Official Title: Digital Therapeutic for Pain Relief through AI-Guided Dynamic Visual Neuromodulation

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[redacted]

GOALS

We are researching a novel neuromodulatory platform using visual stimulation for its impact on nociception. We hypothesize that short abstract videos can be optimized to be used in the modulation of nociception utilizing the process called Dynamic Visual Neuromodulation (DVN). DVN optimization will be performed through an iterative process of choosing different arrangements of concurrent stimulation parameters in order to enhance neurophysiological response. Since pain experiments are challenging, DVN optimization has been designed to be carried out in two stages in order to decrease the burden on participants: (1) In Experiment 1 we aim to develop an optimization procedure for inducing arousal; this experiment requires no pain induction. (2) Using the same general procedure, the Experiment 2 will pursue further optimization of the visual stimuli with the aim of inducing arousal to decrease nociception and the perception of experimentally induced pain in healthy subjects.

OBJECTIVES

The objective of the current research is to develop a visual stimulation platform capable of modulating nociception and alleviating perceived pain intensity. Dandelion Science (the Sponsor) hypothesizes that controlling the level of arousal through DVN can reduce nociceptive effects caused by experimentally produced painful stimuli in healthy participants.

- Aim 1: Find dynamic visual stimuli capable of reliably modulating physiologic arousal.

  [redacted]

- Aim 2: Validate EEG, GSR, ECG, and EMG, biomarkers of pain.

[redacted]

- Aim 3: Demonstrate that optimized DVN can modulate nociception and mitigate or modify pain perception in healthy participants*.

[redacted]

BACKGROUND

In 2017, 11 million of the 191 million prescriptions written for opioid pain medications were misused; 35% of opioid-related deaths (nearly 17,000 cases) were connected to these prescriptions (*7 Staggering Statistics About America's Opioid Epidemic*, 2016). Researchers have been looking - with limited success (Nascimento et al., 2019) - for reliably safe and effective opioid-sparing therapies. The challenge is the complexity of pain (Murphy et al., 2017). Pain comes in many forms, is highly subjective (Fillingim, 2017; Krupić et al., 2019; Pisanu et al., 2019), and arises from complex neural data-processing across multiple regions of the brain (Fenton et al., 2015; Wiech, 2016). This complexity makes it challenging to deliver pain relief that is both safe and effective. Opioids offer efficacy but not safety. While clinical pain-relief interventions (e.g. cognitive behavioral therapy, CBT) and digital behavioral methods (e.g. guided meditation, distraction, and electronic CBT) are safe, none so far has been fully successful (Nascimento et al., 2019). [redacted] The technology platform most compatible with this approach is neuromodulation, which makes use of direct, reproducible input - typically electrical or magnetic stimuli (Kumar & Rizvi, 2014) - and interacts with the CNS as a system of complex data-processing neural networks (Herculano-Houzel, 2009). [redacted] Preliminary study data show that visual stimuli with certain dynamic features are able to induce neurologic and physiologic state changes.

INCLUSION AND EXCLUSION CRITERIA FOR THE EXPERIMENTS

Participants will be recruited at the Dandelion Science's lab [redacted] The details pertaining to the recruitment procedures will be submitted in site-specific applications to the IRB. On the day of the experiment the participants will be encouraged to have a good night sleep and instructed to abstain from consuming caffeinated beverages and medical drugs.

INCLUSION CRITERIA

- Participants of both sexes
- Participants of diverse ethnic and racial backgrounds
- Subjects who speak, read, and understand English and are willing and able to provide written informed consent on an IRB-approved form prior to the initiation of any study procedures
- Age range: 18-50

The age limitation reflects differences in pain response thresholds both in terms of mean and variance, across different developmental groups (González-Roldán et al., 2020; Tumi et al., 2017). Moreover, the age range stated above is the target group of individuals of greatest interest for this future intervention (Salmond & Allread, 2019).

EXCLUSION CRITERIA

A medical history questionnaire will be provided to determine which participants will need to be excluded.

