocaine-induced internal states (i.e., craving and euphoria) than breathing features. We further dive deeper into a detailed feature importance analysis, where we show that two different groups of the morphological descriptors are informative about craving and euphoria. Lastly, we have a key demographic factor that can impact the performance of our VAS Craving and Euphoria models.

We show strong results on predicting drug-seeking behavior i.e., the times when a subject requests another drug dose (i.e., by temporally recorded button clicks to the drug infusion pump). With a logistic regression model trained on a set of highly informative, morphology-related ECG and breathing features, we classified click vs. no-click on a "minute by minute" level with an F1 score of 0.80 and precision, recall of 0.79 and 0.82. The results from this model are then used to infer click density i.e., the rate at which an individual clicked to request drug infusions on a scale 0-10. We observed that it is highly correlated with ground truth click density with a ρ of 0.85 and an *RMSE* of 1.79. Overall, with these results, we demonstrate that it is indeed possible to develop mobile and ubiquitous technology that can passively and continuously monitor an addict's craving and euphoria level, as well as drug-seeking behavior. As such, our wearable solution shows considerable promise for monitoring and potentially developing holistic models of the complex relationships between drug craving, euphoria, and drug seeking in the real world.

In summary, our contributions are:

- With the information contained by the morphology of cardiac and respiratory signals from a wearable chest band, we have developed a machine learning model that predicts subjective self-reports of cocaine craving and euphoria. While there are some prior works on modeling craving in the context of smoking [13], we are unaware of any prior work on continuous and passive sensing of craving and euphoria for cocaine use with mobile and ubiquitous technology.

- We present a detailed analysis of the relative feature importance of different morphological descriptors of ECG and Breathing signal for cocaine craving and euphoria modeling. Two distinctly different sets of morphological descriptors are important for craving and euphoria.
- We systematically analyze a set of key demographic factors and identified that "average dollar spent per use" impacts how one would score craving and euphoria. Just by using this factor as an additional input, our craving and euphoria models could fine-tune their predictions and attain better performance.
- Lastly, using cardio-respiratory signal we predict participant's "minute-by-minute" clicks and subsequently click density. In our laboratory model, we employ button click density as an objective measure for drug-seeking behavior which is found to be highly correlated with ground truth VAS Craving values.

2 RELATED WORK

Addiction Type	Literature	Sensors Data	Obtrusiveness	Craving	Seeking Behavior	Administration	Euphoria
Cocaine	Risinger et al. [45], Bonson et al. [9]	fMRI	High	✓	×	×	×
Opioid, Cocaine	Redish et al. [44], Lu et al. [31]	Neuroimaging, Electrophysiological	High	×	✓	×	×
Alcohol	Ehlers et al. [17]	Electroencephalography (EEG)	High	×	×	×	✓
Cocaine	Mannelli et al. [33]	EEG and Heart rate	High	×	×	×	✓
Smoking	Chatterjee et al. [13]	ECG, Accelerometer, Respiration	Low	✓	×	×	×
Alcohol	Shi et al. [46], Sun et al. [50]	ECG, Accelerometer, Respiration and skin temperature	Low	✓	×	×	×
Opioid	Boyer et al. [10]	Electrodermal Activity (EDA) , Body Motion, Skin Temperature and Heart rate	Low	✓	×	×	×
Smoking	Ali et al. [4]	Respiration	Low	×	×	✓	×
Alcohol	Bernstein et al. [8], Zhang et al. [59] , Wang et al. [55]	ECG, Accelerometer, Respiration and skin temperature	Low	×	×	✓	×
Opioid	Carreiro et al. [11], Mahmud et al. [32]	EDA, Body Motion, Accelerometer Skin Temperature and Locomotion	Low	×	×	✓	×
Cocaine	Natarajan et al. [38, 40], Hossain et al. [21]	ECG, Accelerometer and Heart rate	Low	×	×	✓	×
Cocaine	**Our work**	ECG and Respiration	Low	✓	✓	×	✓

Table 1. Overview of the existing literature on modeling drug craving, drug-seeking behavior, drug administration and drug euphoria for different types of addictive substances.

2.1 Craving

The term craving can be understood as a "wanting" [26] of a desired outcome (e.g., reward), or in the case of the current study, cocaine. Craving has been studied by researchers with both medical and computational backgrounds. From a medical perspective, fMRI brain imaging has been extensively applied to neurobiological studies of cocaine craving physiology and modeling. These studies suggest that craving is associated with dopamine release in the brain [53], activation of limbic brain regions [15], and changes in patterns of regional brain activation in circuits involved in the processing and prediction of rewards. Several studies have used fMRI imaging to capture changes in neural activities to model cocaine craving moments [9, 45]. However, fMRI techniques are highly intrusive, and as a result, such experiments are typically limited within a constrained neuroimaging setting and thus do not lend themselves to a mobile and ubiquitous approach. The feasibility of

sensors for modeling craving has been explored in other substance addiction problems. In the case of cigarette craving, Chatterjee et al., [13] proposed a Conditional Random Field-based model to predict the self-reported craving scores using ECG, respiration and 3-axis accelerometer. It was observed that stress level and time of the day provide sufficient information for estimating cigarette craving. In the case of opioid and alcohol, various studies have been designed and conducted to collect craving data in the form of self-assessments using sensors [46, 50], and a few other studies discussed the computational models which can be used to predict craving [10]. However, none have deployed a fully functioning system capable of inferring craving except in the case of smoking. As relates to cocaine, there are a few studies which have discussed the effect of craving on sensory data. Carter and Tiffany [12] have shown that drug craving gives rise to a significant increase in heart-rate, sweat-gland activity, and skin temperature in response to drug-related cues. Sinha et al. [47] observed that acute stress (i.e., in the form of imagery-guided scripts) leads to an increase in self-reported cocaine craving scores and heart rate. To our knowledge, however, ours the first work that attempts to infer (i.e., predict) self-reported craving scores for cocaine using sensory data (i.e., ECG and RIP).

2.2 Drug-seeking behavior

Drug-seeking behavior is central to addictive disorders, particularly as it relates to issues of recurrent use (i.e., relapse) [56] and drug withdrawal [51]. To date, the vast majority of research into the neural substrates of drug-seeking behavior and reinstatement of drug self-administration derive from preclinical experiments and the modeling of data from laboratory animals (e.g., rodents) [18, 31]. While similarities in drug-related behaviors across rodents and humans exist, distinct differences have also been identified [6]. Thus, there remains an important role for clinical translational studies of human drug-administration and related behaviors in humans. In the current study, we employed a safe and previously validated human laboratory paradigm of self-regulated (i.e., "binge") cocaine administration in experienced users of the drug for the purpose of trying to identify physiological predictors of cocaine-induced subjective effects (e.g., craving and euphoria) and drug-seeking behavior (operationalized as button presses for drug infusions).

2.3 Drug Administration

Although manual logging in a diary or smartphone apps has been traditionally used to keep track of the consumption or administration of substances of use or abuse [7, 35, 41], several recent efforts have explored the use of mobile sensing technologies. Some of these technologies require active participation from the users. For example, SoberDiary [55] has used a Bluetooth breathalyzer to assist participants in self-monitoring their alcohol consumption behavior by measuring breath alcohol concentration. In another study, You et al. [58] tested ketamine administration by analyzing saliva through a Bluetooth-enabled device. Voss et al. [54] used a human body odor sensing mechanism to recognize cannabis administration. Several recent works focused on wearable sensors that passively and continuously (i.e., without needing users' active participation) captures different relevant physiological parameters to predict whether the user has consumed a particular drug. Zhang et al.[59] developed a system that uses ECG and respiration signal from a smart sensor shirt [2] to detect alcohol administration. In this study, ECG features alone were found to be sufficient to achieve an accuracy of 71%. Similarly, Bernstein et al. [8] proposed convolutional neural networks (CNN) trained on the spectrogram of 1D heart rate data to detect alcohol administration and attained an accuracy of 74%. In the case of opioids, Carreiro et al. [11] and Mahmud et al. [32] have used Affectiva wristband with built-in electrodermal activity (EDA), accelerometer and skin temperature sensors to detect opioid administration with an accuracy of up to 99%. Skin temperature and accelerometer sensor data were found to be the most important modality for differentiating between pre and post opioid intake moments. Smoking detection has been performed by Ali et al. [4] using respiration features alone and were able to achieve an accuracy of up to 86%. Finally, in the case of cocaine

administration, Natarajan et al. [38, 40] used ECG based features and Hossain et al. [21] used accelerometer and heart rate for cocaine administration. These experiments were done both in the lab and field setting, and an average area under the curve (AUC) of 0.80 has been achieved.

While prior work has primarily explored the detection of drug administration, our focus is on subjective measures such as craving and euphoria. The ability to predict subjective variables is particularly important in order to model the addiction loop at an individual level.

2.4 Euphoria

Drugs of abuse can have numerous and diverse physiological effects on the body depending on their specific underlying pharmacology. However, common to many (but not necessarily all) drugs of abuse, including cocaine, is the experience of a positive subjective experience euphoria [20]. Depending on the drug, subjects can describe such states variably (e.g., "drunkenness" for alcohol or "high" for cocaine). The study of physiologic correlates of subjective euphoria using on-body sensors has been performed for alcohol and cocaine. In the case of alcohol, Ehlers et al. [17] showed that drunkenness is associated with significant changes in Electroencephalography (EEG) power in the slow alpha frequency range. Mannelli et al. [33] observed that during combined alcohol and cocaine administration, euphoric effects could be identified by EEG power spectral analysis in alpha and beta activity. There have also been several works which related 'high' in cocaine with increased heart rate [5, 36, 42]. Although it is possible that the pharmacological properties of a drug of abuse may exert its central behavioral (e.g., brain) and peripheral physiological (e.g., heart) effects via shared pharmacological mechanisms (e.g., monoamine reuptake blockade in the case of cocaine), it is almost certainly the case that relationships between these measures primarily reflect temporal correlations of drug effects on organ-specific systems/physiologies (e.g., mesolimbic dopamine circuits and cardiac ion channel or sympathetic nervous system norepinephrine, respectively). Importantly, however, such correlations with peripheral measures nonetheless hold significant potential, we believe for inferring central subjective states of relevance to the pathophysiology and treatment of substance use disorders, In this regard, the current work differs in two crucial ways. First, we try to model euphoria with ECG and respiration using unobtrusive sensors. Second, prior work has not used such sensor data to try to quantitatively infer (i.e., on a 0-10 scale) levels of euphoria (e.g., which we refer to as the VAS Euphoria hereafter) vs. mere qualitative differentiation of euphoric and non-euphoric states.

