Effects of Transdermal Electrical Nerve Stimulation on Sleep and Mood

by

Ceasar Udave

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved November 2018 by the
Graduate Supervisory Committee:

William Tyler, Chair
Christopher Buneo
Sarah Wyckoff

ARIZONA STATE UNIVERSITY

December 2018

ABSTRACT

Sleep is an essential human function. Modern day society has made it so that sleep is prioritized less and less. Professionals in critical positions such as doctors, nurses, and emergency medical technicians can often have hectic schedules that are unforgiving toward sleep due to the increase in shift work that dominates these fields. Sleep deficits can have detrimental effects on one's psyche and mood. Depression and anxiety both have high comorbidity rates with insomnia because of sleeping deficits. Transdermal Electrical Nerve Stimulation (TENS) offers a potential solution to improving sleep quality and mood by modulating the ascending reticular activating system (RAS). This system starts in the anterior portion of the head with trigeminal nerve branches and is stimulated using a 500-550 Hz waveform.

In this experiment Positive Affect and Negative Affect Schedule (PANAS) scores are recorded daily to monitor mood differences between pre and post treatment (TENS vs Sham). PANAS scores were found to be insignificant between groups. Pittsburgh Sleep Quality Index (PSQI), and Fitbit were chosen to study perceived sleep, and objective sleep. Both PSQI, and Fitbit found insignificant differences between TENS and Sham. Finally, the Beck Depression and Beck Anxiety Inventories were administered weekly to determine if there are immediate changes to depressive and anxiety symptom, after a week of treatment (TENS vs Sham). A significant difference was found between the pre and post of the TENS treatment group. The TENS group was not found to be significantly different from Sham, potentially the result of a placebo effect. These results were found with n=10 participants in the TENS treatment group and n=6 in the sham group.

ACKNOWLEDGMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Sleep is an essential part of everyday life, yet society is developing in such a way that sleep is prioritized less and less. Ferrie et al. propose that society is quickly becoming a 24/7 endeavor with people working at all hours (Ferrie,1). The increase in shift work has led to an increase in sleep disorders with over 30% of adults reporting some type of insomnia (Ferrie,1). Policemen, doctors, and even astronauts suffer from sleep deprivation, which can lead to a critical drop in performance ability (Gordon,2). Doctors and nurses that committed to a full overnight shift had a 16% decrease in performance from the beginning of their shift to the end of their on-call shift (Gordon,1). The American Sleep Association reports that 10-15% of fatal car accidents were caused by a drowsy driver (Sleep Statistics,1). Taylor et al. have found that insomnia has proven comorbidities with depression and anxiety (Taylor,1). Those with insomnia were almost 10 times as likely to have depression, and 17 times as likely to have anxiety (Taylor,1). It is apparent that solutions need to be found to help people correct their sleep patterns, and remedy sleep conditions. A solution worth exploring is transdermal electrical nerve stimulation of key cranial nerves.

Non-invasive methods of cranial nerve stimulation have been heavily studied and have been present in the United States of America since the 1960's when the first use of cranial electrotherapy stimulation (CES) was used and referred to as "Electrosleep" (Guleyupoglu,1). The United States Food and Drug Administration (FDA) classified CES devices as class III requiring pre-market approval in 1976 (Federal Register, 3752). After public hearings, the FDA reclassified CES devices as class II with special controls

(Federal Register, 3753). Specifically, any device that is used for the treatment of insomnia and anxiety was classified as a class II device as the devices have shown general effectiveness for use in these areas (Federal Register, 3753). CES devices for use in depression are still classified as class III and require pre-market approval (Federal Register, 3753).

The Neuros device manufactured by Cerevast is a CE, European Conformity, class IIa CES device and is the primary device used in this experiment (Cerevast,2). CES devices operate via TENS and apply electrical current to the user's head to stimulate cranial nerves. Branches of the trigeminal nerve that run through the anterior portion of the head are the primary target of Neuros (Cerevast,3). These branches send signals to the ascending reticular activating system (RAS), a system that receives sensory input and transmits the information to the cortex to regulate sleep wake cycles, arousal, and alertness (Cerevast 3). The RAS originates in the upper brain stem and has connections to key structures such as the pons, thalamus, and terminates at the cortex (Schwarz,2). The RAS includes the pedunculopontine nucleus (PPN) the locus coerleus (LC), and the raphe nuclei (Cerevast,3). These structures are responsible for gate regulation and triggering of sleep/wake cycles, arousal, and awareness due to their connections to and modulation of the reticular nucleus of the thalamus (Schwartz,2). To stimulate the RAS branch, the Neuros stimulator targets the trigeminal sensory nuclear complex (TSNC) by stimulating the trigeminal nerve branches located in the anterior portion of the head (Cerevast, 3). The fact that these branches can be stimulated non-invasively is a large advantage to the device, making it user friendly, and most importantly user safe (Cerevast,4).

2

The experiment was designed to replicate and extend research on the impact of TENS on sleep and mood in the short term as compared to a sham condition during a short-term two-week intervention. The idea that the Neuros can be used to correct sleep and mood in the short term is a novel approach, rather than using stimulation as a solution to insomnia. The idea here being that it can be used to lessen the symptoms of stress based temporary insomnia. Sleep was measured using the traditional Pittsburgh Sleep Quality Index, and the Fitbit-Charge 2 sleep quality module. This module provided values for key metrics such as: time in minutes to sleep onset measured from the completion of stimulation, wake after sleep onset (WASO) total minutes, wake up quantity, and total sleep duration. Mood impacts were measured using three assessments: the Positive Affect and Negative Affect Schedule, the Beck Depression Inventory, and the Beck Anxiety Inventory. A product by the name of Neuros manufactured by Cerevast was used in the treatment condition for subjects.

It is hypothesized that WASO, and wakefulness periods of the sleep cycle will reduce in treatment patients. PANAS scores are expected to tend toward high positive affect values and lower negative affect values. Beck Anxiety and Beck Depression Inventory scores are expected to be in the minimum, or mild ranges of their expected scales after a week of stimulation.

The second experiment involved collecting audio files from participants every day to determine the accuracy in mood reading APIs such as IBM Watson or Beyond Verbal. Scores from these two apps would be used and compared against the clinical mood assessments to determine efficacy of the technology. These results are not presented in this Master's thesis.

3

A tertiary aim for this study was to develop a workflow to scale the study to large scale by developing a software backend for the study with a company named Trialomics. A backend was created that administered and scored surveys, recorded stored and parsed audio files, and aggregated data from Fitbits that were linked to participants individual accounts. By having a software backend that served as a one stop area for all study materials, it is anticipated that subjects will be more compliant and easier to train. Creating a backend that stores data digitally allows the scaling of the study to obtain larger participant populations.

The work presented in this master's thesis builds upon the work of several pre-print open source papers that aim to understand the effects of TENS and determine its usability. In Paneri et al 2016, 100 subjects received a TENS or sham treatment once a day for 5 days (Paneri,5). The main goal of the study was to determine the occurrence of adverse events during TENS (Paneri,1). It was found that there was no significant statistical difference to suggest that active TENS treatment had a higher rate of adverse events than sham in areas such as: mildly tingling (during session), mild burning (during session), itching (within session), headaches (within session), and headache (between sessions) (Paneri, 11-19). Mild burning and mild tingling reported higher in sham groups than in either treatment group (Cerevast,5). Data on sensations felt were also recorded in the current investigation but is not reported in this document.

Tyler et al. conducted a series of experiments designed to determine if TENS can lower criteria on the Profile of Mood State (PMOS) survey (Tyler,1). The stimulator used in this experiment were a predecessor to the Neuros used in the experiments outlined in this paper called Thync that had similar waveform parameters (Tyler,13). Subjects were

4

given a resting period, a treatment period, then asked to fill out the PMOS (Tyler,13-14). This experiment looked at negative sub-scales such as: tension-anxiety, anger-hostility, depression-dejection, fatigue-inertia, and vigor-activity (Tyler,3). The data showed that TENS significantly reduced stress-tension in comparison to sham groups (Tyler,3). In the current study, Beck Anxiety and PANAS surveys are used to monitor mood positivity and negativity as well as anxiety to determine if the results seen in the Tyler investigation are supported. A key difference between the two studies is that Tyler et. all measure an immediate before and after for participant stimulation, in this investigation weekly change is looked at for PANAS and Beck Anxiety.

CHAPTER 2

METHODS

Participants

All participants in this study were human volunteers using protocols that were

approved of by the Arizona State University Institutional Review Board (STUDY

00008350) under the office of Research Integrity and Assurance. Participants were

recruited primarily from the Tyler Lab research subject pool and word or mouth referrals.

Inclusion criteria. General inclusion criteria included: adult males and females

aged 18-65, able to give consent, and a full-time worker, full-time student, OR the

combination of a part-time student and worker. All subjects were screened using an

online questionnaire through REDCap software and brief interview.

Exclusion criteria. Potential participants were excluded from the study if they

endorsed any of the following criteria: no daily access to a PC desktop/laptop or

smartphone with Internet access, currently undergoing treatment or medication for

neurological or psychological disorder, including addiction, a medical implant (such as a

pacemaker, cochlear implant, brain stimulation device), history of migraines or frequent

headaches, history of panic attack or acute anxiety disorder, history of fainting (vaso-

vagal syncope or neurocardiogenic syncope), Raynaud's disease, tempomandibular joint

(TMJ) disorder or other facial neuropathy, history of concussions or brain injury, history

of significant face/head injury or cranial or facial metal plate or screw implants, history

of hospitalization for neurological or psychological disorder, recent hospitalization for

surgery/illness, vision or hearing that is uncorrectable (corrected vision or hearing is

okay), pregnant, recent drug or alcohol treatment, high blood pressure, heart disease, or diabetes, a diagnosed sleep disorder, or taking prescription medication for sleep.

Eligible subjects were scheduled for individualized training sessions where the study and its expectations were thoroughly discussed, and consent was acquired prior to experimentation. All subjects were provided necessary training on the various hardware, apps, and surveys that they would be using. Participants were randomly assigned to the treatment or sham conditions.

Assessments

Positive and Negative Affect Schedule (PANAS). The state version of the PANAS is a self-report 20-item questionnaire that assesses momentary positive and negative emotions on a 1-5 point Likert-Scale (Krohne, Egloff, Kohlmann, & Tausch, 1996). PANAS scores were collected every evening to understand patient mood, and how it changed daily. Daily scores were averaged to produce a Baseline (day 1), Pre-treatment (day 2-8), and Post-treatment (day 9-14) score. Ultimately these scores can show how subjects' moods are variant in the baseline and whether pTES has effects that make their mood more consistent, or improves their mood, in the short term.

Beck Depression Inventory (BDI-II). The BDI-II is a 10-minute, 21-item, self-report questionnaire assessing depression symptoms over a one week period using statements assigned a 0-3 point value (Beck, 1996). The BDI-II scores were collected at three time points: Baseline (day 1), Pre-treatment (day 8), and Post-treatment (day 14) to determine whether there was an effect from the stimulation on depression among the participants.

Beck Anxiety Inventories (BAI). The BAI is a 10-minute, 21-item, self-report questionnaire assessing anxiety symptoms over a one week period using a 0-3 rating scale corresponding to a response of "not at all", "mildly", "moderately", and "severely" (Beck, 1990). The BAI scores were collected at three time points: Baseline (day 1), Pre-treatment (day 8), and Post-treatment (day 14) to determine whether there was an effect from the stimulation on anxiety among the participants.