The following criteria will be used to exclude people from the study:

- Patients with neurologic, endocrine, renal, gastrointestinal, and chronic pain disease
- Participants who use unprescribed drugs or medications (a urine drug test will be administered on the day of the experiment to verify compliance)
- Chronically medicated participants
- Participants with photosensitivity and patients with epileptic seizures
- Participants who have undergone major surgery within two months of the experiment date
- Patients with cardiac disorders
- Women who are pregnant
- Prisoners
- People who are unable to provide consent
- Individuals diagnosed with a psychiatric disorder that is likely to interfere with the conduct of the study
- Participants with implanted electronic devices of any kind, including pace-makers, electronic infusion pumps, stimulators, defibrillators or similar

STUDY-WIDE NUMBER OF PARTICIPANTS

Up to 120 participants

STUDY-WIDE RECRUITMENT METHODS

Participants for the study will be recruited by the Dandelion's personnel using social networks and personal communications.

STUDY TIMELINES

	Stages	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
	Recruitment												
Arousal optimization	Experiment												
	Analysis												
	Recruitment												
Pain optimization	Experiment												
	Analysis												

STUDY ENDPOINTS*

Successful control of the arousal reduction of pain perception as measured by VAS and ERP for either thermal (CHEPs) or electric shock pain induction. While there is no single criterion for determining a clinically significant threshold, Dandelion Science has adopted the reported criterion of 20% reduction in pain intensity and expects to achieve a pain perception reduction of 20% on VAS scale for AI-guided visual stimulation as compared with no-visual-stimulation in response to at least one of the nociceptive conditions (CHEPs stimulation).

PROCEDURES INVOLVED

The study consists of 2 experiments:

Experiment 1. Optimization of visual stimulation for arousal

In this experiment we will use the participant's response to dynamic visual stimulation to modify and adapt the stimuli to drive a stronger arousal response. The goal is to show that visual stimulation can affect participants by both raising and lowering their arousal level.

Location	Dandelions Science Research Facilities [redacted]
Estimated number of participants	Up to 100
Estimated experiment duration	2 hr 10 min

Goals

1. Identifying dynamic visual stimuli that are effective in manipulating arousal
2. Developing and testing the platform: integration of neurophysiologic, behavioral and visual stimulation components

Equipment and instruments

1. Neurophysiologic assessment: EEG, GSR, EMG, ECG
2. Behavioral assessment: self-assessment manikin (SAM)
3. Visual stimulation: DVN presented on a display
4. Infrastructure: 2 laptops / PCs for rendering & processing of the data

Conditions

1. Optimized visual stimulation (***OVS***)
2. Random visual stimulation control (***RVS***)

Experiment structure

Stages of experiment:

1. Measuring temperature and a short COVID symptom questionnaire
2. Signing of informed consent
3. Urine drug test
4. Filling out the demographic questionnaire (5 minutes)
5. Filling out Perceived Stress Scale (Cohen, 1988)
6. Sensor setup (~30 minutes)
7. Sensor calibration (~5 minutes)
8. Instructions (~2 minutes)
9. Training block (~2.5 minutes)
10. 25 Experimental blocks (~3 minutes per block). The blocks will be separated by breaks of 45 seconds.

Approximate trial and block structure

1. Fixation cross - 1 second.
2. Stimulation - 5 to 15 seconds total.
3. Behavioral response - 5 to 15 seconds.

Data Analysis

Optimization method

In the optimization procedure, Dandelion Science defines the visual stimulation (VS) parameters and, while they are presented, monitor the response to them. Once the response is registered, we select the next set of parameters that is expected to achieve one or more of the following goals:

- identify and explore in detail VS parameters that affect a specific biomarker (i.e. that cause a significant shift in the biomarker in comparison with its baseline value);
- find the specific values for VS parameters that drive a combination of biomarkers to a predefined state ("target state");
- improve our general predictive model of the relationship between VS parameters and bioresponse.

Effectiveness of DVN in controlling arousal

Dandelion Science will also collect the responses to randomly chosen parameters. This data will be used to estimate the quality of the signal and variance in responses and serve as a prior distribution for the Bayesian model.