3 USER STUDY DESIGN

Our dataset was collected from a National Institute on Drug Abuse (NIDA) funded research study conducted at the Yale University School of Medicine. In this study, we were looking for individuals who are medically healthy, non-treatment seeking, and experienced cocaine users. For each subject successfully enrolled in the study, we first had to phone screen roughly 60 individuals. Here we asked questions about demographics such as age, their frequency/routes of cocaine use, whether they used other drugs, whether they had any other co-morbid psychiatric or medical problems, and whether they were taking any psychotropic medications that would exclude them from the study. From these 60 individuals, we had roughly 5-10 potential participants who were brought to the in-person screening where we performed a physical examination, blood work including pregnancy test (when applicable), electrocardiogram (ECG), urinalysis, urine toxicology and excluded individuals not eligible because of medical, psychiatric, or other conditions. This process usually yielded 1-2 eligible participants who could actually participate in our laboratory study. These individuals were typically scheduled in advance (up to a month). Thus we identified 10 individuals (with an average rate of 1 subject per month) who were then individually studied as part of a 6-hour human laboratory session in Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center (CMHC). During the study, they were allowed to self-administer cocaine while wearing on-body physiological sensors. We have collected approximately 60 hours of sensors data from our study. The

cocaine study was IRB approved and shown previously to be safe, well tolerated, valid, behaviorally relevant, and test-retest reliable [49], and was conducted in the presence of a study physician, advanced cardiac life support certified research nurse, and a basic life support research assistant. We had a research pharmacist who prepared the drug for IV administration. Note that while the sample size of 10 appears small compared to typical user studies with wearables, studies involving cocaine administration [27, 29, 34] usually publish samples in the teens (10-20), both given the cost/subject (approximately $10-20K USD per subject) and large pharmacological effect sizes.

3.1 On-body Wearable Sensor

The *Zephyr Bioharness 3* chest band [3] (shown in Figure 2) was used as the on-body wearable sensor. Each of our 10 participants wore it throughout the entire study (approximately 6 hours) while *Zephyr* captures cardiac and respiratory signal in a passive, continuous and relatively unobtrusive (for example, compared to Holter monitor) manner. The electrode on the chest band can non-invasively detect electrocardiogram (ECG) signals. Similarly, with the help of the built-in pressure sensor pad in the chest band on the subject's left-hand side, it can also capture the expansion and contraction of the rib cage due to breathing. The companion application further processes the raw data to estimate RR interval (i.e., The QRS complex is the name given to the combination of three graphical deflections observed on a typical ECG. The distance between the peak of one QRS complex to the next is called the RR interval) , heart rate, respiratory frequency measurements. For our research in this paper, we have used the raw ECG and breathing waveform data to extract different features which are then used to model craving, euphoria, and drug-seeking behavior. The raw data is stored both in the local memory of the chest band and in the smartphone with the help of a companion app. The data on the sensor is downloaded at the end of each day and uploaded to a secure server while the sensor data stored in the smartphone helped us to salvage data on occasions when the chest band platform failed to log the data correctly in its local memory. Out of ten participants, three participants had highly corrupted/noisy or missing breathing data. As a result, we could only use the ECG data from these three participants. This procedure has been detailed in Section 4.2.1.

3.2 Cocaine Study Protocol

Participants upon admission to the research unit go through a "wash-out" period where they stay abstinent from the drugs for 2-5 days and get accustomed to the daily activities and on-body sensors. This unit is equipped with 24 X 7 medical and nursing coverage, allowing for ongoing monitoring of abstinence (i.e., supervision of subjects, screening of visitors, and compliance with inpatient requirements). This step ensures that absolutely no drug is present in the body of our participants and that the results of this study are not affected by any acute influence of previous drug use. After the "wash-out" period, each subject participated in a 6-hour cocaine study. This 6-hour study was comprised of three distinct periods, in the following order: a) an initial drug-free baseline period, b) a subsequent fixed-order, escalating dose, bolus cocaine administration period, and c) a final self-regulated/administrated, ad-libitum (i.e., "binge") cocaine administration period. The participants wore *Zephyr* throughout the entire study which continuously and passively recorded raw ECG and breathing waveform data, as described in section 3.1. In addition, self-ratings of craving and euphoria were captured by visual analog scale (VAS) every five minutes throughout the study.

Baseline and Fixed Dosage Periods: The study is started with a 30-minute baseline period during which the participant did not receive any cocaine. The baseline period is followed by the fixed dosage period where three, separate bolus intravenous (IV) cocaine doses are administered as a fixed order in an escalating dose regiment. Specifically, a single bolus of 8, 16, and 32 mg IV per 70kg body weight (with a 100 kg maximum cap) are given with an interval of 20 minutes between each of them.

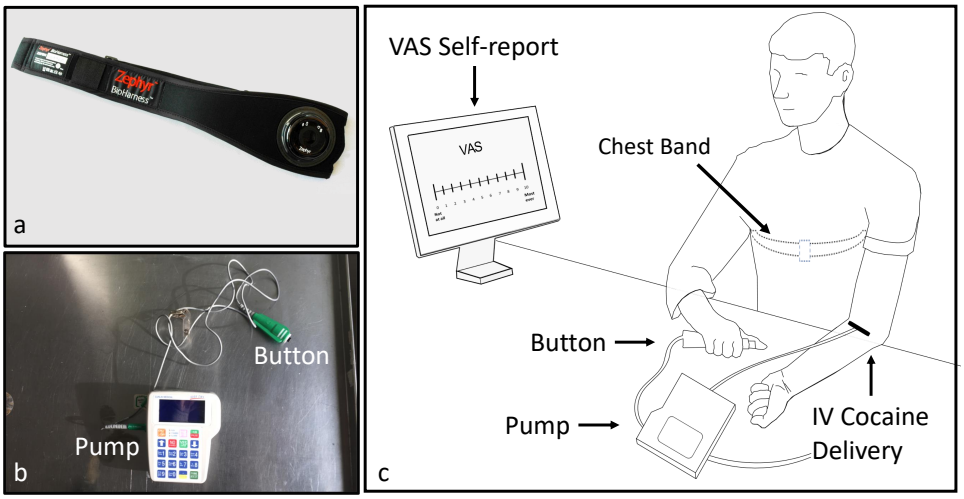


Fig. 2. a) Zephyr chest band. b) Infusion Pump button, used to request cocaine in Self-administration period. c) Brief sketch of participant during the Self-administration period of the study.

The primary purpose of the baseline period was to establish a stable behavioral and cardiovascular baseline against which subsequent cocaine-related measures might be compared. The primary purpose of the fixed-order, escalating dose period was to establish the ability of the study to safely tolerate the cardiovascular effects of the doses of cocaine employed in the study. Specifically, subjects who exhibited a heart rate greater than 160 beats per minute, diastolic blood pressure greater than 110 mm Hg, systolic blood pressure greater than 180 mm Hg, or had evidence of clinically significant cardiac ectopy, arrhythmia, or other dangerous symptoms were excluded from the subsequent "binge" cocaine self-administration procedures.

Self-administration Period: As the name “self-administration” indicates, this period was designed to simulate a period of self-regulated, "binge" cocaine consumption. The participants obtain cocaine via self-initiated presses of a corded infusion pump button (shown in Figure 2). Button presses elicit an audible beep from the pump as feedback of subject’s request, after which the pump would infuse cocaine as a 30-second bolus according to a fixed-ratio 1:5-minute timeout schedule (i.e., every button press resulted in a bolus injection of cocaine except for presses occurring during the 5-min period following an active cocaine infusion). This single-blind schedule is preprogrammed into the pump and used as a safety feature to allow sufficient time for subjects to experience the subjective effects of a given cocaine bolus before a subsequent infusion was delivered. Specifically, button presses during the 5-min timeout period, despite eliciting audible beeps, did not result in an active cocaine infusion. As a result, button presses are comprised of two types, including both infusion and non-infusion clicks. Thus, participants were allowed to receive as many as 12 IV infusions of the drug during a given 1-hour period depending on their desire for any given dosage (limited only by rare instances in which pre-established vital sign safety thresholds were exceeded and the pump button temporarily taken from subjects). Subjects were allowed to press the button as they desired without instruction from the study staff beyond taking cocaine as they desired. All the cocaine self-administration procedure was conducted under the supervision of a study physician. Data on button presses and infusions were recorded by the pump itself and served as primary behavioral outcome measures for understanding potential relationships between drug consumption (i.e., infusions), desire for drug (i.e., button presses; our operational measure of drug-seeking behavior) and other cocaine-induced subjective effects (e.g., self-reported VAS ratings of craving and euphoria).

The self-administration period consisted of three, one-hour sessions, during which subjects received each of the three cocaine dosage types (i.e., 8mg, 16mg or 32mg/70kg IV) under a fully-randomized, double-blind schedule. The double-blind was ensured through the following process. Research nurse would first receive three bags labeled 1, 2, and 3 stating the sequence in which they needed to be administered. Neither the participant nor research nurse/study physician knew the dosage of cocaine present in either of the bags. At the end of the study, the research pharmacy unblinded it to the research nurse and study physician. During a given 1 hr self-administration session only a single dosage type is available to the subject and would receive this amount for each bolus in that session. Subjects are unaware of the variable order in which dosage types are available to them. However, across all the three self-administration sessions, each participant gets to experience all three dosage levels, and the ordering of these dosage levels among sessions is randomly assigned. For example, participant 1 may get respectively 8-16-32 mg dosage sequence in the three consecutive self-administration sessions while participant 2 might get 16-8-32 mg sequence. Each Self-administration sessions were separated by a break of approximately 20 minutes.

3.3 Craving and Euphoria Self-reports

Throughout the study, the participants are asked to self-report their craving and euphoria every 5 minutes according to a visual analog scale (VAS) between 0 ("not at all") to 10 ("most ever"). Below please find the list of questions, their scale, and their acronym. In order to refer to the craving or euphoria/high self-reports, we will use the terms respectively **VAS Craving** and **VAS Euphoria** throughout the paper.

- **VAS Craving** (scale 0-10): how much are you *craving for cocaine* now?
- **VAS Euphoria** (scale 0-10): how *high or euphoric* are you feeling now?

Figure 2 shows the *Zephyr* chest band sensor used, infusion pump button, and finally a brief sketch of participant during the study.

3.4 Example Sensor Data from a Participant

We now show a limited visualization of the sensor data to illustrate that there are interesting trends in the data but also that there are challenges given the noise and variability.

Figure 3 shows the sensor data across all the periods of the cocaine study collected from one of our participants. The start and end times of all the periods including the baseline period, fixed-dosage period, self-administration period, and break times have been marked on the figure. All the click events (both infusion and non-infusion clicks) can also be visualized on the first sub-figure in Figure 3. This figure also shows one sample cardiac activity feature (i.e., mean RR distance), one sample respiratory activity feature (i.e., mean inhalation time), and the two visual analog scale scores for cocaine craving and euphoria. Here, we have displayed one cardiac activity, and one respiratory activity feature as the raw ECG and breathing waveform cannot be properly visualized in this timescale of several hours. The RR distance essentially represents the distance between two large peaks in the raw ECG data, hence captures the heartbeat period (i.e., heart rate). A detailed description of the ECG data preprocessing and feature extraction can be found in section 4.

VAS Craving and Euphoria Scores: The first observation is that there are some very clear trends in the VAS Craving and VAS Euphoria scores, particularly the latter. The participant reported a high level of craving (VAS Craving) while reporting a low level of high or euphoria (VAS Euphoria) during the baseline period. The high craving level is not surprising since the participant had to go through a rigorous "wash-out" phase without any drug for several days preceding the study, leading to high anticipation levels. During the fixed dosage period, the participant self-reported increasing VAS Euphoria scores, consistent with the predicted effects of cocaine.