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a seven domain (19 item) self-rated questionnaire evaluating usual sleep habits during the last week. The seven domain scores including: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, daytime dysfunction, sleep fragmentation, and use of sleep aid medications; and combine to provide a global sleep quality index score. The possible scores range from 0–21. PSQI scores were collected at three time points: Baseline (day 1), Pre-treatment (day 8), and Post-treatment (day 14) to determine whether there was an effect from the stimulation on sleep among the participants. All surveys are administered and processed for scoring in a database created for the survey by Picard.io, a HIPPA compliant software company. Picard's integration is explained in figure 1. An example of Picard's user interface is seen in figure 2.
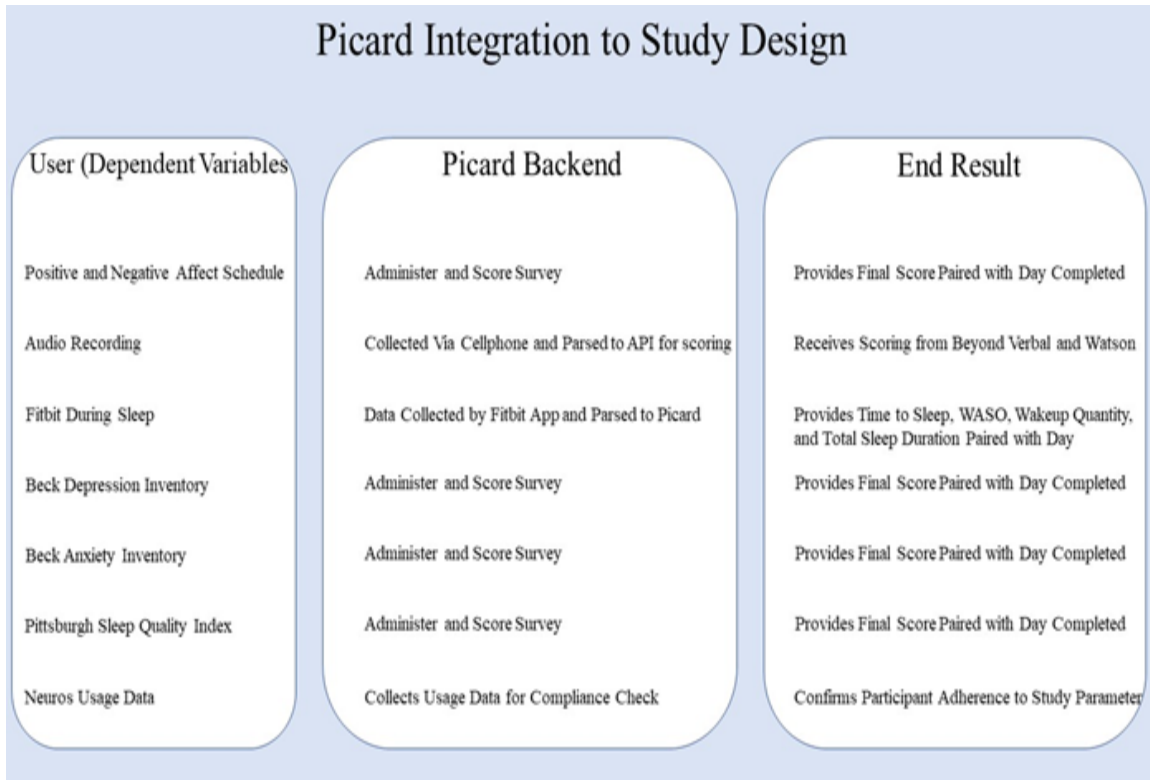
Figure. 1. Picard Integration to Study Design. A block diagram explaining the needs Picard fills in the study. Rather than administer all the surveys by paper, Picard builds a database that holds and scores the surveys. An additional benefit of Picard is its ability to integrate multiple platforms such as directly from user, Fitbit, and Cerevast's Neuros

Neuros Model 1 Feedback Questionnaire. This is a 5-item self-report questionnaire to elicit user feedback about the Neuros the manual/tutorials, stimulation intensity settings, operational ease, sensation/tolerability, and effectiveness. This assessment was emailed to participants following the completion of the study.

User	1	2	3	4	5	6	7	8	9	10	11	12	13	14
PANAS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PSQI	✓						✓							✓
Beck Anxiety	✓						✓							✓
Beck Depression	✓						✓							✓
Audio	▶	▶	▶	▶	▶	▶	▶	▶	▶	▶	▶	▶	▶	▶
Neuros	✗	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✓	✓	✓
Fitbit	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗

Figure. 2. Example Compliance Screenshot. An example how integrating all the user data into a single table can be used to check compliance of individual participants. Picard also provides the ability to email participants in the event they are at risk of failing to comply.

Devices

Fitbit. Fitbit was used as a method of actigraphy to determine participant sleep quality. Four metrics were collected: time in minutes to sleep onset measured from the completion of the Neuros session (only examined during days 8-14), wake after sleep onset (WASO), quantity of wakeups, and sleep duration. According to Fitbit documentation, the variable "startTime" is an indicator of when the user fell asleep. Time in minutes to sleep onset was measured from the time the Neuros stimulation began to the time that Fitbit "startTime" begins, 15 minutes are subtracted from this value because that is the length of one Neuros session. WASO was collected using a variable called "ToFallAsleep". Quantity of wakeups was measured using the variable

"summary.awake". Lastly, total sleep duration was measured with a variable called "duration". Participants were required to wear the Fitbit during sleep throughout the study (day 1-14). Scores were averaged at three time points for the above metrics: baseline (day 1), Pre-Treatment (days 2-7), Post-Treatment (days 8-14).

   Neuros. The Neuros device, seen in figure 1, manufactured by Cerevast is a CE, European Conformity, class IIa CES device that uses low-energy, pulsed electrical stimulation to enhance relaxation and sleep [7,8]. The stimulation created by the hardware was a biphasic, or pulsed, current of 4 mA on average with a frequency of 500-550 Hz. Stimulation levels were adjustable, and each participant was told to adjust to their comfort level. Participants were required to use the study device for 15 minutes prior to bed during the second week of the study (day 8-14). Figure 3 shows the placement of Neuros on the participant.
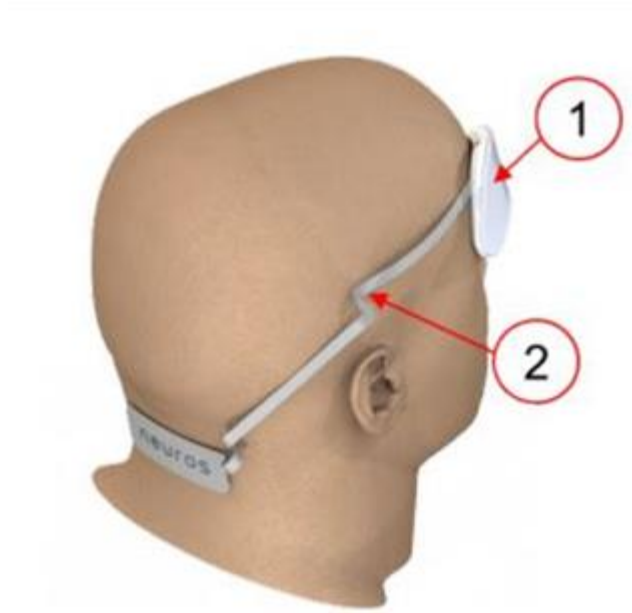
Figure. 3. Neuros Placement Graphic. This graphic was used with permission from Cerevast. Placement of the Neuros as recommended by the manufacturer Cerevast, 1 shows the Neuros module which contains the electronics, rechargeable battery, and connects to the limited use strip electrode assembly, or strip, at arrow 2. The strip contains the electrodes needed to stimulate trigeminal nerves (V1, V2) and the cervical nerves near vertebrae C2 and C3.

CHAPTER 3

RESULTS

The primary aim for this study was to determine effect of TENS on sleep habits

and quality. The PSQI is a clinically validated self-reported sleep assessment that was

given to participants weekly, and the results of this survey are shown in table 1. The

results of the self-reported sleep assessment show that there were no significant

differences between groups initially. The overall time, group interaction shows

significance with a p-value of 0.013 but there were no significant changes between

groups for TENS treatment versus sham treatment and there were no significant

differences for before and after results for active treatment but sham treatment

approaches significance. The TENS treatment had no significant effects on perceived

sleep quality in a week. Fitbit data was also recorded, and several metrics were used to

determine objective quantitative sleep data. Table 2 shows a summation of the statistics

regarding Fitbit. Fitbit echoes the results of the PSQI with only light sleep minutes being

statistically significant in the time, group interaction. There were no significant

differences between groups for any of the metrics measured with Fitbit. There was a

significant decrease in light sleep for the sham group in time, but this was not significant

compared to the active treatment group.

Table. 1.

Results of a mixed model repeated measures statistical analysis. Time and Group were treated as covariates, with treatment (TENS or Sham) as independent variables and results of the PSQI as the dependent variable. Significance was seen in the time group interaction with a p-value of 0.013, and near significance was seen in the time comparison of the sham group. Neither result was statistically significant between groups.

Main Effects		Time				Time * Group				Group		
		df	F	p		df	F	p		df	F	p
Pittsburgh Sleep Quality Index		2,13	0.301	0.745		2,13	2.727	0.013		1,14	1.047	0.323

Between Goup Effects	Active Group M(SD)			Sham Group M(SD)				Baseline		Pre		Post	
	Baseline	Pre	Post	Baseline	Pre	Post	df	F	p	F	p	F	p
Pittsburgh Sleep Quality Index	10.30 (5.50)	10.60 (6.36)	7.40 (5.13)	6.50 (1.52)	6.83 (2.79)	8.17 (3.43)	1,14	2.673	1.24	1.847	0.196	0.105	0.751

With Groups Effects (Time)	Active Group			BL - Pre		Pre - Post		Sham Group M(SD)		BL - Pre		Pre - Post	
	df	F	p	Dif	p	Dif	p	F	p	Dif	p	Dif	p
Pittsburgh Sleep Quality Index	2,8	2.256	0.167	-.03	0.807	3.2	0.103	2.336	0.213	-0.333	0.709	-1.333	0.062

Table. 2.

Results of a mixed model repeated measures statistical analysis. Time and Group were treated as covariates, with treatment (TENS or Sham) as independent variables and results of the Fitbit metrics as the dependent variables. Significance was seen in the time group interaction of light sleep duration with a p-value of 0.03 and was seen in the time comparison of the sham group with a p-value of 0.014. Neither result was statistically significant between groups.

Main Effects	Time				Time * Group				Group		
	df	F	p		df	F	p		df	F	p
FITwazo	1,14	0.451	0.513		1,14	1.056	0.322		1,14	0.11	0.745
FITwakeup	1,14	1.913	0.188		1,14	0.148	0.706		1,14	0.604	0.45
FITduration	1,14	0.247	0.627		1,14	0.546	0.472		1,14	0.016	0.9
FITrem	1,14	0.165	0.691		1,14	0.708	0.414		1,14	0.1	0.757
FITlight	1,14	1.768	0.205		1,14	5.867	0.03		1,14	0.469	0.505
FITdeep	1,14	0.387	0.544		1,14	2.992	0.106		1,14	1.209	0.29

Between Goup Effects	Active Group M(SD)			Sham Group M(SD)					Pre		Post
	Pre	Post		Pre	Post		df	F	p	F	p
FITwazo	57.61 (13.23)	56..69 (11.73)		56.76 (8.23)	61.14 (11.38)		1,14	0.02	0.89	0.551	0.47
FITwakeup	25.18 (6.00)	26.05 (6.37)		26.96 (4.58)	28.5 (3.6)		1,14	0.388	0.543	0.734	0.406
FITduration	395.77 (42.96)	339.48 (50.80)		391.38 (38.12)	403.05 (31.73)		1,14	0.042	0.84	0.17	0.686
FITrem	76.07 (19.28)	78.28 (17.71)		82.81 (13.27)	76.49 (20.55)		1,14	0.564	0.465	0.034	0.856
FITlight	257.81 (42.46)	249.77 (39.24)		227.34 (33.50)	254.83 (35.90)		1,14	2.247	0.156	0.066	0.801
FITdeep	68.14 (14.1)	71.88 (11.39)		81.33 (15.35)	73.40 (18.78)		1,14	3.079	0.101	0.041	0.842

With Groups Effects (Time)	Active Group					Sham Group M(SD)			
	df	F	Pre-Post Dif	p		df	F	Pre-Post Dif	p
FITwazo	1,9	0.059	0.919	0.814		1,5	5.649	-4.382	0.063
FITwakeup	1,9	0.475	-0.87	0.508		1,5	4.479	1.5	0.088
FITduration	1,9	0.03	2.281	0.866		1,5	1.303	-11.668	0.305
FITrem	1,9	0.118	-2.206	0.739		1,5	0.711	6.322	0.438
FITlight	1,9	0.601	8.035	0.458		1,5	13.483	-27.593	0.014
FITdeep	1,9	0.682	-3.736	0.43		1,5	3.449	-7.937	0.122

Quality of life improvement was another aim for the study using Positive and Negative Affect Schedule scores to determine day to day differences, if any, from figure 4 and figure 5. The PANAS results report that there are no statistical differences between the sham group and treatment group for positive mood scores or negative mood scores. There were no significant differences prior to administering the treatments, nor were there significant differences after the participants began to be monitored. These results do show that positive affect trended toward being statistically significant between the two groups, according to the mixed model repeated measure results in table 3. Both had a mean increase in positive affect, but the treatment group tends toward having a greater impact. Figures 4 and 5 show the group interactions overtime. Positive affect trends positively, away from baseline and sham that trend negatively and follow each other. These graphs have no statistically significant values but offer an alternative way to see the data. It is also interesting to note that the negative affect graph shows that the active treatment group stay, on average, below the sham group.