After we collect data for the baseline, we will compare the average response curve (a biomarker value for multiple participants over the course of random stimulation) with the response curve during the optimization procedure. We expect that after a few iterations, the biomarker values will diverge from the baseline. The required number of iterations to observe the effect is yet to be defined.

We want to test whether optimization leads to the gradual improvement in the ability of stimulation to cause change in arousal as registered by the biomarkers. To do so we will analyze how the biomarker changed with control stimulation (RVS) versus optimized stimulation (OVS). The divergence of the time series will be calculated using the ARIMA model, and the significance of the diversion will be assessed using the Chow Test.

Pilot

To assess the effectiveness of the optimization process, a baseline response will be collected to serve as a control condition. Prior to the main experiment we will run a pilot experiment on 5 to 10 participants following the same structure as in the main experiment but with the visual stimulation parameters being chosen randomly during each iteration.
In addition, up to 5 participants will take part in pilot experiments with the cold pressor test (Lamotte et al., 2021), a simple and validated test that has been used in clinical and research settings to evaluate non-baroreflex-mediated sympathetic neural control in humans. During the test the subject immerses one hand or foot into ice water for up to 3 min while blood pressure and heart rate are monitored.

Experiment 2. Optimization of visual stimulation for pain perception

In this experiment we will optimize visual stimulation with the goal of reducing pain perception. To reduce the burden on participants, optimization has been designed as a two-step process, with the first step (implemented in Experiment 1) requiring no pain induction. Our preliminary hypothesis is that arousal-inducing visual stimuli will reduce the perception of acute pain, based on the well-known phenomenon of stress-induced analgesia (Vachon-Presseau et al., 2013; Yilmaz et al., 2010). Thus, once we optimize the stimuli to affect arousal state in Experiment 1, we will test the effectiveness of the optimized visual stimuli (OVS) in reducing pain perception and carry out additional adjustments to further increase their impact.

Location	Dandelions Science Laboratory [redacted]
Estimated number of participants	20 participants
Estimated experiment duration	2 hr

Goals

1. Find optimized visual stimuli
2. Determine optimization curve
3. Disentangle anxiety and pain responses

Equipment and instruments

1. Neurophysiological assessment: EEG, GSR, EMG, ECG
2. Behavioral assessment: VAS

3. Visual stimulation: DVN presented on a display
4. Infrastructure: 2 laptops / PCs for rendering & processing of the data
5. Nociception: Contact Heat Evoked Potentials (CHEPs)

Conditions

Up to three pain intensities levels (cold: 3°C, innocuous: 35°C, hot: 52°C) with OVS.

Experiment structure

1. Measuring temperature and a short COVID symptom questionnaire
2. Signing of informed consent
3. Urine drug test
4. Signing of informed consent
5. Filling out the demographic questionnaire (5 minutes)
6. Filling out Perceived Stress Scale (Cohen, 1988)
7. Sensor setup (~30 minutes)
8. Sensor calibration (~5 minutes)
9. Instructions (~2 minutes)
10. Validating pain levels using step method
11. Training block (~2.5 minutes)
12. 12 Experimental blocks (~4 minutes per block; 8 stimuli). The blocks will be separated by breaks of 45 seconds.

Approximate trial structure

1. Fixation cross 0.5 seconds
2. Stimulation 0.5 - 15.5 (15 seconds total)
3. Pain stimulation jitter window: 2 - 5 (pain stimulation of up to 800 ms can occur uniformly at any point within this window)
4. Behavioral response window: 15.5 to 30 seconds.

Block structure

8 trials of 30 seconds = 4 minutes

Data analysis

Optimization method
To facilitate the search for effective visual stimulation we will use a Bayesian model, pretrained on the data collected in Experiment 1.

Description of the procedures used in the study

Nociceptive protocols: Participants will be attached to the biosensors and seated in front of a digital display. Pain induction will be carried out as follows.

