Graduate Theses, Dissertations, and Problem Reports

2023

Cue Reactivity in Electronic Cigarette Users with Sign-Tracking or Goal-Tracking Behaviors

Polina Krom
West Virginia University, pk00013@mix.wvu.edu

Follow this and additional works at: https://researchrepository.wvu.edu/etd

Part of the Behavioral Neurobiology Commons, Cognitive Neuroscience Commons, and the Other Psychology Commons

Recommended Citation

Cue Reactivity in Electronic Cigarette Users with Sign-Tracking or Goal-Tracking Behaviors

Polina Krom

Thesis submitted to the Eberly College of Arts and Sciences at West Virginia University

in partial fulfillment of the requirements for the degree of

Master of Science in Psychology

Mariya Cherkasova, Ph.D., Chair

Melissa Blank, Ph.D., Member

Julie Brefczynski-Lewis, Ph.D., Member

Department of Psychology

West Virginia University
Morgantown, West Virginia
2023

Abstract

Cue Reactivity in Electronic Cigarette Users with Sign-Tracking or Goal-Tracking Behaviors

Polina Krom

Cue reactivity is an important predictor of addiction course and relapse. However, cue reactivity is only observed after an addiction develops. As such, it is unclear to what degree cue reactivity represents a state stemming from the addiction process versus a trait-like propensity towards developing cue-reward associations. Work in animal models has pointed to important individual differences in trait-like inclination to attribute incentive salience to reward-predictive cues that is associated with addiction-relevant behavioral and neurobiological features. These individual differences manifest as sign-tracking (ST) and goal-tracking (GT) behaviors during Pavlovian conditioning. Little research has attempted to translate ST and GT phenotypes to humans or relate them to cue reactivity in addictive disorders. The current study examined electronic cigarette (ECIG) cue reactivity in human participants as a function of a tendency to sign-track. Regular ECIG users were characterized in terms of their sign-/ goal-tracking propensity based on a Pavlovian conditioning paradigm accompanied by eye-tracking and were exposed to two different cue types: ECIG cues (e.g., devices, vape clouds) and neutral cues (water) in separate testing sessions. Our analysis focused on tendencies for sign-tracking / goal-tracking in relation to ECIG cue reactivity, measured as cue-induced cravings and neural responses captured through electroencephalography (EEG). The study found that participants with a higher gaze index, indicating a stronger tendency for sign-tracking, reported increased cravings (assessed by the Schuh-Stitzer questionnaire) in response to ECIG cues compared to neutral cues, consistent with our hypothesis. This finding was only significant in the analyses removing influential observations. Some trend-level effects also pointed to a possibility that contrary to our hypothesis participants with a greater sign-tracking propensity tended to have higher EEG amplitudes in response to neutral cues and lower amplitudes in response to ECIG cues in P300 and LPP components. It is important to note that the data collection is incomplete, and these results may change. Future research could explore alternative measures for sign- and goal-tracking tendencies and tailor ECIG cue stimuli to participants' specific devices.

Table of Contents

INTRODUCTION

Cue Reactivity

Cue reactivity refers to different responses that people suffering from addictive disorders exhibit when exposed to a stimulus associated with their addiction (e.g. syringes, lighters, bottle-openers) (Rohsenow et al., 1990). Responses to addiction-related cues may be psychological (cravings) (Niaura et al., 1988; Norberg et al., 2016), physiological (increased breathing, heart rate) (Carter & Tiffany, 1999; Drummond & Glautier, 1994), neural (activation of the brain's reward circuitry) (Filbey et al., 2008), cognitive (attentional biases) (Garland et al., 2012), and/or behavioral (drug-seeking) (Starcke et al., 2018).