Table. 3. Results of a mixed model repeated measures statistical analysis. Time and Group were treated as covariates, with treatment (TENS or Sham) as independent variables and results of the PANAS positive affect (PANAS+) and negative affect (PANAS-) as the dependent variables. Near significance was seen between groups in the PANAS+ scores.

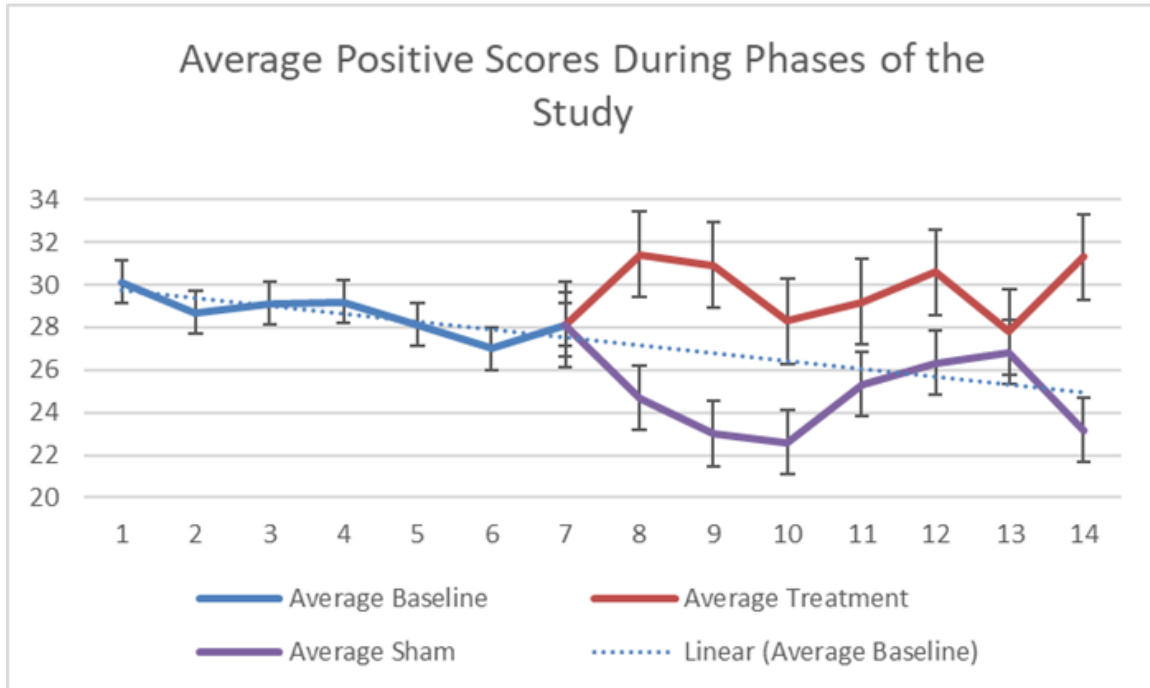| Main Effects	Time				Time * Group				Group		
	df	F	p		df	F	p		df	F	p
PANAS+	1,14	0.314	0.584		1,14	0.246	0.628		1,14	3.56	0.08
PANAS-	1,14	0.774	0.394		1,14	1.386	0.259		1,14	0.056	0.817
Between Goup Effects	Active Group M(SD)		Sham Group M(SD)				Pre			Post	
	Pre	Post	Pre	Post		df	F	p		F	p
PANAS+	31.13 (7.08)	29.93 (7.72)	24.45 (3.85)	24.38 (5.94)		1,14	4.457	0.053		2.268	0.154
PANAS-	13.97 (3.66)	12.43 (1.99)	13.40 (2.51)	13.63 (3.42)		1,14	0.111	0.744		0.803	0.385
With Groups Effects (Time)	Active Group					Sham Group M(SD)					
	df	F	Pre-Post Dif	p		df	F	Pre-Post Dif	p		
PANAS+	1,9	0.652	1.2	0.44		1,5	0.002	0.073	0.964		
PANAS-	1,9	2.049	1.542	0.186		1,5	0.11	-0.223	0.753		

Figure. 4. A plot of positive affect PANAS scores over duration of the study. Baseline points are averaged amongst all 16 participants while TENS (Treatment) and Sham only include their respective n's 10 and 6. Error bars were created with one standard deviation of the averages, and a trend line was made to represent the direction the baseline is expected to continue.
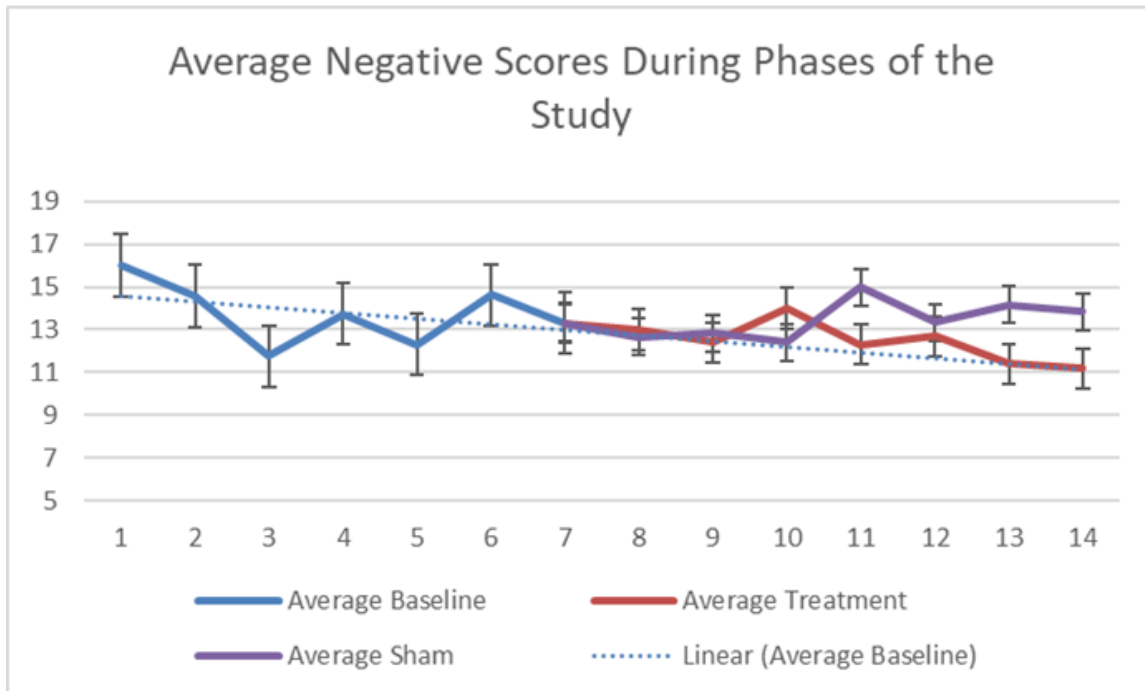
Figure 5. A plot of negative affect PANAS scores over duration of the study. Baseline points are averaged amongst all 16 participants while TENS (Treatment) and Sham only include their respective n's 10 and 6. Error bars were created with one standard deviation of the averages, and a trend line was made to represent the direction the baseline is expected to continue.

Depression and anxiety are co-morbidities as discussed in the introduction of this thesis. Therefore, both were examined using the Beck Depression and Beck Anxiety Inventories. The results for these surveys are shown in table 4. Overall for the Beck Depression and Beck Anxiety groups there were no statistical differences between sham and treatment groups. An interesting result is a statistically significant difference between pre and post Beck Anxiety Inventory scores for TENS treated participants. The TENS group did have reduced anxiety levels, but these were not statistically significant when compared to the sham group.

Table. 4. Results of a mixed model repeated measures statistical analysis. Time and Group were treated as covariates, with treatment (TENS or Sham) as independent variables and results of the Beck Depression Inventory and Beck Anxiety Inventory score metrics as the dependent variables. Significance was seen in the time group interaction of both inventories with a p-values of 0.038 and .01. Neither inventory was significant between groups, but the active sham has significance between pre and post in the time group.

Main Effects	Time				Time * Group				Group			
	df	F	p		df	F	p		df	F	p	
Beck Depression Inventroy	2,13	0.701	0.514		2,13	4.253	0.038		1,14	0.05	0.826	
Beck Anxiety Inventroy	2,13	3.727	0.063		2,13	6.659	0.01		1,14	0.117	0.738	

Between Goup Effects	Active Group M(SD)			Sham Group M(SD)				Baseline		Pre		Post	
	Baseline	Pre	Post	Baseline	Pre	Post	df	F	p	F	p	F	p
Beck Depression Inventroy	4.60 (3.89)	5.50 (4.60)	4.50 (4.43)	6.50 (5.75)	3.00 (3.69)	3.83 (5.62)	1,14	0.628	0.441	1.269	0.279	0.069	0.796
Beck Anxiety Inventroy	7.80 (4.57)	8.20 (8.03)	4.30 (4.99)	7.17 (3.25)	4.50 (2.35)	6.17 (3.55)	1,14	0.088	0.772	1.184	0.295	0.638	0.438

With Groups Effects (Time)	Active Group			BL - Pre		Pre - Post		Sham Group M(SD)		BL - Pre		Pre - Post	
	df	F	p	Dif	p	Dif	p	F	p	Dif	p	Dif	p
Beck Depression Inventroy	2,8	0.968	0.42	-0.9	0.43	1.00	0.213	6.066	0.061	3.5	0.205	-0.833	0.637
Beck Anxiety Inventroy	2,8	14.584	0.002	-0.4	0.827	3.9	0.006	2.362	0.21	2.667	0.121	-1.667	0.141

CHAPTER 4

DISCUSSION

PSQI

An interesting observation in the PSQI data can be seen in the time group interaction. Active PSQI scores trend negatively (higher scores) while sham scores fail to trend at all. One of the recurring weaknesses of the study is the number of individuals enrolled. It could be that there is not enough of a sample size to determine differences in these various metrics, but with the sample size present the beginnings of trends can be seen in every group.

A weakness of the PSQI test is in its self-reporting nature. Many of the participants I talked to would follow up with me and talk to me about how they are feeling during the study. I noticed that many people commented that their sleep was far from ideal yet many reported low PSQI scores. I think one failure of the PSQI as a metric is that the primary participant population were college aged students. Many of whom do not face sleep issues such as "Cannot breathe comfortably" or "Cough or Snore Loudly" that are more common to an older population, or those with sleep apnea. If time permitted, it would be interesting to see statistical differences between groups for each question asked on each assessment. I also anticipated a larger placebo effect on self-reported sleep seeing as the sham did administer a very brief pulse of stimulation to the sham participants, but it appears to have had very little effect on perceived sleep quality. The fact that the sham was active can also be a source of variability. Tyler et al. reported that stimulation of any sort can have tangible effects in subject populations, no matter how short, or shape of the waveform (Tyler,13).