In contrast, the VAS Craving score remains at relatively high levels but starts to reduce towards the end of the self-administration period. This is also not surprising as during early periods, we use low doses of cocaine (e.g.,

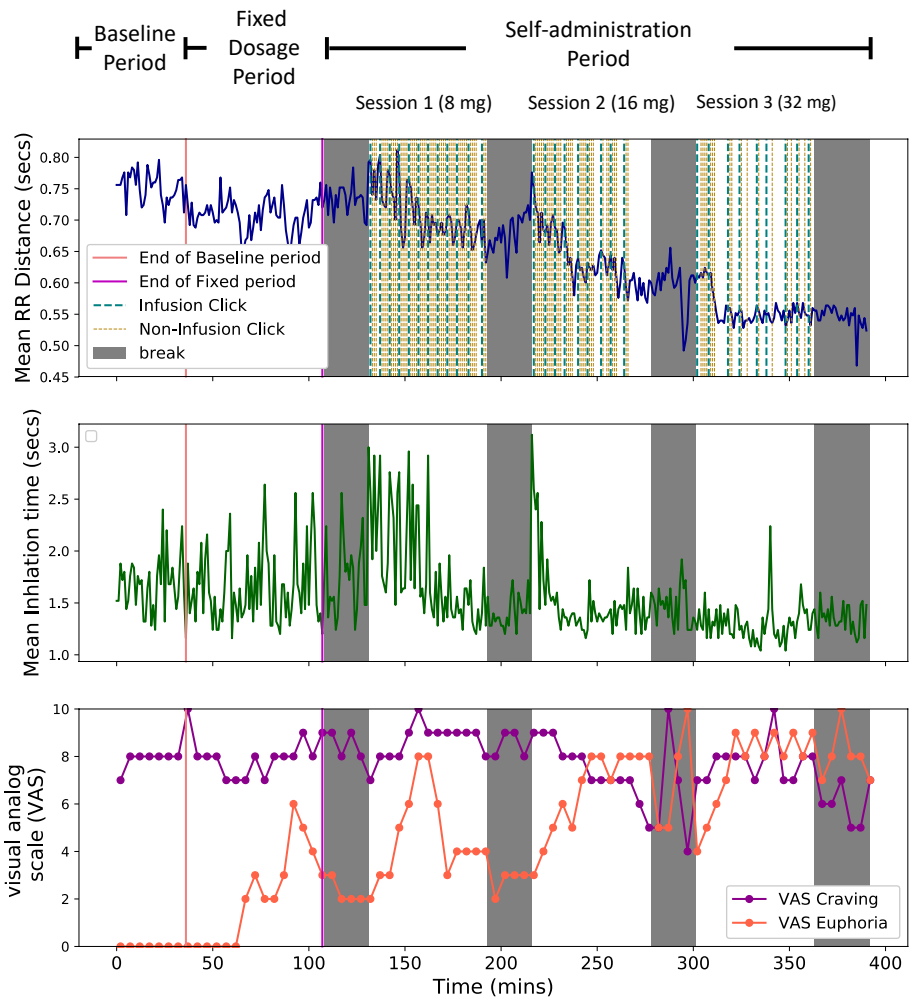


Fig. 3. illustrates the sensor data, click events, and self-reports collected across all the different periods during a 6 hour-long cocaine study with one of our participants. As raw ECG and Breathing data can not be visualized in this time scale (of 6 hours), we have derived one ECG feature (RR distance) and one breathing feature (inhalation time) for visualization purposes.

8 mg) to ensure that there is no adverse reaction but this also produces a smaller than desired drug effect for habituated users. As the dosage increases to larger bolus doses of cocaine (e.g., 32 mg), a reduction in craving ratings can be observed. Interestingly, we see that during a relatively high 16 and 32 mg self-administration session, we can see the two VAS scores crossover. The VAS Euphoria scores increases while VAS Craving score decreases. During the 32 mg self-administration session, the self-reported VAS scores show a high amount of variability.

Two Sample Cardiac and Respiratory Signals: Let us now look at the two features that we have plotted (RR distance and inhalation time) and see how it follows these VAS scores. During the baseline period, the

participant did not get any cocaine which is reflected by the relatively high RR distance. As the participant progresses through the study and consumes more cocaine, RR distance decreases (as can be seen in Figure 3) meaning heart rate increases. During the break or pause period, the RR distance increases slightly as the body can cope with the stimulant effect of the drug. We can also observe a similar pattern in mean inhalation time. In general, as the person consumes more drugs, the inhalation time or period decreases and the breathing process becomes faster. It is clear that we can detect drug administration and estimate dosage level with cardiac signals captured during a typical cocaine period which is also backed up by existing literature [21, 40].

Clicking Behavior: While somewhat hard to observe, the vertical lines in the top plot in Figure 3 show infusion and non-infusion clicks of this participant. One trend that is immediately visible is that the rate of clicks clearly follows the dosage level. For example, the participant clicked a lot in the 8 mg session since the dosage was too low but when the dosage increases (particularly to 32mg), the clicks are increasingly sparse. This clearly demonstrates some kind of regulation of drug-seeking behavior via clicks as a function of the craving and euphoria levels. Also interesting is that the RR distances generally tends to dip after each infusion click but appears to go up before the next infusion.

Thus, we can see that there is clearly useful information in the sensor signals that appear to correlate with the trends observed in VAS Craving and Euphoria levels. However, there are clearly challenges since the features themselves appear to be highly variable and noisy, and we need robust features that accurately capture these trends. The fundamental challenge that this paper tackles is whether we can extract relevant and meaningful information from the cardiac and respiratory signals of relevance to measures of craving and euphoria.

4 PREDICTING VAS CRAVING AND EUPHORIA SELF-REPORTS FROM CARDIAC AND RESPIRATORY SIGNALS

In this section, we describe how we model VAS Craving and VAS Euphoria by extracting features from ECG and respiratory signals. As mentioned in the previous section, our current study captures the cocaine craving and euphoria levels of the participants every 5 minutes throughout the experiment, i.e., we have craving and euphoria information when the subject is not intoxicated at all (baseline period), when the subject is intoxicated at fixed time points (fixed dosage period), and when the subject self-administers and has complete control over when to consume cocaine (self-administration period), as well as during break periods. Apart from all these, cardiac information via ECG and respiratory information is also captured continuously and passively throughout the study. In total, during a 6 hour study, we received approximately 72 VAS Craving and 72 VAS Euphoria scores from each participant. Using all this data we ask a straightforward question: *how well can we predict self-reported craving and euphoria scores using information captured by ECG and Respiratory signals?*

4.1 Model Architecture

Our overall model architecture for predicting VAS Craving and VAS Euphoria scores is shown in Figure 4. We model VAS score prediction as a regression problem, where we predict what the subject answered for the self-report questions using ECG and Breathing (BR) information from that minute and past N-1 minutes. We define a window, which comprises of this N minute ECG and BR information. Since both VAS Craving and Euphoria questions are asked simultaneously with the same fixed frequency, the model for each of these is identical and uses the same window size parameters.

ECG and BR signals are fast changing periodic signals. As a result, the properties or characteristics of these signals can completely change in a much shorter span of time, compared to the typical length of a window. In order to capture the temporal changes of ECG and BR signal properties, we break down each window into frames and features are extracted from these frames. Extracting and feeding a sequence of frame-level features to the model allows us to retain the temporal changes of the ECG and BR features over the course of a window.

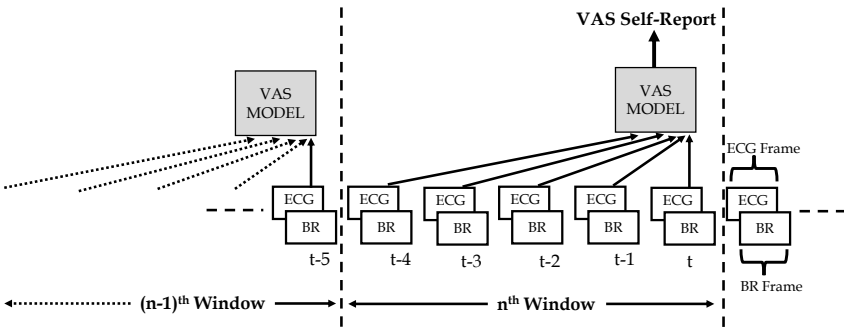


Fig. 4. illustrates the modeling approach we used for subjective VAS Craving and Euphoria self-reports. Here we show a sample model with a window length of 5 minutes and the frame length of 1 minute for both ECG and Breathing (BR).

The window and frame lengths are considered as hyperparameters to the model. For our VAS prediction models we used integer length window sizes, N ranging from 1-5 minutes and selected frame lengths from $[0.5,1,N/2,N]$ minutes. As ECG and BR signals are intrinsically at different rates and have different types of information, the optimal window and frame length of ECG can be different from the optimal window and frame length of BR. For this reason, we had separate hyperparameters for ECG and BR.

4.2 Feature Engineering Pipeline

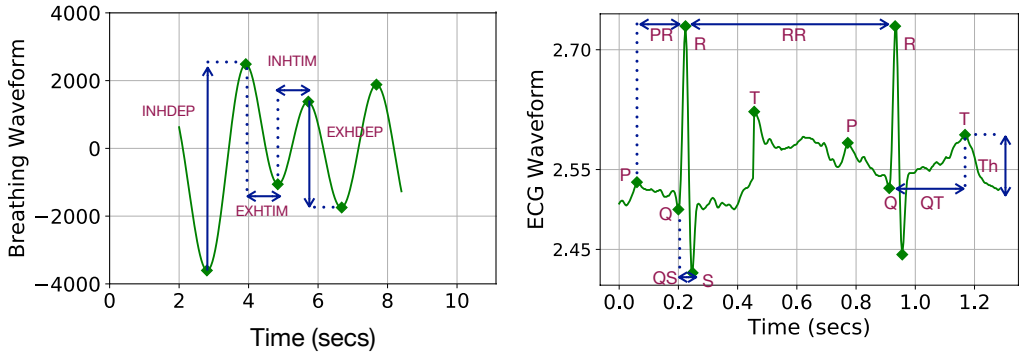
The feature engineering pipeline aims to extract relevant information from the noisy raw ECG and BR data to model cocaine craving and euphoria. This pipeline includes several essential steps: de-noising the raw ECG and BR signals, detection of different characteristic anchor points on both the BR and ECG waveforms, extracting meaningful features capturing structure and rate of change in cardiac and respiratory activities, selecting highly important features from the initial feature pool. Although the exact feature sets used for modeling self-reports of craving and euphoria (i.e., VAS scores) are different, the feature engineering pipeline remains the same.

4.2.1 Data Cleaning: Since the *Zephyr* chestband continuously collects data during the entire period of our user study, the raw wearable ECG and BR signals include various sources of noise including motion artifacts, change of coupling between the sensor and the body due to different body posture, signal dropouts, and errors occurring during transfer of data from sensors to the device. As a result, cleaning the raw signal by using various denoising algorithms is necessary to ensure a high quality of features.