1. Cold pressor Test:

The cold pressor test is a simple and validated test in which the subject immerses one hand or foot into ice water for up to 3 min while blood pressure (BP) and heart rate are monitored. The cold stimulus activates afferent sensory pathways that, in turn, trigger a sympathetic response resulting in an increase in BP. The cold pressor test has been used in clinical and research settings to evaluate non-baroreflex-mediated sympathetic neural control in humans (Lamotte et al., 2021).

2. Contact Heat Evoked Potentials (CHEPs):

A contact heat stimulator will be employed to deliver stimulation (Pathway, Medoc, RamatYishai, Israel). The CHEPs thermode surface (diameter: 27 mm) consists of a heating thermo-foil covered with a layer of thermo-conductive plastic. The nominal heating rate of this device is 70 °C/ s, with a cooling rate of 40 °C/ s. The temperature of the thermode will be controlled through dedicated software, designed for optimization purposes. The thermode was attached to the participant's nondominant volar forearm. The stimulation will be conducted within the range of 40 °C for cold stimuli and 52 °C for hot stimuli. The duration of a single stimulation event will range from 800 ms to 10 seconds depending on the stimulation paradigm.

Biochemical Test:

1. 12 Panel Urine Drug Test Cup (Prime Screen ™ or a compatible alternative)

Neurophysiologic measurements:

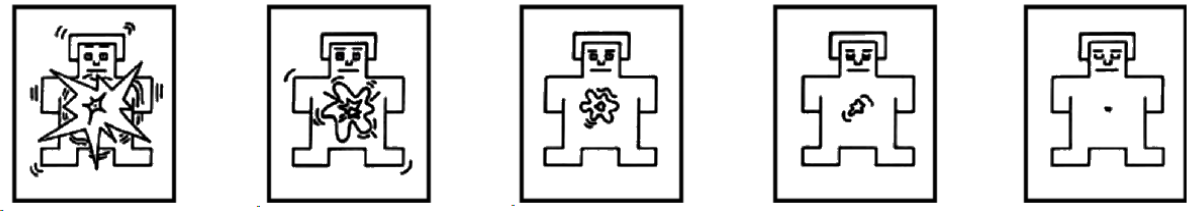
1. EEG/ERP will be performed using a commercial active 32-electrode system (Biosemi). Before every session a participant will be fitted with a comfortable cap matching their head size. Conductance will be enhanced through the use of the standard EEG gel, which will be injected into the electrodes using plastic syringes with plastic tips. The experimental system will be powered by a low-voltage battery to avoid electrocution.
2. GSR will be measured using a common commercial system ((Biosemi) using two electrodes and applying low voltage between them. The electrodes will be attached to the palm of the dominant hand. The device will be powered by a low-voltage battery.

3. ECG will be measured by a common commercial system (Biosemi) consisting of one active electrode attached to the dominant hand. EMG will be measured by a common commercial system (Biosemi) consisting of two active pair of electrodes attached to participants face above right brow to measure corrugator activity and on the right cheek to measure zygomatic activity. Alternatively the electrodes may be placed on the participant's dominant hand to measure arm muscles' activity.

Self-reports:

1. Self-assessment manikin (SAM):

Using a computerized questionnaire, participants will rate their subjective physiological arousal level by selecting one of the 5 figures representing decreasing levels of arousal (Bynion & Feldner, 2017; Handayani et al., 2015).