Additionally, due to issues with the backend development several scores reported -1 for PSQI. -1 is not a valid value and at the time of writing this thesis the cause of the bug is unknown. An assumption was made that the -1 values were meant to be 0 for processing the data, should the bug be corrected the thesis will be corrected with new results.

Fitbit

The Fitbit results are metrics that do not look like they will benefit from additional subjects. The primary aim of using the Fitbit was to objectively see if periods of wakefulness while asleep decreased and if total sleep duration became more normal 420-480 minutes, 7-8 hours, of sleep per night is the recommended average sleep duration one should have. WASO and number of wakeups were key metrics in this study. Sham treatment was the only group that approached significance in any of its values, with light sleep having a significant pre/post difference. There is no way to measure sleep without the Fitbit but based on feedback from participants some found it more difficult to sleep while wearing the Fitbit, with one participant even claiming, "I almost quit the study because I hated the feeling of the Fitbit."

Lastly the Picard data collection service that was used to collect Fitbit seemed to randomly drop days from participants. Originally Picard would only remove data if the participant went to sleep after 3am or slept for less than 4 hours yet data was still missing even in subjects that confirmed they met these criteria. This is one of a few bugs that were encountered in the data collection process that may have impacted the results of this study.

Another factor to consider was that in the weeks of September and October in which these participants' data were being collected, midterms were common. Two participants dropped from the study due to failing to sleep more than 4 hours for two nights. These two were filtered out but there could have been others that slept just long enough to still qualify for the study, while sacrificing sleep to prepare for midterm exams. used to collect Fitbit seemed to randomly drop days from participants. Originally Picard would only remove data if the participant went to sleep after 3am or slept for less than 4 hours yet data was still missing even in subjects that confirmed they met these criteria. This is one of a few bugs that were encountered in the data collection process that may have impacted the results of this study.

PANAS

PANAS scores were one of the major metrics to indicate how mood was changing in the short term due to their daily measurement. One weakness in the PANAS analysis could have been averaging weekly values and comparing pre/post. Perhaps any change is being lost in the process of averaging the data due to some participants starting with fairly high scores in the 30's and some starting in low twenties. A participant who starts high would not be expected to increase by much. An inclusion criterion could be added for participants that believe their sleep quality is affecting their mood but there is no way to check this. The point may also be moot since many people that signed up and completed this study would agree with this statement, only a small percentage of the participants (1-3 of 16) claimed to be sleeping enough before the study.

PANAS scores were also recorded from participants at the same time audio recordings took place. A significant factor to consider is that some participants had

phones that were not compatible with Picard's mobile recording, mostly older model iPhones. These participants tried many times to record and could not and would end up emailing me in frustration. This combined with several Android glitches that caused timers to misrepresent time or force participants to re-record 2 minutes of audio may have affected the PANAS scores that were recorded the same day. I did not ask participants in what order they submitted their audio and PANAS but it is very likely that a participant could have struggled to submit an audio file, which in turn caused them to fill out their PANAS form in frustration and skewed the results.

Overall the PANAS does show some trending so perhaps the issue lays in sample size of the population.

Beck Depression and Beck Anxiety Inventories

There was one group, TENS group and Beck Anxiety Inventory, where there was a significant increase in the score. This contradicts the hypothesis of this study and results found in other publications. This could be due to several reasons including: midterm exams taking place during the study, participants feeling uncomfortable with the stimulator technology or sensation, or general fluctuations week to week since the increase was not statistically different from the sham group. The p-value for differences between sham and treatment was 0.738 which is not close to the target 0.05 which further suggests that the significance found for the group was likely an adverse effect.

The Beck Anxiety inventory could have been affected by participants worrying about filling the form out. Many participants were unsure if their data was coming through and were anxious despite my telling them they were compliant. It is impossible to know what the scores on the surveys would show if filling them out didn't add a

worrisome obligation, especially on a platform that may fail in other aspects such as the audio recording.

The Beck Depression inventory was wholly uneventful with only the overall time group interaction showing significance but no significance upon further inspection between groups or within groups.

CHAPTER 5

CONCLUSION

Though the experiment yielded negative results there are several things that can be approved upon in future study design. As this thesis is being written there are more participants providing data to increases sample sizes. Given more time to test and develop the back end with Picard could reduce participant frustration with submitting their surveys and remove the possibility that participating in the study has an inherent influence on the measures. In follow-up studies a more diverse population should be chosen. Though exclusion criteria allow for a diverse group, college students should be considered for exclusion since their schedules are inherently fluctuating. The author is confident that this study has laid out preliminary groundwork for a future study that is more in-depth amongst a greater population of people.

REFERENCES

Boasso, Alyssa M., et al. "Transdermal Electrical Neuromodulation of the Trigeminal Sensory Nuclear Complex Improves Sleep Quality and Mood." *BioRxiv*, 2016, doi:10.1101/043901.

Cerevast Medical, Pulsed Transdermal Electrical Stimulation (pTES): An Overview. Cerevast Medical inc., 2018, pp. 1-21.

Ferrie, J. E., et al. "Sleep Epidemiology--a Rapidly Growing Field." *International Journal of Epidemiology*, vol. 40, no. 6, Jan. 2011, pp. 1431–1437., doi:10.1093/ije/dyr203.

Gordon, James A., et al. "Does Simulator-Based Clinical Performance Correlate With Actual Hospital Behavior? The Effect of Extended Work Hours on Patient Care Provided by Medical Interns." *Academic Medicine*, vol. 85, no. 10, 2010, pp. 1583–1588., doi:10.1097/acm.0b013e3181f073f0.

Guleyupoglu, Berkan, et al. "Classification of Methods in Transcranial Electrical Stimulation (TES) and Evolving Strategy from Historical Approaches to Contemporary Innovations." *Journal of Neuroscience Methods*, vol. 219, no. 2, 2013, pp. 297–311., doi:10.1016/j.jneumeth.2013.07.016.

"Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Intended To Treat Insomnia and/or Anxiety; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Intended To Treat Depression." *Federal Register*, 22 Jan. 2016, www.federalregister.gov/documents/2016/01/22/2016-01173/neurological-devices-reclassification-of-cranial-electrotherapy-stimulator-intended-to-treat.

Paneri, Bhaskar, et al. "The Tolerability of Transcranial Electrical Stimulation Used across Extended Periods in a Naturalistic Context by Healthy Individuals." Apr. 2015, doi:10.7287/peerj.preprints.1097.

Schwartz, Jonathan, and Thomas Roth. "Neurophysiology of Sleep and Wakefulness: Basic Science and Clinical Implications." *Current Neuropharmacology*, vol. 6, no. 4, Jan. 2008, pp. 367–378., doi:10.2174/157015908787386050.

"Sleep Statistics - Research & Treatments | American Sleep Assoc." *American Sleep Association*, www.sleepassociation.org/about-sleep/sleep-statistics/.

Taylor, Daniel J., et al. "Epidemiology of Insomnia, Depression, and Anxiety." *Sleep*, vol. 28, no. 11, 2005, pp. 1457–1464., doi:10.1093/sleep/28.11.1457.

Tyler, William J., et al. "Transdermal Neuromodulation of Noradrenergic Activity Suppresses Psychophysiological and Biochemical Stress Responses in Humans." *Scientific Reports*, vol. 5, no. 1, Oct. 2015, doi:10.1038/srep13865.

APPENDIX A

DEFENSE SLIDES

Effects of Transdermal Electrical Nerve Stimulation (TENS) on Sleep and Mood

CEASAR UDAVE

The Problem

- ▶ Prioritization of sleep has been reduced.
- ▶ Some level of insomnia due to shift work in adults: 30%
- ▶ Chronic insomnia in adults: 10%
- ▶ Fatal motor-vehicle crashes due to sleepiness: 10-15%
- ▶ Predicted number of global motor vehicle deaths: 2.3 Million
- ▶ Number of deaths in US due to medical errors: 100,000
- ▶ Decrease in doctor's performance from beginning of on-call to end of on call (can be up to 30 hours): 20%

Summarized from [1], [2], [3], [4]

Background

- The Reticular Activating System (RAS) regulates sensory input information from the brainstem to the cortex.
- By regulating sensory input sleep/wake cycles, arousal, alertness, attention, and sensorimotor activity are also regulated.
- Includes:
  - Cholinergic neurons of Pedunculopontine Nucleus (PPN). Shown to mediate REM.
  - Noradrenergic neurons of Locus Coeruleus (LC) shown to trigger sleep/wake states.
 - Serotonergic neurons of the Raphi Nuclei (RN)

[5],[6],[7],[8],[9]

Background

Reticular Activating System

Projections into cerebral cortex

Visual impulses

Auditory impulses

Reticular formation

Ascending sensory tracts (pain, touch, temperature)

Descending motor signals to spinal cord
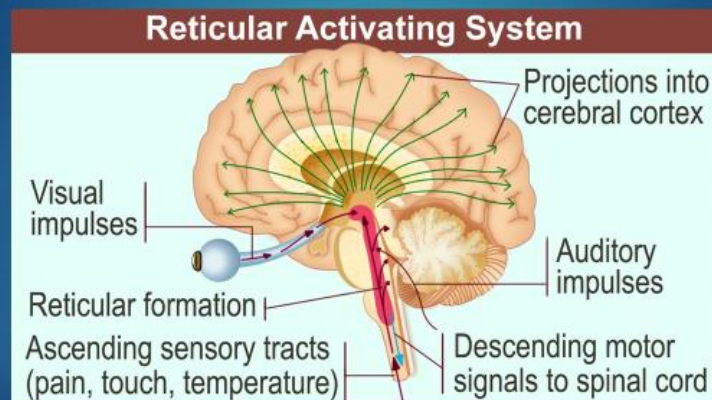
Graphic from bodytonomy.com

The Device- Neuros

1. The Neuros module which contains the electronics, rechargeable battery, and connects to the limited use strip electrode assembly.

2. The strip contains the electrodes needed to stimulate trigeminal nerves (V1, V2) and the cervical nerves near vertebrae C2 and C3.
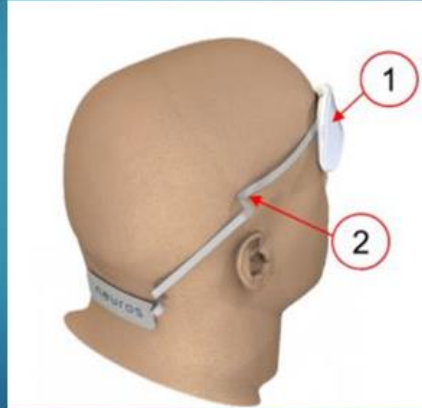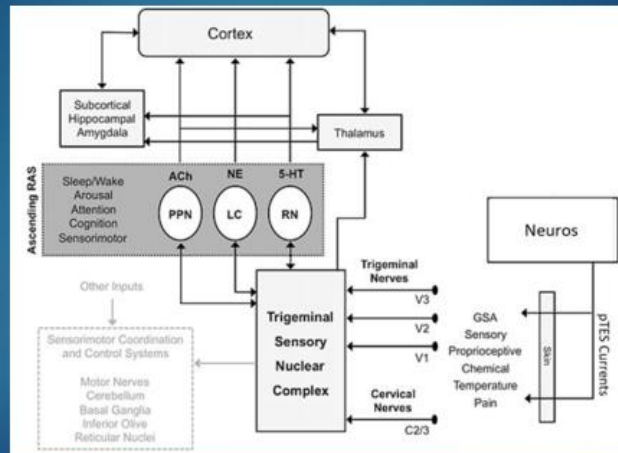

Used with permission from Cerevast. [5]

The Device cont.

▶ Specifications of the Neuros:
- ▶ Current: 0- 4 mA, 20 steps of intensity
- ▶ Recommended Current: 1.6 mA (intensity of 8)
- ▶ Frequency: 500-550 Hz
- ▶ Duty Cycle- Not Specified for Neuros, 50% Duty Cycle for previous model, Thync.