Before cleaning the raw data, we used two simple rules to determine the usefulness of wearable sensor data from a subject: (1) Data scarcity – if data is available only for a small temporal window for a user then we refrained from using that stream of sensor data for the respective user; (2) Signal Quality – if the signal to noise ratio is small then this suggests that the wearable sensor data carries little to no information. We computed these two metrics for both ECG and respiratory waveforms for each user. In our dataset, these two rules led to discarding respiratory waveforms for the three users since they were only available for a tiny fraction of time ($\sim$ 2%).

After removing the noisy data using the above two simple rules, our next step was cleaning the ECG and BR data. In order to clean raw ECG data, we leveraged methods from Natarajan et.al [40] to process ECG signals for use in cocaine use detection. The noise removal process works by first removing noise from dropout by identifying the R peaks. The distances between consecutive R peaks are then calculated. As heart rate is an

inverse measure of RR distances, all the intervals which have RR distance corresponding to implausible heart rate are filtered out. Since we use BR data in addition to ECG, we added a filtering pipeline for this signal. To clean raw BR data, we subtracted the mean from the raw signal to get rid of the DC components and then passed the data through a 5th order bandpass Butterworth filter with a lower 3dB cutoff frequency of 0.0833 Hz and an upper 3dB cutoff frequency of 0.5 Hz. The particular values for lower and upper cutoff frequencies were selected so that we can capture all the breathing signals with rates between 5 to 30 breaths per minute.



(a) (b)

Fig. 5. shows different morphological features extracted from one period of (a) Breathing (BR) and (b) ECG waveform.

4.3 Feature Extraction

After the raw ECG and BR signals have been denoised, we extract necessary features from these signals. Our feature extraction can be divided into two stages. In the first stage, we extract morphological features at the granularity of each ECG or BR waveform (e.g., QT interval, T Height, Inhalation time). These features capture the structural information present in each beat of the signal. However, as we described earlier, this information is too detailed to directly input to a classifier since we have limited number of labels. So, we need to aggregate beat-level information into a more representative frame-level features which can be used as input to the classifier. In order to do so, in the second stage, we apply statistical quantifiers on the morphological descriptors to approximate the distribution of features within each frame. The statistical quantifier aims to estimate the distribution of the morphological features (e.g., 67 percentile of QT interval) in a larger time period i.e., a frame.

4.3.1 Morphological features for each beat: In order to estimate the morphological descriptors of ECG and BR waveform, the first step is to detect the characteristic points/peaks from the denoised waveform. For example, the PQRST complex (P-wave, QRS complex, T-wave) which represents one complete heartbeat in the ECG is a systematic method of interpreting ECG rhythm and marks a series of different cardiac activities. Figure 5b shows the PQRST complex on a 1.2-second long sample of denoised ECG data collected in our study. In this paper, we leverage the PQRST detection algorithm proposed by a recently published work of Natarajan et.al [39]. After detecting the PQRST peaks, we estimated different distance (or interval) and height information capturing the structure of the ECG waveform.

The morphological descriptors of the BR signal are also estimated in a similar fashion. At first, we estimate the peaks and troughs in the bandpass-filtered breathing waveform. The peaks and troughs represent the maximum expansion and contraction of chest or diaphragm due to inhalation and exhalation. Once we identify the peaks and troughs, we estimate the morphological descriptors of breathing waveform by estimating the inhalation and

Data	Morphological Descriptors	Acronym
ECG	RR Distance	RR
	QT interval	QT
	PR interval	PR
	QRS interval	QRS
	QTc interval	QTc
	T Height	Th
BR	Inhalation time	INHTIM
	Exhalation time	EXHTIM
	Inhalation depth	INHDEP
	Exhalation depth	EXHDEP
	Respiration Duration	RD

(a)

Statistical Quantifiers	Acronym
Minimum	min
33 Percentile	33%
Median	med
67 Percentile	67%
Maximum	max
Standard Deviation	std
Skewness	skew
Kurtosis	kurt

(b)

Table 2. (a) The list of morphological descriptors extracted from ECG and Breathing (BR) waveform. (b) The list of statistical quantifiers applied on all the morphological descriptors to extract frame-level features.

exhalation time, inhalation and exhalation depth and respiration duration which is the sum of inhalation and exhalation time. Figure 5a shows all the morphological descriptors from a few seconds of BR data from our user study. All the ECG and BR-based morphological descriptors are listed in Table 2a.

4.3.2 Statistical quantifiers for each frame: We get a morphological descriptor from every period of ECG (the length of a heartbeat) and BR (the total duration of an inhalation and an exhalation) data. However, each morphological descriptor extracted from a heartbeat or a breathing cycle cannot directly be used as a feature as it is noisy and does not holistically capture the trends over time. By applying the statistical quantifiers listed in Table 2b on all the morphological descriptors estimated from all the heartbeats and breathing periods in a frame, we can capture the summary statistics that are both robust to noise and representative of the underlying trend. One example feature can be the median of QT interval. From one ECG and BR frame, with a total of 11 morphological descriptors, we get 88 statistical quantifiers which are used as a features to our model.

4.3.3 Feature Normalization and Selection: Different frame level features estimated with different combinations of morphological descriptors and statistical quantifiers have different ranges. For example, the median value of QRS typically ranges between 0 and 0.5, but median respiration duration typically ranges between 3 and 5. In order to keep all features in the same range between 0 and 1, we normalized the features with the help of Min-Max scaling.

As a feature selection algorithm, recursive feature elimination algorithm [19] was used. This recursive algorithm starts with a model trained with all the features and iteratively removes the least important feature to optimize the performance (i.e., RMSE) of the model. We continue this process until the required number of features is reached. For all our VAS models, number of features required is a hyperparameter and is selected from [5, 10, 15, 20, 25, 30].

5 RESULTS: VAS CRAVING AND EUPHORIA PREDICTION

As described in section 4, we model VAS Craving and VAS Euphoria score prediction as a regression problem. We explore four different models for prediction — linear regression, one layer Neural network (1lnn), Support Vector Regression (SVR) and Random Forests (RF). We compare these approaches against a baseline model which does

		VAS Craving			VAS Euphoria		
Features	**Models**	ρ	*RMSE*	*MAE*	ρ	*RMSE*	*MAE*
-	Baseline	0.00	4.77	3.99	0.00	4.87	4.06
ECG+BR	Random Forest	0.31	3.02	2.81	0.62	2.98	2.56
ECG+BR	Neural Network (1 lnn)	0.49	1.95	1.74	0.70	1.91	1.52
ECG+BR	Support Vector Regression	0.40	2.27	2.09	0.64	2.91	2.57
ECG+BR	Linear Regression	0.49	1.76	1.40	0.73	1.67	1.34

Table 3. The performance of VAS Craving and VAS Euphoria regression models trained with different feature subsets from Leave-One-Subject-Out Cross-Validation (LOSOXV) experiments. The performance was measured in terms of average Pearson correlation coefficient (ρ), Root-Mean Square Error (RMSE), Mean Absolute Error (MAE) across participants.

not use any of the sensor signals for prediction. This model simply uses the self-report score distribution from the training data and randomly generates scores for test subject from this distribution. We use Leave-One-Subject-Out Cross-Validation (LOSOXV) experiments for all the analysis. The LOSOXV experiment is performed on the seven participants whose ECG and BR data is available. The performance was measured in terms of average Pearson correlation coefficient (ρ), Root-Mean Square Error (RMSE), Mean Absolute Error (MAE) across all the participants. Before training our models, we used synthetic minority oversampling technique (SMOTE) [14] in data preprocessing step as the number of data instances for each VAS score class is uneven and we do not want our model to be biased towards the majority class.

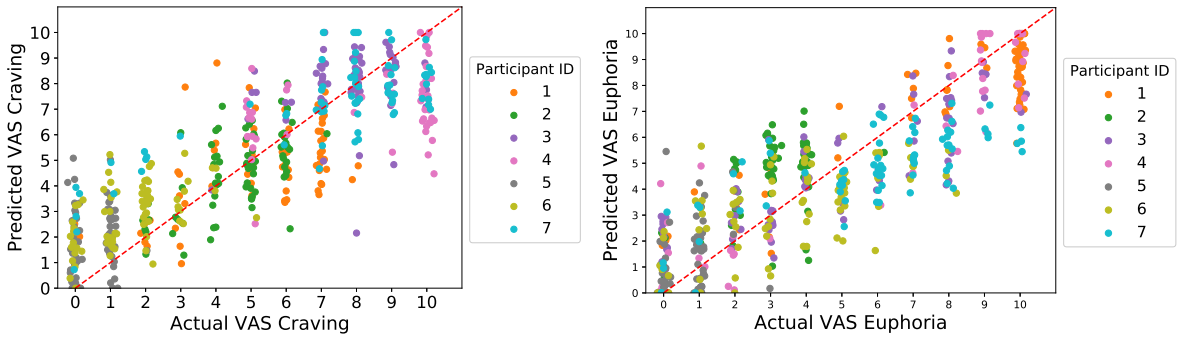
Table 3 shows the performance of different regression models for predicting self-reported VAS Craving and VAS Euphoria scores. Overall, the linear regression model that used a combination of ECG and BR features gave us the least RMSE and best Pearson correlation coefficient for both craving and euphoria self-report prediction. For craving, the linear regression model trained with both ECG and BR features attains a Pearson correlation coefficient (ρ) of 0.49 and an *RMSE* of 1.76. As the range of the VAS score is 0-10 by definition, the normalized root mean squared error (*NRMSE*) is 17.6%. It indicates that the predicted VAS Craving is highly likely to be within 17.6% of the reference VAS score. For VAS Euphoria modeling, we achieved an even stronger result with the ρ of 0.73, *RMSE* of 1.67 and *NRMSE* of 16.7%. Our results show that a simpler model outperforms the other higher complexity models. It is not surprising since the number of labels (i.e., self-reported VAS scores) are relatively small. As a result, more complex models can over-fit to the data which may reduce performance.

We optimize the performance of our best model with respect to several hyperparameters including window, and frame length of ECG and BR. With respect to best models shown in Table 3, we find that the optimal window length for both VAS Craving and Euphoria modeling is 5 minutes. The optimal frame length for ECG and BR features are 30 seconds and 1 minute respectively in both VAS predictions. As the period of the ECG signal is significantly shorter than that of BR signal, a shorter frame length can sufficiently extract meaningful and informative ECG features. For VAS Craving and Euphoria modeling, the feature selection algorithm selects 10 and 30 features respectively .