At the neural level, regions involved in reward and motivational processing (the ventral striatum, the anterior cingulate cortex, the insula, the medial prefrontal cortex) and habit-formation (such as the dorsal striatum) are implicated in cue reactivity (Gerdeman et al., 2003; Kühn & Gallinat, 2011; Schacht et al., 2013). Motivational processing mobilizes goal-directed behaviors to obtain an anticipated reward (or avoid aversive outcomes),which can be experienced as "wanting (Berridge & Robinson, 2016; Kim, 2013). Conversely, habitual behavior depends on well-established (automated) associations between a stimulus and a response and may be independent of goal pursuit and wanting; an example would be turning off lights as one exits the room (Vandaele & Janak, 2018). In individuals with SUDs, cue reactivity may reflect both motivational and habitual processes (Carter & Tiffany, 1999; Cousijn et al., 2013). In addition, regions involved in emotional responses (such as the amygdala and the inferior parietal gyrus) have also been implicated (Devoto et al., 2020; Lin et al., 2020; Noori et al., 2016). Cue reactivity predicts drug-seeking behavior and relapse. According to a recent meta-analysis, cue exposure, cue-induced craving, and physiological (including neural) cue

reactivity all strongly predicted drug use and relapse, with a 1 unit increase in these cue reactivity indicators more than doubling the odds of consumption and relapse (Vafaie & Kober, 2022).

Cue Reactivity Mechanisms

Cue reactivity can be explained through theoretical accounts of classical conditioning (LaRowe et al., 2007; Tiffany, 1995), and incentive sensitization (Robinson & Berridge, 1993). Through repeated pairings with drug rewards, previously neutral stimuli (drug-related cues such as environments, smells, drug paraphernalia) become Pavlovian conditioned stimuli capable of eliciting conditioned responses. Simply seeing, smelling, or feeling things that were conditioned with drug use may elicit a conditioned motivational state marked by a desire for and seeking of the drug (Niaura et al., 1988; Rohsenow et al., 1990). The incentive sensitization theory of addiction explains mechanisms underpinning this conditioned motivational state. According to the incentive sensitization theory, drug-related stimuli acquire incentive motivational properties (or 'incentive salience') through the sensitization of the mesolimbic dopamine system occurring with repeated drug use (Robinson & Berridge, 1993, 2008). The incentive sensitization theory of addiction focuses on explaining how the mechanisms of "wanting" (craving) a drug are amplified at the neural level with repeated exposures to drugs and the accompanying cues. Hence, drug cues imbued with incentive salience come to elicit states of excessive craving or "wanting" (Robinson & Berridge, 1993). "Wanting" is distinct from "liking", which signifies the pleasure experienced with drug consumption. While drug liking and wanting are often experienced together, it is also possible to experience "wanting" without "liking", and "liking" without "wanting" (Peciña et al., 2003; Wyvell & Berridge, 2000).

Individual Differences in Trait-Like Cue Reactivity

Although individual differences in cue reactivity are associated with addiction course and outcome (e.g.Vafaie & Kober, 2022), it is unclear to what degree cue reactivity represents a state stemming from the addiction process versus a trait-like propensity towards developing cue-reward associations. Work in animal models has uncovered meaningful individual variation in trait-like tendency to attribute incentive salience to reward-predictive cues that is associated with addiction-relevant behavioral and neurobiological features (J. D. Morrow et al., 2011). Such variation is observed during Pavlovian conditioning: rodents are presented with a lever cue (conditioned stimulus), which predicts the delivery of food pellet rewards into the food tray (Flagel et al., 2009; Robinson et al., 2014). The rats do not need to interact with the lever to receive food pellets. However, during Pavlovian learning, individual differences emerge in how the rats respond to the presentation of this lever cue. Some of the animals develop a conditioned approach behavior to the lever cue and interact with it in an appetitive way (e.g., biting), suggesting the cue had acquired incentive motivational properties for these animals. These animals have been termed *sign-trackers* (ST). Other animals approach the food magazine in response to the lever presentation, suggesting that for them, the lever cue acquires purely informational rather than motivational significance. These animals have been termed *goal-trackers* (GT). Animals who display both sign- and goal-tracking behaviors some of the time have been termed *intermediates*.