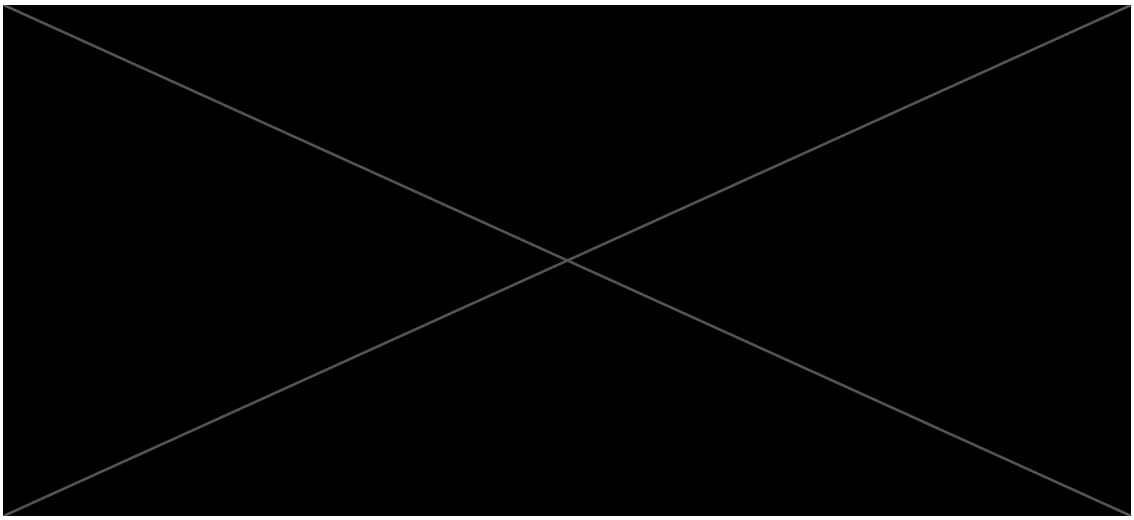
2. Visual analogue scale (VAS)*:

Participants will rate their experienced pain level on a standard computerized scale by choosing a point on a line (Ergin et al., 2015; Jamison et al., 2002).

3. The Perceived Stress Scale (Cohen, 1988):
   A 14-item scale to measure general mental wellbeing (see attached).
4. Demographic/situational questionnaire to access basic demographic information and compliance with the experimental requirements.

Dynamic visual stimulation:

DVN will consist of 15-second-long non-figurative dynamic visual patterns (see screenshot examples bellow):



Screenshots from a visual stimulation clip.

DATA AND SPECIMEN BANKING

The personnel responsible for collecting and storing data will be specified in the site-specific protocols. The PI is responsible for all information collected on subjects enrolled in this study. All data collected during this study must be reviewed and verified for completeness and accuracy by the PI. PI will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject participating in the study. In general data obtained from the participants will be recorded and stored in a HIPAA-compliant manner by a designated staff member. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials. All questionnaire results will be coded as to the identity of the study participants in a HIPAA-compliant manner and therefore the study participants will not be identified with the recorded data. No such identifying information will be shared with anyone outside of the study sites. Obtained de-identified data will be used in secondary analyses. The consent form will include a request for secondary data utilization without an expiration date. All team members will be trained and certified in the HIPAA requirements for research involving human subjects.

DATA MANAGEMENT

Data obtained from the participants will be recorded and stored in a HIPAA-compliant manner. Specifically, the data will be de-identified and ID numbers assigned by the responsible investigator at the site will be used.

Dandelion Science Corp intends to share the analysis results with the NIH and appropriate organization/entities that have oversight (e.g., IRB, safety officer). Any data that falls under the

Dandelion Science Corp intellectual property will not be shared. Prior to any type of sharing, Dandelion Science Corp will de-identify and strip data of any information that can link the data with a particular participant. All the data will be stored and transferred in a HIPAA-compliant manner. The de-identified data may be shared in a HIPAA-compliant fashion with consultants and contractors who have a signed confidentiality agreement with Dandelion Science Corp.

EEG data preprocessing:

Cleaning EEG data involves removing artifacts from the EEG signal. Although the EEG system is designed to record neural activity, it also records electrical activity arising from physiological entities such as eye blinking or jaw clenching. The EEG will be digitized continuously at a 512 Hz sampling rate. Data will be downsampled to 256 Hz and bandpass filtered using a 0.1 Hz high-pass cut-off (12db/octave) to reduce low-frequency noise such as drifting, and a 30 Hz low-pass cut-off (24db/octave) to reduce high-frequency noise such as muscle tension. Following this step, data will then be re-referenced to the average of all channels. Then a time-frequency analysis will be performed to extract temporal dynamics of the major EEG wave bands (alpha, beta, theta and gamma). Signal processing will be performed using the MNE toolbox (Gramfort et al., 2013)and performed in Python. In addition, the painful stimulation-onset ERPs will be computed and the areas of N2 and P2 components will be used for the analysis.