5.1 Performance breakdown across the VAS scale

To evaluate how well we capture craving and euphoria across the VAS range, we show two scatter plots in Figure 6. These plots show how well the predicted VAS scores matches with the actual ones at different points on the scale. Ideally, if all the predicted VAS scores exactly match with the actual ones, all the points will fall on the diagonal red dash line. In our case, for both craving and euphoria VAS models, the predicted scores generally follow the actual values. As the actual VAS scores increases, the predicted values also increase. This indicates that our VAS Craving and Euphoria model can learn the subjective VAS scores across different regions on the scale

and can be effective in distinguishes between sub-ranges such as high craving or euphoria. While our results



(a) VAS Craving model

(b) VAS Euphoria model

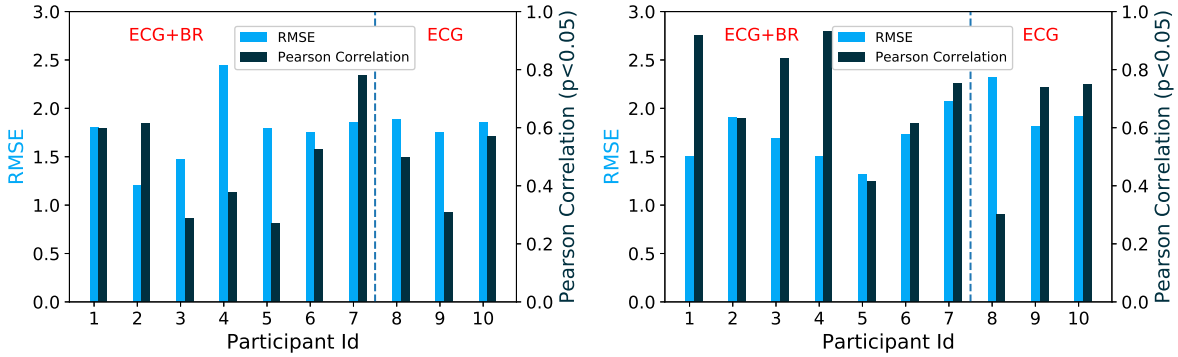
Fig. 6. shows two scatter plots: (a) between predicted and actual VAS Craving scores, (b) between predicted and actual VAS Euphoria scores for different participants (encoded in different colors). Added small Gaussian noise to the actual VAS scores to help with the visualization.

report the average performance across all VAS levels, we are generally more concerned with identifying the higher levels of craving and euphoria. There are two reasons for this: 1) higher levels of craving and euphoria are generally indicative of more addictive behavior and can help identify situations when interventions are required, and b) many medications for treatment of cocaine dependence (e.g. Modafinil) work by blocking craving and euphoria via modulation on various neurotransmitters such as dopamine, glutamate/GABA and others. Thus, if we are able to identify higher levels of craving and euphoria, these can help us identify both intervention points as well as efficacy of pharmacological treatment. If we use the VAS Craving and Euphoria linear regression models for binary classification between $VAS\ score >= 6$ (High) and $VAS\ score < 6$ (Low), we achieve an average F1 score of 0.83 for both VAS Craving and VAS Euphoria from LOSOXV experiment.

5.2 Performance breakdown across participants

The next question we ask is how the performance of our models vary across participants. Since different individuals can have widely varying cardiovascular response to cocaine (due to factors like habituation), we expect some variation across the individuals in our study. Figure 7 shows the performance of our best model with respect to RMSE and Pearson correlation coefficient for VAS craving and euphoria across different participants. For the first seven participants, whose ECG and BR data is available, we reported the performance of the best model with both these features. For the remaining three participants with ID-{8,9,10} whose BR data is not available, we reported their performance by using the best model with just ECG features with LOSOXV done on all ten participants. Later in section 5.3, we will demonstrate that ECG features, in the absence of BR features, can alone be used for subjective VAS Craving and Euphoria modeling as BR features marginally improve the performance.

The results, shown in Figure 7, suggest that the VAS prediction models have reasonably consistent performance across all participants. For most of the participants, the RMSE is less than 2 for both craving and euphoria where the actual VAS score ranges between 0 and 10. It indicates that our prediction is not far from the actual score and we are almost always within ±2 of the actual score for both VAS Craving and Euphoria prediction. However, for some of the participants our model does not perform well. For example, the VAS Craving model for participant 4 yields a high RMSE (with a value greater than 2, as can be seen in Figure 7a). The participant 4 has reported a



(a) VAS Craving model

(b) VAS Euphoria model

Fig. 7. shows the performance of (a) the VAS Craving model and (b) the VAS Euphoria model across different participants with respect to Pearson correlation coefficient and RMSE. For participants 1 to 7, a linear regression model with ECG and BR feature was used. The participants 8 to 10 only had ECG data, so a linear regression model with only ECG features is used for these three participants.

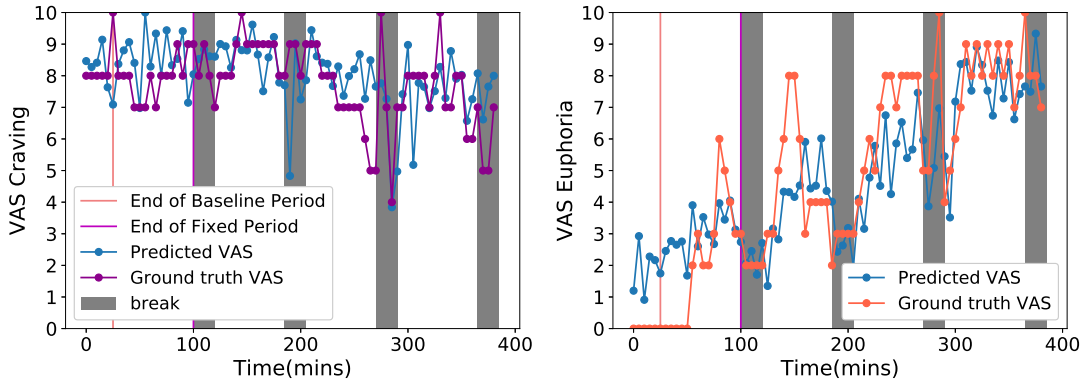


Fig. 8. (a) Bar plots showing Predicted vs Ground truth for VAS Craving and VAS Euphoria a for Participant ID-3 .

score of 10 for VAS Craving 70% of the time. As our participants rarely reported a VAS Craving score of 10, our craving model under performs on the upper extremity of the scale in comparison to the lower and middle values.

We illustrate the result for one specific individual in Figure 8. The individual we select is Participant Id-3, for whom we get roughly average performance i.e. neither the best nor the worst performance among all participants. The plots show the Predicted VAS score and the Actual VAS score. We see that the predicted VAS scores follow the trend of ground truth VAS scores. Although the two lines do not perfectly align, they are relatively close and the trends are accurate. We can see that the increasing and decreasing trend of the predicted VAS scores tends to follow ground truth trends.

5.3 Feature Importance Analysis

We now look at which features are most informative for prediction of VAS scores. We breakdown the performance of the best model, linear Regression, by the specific feature sets and evaluate its performance when using features solely from ECG, solely from BR, and both (Table 3).

		VAS Craving			VAS Euphoria		
Features	**Models**	ρ	*RMSE*	*MAE*	ρ	*RMSE*	*MAE*
ECG+BR	Linear Regression	0.49	1.76	1.40	0.73	1.67	1.34
ECG	Linear Regression	0.41	1.86	1.46	0.72	1.99	1.58
BR	Linear Regression	0.23	2.33	1.86	0.37	2.66	2.18

Table 4. Breakdown of the contribution of each feature block to overall performance. Values reported are after we average them across participants.

The results are shown in Table 4 and we used seven participants whose ECG and BR data are available for this analysis. We see that the linear Regression model trained only on ECG features outperforms the BR feature-based model for both craving and euphoria self-report prediction. This tells us that ECG features contain more information than BR features about craving and euphoria. For VAS Craving prediction, the linear regression model trained with only ECG features can reach a ρ of 0.41 and *RMSE* of 1.86 while the corresponding model trained with BR features alone performs very poorly with ρ of 0.23 and *RMSE* of 2.33. Similarly, for VAS Euphoria prediction, the linear regression model trained with only ECG features can reach a ρ of 0.72 and *RMSE* of 1.99 while the corresponding model trained with BR features alone performs very poorly with ρ of 0.37 and *RMSE* of 2.66. When it comes to VAS Craving prediction, BR features contribute complementary information on top of the information captured by the ECG features and we can observe an increase in the ρ from 0.41 to 0.49 when using ECG+BR feature based model over ECG feature based model. However, when it comes to VAS Euphoria prediction, ECG+BR feature based model has only a slight improvement over the ECG only model from 0.72 to 0.73 in ρ (though we can observe some improvement in *RMSE*). We now drill-down further and look at which features within the ECG and BR feature groups are more important to prediction. In order to systematically answer this question, we grouped the features with respect to the corresponding morphological descriptors and estimated the importance. The results are shown in Figure 9a. In order to evaluate the worth of a morphological descriptor, we remove all the features corresponding to that descriptor from the full feature set. We then run feature selection, train the model, and evaluate the performance of the VAS model with respect to *RMSE* with the help of a LOSOXV experiment. The *RMSE* increase due to the removal of all the features corresponding to the morphological descriptors gives us a measure of the importance of that morphological descriptor. We considered our best models which is ECG+BR feature based linear regression model both for craving and euphoria in this experiment.

Figure 9a tells us that for the case of VAS Craving, *Th* descriptor is the single most dominating feature as it caused the highest jump in *RMSE* after removing. Similarly, for VAS Euphoria both QRS and RR descriptors caused a big rise in *RMSE*. The statistical quantifiers which were selected after feature selection corresponding to these descriptors are analyzed and we demonstrate cumulative distribution function (CDF) of these features for 3 groups of scores- [0-3],[4-7],[8-10] with respect to the best statistical quantifier in Figure 9b and 9c.

5.4 Influence from Demographic related Factors

During the initial screening process we have gathered information about several demographic factors which include age, weight, number of years of cocaine use, average days of cocaine use in a month, and average dollar ($) spent per cocaine use. The demographic factors and their distribution are listed in Table 5.