[5]

Neuros Interface

Used with Permission from Cerevast. [5]

Picard Integration to Study Design

User (Dependent Variables)	Picard Backend	End Result
Positive and Negative Affect Schedule	Administer and Score Survey	Provides Final Score Paired with Day Completed
Audio Recording	Collected Via Cellphone and Parsed to API for scoring	Receives Scoring from Beyond Verbal and Watson
Fitbit During Sleep	Data Collected by Fitbit App and Parsed to Picard	Provides Time to Sleep, WASO, Wakeup Quantity, and Total Sleep Duration Paired with Day
Beck Depression Inventory	Administer and Score Survey	Provides Final Score Paired with Day Completed
Beck Anxiety Inventory	Administer and Score Survey	Provides Final Score Paired with Day Completed
Pittsburgh Sleep Quality Index	Administer and Score Survey	Provides Final Score Paired with Day Completed
Neuros Usage Data	Collects Usage Data for Compliance Check	Confirms Participant Adherence to Study Parameter

Results- PSQI

Main Effects	Time				Time * Group				Group		
	df	F	p		df	F	p		df	F	p
Pittsburgh Sleep Quality Index	2.13	0.301	0.745		2.13	2.727	0.013		1.14	1.047	0.323

Between Goup Effects	Active Group M(SD)			Sham Group M(SD)				Baseline		Pre		Post	
	Baseline	Pre	Post	Baseline	Pre	Post	df	F	p	F	p	F	p
Pittsburgh Sleep Quality Index	10.30 (5.50)	10.60 (6.36)	7.40 (5.13)	6.50 (1.52)	6.83 (2.79)	8.17 (3.43)	1.14	2.673	1.24	1.847	0.196	0.105	0.751

With Groups Effects (Time)	Active Group			BL - Pre		Pre - Post		Sham Group M(SD)		BL - Pre		Pre - Post	
	df	F	p	Dif	p	Dif	p	F	p	Dif	p	Dif	p
Pittsburgh Sleep Quality Index	2.8	2.256	0.167	-0.3	0.807	3.2	0.103	2.336	0.213	-0.333	0.709	-1.333	0.062

Results Fitibit

Main Effects	Time				Time * Group				Group		
	df	F	p		df	F	p		df	F	p
FITwaso	1,14	0.451	0.513		1,14	1.056	0.322		1,14	0.11	0.745
FITwakeup	1,14	1.913	0.188		1,14	0.148	0.706		1,14	0.604	0.45
FITduration	1,14	0.247	0.627		1,14	0.546	0.472		1,14	0.016	0.9
FITrem	1,14	0.165	0.691		1,14	0.708	0.414		1,14	0.1	0.757
FITlight	1,14	1.768	0.205		1,14	5.867	0.03		1,14	0.469	0.505
FITdeep	1,14	0.387	0.544		1,14	2.992	0.106		1,14	1.209	0.29

Between Goup Effects	Active Group M(SD)			Sham Group M(SD)			Pre		Post	
	Pre	Post		Pre	Post	df	F	p	F	p
FITwaso	57.61 (13.23)	56..69 (11.73)		56.76 (8.23)	61.14 (11.38)	1,14	0.02	0.89	0.551	0.47
FITwakeup	25.18 (6.00)	26.05 (6.37)		26.96 (4.58)	28.5 (3.6)	1,14	0.388	0.543	0.734	0.406
FITduration	395.77 (42.96)	339.48 (50.80)		391.38 (38.12)	403.05 (31.73)	1,14	0.042	0.84	0.17	0.686
FITrem	76.07 (19.28)	78.28 (17.71)		82.81 (13.27)	76.49 (20.55)	1,14	0.564	0.465	0.034	0.856
FITlight	257.81 (42.46)	249.77 (39.24)		227.34 (33.50)	254.83 (35.90)	1,14	2.247	0.156	0.066	0.801
FITdeep	68.14 (14.1)	71.88 (11.39)		81.33 (15.35)	73.40 (18.78)	1,14	3.079	0.101	0.041	0.842

With Groups Effects (Time)	Active Group				Sham Group M(SD)			
	df	F	Pre-Post Dif	p	df	F	Pre-Post Dif	p
FITwaso	1,9	0.059	0.919	0.814	1,5	5.649	-4.382	0.063
FITwakeup	1,9	0.475	-0.87	0.508	1,5	4.479	1.5	0.088
FITduration	1,9	0.03	2.281	0.866	1,5	1.303	-11.668	0.305
FITrem	1,9	0.118	-2.206	0.739	1,5	0.711	6.322	0.438
FITlight	1,9	0.601	8.035	0.458	1,5	13.483	-27.593	0.014
FITdeep	1,9	0.682	-3.736	0.43	1,5	3.449	-7.937	0.122

Results PANAS

Main Effects	Time				Time * Group				Group		
	df	F	p		df	F	p		df	F	p
PANAS+	1,14	0.314	0.584		1,14	0.246	0.628		1,14	3.56	0.08
PANAS-	1,14	0.774	0.394		1,14	1.386	0.259		1,14	0.056	0.817

Between Goup Effects	Active Group M(SD)		Sham Group M(SD)			Pre			Post	
	Pre	Post	Pre	Post		df	F	p	F	p
PANAS+	31.13 (7.08)	29.93 (7.72)	24.45 (3.85)	24.38 (5.94)		1,14	4.457	0.053	2.268	0.154
PANAS-	13.97 (3.66)	12.43 (1.99)	13.40 (2.51)	13.63 (3.42)		1,14	0.111	0.744	0.803	0.385

With Groups Effects (Time)	Active Group				Sham Group M(SD)			
	df	F	Pre-Post Dif	p	df	F	Pre-Post Dif	p
PANAS+	1,9	0.652	1.2	0.44	1,5	0.002	0.073	0.964
PANAS-	1,9	2.049	1.542	0.186	1,5	0.11	-0.223	0.753

Results PANAS cont.

Average Positive Scores During Phases of the Study

Average Negative Scores During Phases of the Study
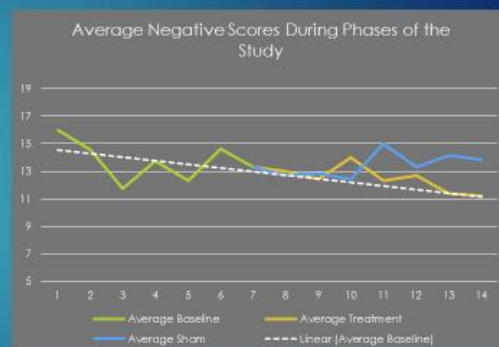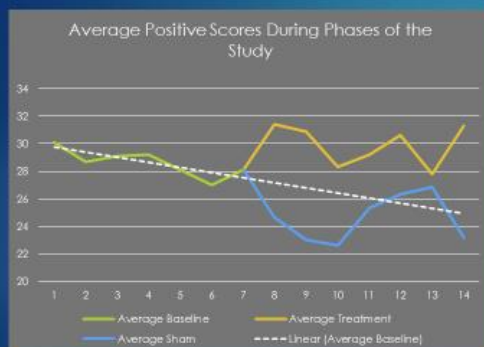
Results Beck Anxiety/Depression Inventory

Main Effects	Time			Time * Group			Group		
	df	F	p	df	F	p	df	F	p
Beck Depression Inventroy	2.13	0.701	0.514	2.13	4.253	0.038	1,14	0.05	0.826
Beck Anxiety Inventroy	2.13	3.727	0.053	2.13	6.659	0.01	1,14	0.117	0.738

Between Goup Effects	Active Group M(SD)			Sham Group M(SD)			Baseline			Pre		Post	
	Baseline	Pre	Post	Baseline	Pre	Post	df	F	p	F	p	F	p
Beck Depression Inventroy	4.60 (3.89)	5.50 (4.60)	4.50 (4.43)	6.50 (5.75)	3.00 (3.69)	3.83 (5.62)	1,14	0.628	0.441	1.269	0.279	0.069	0.796
Beck Anxiety Inventroy	7.80 (4.57)	8.20 (6.03)	4.30 (4.99)	7.17 (3.25)	4.50 (2.35)	6.17 (3.55)	1,14	0.088	0.772	1.184	0.295	0.638	0.438

With Groups Effects (Time)	Active Group			BL - Pre		Pre - Post		Sham Group M(SD)		BL - Pre		Pre - Post	
	df	F	p	Dif	p	Dif	p	F	p	Dif	p	Dif	p
Beck Depression Inventroy	2.8	0.968	0.42	-0.9	0.43	1.00	0.213	6.066	0.061	3.5	0.205	-0.833	0.637
Beck Anxiety Inventroy	2.8	14.584	0.002	-0.4	0.827	3.9	0.004	2.362	0.21	2.667	0.121	-1.667	0.141

Improvements

- Low N
- Addition of time to sleep onset as metric
- Backend Glitches, Improvements
  - Fitbit data truncated if participant sleeps in "incorrect" position
  - Allow participant to see previous day's tasks.
  - Keep running statistics for all participants, and all data.
- Participant reporting of abnormalities
  - I went to a party last night.
  - I had just received some bad news about work.
  - My midterm was the next day.
- Stricter Adherence guidelines
  - Try to choose time frames to eliminate important dates to the participant.
- Check for other ways to normalize data.
- Active Sham, use of placebo sham (inactive sham)
- Long term effects

Sources

[1] J. Ferrie, M. Kumari, P. Salo, A. Singh-Manoux and M. Kivimaki, "Sleep epidemiology--a rapidly growing field", *International Journal of Epidemiology*, vol. 40, no. 6, pp. 1431-1437, 2011.

[2] J. Gordon, E. Alexander, S. Lockley, E. Flynn-Evans, S. Venkatan, C. Landrigan and C. Czeisler, "Does Simulator-Based Clinical Performance Correlate With Actual Hospital Behavior? The Effect of Extended Work Hours on Patient Care Provided by Medical Interns", *Academic Medicine*, vol. 85, no. 10, pp. 1583-1588, 2010.

[3] "Sleep Statistics - Research & Treatments | American Sleep Assoc", *American Sleep Association, 2018*. [Online]. Available: https://www.sleepassociation.org/about-sleep/sleep-statistics/. [Accessed: 20- Sep- 2018].

[4] Taylor, Daniel & L Lichstein, Kenneth & Durrence, Heith & W Reidel, Brant & Bush, Andrew. (2005). Epidemiology of Insomnia, Depression, and Anxiety. Sleep. 28. 1457-64. 10.1093/sleep/28.11.1457.

[5] Pulsed Transdermal Electrical Stimulation (pTES): An Overview. Cerevast Medical Inc., 2018, pp. 1-21.

[6] A. Boasso, H. Mortimore, R. Silva, L. Aven and W. Tyler, "Transdermal Electrical Neuromodulation of the Trigeminal Sensory Nuclear Complex Improves Sleep Quality and Mood", *bioRxiv*, 2016.

[7] J. Schwartz and T. Roth, "Neurophysiology of Sleep and Wakefulness: Basic Science and Clinical Implications", *Current Neuropharmacology*, vol. 6, no. 4, pp. 367-378, 2008.

[8] Paneri B, Khadka N, Patel V, Thomas C, Tyler W, Parra LC, Bikson M. (2015) "The tolerability of transcranial electrical stimulation used across extended periods in a naturalistic context by healthy individuals". *PeerJ PrePrints* 3:e1097v2 https://doi.org/10.7287/peerj.preprints.1097v2

[9] W. Tyler, A. Boasso, H. Mortimore, R. Silva, J. Charlesworth, M. Marlin, K. Aebersold, L. Aven, D. Wetmore and S. Pal, "Transdermal neuromodulation of noradrenergic activity suppresses psychophysiological and biochemical stress responses in humans", *Scientific Reports*, vol. 5, no. 1, 2015.

APPENDIX B

IRB AND IRB RELATED DOCUMENTS

IRB Number: HRP 503b

1 Protocol Title

Effects of Transdermal Electrical Nerve Stimulation (TENS) on Sleep and Mood

2 Background and Objectives

Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

- Describe the purpose, specific aims, or objectives.
- State the hypotheses to be tested.
- Describe the relevant prior experience and gaps in current knowledge.
- Describe any relevant preliminary data.