ST and GT differ in addiction-relevant behavior. Compared with GT rodents, ST rodents acquire the drug-taking response more rapidly and then are observed to self-administer cocaine, ethanol, and opioids more readily, along with exhibiting increased reinstatement of cocaine-seeking behaviors (Krank, 2003; Saunders et al., 2013; Tomie & Morrow, 2018; Tunstall & Kearns, 2015; Yager & Robinson, 2015). Notably, sign-trackers that sign-tracked to a food-

related cue reward also sign-tracked to a stimulus associated with a cocaine infusion; goal-tracking animals were not observed to exhibit such behavior (Robinson & Flagel, 2009). Additionally, rodents that sign-tracked to a food-predicting cue were more likely to choose cocaine over food (when presented with cocaine/food levers) compared to rodents that goal-tracked to the same food-predicting cue (Tunstall & Kearns, 2015). Although the preponderance of research has pointed to ST being the more addiction-vulnerable phenotype, goal-trackers were found to be to be more susceptible to the effects of contextual cues on drug-related behavior: GT showed more context-conditioned hyperactivity and context-induced reinstatement of cocaine-seeking behavior (Robinson et al., 2014; Saunders & Robinson, 2011). This means that GT are more reactive to contextual (environmental) cues, such as places or situations that remind a person of their behavior (e.g., being at a bar, being at a vape shop). This could have potential treatment implications when attempting to choose a patient-tailored abstinence/treatment approach (e.g., opting for exposure therapy as a treatment option if a patient is a GT as they are less resistant to extinction compared to ST (Colaizzi et al., 2020; Gillis & Morrison, 2019)).

Sign- and goal-trackers may rely on different mechanisms for processing motivational information (Robinson et al., 2014). This notion is underscored by the findings suggesting that sign-tracking and goal-tracking CRs rely on different neurobiological substrates. Rodent models have shown that, sign-tracking behavior relies on dopamine signaling in the nucleus accumbens. Learning the association between the reward and the cue predicting the reward depends on dopamine signaling in the nucleus accumbens in ST but not in GT (Flagel, Clark, et al., 2011; Flagel et al., 2010). The manifestation and maintenance of sign-tracking relies on the activation of dopamine receptors and is blocked by dopamine receptor antagonist, which is not the case for goal-tracking (Flagel, Clark, et al., 2011; Saunders & Robinson, 2012). Additionally, exposure to

conditioned stimuli elevated levels of c-FOS (a marker of neuronal activity (Bullitt, 1990) in the striatum and thalamus more in sign-trackers compared to goal-trackers (Flagel, Cameron, et al., 2011). Goal-tracking, on the other hand, appears to not be subcortical dopamine dependent and to rely on alternative neural mechanisms, such as top-down cortical control (Haight et al., 2017). Goal-trackers are superior in cognitive performance, with greater attentional control and the frontal dopamine system that is less responsive to drug cues (Sarter & Phillips, 2018). In sign trackers, top-down cortical control mechanisms are shown to be impaired relative to goal-trackers (Haight et al., 2017). Sign-trackers showed greater resistance to extinction of sign-tracking and cue-evoked activity, whereas goal-trackers rapidly reduced their goal-tracking behavior in extinction (Ahrens et al., 2016; Gillis & Morrison, 2019). After cue exposure, it was observed that GT but not ST showed a substantial increase in drug-seeking behavior after the paraventricular nucleus (PVT) inactivation (PVT is a structure that mediates cue-motivated behaviors) (Kuhn et al., 2018). It has been hypothesized that sign-tracking behaviors may be explained by hyperactive subcortical processes that interfere with top-down control mechanisms (Colaizzi et al., 2020). These individual differences observed in rodents could potentially be important in informing the study of individual differences in addiction in humans.

Only a minority of individuals who use a certain drug recreationally will go on to develop a substance use disorder. For example, about 8000 teenagers try illicit substances every day, but only 5–14% of them progress to develop a substance use disorder (Jordan & Andersen, 2017). Likewise, while many people report recovering from addiction with minimal treatment, for others, addiction has a chronic, recurrent course and is sometimes resistant to treatment (M. Dennis & Scott, 2007; White & Kurtz, 2005). What is it that makes some people and not others vulnerable to developing and sustaining addictive disorders? Through a combination of human