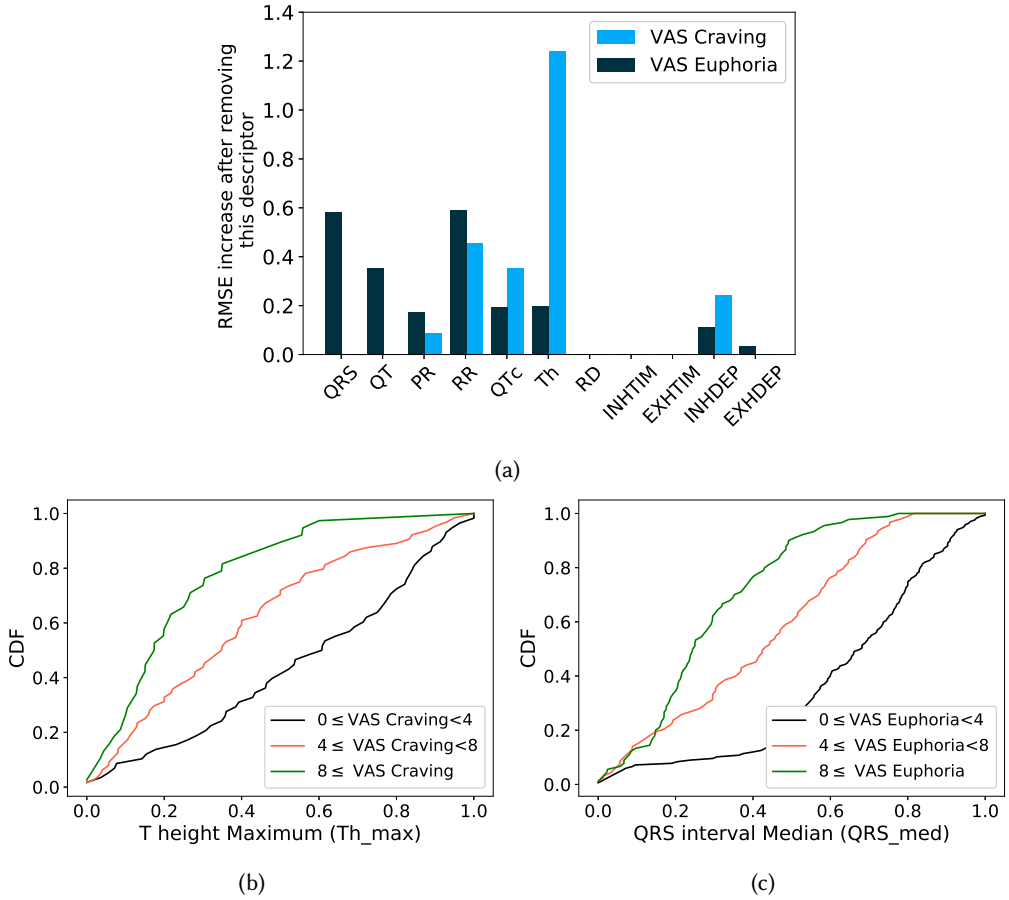


Fig. 9. (a) The importance of features corresponding to different morphological descriptors of ECG and BR for VAS Craving and Euphoria. The RMSE increase due to the removal of all the features corresponding to the morphological descriptors gives us a measure of the importance of that morphological descriptor. (b) The Cumulative Distribution Function (CDF) of the Maximum value of T Height which is normalized, with respect to VAS Craving score in three different ranges. (c) The CDF of the Median value of QRS interval which is normalized, with respect to VAS Euphoria score in three different ranges.

In this section, we aim to identify the key demographic factors that can impact the performance of our VAS Craving and Euphoria models by providing complementary information to the cardiac and respiratory features. We have added a demographic factor as an additional input to the model in addition to the top selected feature subset and observed the change in RMSE. A factor that brings important complementary information to the top selected feature subset will help the VAS Craving and Euphoria model to achieve higher performance (i.e., decrease RMSE). Rather than directly using the value of the demographic factor, we grouped subjects into two groups based on the median of this demographic factor and used the group id as an additional input. We have considered all 10 subjects data for this analysis. Figure 10a and 10b show the RMSE of different models where each of the demographic factors are used as an additional input. With the dashed line, these figures also show the RMSE of the best performing VAS Craving and Euphoria models with top selected feature subset without any

Factors		Statistics
Gender, n (%)	Male	8 (80)
	Female	2 (20)
Age, mean (SD)		43.1 (6.1)
Weight (lbs), mean (SD)		190.8 (29.7)
Years of Cocaine use, mean (SD)		19 (7.1)
Average dollar($) per cocaine use, mean (SD)		121.5 (75.3)
Average days of cocaine use per month, mean (SD)		19.3 (8.4)

Table 5. Demographic factors and statistics of 10 subjects. The statistics is presented either in the form of mean and standard deviation (SD) values or count and percentage values.

demographic factors.

Our analysis suggests that for both VAS Craving and VAS Euphoria, "Average $/use" as an additional feature yields the significant decrease in RMSE. The RMSE dropped from 1.93 to 1.85 in the case of VAS Craving and from 1.89 to 1.78 in VAS Euphoria. All the other demographic factor fails to yield a decrease in the RMSE for VAS Craving and Euphoria prediction. The average $ per use is a psychologically salient/convenient proxy for the amount of cocaine use (e.g., as compared to grams). It may reflect different cocaine use related phenomena, including severity of use and can also reflect tolerance and/or pharmacokinetic factors. In order to further investigate why exactly average $ per use helps to refine our cardiac and respiratory signal-based model and yields a lower RMSE, we explore if there is a statistically significant main effect between average $ per use and the VAS scores that they have reported. We categorize the average $ per use into two groups based on the median value. As can be seen in Figure 10c, Group 1, who spends more than median, tends to crave more as compared to Group 2, who spends less than the median. There is a statistically significant difference between the two groups ($p<0.05$). The members of Group 1, can be thought of as heavy cocaine users who are used to the high amount of cocaine. The heavy users in Group 1 tend to report a higher level of VAS Craving values. As a result, when average $ per cocaine use is used as an additional input feature, the VAS Craving model learned to adjust its craving inferences based on the factor. We also observed a similar statistically significant difference in the VAS Euphoria values between Group 1 and 2. The members of Group 1 who spend a higher $ amount on cocaine per use also clicked at a higher rate leading to a greater number of infusions during the self-administration session. This is most evident during the 32 mg session. More specifically, Group 1 reported higher VAS Euphoria values than Group 2 (as can be seen in Figure 10d). The latter findings are not consistent with tolerance or pharmacokinetic effects, but rather, suggest that Group 1 subjects are heavier users with attendantly larger levels of Craving and Euphoria.

6 PREDICTING DRUG-SEEKING BEHAVIOR VIA CLICK DENSITY

One intriguing signal that we obtain in our self-administration period is drug-seeking behavior, i.e., the pattern of clicks by the subject to request or seek an additional bolus of the drug. This drug-seeking behavior has been studied in animal behavior studies, particularly in rats [43, 52], but we are unaware of work that explores whether such drug-seeking behavior can be predicted using physiological sensor signals in human trials. While there are certain to be differences between drug-seeking via clicks in a lab study versus self-administration in a real-world setting, our exploration can provide initial insights into whether this behavior is predictable.

6.1 Relation between drug-seeking and craving

The first question we ask is whether intensity of drug-seeking behavior follows the intensity of craving. The link between drug-seeking and drug craving has been well-established and is illustrated by the addiction loop in

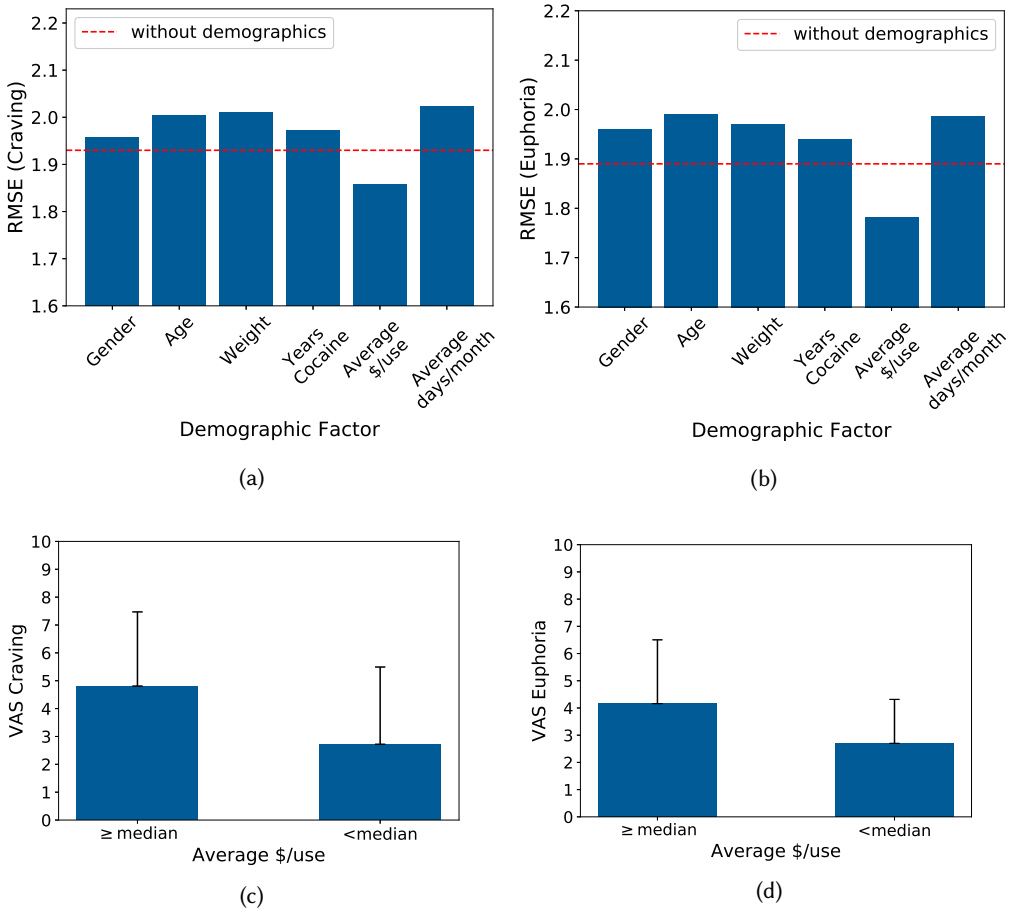


Fig. 10. (a) The influence of demographic factors on VAS Craving. The RMSE change due to the addition of a factor gives us a measure of the importance of that factor. Here we can see that only the addition of "Average $/use" decreases the RMSE from the model without any demographic factor (marked by the horizontal dotted red line). (b) The influence of demographic factors on VAS Euphoria. Similar to VAS Craving, we can see addition of "Average $/use" decreases the RMSE. (c) The bar plot showing that subjects whose "Average $/use" ≥ median on average crave more as compared to subjects with "Average $/use" < median ($p<0.05$) . (d) The bar plot showing that subjects whose "Average $/use" ≥ median on average feel more euphoric as compared to subjects with "Average $/use" < median ($p<0.05$) .

Figure 1[16]. This means our study should show some relation between VAS Craving and click frequency/density. In other words, if the subject experiences high craving, this should, in principle, lead to more intense drug-seeking behavior. We show that there is indeed a strong connection between the two variables i.e. when participants reported a higher craving level, they tended to click more frequently.

The error bars in Figure 11 show that click density increases with an increase in VAS Craving score. In order to explore whether the relationship between VAS Craving scores and click density is statistically significant, We conducted a one-way between subjects ANOVA between VAS Craving scores and click density across all the 0-10 VAS craving levels. Here, we compute click density as the total number of clicks in the ten minute window

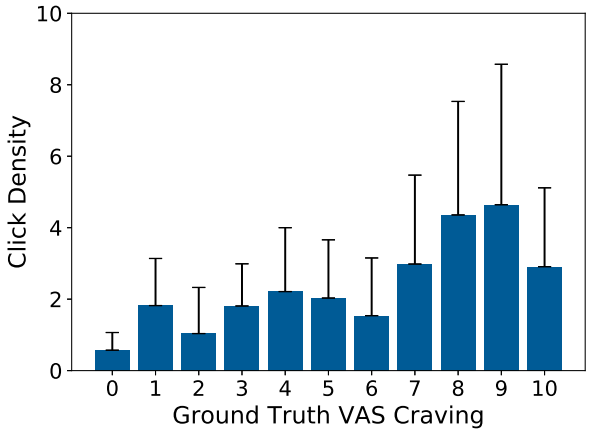


Fig. 11. shows the error bars of click density at different VAS Craving scores (0-10). The height of the bar represent the mean click density while the thin black line represents one standard deviation from the mean value.

prior to VAS Craving self-report. Our results showed that there was a significant main effect of VAS Craving on click density at the p<.0001 for all the 11 levels [F(10, 348) = 8.62, p = 1.31e-12]. Post hoc comparisons using the Tukey HSD test indicated that the mean score for the click densities associated with VAS Craving score of 8 and 9 is significantly different from the click densities associated with VAS Craving scores of less than 8. We note that the average click density of VAS Craving score of 10 does not follow the trend. This is primarily because very few participants reported a VAS Craving score of 10, which resulted in too few data points to draw a strong conclusion. Thus, our results suggest that our participants tend to click more as they report to feel a high level of craving via VAS Craving score.