Transdermal electrical nerve stimulation (TENS) and pulsed transdermal electrical stimulation (pTES) devices are becoming increasingly popular therapeutic options due to their low invasiveness and low associated risk of use. For these same reasons, the FDA has approved many electrotherapy stimulation devices for use in the fields of pain relief, anxiety, depression, and sleep assistance. Many devices are even approved as recreational devices due to their low risk of adverse effects.

Many studies done on the topic of nerve stimulation look for results in the long-term and specify through continued use of the devices that results are seen. An interesting question that should be addressed is whether these devices produce short-term impacts that can help users adjust sleep and behavior. A long-term study using a device called Thync showed that over a time of 1,386 days improvement in sleep was seen when the Thync device was used to stimulate the trigeminal sensory nuclear complex in 99 healthy individuals (Boasso et al., 2016). Thync has since restructured into a new device called Neuros created by Cerevast Medical Inc. It is with these devices that a follow up study should be conducted with similar experiments testing sleep quality, anxiety, and depression in the short-term. If improvements are seen and sustained in a short-term context then psychologically people can become less dependent on the devices and can treat them as an as needed therapy.

Another interesting aspect of this study is the use of machine learning applications that determine mood based on subjects' voices (Beyond Verbal, IBM Watson, etc.) and text (IBM Watson). This data will be analyzed and compared to gold standards such as Positive and Negative Affect Schedule, Beck Anxiety Inventory, and Beck Depression Inventory. Beyond Verbal is the only application thus far to be a clinically proven application for vocal biomarkers in depression. By comparing the other applications to gold standards, a small review of these methods can be compiled and commentary on the reliability of these applications in their current state can be made.

The primary purpose of this study is to add knowledge on the short-term effects of these therapies. The treatments themselves have already been FDA approved and long-term effects have already shown clinical significance. Using the knowledge from this study, nerve stimulating devices such as Neuros may be able to recommend different therapy regiments for healthy individuals who need temporary assistance adjusting their sleep cycles or find themselves in a bout of depression. There is a lot to be learned from these minimal risk devices.

References
Ben-Menachem E (2001) Vagus Nerve Stimulation, Side Effects, and Long-Term Safety. Journal of Clinical Neurophysiology 18:415-418.
Ben-Menachem E, Revesz D, Simon BJ, Silberstein S (2015) Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. Eur J Neurol 22:1260-1268.
Boasso AM, Mortimore H, Silva R, Aven L, Tyler WJ (2016) Transdermal electrical neuromodulation of the trigeminal sensory nuclear complex improves sleep quality and mood. bioRxiv.
Merrill DR, Bikson M, Jefferys JG (2005) Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J Neurosci Methods 141:171-198.

3   Data Use

Describe how the data will be used. Examples include:
- Dissertation, Thesis, Undergraduate honors project
- Publication/journal article, conferences/presentations
- Results released to agency or organization
- Results released to participants/parents
- Results released to employer or school
- Other (describe)

The data collected in this study will primarily be used as a master's thesis by Ceasar Udave in the School of Biological and Health Systems Engineering Biomedical Engineering master's program. Upon completion of thesis defense, the thesis will be submitted for publication in November 2018 to peer reviewed journals related to engineering, neuromodulation, and neurosciences.

4	**Inclusion and Exclusion Criteria**
	Describe the inclusion and the exclusion criteria for the study.
	Describe how individuals will be screened for eligibility.
	Indicate specifically whether you will target or exclude each of the following special populations:
	• Minors (individuals who are under the age of 18)
	• Adults who are unable to consent
	• Pregnant women
	• Prisoners
	• Native Americans
	• Undocumented individuals

Inclusion criteria
- Only adult males and females aged 18-65 will be enrolled.
- All adults will be able to give consent.
- Be full-time worker, full-time student, OR the combination of a part-time student and worker discussed in the phone interview.
- All eligible study participants will be screened for eligibility using an online questionnaire through REDCap software or telephone interview prior to scheduling, consent, and enrollment or exclusion.

Exclusion criteria
- No daily access to a PC desktop/laptop or smartphone with Internet access.
- Currently undergoing treatment or medication for neurological or psychological disorder, including addiction
- Has a medical implant (such as a pacemaker, cochlear implant, brain stimulation device)
- History of migraines or frequent headaches
- History of panic attack or acute anxiety disorder
- Fainting (vaso-vagal syncope or neurocardiogenic syncope)
- Raynaud's disease
- Tempomandibular joint (TMJ) disorder or other facial neuropathy
- History of concussions or brain injury
- History of significant face/head injury or if you have cranial or facial metal plate or screw implants
- History of hospitalization for neurological or psychological disorder
- Recent hospitalization for surgery/illness
- Vision or hearing that is uncorrectable (corrected vision or hearing is okay)
- Pregnant
- Recent drug or alcohol treatment
- High blood pressure, heart disease, or diabetes
- Diagnosed with sleep disorder
- Taking prescription medication for sleep

5	**Number of Participants**
	Indicate the total number of participants to be recruited and enrolled
	• Provide a rationale for the proposed enrollment number
	• What percentage of screened individuals will likely qualify for the study?

For this study 50 total participants will be the target number. According to power analysis run in RStudio a minimum participant number of 16 is necessary to show an effect of approximately 10% with 90% confidence. We anticipate that 100 people will need to be screened to meet the exclusion criteria. Subjects will be enrolled in the study 10 participants at a time to ensure all participants have all required materials.

6	**Recruitment Methods**
	• Describe when, where, and how potential participants will be identified and recruited.
	• Describe materials that will be used to recruit participants. (Attach copies of these documents with the application.)
	• Does any member have a dual role with the study population?

Participants will be recruited mostly through word of mouth and by email to a registry of students who have previously participated in the lab's studies. Flyers for general advertisement and electronic advertisement have been created and attached to this IRB along with a sample email for recruiting from previous lab participants.

7	**Study Timelines**
	Describe:
	• The duration of an individual participant's participation in the study.
	• The duration anticipated to enroll all study participants.
	• The estimated date for the investigators to complete this study (up to and including primary analyses).

The primary planning for the study occurred from January to May. The IRB submission/revision process is scheduled June to August. S Upon IRB approval (August 2018) subjects will be recruited, informed, and data collection will begin. After 2 weeks of data collection the data will be analyzed and processed over the following 6 weeks. November 2018 is the goal for a competed thesis and December 2018 will be the conclusion of the study with a thesis defense to a committee of representatives from the School of Biological and Health Systems Engineering. Upon completion of thesis defense, the thesis will be submitted for publication in 2018/2019 peer reviewed journals related to engineering, neuromodulation, and neurosciences.

8	**Procedures Involved**
	Describe and explain the study design. Provide a description of all research procedures being performed and when they are performed. Describe procedures including:
	• The documents/ measures / devices/ records /sampling that will be used to collect data about participants. (Attach all surveys, scripts, and data collection forms.)
	• What data will be collected including long-term follow-up?
	• All drugs and medical devices used in the research and the purpose of their use, and their regulatory approval status.
	• Describe the available compensation (monetary or credit that will be provided to research participants).
	• Describe any costs that participants may be responsible for because of participation in the research.

The primary methods of data collection will be through survey. The Positive Affect and Negative Affect Schedule (PANAS) Questionnaire will be used daily to record ratings on subject daily moods. A daily sleep diary survey will also be used daily to allow subjects to self-report sleep quality daily over the course of the study. In conjunction with the sleep diary a Fitbit will be worn by the participants for most of the day (excluding shower, swimming, etc) to collect data on sleep quality, and heart rate. Weekly, subjects will take the Beck Anxiety Inventory, and the Beck Depression Inventory to determine if their depression and anxiety scores have reduced with use of trigeminal nerve stimulation. Daily, the Pittsburgh Sleep Quality Assessment and Fitbit actigraphy will be used to assess sleep quality data. All subjects will be trained on all procedures prior to study start date. A resource list of emergency contacts will be provided to all subjects in the event that any subject feels depressed or believes they have suicidal tendencies. Following the end of the treatment period research participants will be asked to complete a computerized questionnaire asking them to rate their experience with the study device/treatment.

The stimulator that will be used is an over the counter pulsed transdermal electrical stimulation (pTES) unit called Neuros created by Cerevast Medical Inc. The maximum current used by the device is up to 4mA which is approx. 1/10th that of the highest allowable current for safety in humans approved by the FDA. Many over the counter TENS units operate at a higher current and have proven to be safe for use with humans. The stimulator will be used for the recommended 15 minutes daily before sleep and subjects will be taught how to properly use the device. All subject questions and concerns will be addressed before the device is provided for use.

Transcutaneous electrical stimulation of peripheral nerves including cranial nerves like the trigeminal and vagal nerve is a noninvasive procedure that involves minimal risk by transmitting weak electrical impulses across the skin to underlying nerves using transdermal electrodes. Transcutaneous electrical nerve stimulation (TENS) using weak pulsed currents to noninvasively stimulate nerves have a long safety record dating back decades. The basic procedure involves the positioning and placement of standard transcutaneous neurostimulation electrodes with hydrogel. Targeting of the trigeminal and cervical nerves will be achieved using previously described procedures where electrodes are placed at the base of the neck and the side of the forehead or face (Tyler et al., 2015).

Over-the-counter and cosmetic TENS devices, such as Rejuvenique Face Toning Mask (RJV10), NuFace Trinity, Strivectin Facial Toner, IcyHot Smart Relief, Aleve Direct Therapy and numerous others have maximum current outputs up to 100 mA into a 500-ohm load with peak voltages up to 80 V. Other transdermal electrical stimulators like electrical muscle stimulators (EMS), such as the Compex Sport Elite or neuromuscular electrical stimulators (NMES) used for lifestyle, recreational, or cosmetic applications have current outputs that exceed 120 mA with peak voltages up to 200 V.

Pulse widths on peripheral nerve stimulators can range from 3 microseconds to several milliseconds depending on a given stimulus protocol and intended use. Prescription, over-the-counter, and direct-to-consumer peripheral nerve stimulation devices generate stimulus waveforms that span a diverse range of pulse frequencies from 1 Hz to 20 kHz. The low-risk designation of TENS, EMS, NMES, electroacupuncture, and other devices used for medical, lifestyle, or cosmetic applications has led to the FDA-exemption of similar, consumer neurostimulation products intended for general health or wellness purposes.

All pulse parameters used for transcutaneous nerve stimulation of the trigeminal and cervical nerves will be within safe ranges referenced above. Pulsed stimuli used for TENS will have variable intensities with peak amplitudes < 20 mA at frequencies ranging from 10 Hz to 5 kHz. As recommended for safe application of TENS the current density will remain less than 2 mA/cm2. TENS electrodes will be made of biocompatible polymers, such as conductive silicon or carbon fiber and have an insulating layer comprised of a hydrogel. Electrodes will be standard to the Neuros device from Cerevast Medical Inc.. Electrodes will be positioned to target branches of the trigeminal and cervical nerves as previously described (Tyler, 2015). Users will be able to exert control over the stimulus amplitude (TENS intensity) such that they can maintain a
comfortable level of stimulation throughout the experimental protocol. Each participant will be exposed to no more than 20 minutes of stimulation per day which is within the recommended range of over-the-counter TENS devices.

Lastly a software combination of Beyond Verbal API and IBM Watson Text to Speech API will be used to assess daily mood by asking the subject how they felt that day. The data collected by these APIs will be deidentified and stored in a private cloud maintained by the Tyler Lab. All data will be de-identified in a cloud storage service called Picard.io. Picard is a HIPAA compliant data storage and collection platform.