GSR data preprocessing:

First, GSR artifacts will be detected by automatically identifying large, sharp changes in the amplitude, defined as an absolute value change of the derivative larger than 10. These artifacts will be corrected using cubic splines. Then the tonic and phasic components will be separated through FIR filtering. Then through application of a threshold a number of peaks will be calculated.

ECG data preprocessing:

The ECG data will be downsampled to 500 Hz. The QRS complex will be identified using Hilbert transform procedure and the R-R intervals will be computed.

EMG data preprocessing:

Analog band pass filter (20Hz to 500 Hz) will be applied to the raw signal before it is digitized. Then wavelet transform will be used to perform a time-frequency analysis on EMG data.

Optimization training and testing*:
During the optimization procedure, we will use alpha and beta EEG bands, number of peaks in GSR, heart-rate variability and facial EMG spectrum, among other features, to guide the arousal and pain-control optimization procedure. The success of the optimized stimuli in reducing pain

perception will be evaluated using VAS. Prior data indicate that the minimal clinically relevant change in pain self-report should be 20%. In our study this effect will correspond to roughly an 8 mm change on the 100mm VAS. If the true difference in the mean response of matched pairs is 8 mm, we will need a sample of 30 participants to be able to reject the null hypothesis that the response difference is zero with a probability (power) of 0.8. The Type 1 error probability of this test is 0.05.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

The purpose of this study is to develop a novel treatment to help reduce pain through dynamic AI-guided visual stimuli. The Data and Safety Monitoring Plan (DSMP) outlined below for this Phase I grant proposal will adhere to the protocol approved by the IRB, as well as by all other committees that have oversight responsibilities for this research. Since the study entails only minimum risk to the participants, the PI will monitor the safety of the participants. The Study team members will compile data and report to PI, as well as to the funder.

Our biosensor recordings have the potential to pick up abnormalities, including signs of focal and general epileptiform and non-epileptiform waveforms (EEG); arrhythmias, ischemia, and conduction abnormalities (ECG); and radicular abnormalities and metabolic-related conduction disorders (EMG).

Adverse Events associated with Experiment 1

Regarding the visual stimuli, adverse events are:

- seizure, defined as jerking movements of the limbs and/or loss of consciousness,
- dizziness/vertigo as defined by verbal complaints and loss of balance, and syncope.

Adverse Events associated with Experiments 2

We are concerned that pain induction and visual stimulation each has the potential for creating adverse effects, although they are unlikely to occur. CHEPs stimulation is commonly used pain-induction models for experimental purposes. It has been well described and are known to have a very low potential for harm to study volunteers because the stimuli can be precisely controlled. Within the individually predetermined range of nociceptive stimulation, participants are expected to experience neither psychological distress nor tissue injury. The latter will be verified by study personnel through inspection of the involved skin after the first test stimuli are administered (during the initial demonstration of study procedures to participants) as well as after all nociceptive stimulation has concluded. Furthermore, the study team members involved in pain induction will be present throughout and observe the participants directly during the entire process. In the highly unlikely event of equipment malfunction or misapplication, both of which

would trigger the need for reporting, arrangements will be made for participants to be evaluated by the on-site physician as stipulated in the protocol.

With regard to pain stimuli, adverse events are:

• excessive intensity of induced pain, defined as 80-100mm on VAS,
• anxiety/fear, defined as a 100% increase (i.e., doubling) in heart rate or >135 beats per minute, and
• injury to skin, likely in the form of a burn, defined as skin discoloration (i.e., red, white and/or brown) that does not resolve within 10 minutes of stimulus discontinuation.

WITHDRAWAL OF PARTICIPANTS

There are minimal risks to be incurred from participating in this study. Specific risks related to the clinical and cognitive assessments (study questionnaires), visual stimulation are described below.