6.2 Predicting drug-seeking from physiological signals

The strong relationship between VAS Craving and click density suggests that click density may be predictable from physiological sensor signals. This leads to the following questions: *Can we detect whether the participant will click in the current minute with the cardiac and respiratory signals? Do the cardiac and respiratory signals contain information about the participant's aggregate clicking behavior?* In this section we will demonstrate that the ECG and BR signals not only can capture the subjective feelings of cocaine craving and euphoria but also can explain drug-seeking behavior which is captured by the button clicking behavior of participants in our user study.

Figure 12 illustrates our click prediction model. The model has two stages – in the first stage, we train a binary click vs. no click classifier that predicts whether the person will click in a certain minute. In the second stage, the minute by minute click vs. no click inferences are then accumulated over a larger period of time to estimate click density. The model architecture for click prediction is very similar to the VAS model, with the only difference being click prediction is done for every minute (since the frequency is high) whereas VAS Craving and Euphoria predictions are done every five minutes. Similar to the VAS model, we run the same feature selection algorithm to select highly informative ECG and BR features which are then used to train the binary classifier. The click model also captures temporal changes of features by incorporating all the frames in the current and $(N-1)$ previous minutes, where N is the length of the window.

6.2.1 Click vs. No Click Classification. The binary click vs. no click classifier uses the cardiac and respiratory signals to predict whether a participant clicked in a certain minute or not. We find that our participants tend

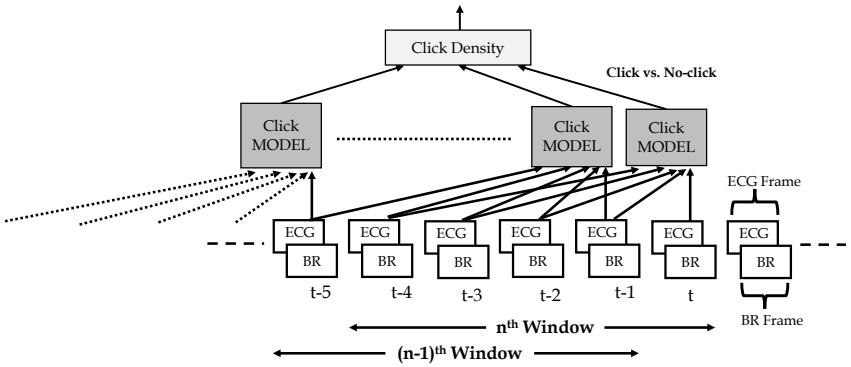


Fig. 12. illustrates the modeling approach we used for click prediction. Here we use a Window , N=5 minutes. The frame length = 1 minute, number of frames= 5. In each frame we are using ECG+BR features (the output of statistical quantifiers) as input to the model.

to click differently across sessions with different dosage levels. In sessions with lower dosage level (e.g., 8mg), our participants clicked twice as much as they clicked in session with higher dosage levels (e.g., 32mg). This observation can be intuitively explained. In lower dosage sessions, the small amount of cocaine in each bolus fails to satisfy the participants which results in clicking more frequently. In order to understand the usefulness of dosage information for click classification, we considered two types of models: a) Dosage Independent Click Model, and b) Dosage Dependent Click Model. In the Dosage Independent Model, we train a single model for click classification while in the Dosage Dependent Model we used three different models for each dosage levels (i.e., for 8, 16, and 32 mg). The predictions from these three models are combined to get complete click prediction for whole self-administration period and compare against dosage independent model. Similar to VAS models, we used SMOTE algorithm to balance the data instances for both the classes.

Type	Features	Model	F1 Score	Precision	Recall
Dosage Independent	-	Baseline	0.49	0.49	0.49
Dosage Independent	ECG+BR	Random Forest	0.54	0.54	0.55
Dosage Independent	ECG+BR	Neural Network (1 lnn)	0.65	0.63	0.65
Dosage Independent	ECG+BR	Support Vector Machine	0.68	0.67	0.70
Dosage Independent	ECG+BR	Logistic Regression	0.72	0.70	0.74
Dosage Independent	ECG	Logistic Regression	0.67	0.66	0.71
Dosage Independent	BR	Logistic Regression	0.58	0.58	0.59
Dosage Dependent	-	Baseline	0.56	0.55	0.56
Dosage Dependent	ECG+BR	Logistic Regression	0.80	0.79	0.82
Dosage Dependent	ECG	Logistic Regression	0.76	0.74	0.75
Dosage Dependent	BR	Logistic Regression	0.68	0.67	0.68

Table 6. The performance of binary click vs. no click classifier with different models and features. Values reported are after we average them across participants

Table 6 shows the performance of these two types of models with different feature groups in terms of average F1 Score, Precision and Recall from Leave-One-Subject-Out Cross-Validation (LOSOXV) experiments. Here, from

each participant we used 180 minutes of self-administration data with 60 minutes from each dosage level. As a baseline, we used a model very similar to the VAS baseline, where based on the training data, we learned the distribution of clicks and no-clicks. We then randomly predicted for test participant using this distribution.

Let us first look at the performance of the dosage independent model. The first observation we can make is that the random baseline model performs very poorly with a F1 score 0.49. Thus, prior click distribution alone fails to predict the clicking behavior whereas all dosage independent models outperform the random baseline model. However, the ECG and BR features do contain information about the click behavior that allows us to classify clicks significantly more accurately than random baseline. The best dosage independent model is a logistic regression model that uses both ECG and BR features. As can be seen in Table 6, this classifier achieves a F1 score of 0.72 with corresponding precision and recall being 0.70 and 0.74. We note that the reason for this model outperforming other more complex variants such as neural network, SVM and Random Forest could simply be because we have limited data to fit more complex models. Let us now look at the performance of the dosage dependent click model. As can be seen in Table 6, the dosage dependent model trained on top selected ECG and BR features outperforms the best dosage independent model by about 8% in F1 score. This model achieves an F1 score, precision and recall of 0.80, 0.79 and 0.82 respectively. These results confirm our previous observation that dosage level is indeed an important factor that effects clicking behavior. However, in order to know which among the three dosage level models to be used for a given data instance, we can use an automatic dosage or bolus amount detection model. In a recent work, Natarajan et al.[40] demonstrated that we can differentiate between different dosage levels of cocaine administration or usage with ECG features [40]. We can use the output of the dosage level detector as an input in the dosage dependent model.

In terms of feature importance we see the same trend as we have observed in VAS modeling. ECG features are generally more informative than BR features for click classification for both Dosage Independent and Dependent models. However, the fusion of ECG and BR features improves over just using ECG features showing that there is complementary information being captured in BR features.

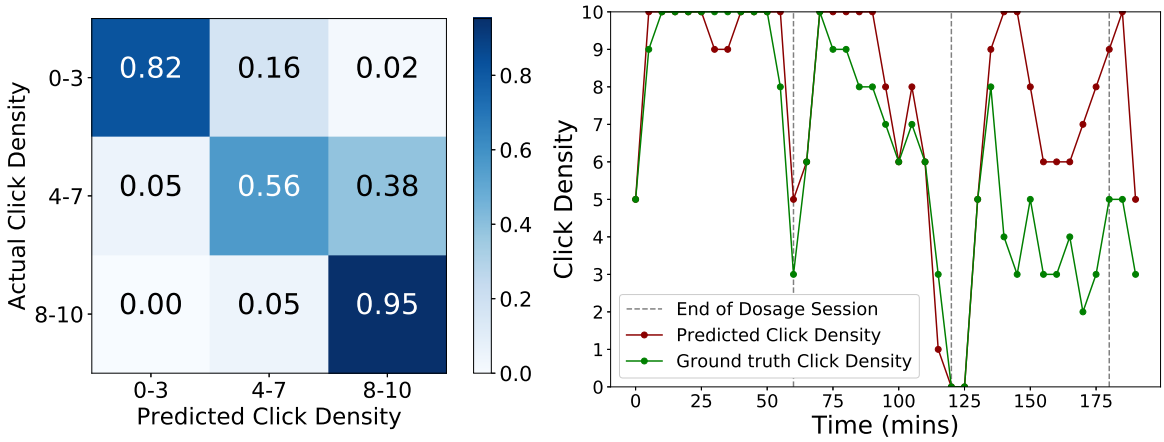


Fig. 13. (a) shows the confusion matrix of the click density across three different range bins. (b) shows over 3 hours of predicted and ground truth click density from the cardiac and respiratory data captured from participant id-3. Break period has been omitted from this timeline as participants cannot click then.

6.2.2 Click Density Estimation. We now look at how well we can estimate click density by aggregating the results from click classification. The click density is estimated by the total number of clicks in a time period of ten minutes. We run a LOSOXV experiment to classify clicks and estimate click density on the unseen participant. With the best dosage dependent click classifier, we find that the estimated click density is strongly correlated with the ground truth values with a Pearson correlation coefficient of 0.85 and an *RMSE* of 1.79. As we considered ten minute window to capture click density which means our click density score is in 0-10 range, the normalized root mean squared error (*NRMSE*) is 17.9%. Thus, our results suggest that our proposed dosage dependent click model can accurately predict the click density by using cardiac and respiratory features. With the best dosage independent classifier, we can predict the click density with a Pearson correlation coefficient of 0.78, *RMSE* of 2.15, and *NRMSE* of 21.5%. The dosage independent model performs slightly worse than dosage dependent model for click density estimation. However, only marginal decrease in the correlation coefficient and increase in *NRMSE* indicates that the overall click density trend can be captured reasonably accurately with the dosage independent click classifier as well.

We further investigate whether the predicted click density matches up with the ground truth values across different levels of click density. We binned click density scores into three groups [0-3],[4-7], and [8-10] and report the confusion matrix between predicted and actual click density in Figure 13a using best Dosage Dependent click model. It is evident from this confusion matrix that our click model performs very well when predicting scores in the range [0-3], and [8-10] with performance in [8-10] range being the best. While predicting in [4-7], our model gets confused with [8-10] scores but still largely does well.

To illustrate, Figure 13b shows the predicted and ground truth click density corresponding to the participant ID-3 for the entire duration of three self-administration sessions using best dosage dependent model. The predicted click density closely follows the trend of the ground truth values.