Research participants will be compensated $50 a week for approximately 10 hours of commitment. The maximum compensation is $100 for the completion of the two-week study. The subjects will face no expenses of their own as each will be loaned the materials that are needed to conduct the study. The compensation shall be paid at the end of the two week period given that the subjects are not removed from the study for compliance issues including: not filling out required forms, skipping use Cerevast Neuros devices, etc. Participant funding is supported by ASU internal Weartech program funds. Participants will be compensated after all study related devices are returned and the ASU Petty Cash Fund Expenditure Register Form is signed. Participants expected to earn more than $600 in a calendar year for human subjects research at ASU will be asked to completed applicable tax forms (e.g. ASU Substitute W-9 or W-8BEN) in compliance with ASU FIN 421-05.

---

9   **Withdrawal of Participants**
Describe anticipated circumstances under which participants will be withdrawn from the research without their
consent.
Describe procedures that will be followed when participants withdraw from the research, including partial
withdrawal from procedures with continued data collection.

Participants are free to withdraw from the study at any time. Since only able-bodied participants will be accepted there are no circumstances under which we would expect a participant to withdraw. If the participant does withdraw during data collection, then we may still use the data collected from the participant, with the participant's verbal consent.

10 Risks to Participants

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related the participants' participation in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks. Reference this information when appropriate.

- If applicable, indicate which procedures may have risks to an embryo or fetus should the participant be or become pregnant.
- If applicable, describe risks to others who are not subjects.

TENS is considered a low risk procedure and is routinely used in research, for medical indications, and in over-the-counter or direct-to-consumer applications. With respect to the safety, there exists a wealth of primary data and clinical endpoints demonstrating broad safety margins for electrical stimulation of peripheral nerves including cranial nerves like the vagus and trigeminal nerves (McCreery et al., 1990, Ben-Menachem, 2001, Merrill et al., 2005, Ben-Menachem et al., 2015). These noninvasive cranial nerve TENS approaches are also used in direct-to-consumer devices intended to relieve stress or promote relaxation. This latter use of TENS is what this study will primarily use.

Transcutaneous electrical stimulation of peripheral nerves including cranial nerves like the trigeminal and vagal nerves is a noninvasive procedure that involves minimal risk by transmitting weak electrical impulses across the skin to underlying nerves using transdermal electrodes. Transcutaneous electrical nerve stimulation (TENS) using weak pulsed currents to noninvasively stimulate nerves have a long safety record dating back decades as previously described. The basic procedure involves the positioning and placement of standard transcutaneous neurostimulation electrodes having a hydrogel. Targeting of the trigeminal and cervical nerves will be achieved using previously described procedures where electrodes are placed at the base of the neck and the side of the forehead or face (Tyler et al., 2015).

There have been no known severe adverse events associated with the use of TENS. However, there is a low-risk for some minor side-effects or adverse reactions. Subjects with sensitive skin may experience skin irritation in the area where electrodes are applied. Some subjects may experience a headache and other painful sensations during or following the application of electrical stimulation. Some subjects may experience a sensation of hearing ringing tones after electrical stimulation.

Skin Irritation Risk
Minor skin irritation can occur if electrodes are placed over broken skin or wounds. We will avoid placing electrodes over these areas. Moreover, we will inspect the skin prior to electrode placement to further reduce the potential for minor irritation. Mild redness has been reported at the site of electrode placement, but this is an acute effect of vasodilation as opposed to inflammation and thus does not indicate damage.

Skin Discomfort Risk
Skin sensations during TENS are transient, most prominent at the onset and offset of stimulation and do not persist beyond the timeframe of stimulation. With proper use the most common sensation from TENS is tingling at the electrode site, which is not uncomfortable or painful. However, depending on the amplitude of the current, uncomfortable sensations may occur, including a sensation of pain or heat. To minimize these sensations, we are using electrodes that have been specially designed to distribute current across the electrode-skin interface. In addition subjects will be able to decrease the current amplitude or abort the stimulation paradigm if they become uncomfortable at any time.

Headache
A rare side effect of TENS and transdermal cranial nerve modulation is the occurrence of a mild headache. This occurs in less than about 10% of subjects at incidence rates similar to sham procedures during both acute and repeated use procedures. Mild headaches typically resolve within a couple hours with no further complications. If a subject experiences a headache or discomfort, they may discontinue use at any time.

There are no other known risks associated with this study. Participation is completely voluntary and participants are free to ask questions, ask for a break or withdraw from the study without penalty. A signed copy of the consent form will be given to each participant for each session.

11 Potential Benefits to Participants
Realistically describe the potential benefits that individual subjects may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit. Do not include compensation or benefits to society or others.

By taking an active role in this study participants will be able to see their own changes in mood and sleep based on their Fitbit readings and feedback from their sleep journals.

12 Setting

Describe the sites or locations where your research team will conduct the research.
- Identify where research procedures will be performed.
- For research conducted outside of the ASU describe:
  - Site-specific regulations or customs affecting the research.
  - Local scientific and ethical review structures in place.

There will be an initial training session at ASU where the participants will be taught how to access the surveys, how to use the Neuros device, and baseline personality profiles will be taken. The remainder of the data will be collected through picard.io and REDCap software remotely from the participants' location. Each participant will be free to conduct the protocols at home since they are simple. Email reminders will be used to make sure the participants are recording necessary data when needed.

13 Multi-Site Research

If this is a multi-site study where you are the lead investigator, describe the processes you will use to ensure communication among sites, such as:
- Each site has the most current version of the protocol, consent document, and HIPAA authorization.
- Required approvals have been obtained at each site (including approval by the site's IRB of record).
- Describe processes you will use to communicate with participating sites.
- Participating sites will safeguard data as required by local information security policies.
- Local site investigators conduct the study appropriately.

NA

14 Resources Available

Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform your roles. When applicable describe knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.
Describe other resources available to conduct the research: For example, as appropriate:
- Describe your facilities.
- Describe the availability of medical or psychological resources that participants might need as a result of any anticipated consequences of the human research.
- Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

The research will be conducted under the supervision of Dr. William Tyler. The PI has more than ten years' experience investigating and developing noninvasive neuromodulation methods, devices, and systems. These investigations include the development of methods for optimizing transcranial magnetic stimulation and the development of transcranial focused ultrasound for neuromodulation. In addition, the PI has had independent experience in leading a company from product conceptualization to launching a direct-to-consumer neuromodulation device (transdermal electrical neuromodulation device), which was exempted from regulatory enforcement by the FDA under a 513.g precedent decision. In addition to industry efforts and academic research, the PI is an authority and published expert on the safety of noninvasive neuromodulation devices including forthcoming industry guidelines for direct-to-consumer devices. The PI also has experience training undergraduate students, graduate students,
postdoctoral scholars, professors, and other users on a variety of noninvasive neuromodulation methods for diverse applications.

The Tyler Laboratory is equipped with the necessary materials such as Neuros devices, mood inventories, Fitbits, and sleep inventories for subjects to take with them. The Tyler Lab will train subjects to use all materials safely and comfortably prior to the beginning of the study via in person workshops.

Graduate students and postdoctoral fellows to be involved in the research will provide required CITI documentation and will be trained on specific laboratory procedures before being added to the IRB protocol. Research training records will be maintained in the laboratory with other safety
training procedures.

Attached to the consent form that participants take with them will be a list of mental health services in the event that a participant feels they have significant mood changes or disturbances.

---

15 Prior Approvals
Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site, funding agency, laboratory, radiation safety, or biosafety approval.)

The local ASU IRB is the only approval that is needed for this research.

---

16 Data Management and Confidentiality
Describe the data analysis plan, including procedures for statistical analysis.
Describe the steps that will be taken to secure the data during storage, use, and transmission.
- Training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data

Describe how data and any specimens will be handled:
- What personal identifiers will be included in that data or associated with the specimens?
- Where and how data or specimens will be stored?
- How long the data or specimens will be stored?
- Who will have access to the data or specimens?
- Who is responsible for receipt or transmission of the data or specimens?
- How will data and specimens be transported?
- If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.
- Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

A master contact list containing participant names, email addresses, and phone numbers will be stored in a locked file cabinet separate from the consents, questionnaires, physiological, and audio data. Consents forms will also be stored in a locked file cabinet separate from the master contact list. Participants will be assigned a Study ID (e.g. P1, P2, P3...) and User Login ID (e.g. weartech1@asu.edu, weartech2@asu.edu...) that will be used to create/track audio recordings, Fitbit tracking accounts, and Neuros training accounts. Data and audio files will be exported without any participant identifiers and stored in computer memory and digital storage backup drives for up to 10 years. The computer memory will be accessible via secure login only to study personnel named in this document; data and audio will remain secured on Arizona State University property in the Tyler Laboratory PEBE rooms 158C, 150, and 220 Digitally stored data (on the computer or in backup drives) will not contain any identifiable information on the participant.

17 Safety Monitoring

This is required when research involves more than Minimal Risk to participants. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor. Describe:

- The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether participants remain safe.
- What data are reviewed, including safety data, untoward events, and efficacy data?
- How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
- Who will review the data?

This study has been designated to have a Minimal Risk Level. There are no other known risks associated with this study. Participation is completely voluntary and participants are free to ask questions, ask for a break or withdraw from the study without penalty. We will hold weekly laboratory meetings with the research personnel involved in this research to discuss any adverse reactions, which may have occurred during the study. We will collect some questionnaire information (REDCap, Picard) at the end of each study treatment session asking participants to describe any adverse reactions. Safety will be continuously tracked and monitored throughout the study by the local research personnel affiliated with the study. An emergency resource list shall be provided to every subject in case of an event that a subject feels depressed or feels that they may have suicidal tendencies based on their answers to the Beck Depression Inventory.

18 Consent Process

Describe the process and procedures process you will use to obtain consent. Include a description of:

- Who will be responsible for consenting participants?
- Where will the consent process take place?
- How will consent be obtained?
- If participants who do not speak English will be enrolled, describe the process to ensure that the oral and/or written information provided to those participants will be in that language. Indicate the language that will be used by those obtaining consent. Translated consent forms should be submitted after the English is approved.

Before the study officially begins a small workshop will be held with the participants. Participants will be provided with the study information, study rationale, risks, potential benefits, and the role of the IRB. All participants will be asked to complete the Informed Consent form in writing; the consent form will be dated and countersigned by the PI, and one copy will be provided to the participant (Consent form is attached). The participant may withdraw from the study at any time. All participants will be English speaking and all will be adults capable of giving informed consent.

19 Investigational New Drug or Devices

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- Identify the hold of the IND/IDE/Abbreviated IDE.
- Explain procedures followed to comply with FDA sponsor requirements for the following:

FDA Regulation	Applicable to:		
	IND Studies	IDE studies	Abbreviated IDE studies
21 CFR 11	X	X	
21 CFR 54	X	X	
21 CFR 210	X		
21 CFR 211	X		
21 CFR 312	X		
21 CFR 812		X	X
21 CFR 820		X	

NA

20 CITI

Provide the date that the members of the research team have taken the CITI training for human participants. This training must be taken within the last 4 years. Additional information can be found at: http://researchintegrity.asu.edu/training/humans

William Tyler
Sarah Wyckoff
Ceasar Udave

Recruitment Email

Hello!

      If you are receiving this email it is because you expressed interest in taking part in future Tyler Lab studies. The Tyler Lab will be conducting a new study on neuromodulation and its effects on sleep and mood. We are working on validating different software packages to detect mood and looking to study short term trends in sleep and mood with normal use of transdermal neurostimulation.

Details:

Must be 18-65 to participate.

Participation is voluntary

Must pass a prescreening phone call or online survey. (Less than 5 minutes).

Study will last approximately 2 weeks with the participant involved no more than 10 hours a week.

Participation will involve:

-Neurostimulation using approved over the counter pulsed transdermal electrical stimulation device for trigeminal nerve stimulation.

-Vocal recordings for use with software packages.

-Filling out mood and depression inventories.

-Keeping a sleep diary.

-Wearing a Fitbit to record sleep activity.

Participants will be given $125 per week of participation.

If interested please email us back at study1@tylerlab.com with the subject "Sleep Study".

Thank you for your time,

Ceasar Udave

Reminder Email

Hello Study Participant!