Participants will be reminded that they may stop participating in the study at any time for any reason with no penalty or loss of benefits to which they are otherwise entitled. Participants will be encouraged to take breaks when needed. They will be reminded that they may refuse to answer any questions on the study questionnaires, and they may stop the nociceptive stimulation session at any time.

During arousal experiments, since the risk of adverse medical effect is extremely low and participants inclusion criterion bars participants with sensitivity to visual stimulation, any adverse effects will be dealt with through usual emergency procedures (calling 911).

Syncope, vasovagal response, signs of seizure, and verbal complaints of dizziness and vertigo will be considered as criteria for terminating the experiment. The Project Coordinator on site will be responsible for reporting all events to the PI and Safety Officer within a day, and these events will then be reported to the NIH and IRB according to the following scheme:

- Unanticipated problems, complaints and serious adverse events will be reported to NIH and IRB within 5 days
- Unanticipated Adverse Device Events and Major deviations within 10 days.
- Minor deviations will be aggregated and reported with continuing review or study closure.

RISKS TO PARTICIPANTS*

The potential risks of this experiment are extremely low. Given mild inconvenience of the CHEPs stimulation we are excluding volunteers with cardiac, neurologic, endocrine, gastrointestinal or renal disease or chronic pain conditions, as well as those with a history of prior major surgery. In addition, the participants will be exposed to visual stimulation which could potentially induce seizures in individuals with heightened light sensitivity. Hence such participants will also be excluded from our study.

POTENTIAL BENEFITS TO PARTICIPANTS

There is no direct benefit of this research to the study participants. The potential benefit of the research is to society in general, through the future development of a safe, effective, and affordable treatment for pain.

VULNERABLE POPULATIONS

No vulnerable population is expected to participate in the study.

MULTI-SITE RESEARCH

The research will be conducted at the Dandelion Science research facilities in Hoboken, NJ.

COMMUNITY-BASED PARTICIPATORY RESEARCH

This type of research is not part of our experimental design

SHARING OF RESULTS WITH PARTICIPANTS

There is a potential for observing abnormalities in our biosensor recordings. For example, with EEG recordings, we can observe signs of focal and general epileptiform and non-epileptiform waveforms; with ECG, we can observe arrhythmias, ischemia, and conduction abnormalities; and with EMG, we can observe radicular abnormalities and/or metabolic-related conduction disorders. Given that records are not performed for diagnostic purposes, if abnormalities are suspected the participant will be informed that such an abnormality was observed and instructed to follow up with their health provider for further investigations.

SETTING

Dandelion Science facilities

Laboratory

Dandelion Science Corp
[redacted]

Dandelion Science maintains its primary office at this location. At this location Dandelion Science maintains space for overall company management, as well as areas appropriate for computer research and computer programming activities. Dandelion Science maintains Internet access and wireless networking capabilities, computer workstations where software developers will be clustered together, beta testing rooms, conference rooms for privacy and larger meetings, video conferencing capabilities, as well as other standard office provisions. Dandelion Science will perform all programming and product development activities on secure company-owned computers.

Scientific Advisory Board

- [redacted]

- [redacted]

[redacted]

Consultants

- [redacted]

- [redacted]

Dandelion Science Management Team

- [redacted]

[redacted]

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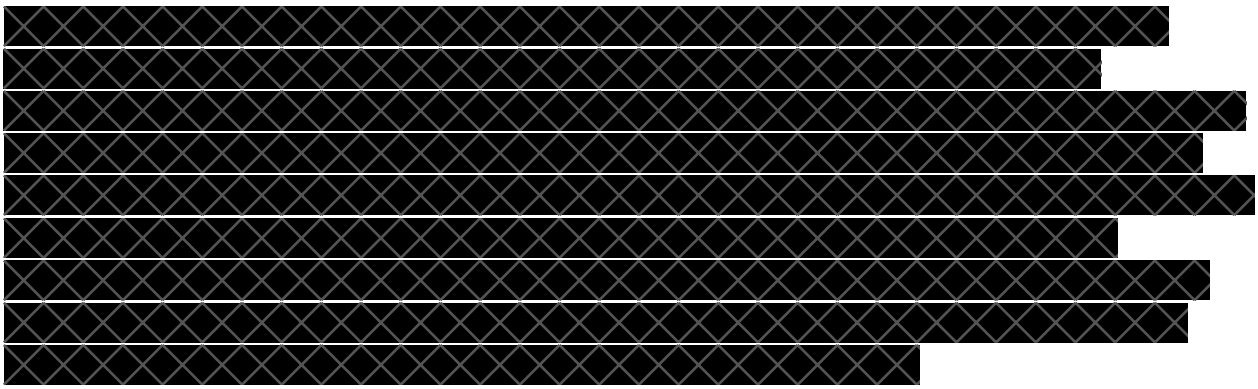