While

6.3 Implications for real-world interventions

Overall, our results suggest that drug-seeking behavior might indeed be predicted from peripheral physiological signals. While many more factors are likely to influence real-world drug-seeking behavior, including proximity to locations where drugs are or were previously available, the current work constitutes a promising first step towards developing sensor-based methods for just-in-time interventions for addictive behavior. Alternatively stated, our current work opens up the possibility to develop a classifier that might reliably and robustly identify (i.e., predict) drug craving states that predispose to relapse - such that clinical interventions might be targeted in a timely fashion so preserve sobriety. While such interventions have shown tremendous promise for other drugs of abuse (e.g., nicotine) to our knowledge, ours is the first to explore their feasibility for cocaine.

7 DISCUSSION

In this discussion section, we aim to highlight the new insights in terms of sensing, features, and methods that we have generated in our work. We will also dive deeper in the technical design and describe how our design could generalize across different application scenarios, different population (i.e., opioid users), different setting (i.e., outpatient) and different on-body wearable sensors with different form factors. Lastly, we will discuss the limitations and future works.

7.1 New Insights and Key Takeaways

There are several new insights and takeaways that we have generated in our work:

- ***The cardiac and respiratory signals contain information about different integral components of the Addiction Loop: Euphoria, Craving and Drug-seeking behavior.*** Most importantly, all the cardiac

and respiratory signals were captured by a low-cost wearable chest band. While there is some prior work on modeling craving in the context of smoking [13], we are unaware of prior work on continuous and passive sensing of craving, euphoria, and drug-seeking behavior for cocaine use with mobile and ubiquitous technology in a controlled laboratory setting.

- ***A significant milestone for our work was that we can accurately predict the Drug-seeking Behaviors (i.e., participant's "minute-by-minute" clicks and subsequently click density) simply from cardiac and respiratory signals.*** This is potentially exciting and surprising development for researchers and developer who aims to develop tools for predicting drug-seeking behavior (including the relapse to such behavior) with mobile and ubiquitous technology. To date, most of the research on understanding drug-seeking behavior has been done through experiments conducted on rodents. Our work was the first to show it is indeed possible to predict drug-seeking behavior in humans using sensor data in a lab setting during the self-administration period (section 6).
- ***The self-administration data collection can also give us further insights into how to measure an addict's micro-behaviors*** that are associated with the actions (i.e., clicks) and subjective feelings (i.e., VAS scores) during multiple binge intake sessions with multiple levels of dosage. ***Our participants tolerated the wearable sensors during Self-administration period*** which is done to model a real-world scenario of "binge" session where subjects have control over when to take cocaine and allows them to take various boluses within a short period of time.
- Instead of focusing on modeling, we focused on crafting and engineering different morphological features of ECG and BR waveforms in our work. ***We present a detailed analysis of the relative importance of physiological features for cocaine craving and euphoria modeling and demonstrate that such feature sets are distinctly different for craving and euphoria***. For example, our analysis shows that overall there is more information in ECG than in the BR channel. We also evaluated contribution of different individual morphological feature of ECG and BR features (section 5.3). With regards to these features, we are not aware of any prior work showing a relationship between the cardio-respiratory data and the drug-related states or behaviors (i.e., craving, euphoria, and drug-seeking behavior) for cocaine.
- ***We have systematically analyzed and identified the key demographic factors that impact the VAS Craving and Euphoria models.*** Our analysis shows that the "average dollar ($) spent per use" is a key background demographic factor that has a statistically significant main effect on how our participants scored VAS Craving and Euphoria value (in section 5.4). Our VAS models can fine tune it's prediction, simply by taking this background demographic factor as an additional input.

7.2 Generalizability across Different Populations, Real-World mHealth Applications and Wearables

The proposed on-body sensing solution for monitoring craving, euphoria and drug-seeking behavior has been validated in the context of a controlled clinical environment. A real-world mHealth application where our work is potentially transferable is to use our methods on abstinent cocaine users and to predict their craving and vulnerability to relapse (i.e., recurrent drug use behavior). Such a passive and continuous craving model could also facilitate early interventions (e.g., the subject receiving a text message asking them to attend a self-help group or, for a patient with opioid use disorder, reminding them risks of overdoses/importance of having a Narcan kit available).

Our method is also potentially transferable to other wearable devices that allow us to capture ECG and breathing accurately. There are several such off-the-shelf solutions in the market, such as Hexoskin smart shirt [2], Equivital LifeMonitor [1]. For example, Hexoskin smart garment (in a form factor of a shirt) can be comfortably worn and can continuously and passively collect ECG and breathing data with its built-in 3-lead ECG (with dry electrodes), Respiration Inductance Plethysmography (RIP) bands. One of the major challenges of *Zephyr* chest band was

that it requires relatively tight contact with the body for capturing high-quality data. Although our participants in the laboratory study have tolerated the chest band well, solutions like Hexoskin smart shirt might be preferred for real-world studies.

Another interesting insight from our work that can inform future prototypes is that ECG is more informative about craving, euphoria and drug-seeking behavior than BR. In recent times, increasingly more wearable devices (e.g., Apple watch or Alphabet's new smartwatch) are enabling customers to take an ECG recording directly from the wrist just with a finger touch. In the future, we aim to validate our models with these new smartwatches. The addition of ECG in the consumer-grade wearable devices will enable us to collect a large-scale ECG dataset with ground truth measurements of craving, euphoria and drug-seeking behavior in the real-world settings. We also aim to develop an app based intervention model which identifies craving or drug-seeking moments and trigger Just-in-Time intervention.

In order to get further insights into the potential generalizability of our findings for the development of real world applications, we conducted informal interviews. We talked with several addiction psychiatrists/addiction experts. Upon explaining our results and findings, we asked these domain experts to share their views on how our findings may or may not apply in the broader context of real world application development. Some of their notable responses are listed below:

- **Addiction Researcher 1:** "I think that a wearable monitor which predicts craving and cocaine self-administration could be very helpful for clinicians. If such a device were found to be reliable, it could be used to monitor early treatment response and therefore could allow clinicians to more rapidly optimize patient care (rather than waiting for patients to relapse as an indication that a given treatment isn't working). Furthermore, wearable monitors are already used in other disciplines (e.g. holter monitors in cardiology) and could easily be extended to addiction care."
- **Addiction Researcher 2:** "If the wearable sensors could predict potential relapse in the short-term, I suppose, it could also be used as a mechanism for patients to receive some form of biofeedback, and then use relapse prevention techniques to prevent relapse. It could also help people to better understand what their triggers for relapse are."
- **Addiction Researcher 3:** "Wearable technology is ubiquitous and acceptable in a variety of situations. Chest straps are routinely worn during exercise and other monitoring. Watches are expanding capabilities to monitor for a variety of heart-related conditions. These wearable technologies may have a major impact on the future of healthcare as so many are now routinely wearing them. Applying this technology to the substance use field, particularly for real-time detection of various physiologic and emotional states, would provide much-needed information that could expand our understanding of substance use disorders."

7.3 Limitations and Future Opportunity

Despite the encouraging results for cardio-respiratory signal-based craving, euphoria and drug-seeking behavior modeling, we need to be cautious while interpreting the result. We have collected the sensor data from 10 expert cocaine users who had at least a decade-long of experience in cocaine use. While the current sample size ($N = 10$) is typical for such a human laboratory study (considering the risk, cost, recruitment difficulties, and large pharmacological effect), we cannot completely rule out the possibility that our findings are unique to the current cohort and that testing of our model in a second human laboratory cohort is warranted. For example, it will be interesting to explore whether the craving and euphoria models trained on expert cocaine users will generalize across new cocaine users. Whether long term cocaine use changes aspects of our brain that causes the heartbeat and breathing signal to change over time, is something that warrants further study in the future.

Another major limitation of our study is that a large outpatient naturalistic design was not employed. While the controlled experiments allowed us to monitor the cardio-respiratory changes of our participants during

self-administration sessions in a safe and secure environment while frequently sampling (every 5 minutes) their subjective VAS craving and euphoria scores over a long period of time (i.e., 6 hours), it is not clear if our participants would tolerate that frequent sampling in the real-world setting and whether the frequent sampling would substantially degrade the quality of the VAS scores. Similarly, drug-seeking behavior could be measured through the button click mechanism in our study. Future work would also need to standardize unit measurements in order to have an equivalent outcome of click measure of drug-seeking behavior could be recorded in the real-world setting as well and whether there are any other proxy variable for drug-seeking behavior that can be employed in the real-world. As a result, a new study and ubiquitous computing tools need to be designed to collect both the sensor data and information about the drug-induced internal state from a large population in a scalable manner. For example, most cocaine use in the real world involves smoked (i.e., crack) cocaine and methods for the tracking of outpatient cocaine use (e.g., perhaps methods that combined respiratory, cardiac and psycho-/locomotor approaches) need to be developed. Collecting such a real-world large-scale dataset also requires multi-disciplinary and possibly multi-institutional efforts. We are currently actively working towards such an effort.

From a modeling perspective, there are several things that we aim to do. For example, to make use of the temporal information, we aim to use Conditional Random Field (CRF) and Long Short-Term Memory (LSTM) models. The effectiveness of these relatively more complex models can be properly evaluated only after we collect a larger dataset. Currently, we extracted the ECG and BR features from fixed morphological descriptors which have the advantage of being easier to interpret by the domain experts from Addiction psychiatry and cardiology. In the future, we aim to explore features collected from the wavelet transformation of the physiological signals to capture subtle information of the raw waveform.

8 CONCLUSION

In this paper, we have demonstrated that cardiac and respiratory signals captured from a wearable sensor can be used to predict subjective craving and euphoria levels. While the state-of-the-art ubiquitous computing platforms developed for addiction research primarily focuses on detecting drug use or administration, this paper takes a significant leap by demonstrating that it is possible to accurately model cocaine-induced subjective states (e.g., craving and euphoria) as well as compulsive drug-seeking behavior with continuous and passive physiological measurements. Our wearable solution shows considerable promise for monitoring and potentially developing holistic models of the complex relationships between drug craving, euphoria, and drug-seeking behavior in the real world setting.

We train two linear regression models for VAS craving and euphoria score prediction which achieve a normalized RMSE of respectively 17.6% and 16.7% from LOSOXV experiments. With respect to Pearson correlation coefficient, they achieve 0.49 and 0.73 respectively. The high fidelity of VAS Craving and Euphoria prediction is achieved by simple linear models with carefully designed cardiac and respiratory features which makes them easy to deploy and less susceptible to over-fitting problem. We present a detailed analysis of the relative importance of physiological features for cocaine craving and euphoria modeling and demonstrate that such feature sets are distinctly different for craving and euphoria. The "average dollar ($) per use" is identified as a key demographic factor that can improve the performance of our VAS Craving and Euphoria models. Lastly, we model drug-seeking behavior using cardiac and respiratory signals. Specifically, we demonstrate that the features extracted from physiological signals can be used to predict participant button clicks with an F1 score of 0.80 and estimate different levels of click density with a correlation coefficient of 0.85 and an normalized RMSE of 17.9%.

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