This is a friendly reminder that all surveys need to be completed before midnight. Neuros stimulation must be complete before you go to bed and wear your Fitbit while you sleep. Login with your Weartech credentials to see what still needs to be completed today at:

https://weartech.picard.io

Thank you from the Tyler Lab Staff!

SUBJECT CONSENT FORM

Examination of Pulsed Transdermal Electrical Stimulation (pTES) and its Effects on Sleep and Mood

School of Biological and Health Systems Engineering: Arizona State University

Introduction:

The purpose of this form is to provide you (a prospective research participant) with pertinent information that may affect your decision to participate in this research and to record consent of those who agree to be involved.

Principle Investigator & Research Associates:

William Tyler, Ph.D., (PI, Associate Professor, School of Biological and Health Systems Engineering)

Ceasar Udave (graduate student, SBHSE)

Sarah Wyckoff, Ph.D. (research assistant professor).

Study Purpose:

The purpose of this study is twofold. Primarily, the data collected will be used to determine if regular use of pulsed transdermal electrical stimulation (pTES) has beneficial effects to the sleep of users in a short-term time frame using Fitibit, and the Pittsburgh Sleep Quality Assessment (PSQI). Secondly, mood data collected from gold standard questionnaires such as the Positive Affinity Negative Affect Schedule (PANAS), Depression Anxiety and Stress Scale (DASS21), Beck Anxiety Inventory, and Beck Depression Inventory will be compared against software packages Beyond Verbal, and IBM Watson to determine the validity of these software packages in assessing mood.

Description of Research Study:

You will be one of approximately 20 able-bodied healthy individuals to be asked to participate in this project. You will be asked to perform the following procedures at home with training and continued support from the research faculty.

Testing:
○You will be expected to wear a Fitbit for the duration of the study. Excluding during showers.

○Once daily you will use a Cerevast Neuros pTES units. Training on how to use the device, settings available, best practices, and other information will be provided.

Description of Research Study (cont.):

○Once daily you will take the Positive and Negative Affect Schedule.

○Once weekly you will take the Pittsburgh Sleep Quality Assessment

○Once daily you will make an audio recording responding to a prompt

○Once weekly you will take the Beck Depression Inventory

○Once weekly you will take the Beck Anxiety Inventory

The inventories, schedules, assessments, and scales described above are simple questionnaires that will be filled out through an online service called Picard.io. Picard.io is a HIPAA compliant data collection service that guarantees confidentiality and will provide each subject with their own access portal.

One mandatory training session will be held before the study begins. At this training session subjects will be taught how to access their Picard.io accounts, be assigned their equipment, walked through each of the questionnaires, taught how to use their Fitbits, taught how to use their Cerevast Neuros devices, and taught what to expect in an average day of the study by completing baseline surveys. The estimated time of commitment for each subject will be approx. 10 hours/ week.

Risks:

This study has been designated to have a Minimal Risk Level. There have been no known severe adverse events associated with the use of TENS. There is a low-risk for some minor side-effects or adverse reactions however. Subjects with sensitive skin may experience skin irritation in the area where electrodes are applied. Some subjects may experience a headache and other painful sensations during or following the application of electrical stimulation. Some subjects may experience a sensation of hearing ringing tones after electrical stimulation.

Skin Irritation Risk

Minor skin irritation can occur if electrodes are placed over broken skin or wounds. We will avoid placing electrodes over these areas. Moreover, we will inspect the skin prior to electrode placement to further reduce the potential for minor irritation. Mild redness has been reported at the site of electrode placement, but this is an acute effect of vasodilation as opposed to inflammation and thus does not indicate damage.

Skin Discomfort Risk

Skin sensations during TENS are transient, most prominent at the onset and offset of stimulation and do not persist beyond the timeframe of stimulation. With proper use the most common sensation from TENS is tingling at the electrode site, which is not uncomfortable or painful. However depending on the amplitude of the current, uncomfortable sensations may occur, including a sensation of pain or heat. To minimize these sensations, we are using electrodes that have been specially designed to distribute current across the electrode-skin interface. In addition, subjects will be able to decrease the current amplitude or abort the stimulation paradigm if they become uncomfortable at any time.

Headache

A rare side effect of TENS and transdermal cranial nerve modulation is the occurrence of a mild headache. This occurs in less than about 10% of subjects at incidence rates similar to sham procedures during both acute and repeated use procedures. Mild headaches typically resolve within a couple hours with no further complications. If a subject experiences a headache or discomfort, they may continue use at any time.

Inclusion Criteria:

○Healthy males or females aged 18-65.
○Full time workers or students (or part time combination approved by investigators) with regular sleep schedules.

Exclusion Criteria:

Please check each box acknowledging that you do NOT have this condition or exclusion criteria.

- ❑ Currently undergoing treatment or medication for neurological or psychological disorder, including addiction

- ❑ Has a medical implant (such as a pacemaker, cochlear implant, brain stimulation device)
- ❑ History of migraines or frequent headaches
- ❑ History of panic attack or acute anxiety disorder
- ❑ Fainting (vaso-vagal syncope or neurocardiogenic syncope)
- ❑ Raynaud's disease
- ❑ Tempromandibular joint (TMJ) disorder or other facial neuropathy
- ❑ History of concussions or brain injury
- ❑ History of significant face/head injury or if you have cranial or facial metal plate or screw implants
- ❑ History of hospitalization for neurological or psychological disorder
- ❑ Recent hospitalization for surgery/illness
- ❑ Vision or hearing that is uncorrectable (corrected vision or hearing is okay)
- ❑ Pregnant
- ❑ Recent drug or alcohol treatment
- ❑ High blood pressure, heart disease, or diabetes
- ❑ Diagnosed with sleep disorder
- ❑ Taking prescription medication for sleep

Benefits:

Using the Fitbit data and various mood assessments given in the study, participants will gain a better understanding of their sleep schedules, moods on a weekly and daily basis, and learn awareness of their own health. The data collected in this study will help the investigators understand how an emerging technology can affect the patient population who may use these devices.

New Information:

If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

Confidentiality:

Every effort will be made to maintain the confidentiality of your participation in this project. Each subject's name will be paired with a code number by the principal investigator. This code number will appear on all written materials. The list pairing the subject's name to the assigned code number will be kept separate from all research materials and will be available only to the principal investigator. Confidentiality will be maintained within legal limits.

Withdrawal:

You may choose to withdraw from the study at any time. If you do withdraw, then any data collected from you prior to your withdrawal will only be used under your verbal consent.

Compensation:

Compensation will be $125 per completed week of study requirements. Should any subject fail to comply with the parameters of the study their compensation will be forfeited, and they will be asked to leave the study.

Compensation for Illness and Injury:

If you consent to participate in the study, then your consent does not waive any of your legal rights. However, no funds have been set aside to compensate you in the event of an injury.

Voluntary Consent:

1. I understand that informed consent is required of all persons participating in this project.

2. All procedures have been explained to me and all my questions have been answered to my satisfaction.

3. Any risks and/or discomforts have been explained to me.

4. Any benefits have been explained to me.

5. I understand that any questions that I have concerning the research study or my participation in the research study, before or after my consent, will be answered by William Tyler, Ph.D. or research associates, Tyler Laboratory, School of Biological and Health Systems Engineering, PEBE 158C, at 480-965-9270.

   I also understand that if I have questions about my rights as a subject/participant in this research, or if I feel I have been placed at risk, I can contact the Chair of the Human Subjects Institutional Review Board, through the ASU Research Compliance Office, at 480- 965-6788

6. I have been told that I may refuse to participate or to stop my participation in this project at any time before or during the project. I may also refuse to answer any question.

7. All information that is obtained in connection with this project and that can be identified with me will remain confidential as far as possible within legal limits. Information gained from this study that can be identified with me may be released to no one other than the principal investigator. The results may be published in scientific journals, professional publications, or educational presentations without

identifying me by name.

8. This form explains the nature, demands, benefits and any risk of the project. By signing this form, I agree knowingly to assume any risks involved. My participation is voluntary. I may choose not to participate or to withdraw my consent and discontinue participation at any time without penalty or loss of benefit. In signing this form, I am not waiving any legal claims, rights or remedies. A copy of this consent form will be offered to me.

My signature means that I agree to participate in the study.

_____   _____   _____

Subject's Signature   Printed Name   Date

"I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Research Integrity and Assurance to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document"

Signature of Investigator_____ Date_____

Sleep Study Ad Electronic and Flyer

<div align="center">

Study on

Sleep and Mood Improvement

at Arizona State University

We are investigating noninvasive neuromodulation methods for the
improvement of sleep schedule and quality, as well as improvement in mood
in an acute time frame.

The details:
Must be 18-65 years of age to participate in study.

Must be available for a 2-week time period in June/July.

Must be a full-time student/ Have full time employment during study.

Participation is voluntary.

If interested please email

study1@tylerlab.com with the subject line "Sleep Study"
to request a pre-screening telephone interview/online survey, which should last
less than 5 minutes.

Study period will last approximately 2 weeks.

**Volunteer participation will involve one laboratory visit
training and include:**

-Use of a Fitbit to monitor sleep quality

</div>

-Transcutaneous electrical nerve stimulation of trigeminal/cervical nerves with over the counter therapy device.

-Recording of verbal responses to prompts.

-Computerized questionnaires used to evaluate mood.

-Self-administered questionnaires, nerve stimulation, and Fitbit recordings in the comfort of your own home.

Participants will be compensated with $125 per week of participation.

Counseling Services Information

Counseling Service Providers

ASU Counseling Services staff is available for walk-ins, appointments or to provide consultation anytime between 8 a.m. – 5 p.m. Monday thru Friday. Call (**480) 965-6146** to be connected to any of our four campus locations.

Downtown Phoenix Campus
Phone: 602-496-1155
Street Address
Historic Post Office Building
522 N. Central Avenue, Suite 208
Phoenix, AZ 85004

Polytechnic Campus
Phone: 480-727-1255
Street Address
Academic Center, Suite 92
5988 S. Backus Mall
Mesa, AZ 85212

Tempe Campus
Phone: 480-965-6146
Street Address
Student Services Bldg, Rm 334
1151 S. Forest Ave.
Tempe, AZ 85287

West Campus
Phone:602-543-8125
Street Address
University Center Building, Room 221
4701 West Thunderbird Road
Glendale, AZ 85306

If a crisis occurs outside of business hours call EMPACT's 24-hour ASU-dedicated crisis hotline: **480-921-1006**

Student Advocacy and Assistance in the Dean of Students office guides students in resolving educational, personal and other difficulties by linking students with appropriate university and community resources. Call 8 a.m. – 5 p.m. Monday thru Friday.

Downtown Phoenix Campus
602-496-0670

Tempe Campus
480-965-6547

Polytechnic Campus
480-727-5269

West Campus
602-543-8152

Maricopa Crisis Line You can call for help with a behavioral health crisis 24 hours a day, 7 days a week. It's available for anyone at any time. Crisis Response Network, Inc. (CRN) operates the Crisis Line. Their experienced, professionally trained Crisis Specialists are ready to respond to whatever crisis an individual is facing. They provide immediate and confidential help. If your crisis can't be solved over the phone, CRN may dispatch mobile clinicians to meet you where you are.

Phone: 602-222-9444
1-800-631-1314 (toll free)
www.crisisnetwork.org

National Suicide Prevention Hotline
Phone:1-800-273-8255

For emergency situations, call (9-1-1).

Sleep Surveys

[All surveys were done online through a service called Picard by Trialomics. Please contact the author to obtain copies of the surveys used. All surveys can be found online.]

BIOGRAPHICAL SKETCH

I completed my bachelor's degree here at Arizona State University in Biomedical Engineering. I am currently a 4 + 1 MS thesis student working under Dr. William Tyler. My research was inspired by my brief internship period at NASA, where I learned one of the main issues astronauts still face is a sleep deficit, due to lack of gravity, prolonged days, and abnormal day night cycles. The Tyler Lab is interested to see if transdermal electrical nerve stimulation (TENS) to the trigeminal nerve can help correct sleep patterns and improve mood in the short term. Following graduation, I plan on working in the biomedical industry to continue the tackling issues that will improve quality of life.