and animal research, some individual risk factors for addictive disorders have been identified. Such factors include early substance use (before age 14) (Jordan & Andersen, 2017), childhood adversity (Levenson & Grady, 2016), novelty or sensation seeking (Bardo et al., 1996), impulsivity (de Wit, 2009), genetic factors (Kreek et al., 2005), and an early onset of puberty (Jordan & Andersen, 2017). Possession and/or development of such traits can be a substantial risk factor associated with the likelihood of drug use and/or dependence. Likewise, evidence of blunted dopamine responses to a stimulant challenge in people at high familial risk for addition (Casey et al., 2014) may point to DA system hypofunction being a vulnerability factor. Nonetheless, individual variation in addiction vulnerability, course, and the outcome remains poorly understood. Individual differences in the tendency to attribute incentive salience to reward-associated cues may explain some of the variability (Saunders & Robinson, 2013). To the degree that it does, a better understanding of individual differences in incentive salience attribution could have implications for the development of personalized treatment and prevention approaches.

Sign-Tracking and Goal-Tracking in Humans

Several attempts have been made to translate the sign- / goal-tracking construct to humans. At a theoretical level, it has been hypothesized that certain human traits/ behaviors may be conceptually similar to ST/GT in rodents. These traits include risk-taking, deficits in attentional control (defined as a reduced ability to allocate and shift attention between stimuli in an adaptive and flexible way), and impulsivity (defined as unplanned behaviors occurring as a result of insufficient behavioral inhibition, and behaving with insufficient regard for long-term consequences) (Colaizzi et al., 2020). Impulsivity and novelty-seeking (investigatory behavior often associated with drug experimentation) have been often looked at together in human

research, which creates a potential for exploring sign- and goal-tracking in the context of risky

behaviors and impulsivity in humans (Bardo et al., 1996; Colaizzi et al., 2020; Grant et al.,

2014). Most previous research has operationalized ST and GT in human participants using a

measure of eye gaze fixation on a reward-predictive cue versus the location of the predicted

monetary reward delivery on the screen during Pavlovian conditioning (Garofalo & di

Pellegrino, 2015; Schad et al., 2020a). In both studies, the Pavlovian conditioning task was part

of a Pavlovian Instrumental Transfer (PIT) paradigm. The PIT paradigm measures the influence

of irrelevant Pavlovian-conditioned cues on operant behavior (Lovibond, 1981; Rescorla &

Solomon, 1967; Talmi et al., 2008). In this paradigm, participants learn to associate previously

neutral cues with a reward through Pavlovian conditioning. In an operant conditioning task, they

learn to obtain rewards by performing an operant response. Lastly, motivational influence of

Pavlovian-conditioned cues on operant responding is evaluated as participants perform the

operant task in extinction in the presence of Pavlovian-conditioned cues (Estes, 1948; Holmes et

al., 2010; Rescorla & Solomon, 1967). Individuals classified as ST were found to show stronger

PIT effects (Garofalo & di Pellegrino, 2015; Schad et al., 2020a), paralleling the findings in the

rodent literature (Flagel et al., 2008; Saunders & Robinson, 2013). In addition, higher

impulsivity was self-reported by ST compared to GT (Garofalo & di Pellegrino, 2015), which

again parallels the behavioral patterns observed in animal models. For example, ST rodents

exhibit a faster and more frequent engagement with the lever, which demonstrates a decreased

ability to withhold a lever response in order to receive a reward, and suggests that STs are more

impulsive (Flagel et al., 2010). ST also showed greater reliance on model-free reinforcement

learning mechanisms, which track rewards independent of context, whereas GT relied more on

model-based reinforcement learning mechanisms, which take context into account (Pohořalá et

al., 2021; Schad et al., 2020b), a finding also recently reported in rodents (Moin Afshar et al., 2022). Habitual or compulsive substance use, despite the negative consequences, has been hypothesized to represent an over-reliance on model-free mechanisms (Vandaele & Janak, 2018). Other studies have attempted to operationalize sign-tracking behavior in humans as an approach of both eye gaze fixation and a lever cue in an apparatus resembling the operant chambers used to study ST and GT in rodents (Joyner et al., 2018; J. Morrow et al., 2019). Additional research is needed to establish the translational validity of the ST and GT conditioned responses in humans.