PRIOR APPROVALS

The research will be funded through a NIH grant.

CONFIDENTIALITY

Participation in this research will be kept confidential. In compliance with HIPAA protocols, all presentations of data will be void of unique identifiers in order to ensure that participant confidentiality is maintained. The experiment preparation will be conducted in a dedicated room with only the participants, the experimenter and the assistants present. In the beginning of the experimental setup a participant will be requested to sign a consent form, in which the experimental procedures and their rights as participants will be explained. The participants will be asked to provide general demographic information consisting of their age, gender and race/ethnicity. During the setup the electrodes will be attached to the participant's head, face, hands and palms, so participants will not be required to disrobe. The experiment will be conducted in a separate experimental booth, in which the participant will either be alone or with the experimenter depending on the specific details of the experiment.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

The data will be collected and kept electronically on a computer hard drive. The hard drive will be password protected and will be kept in a locked secure facility. Upon completion of the experiment the data will be transferred to secure and encrypted online storage. All the information pertaining to the identity of the participant will be removed from the data used for analytical and presentation purposes. The demographic and other unique identifiers will be kept in a separate encrypted online storage. An assigned study number, saved with each participant's unique identifiers and with study data, will be used to allow cross-referencing between separately stored information should there be a need to do so in the future.

COMPENSATION FOR RESEARCH-RELATED INJURY

In the event you become injured as a result of participation in this study, medical care will be available. The participants will be expected to pay for such treatment or seek reimbursement by their health insurance provider. Dandelion Science will cover the costs of reasonable and necessary treatment of study-related injuries that are not standard of care while the participants are in the study.

ECONOMIC BURDEN TO PARTICIPANTS

Participants' economic burden should not exceed the costs involved in traveling to the study site and the opportunity costs of participation in the experiment, for which they will be compensated.

CONSENT PROCESS

All participants will be required to provide written informed consent for the planned research. Given that all participants are their own legal guardians, and no deception or blinding will occur in this research, it is expected that each participant will have full understanding of what they are agreeing to. As usual, participants will be informed that they can terminate participation at any time and for any reason, without negative repercussions and without having to state a reason. In addition, the participants will be provided with information regarding the funder of the study, the purpose of the study, expected length of participation, study procedures, participant responsibilities during the experiment, possible risks and discomforts, potential benefits from the research, and reimbursement of expenses (See attached the informed consent form).

PROCESS TO DOCUMENT CONSENT IN WRITING

The outcome of the consenting process will include written documentation to verify participant agreement required in writing.

DEVICES*

The pain stimulation devices will be used only by the authorized study team members and when not in use the equipment will be stored in the locked experimental booth. The OVS will be kept in the stimulation computer and will be assigned a participant id number. The access to the stimulation computer will be limited to the authorized study team members.

Glossary

CHEPs – Contact Heat Evoked Potentials

DVN- Dynamic Visual Neuromodulation, general term for the neuromodulatory visual stimulation performed using Dandelion Science's platform
ECG - Electro-cardiogram
EEG - Electroencephalogram
EMG - Electro-myogram
ERP - Event Related Potentials
GSR - Galvanic Skin Response
OVS - Optimized Visual Stimulation
PI - Principal investigator
RVS - Random Visual Stimulation
SAM - Self Assessment Manikin (arousal and valence assessment)
VAS - Visual Analogue Scale (pain assessment)

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