Despite sign-tracking having emerged as a behavioral marker of addiction vulnerability in animal models, its relationship to addictive disorders in humans has remained unstudied. Evidence demonstrating links between PIT and SUDs hints at the relevance of the sign-tracking construct to addiction in humans. Although not synonymous with sign-tracking, PIT is a closely related construct. In one study, individuals with alcohol use disorder showed stronger PIT effects to aversive, but not appetitive, stimuli compared to healthy controls (Garbusow et al., 2014), although another study did not find differences in PIT between individuals with alcohol use disorder and controls (van Timmeren et al., 2020). It is, therefore, unclear whether and how sign-tracking relates to addiction in humans. Considering that the sign-tracking CR represents a trait-like behavioral reactivity to Pavlovian-conditioned cues in rodents, ST propensity may be an important determinant of individual differences in cue reactivity in humans. In the proposed research, we will evaluate how sign-tracking relates to ECIG cue reactivity in regular users. We will measure cue reactivity as self-reported cue-induced cravings and changes in neural activity measured using electroencephalography (EEG).

Smoking/ ECIGs Cue Reactivity

Cigarette-related cues play an important role in nicotine addiction maintenance, relapse, and treatment outcomes (Erblich & Montgomery, 2012), which underscores the importance of research on the mechanisms underpinning cue reactivity for tobacco and nicotine products. For instance, exposure to cigarette-related cues has been found to increase subjective cravings in smokers (Bedi et al., 2011, p. 20; Betts et al., 2021; Conklin et al., 2015), as well as enhanced mesolimbic activity (Due et al., 2002).

Electronic cigarettes (ECIGs) are a relatively new form of nicotine consumption that has become increasingly popular since their initial emergence, with 14.9% of the adult population worldwide reporting having used ECIGs (Villarroel, 2020). There has been an increasing number of non-smokers who use ECIGs. This is especially the case among teenage and pre-teen users of ECIGs: regular cigarette lifetime use prevalence has now been surpassed by electronic cigarette use among adolescents (Hansen et al., 2020). ECIGs provide a convenient, user-friendly way to consume nicotine by inhaling an aerosol. Electronic cigarette devices have many different names that reflect their variety (e.g., "mods," "pods," "vape pens," "vapes," and "tank systems") but they all share common characteristics in their construction. Most ECIGs consist of an atomizer, a battery, and a cartridge that contains liquid nicotine along with propylene glycol (PG) (which is reported to deliver more flavor and provide a better throat hit) and vegetable glycerin (VG) (which is known to produce more vapor in the exhaled aerosol) (Pauly et al., 2007; Spindle et al., 2018; Wollscheid & Kremzner, 2009). The battery heats up the atomizer, which vaporizes the nicotine, vegetable glycerin, and propylene glycol liquid. Both VG and PG are present in ECIG liquids and carry a function of nicotine delivery, however, the PG:VG ratio in the liquids differ. It is shown that liquids with a higher PG concentration achieve better nicotine delivery along with requiring fewer puffs and reduced puff volume to achieve a certain nicotine concentration,

when compared to liquids with a higher VG concentration (Spindle et al., 2018). Interestingly, liquids with higher PG concentration were reported to be less satisfying to users, which suggests that factors other than efficient nicotine delivery (for example cues such as larger vape clouds, flavors) could be important for ECIG users (Spindle et al., 2018). This suggests that cue reactivity may differ based on the type of PG:VG ratio liquid used by an individual, as the flavor delivery and the amount of vape clouds serving as cues would vary. Although the amount of toxic chemical exposure is much lower when using ECIGs compared to tobacco cigarettes (Farsalinos & Polosa, 2014), there are still significant health risks present. Various liquid flavorings may contain harmful chemicals, and ECIG coils can vaporize harmful metal particles (Williams et al., 2013). Additionally, propylene glycol, a solubilizing agent approved by the Federal Drug Administration and used in ECIGs to create vapor, can potentially contain other harmful chemicals (such as formaldehyde) and cause upper airway and ocular irritation (Bhatnagar et al., 2014; Palazzolo, 2013; Sleiman et al., 2016). Experienced tobacco cigarette users reported that switching to ECIGs has helped them quit using tobacco cigarettes (Caponnetto et al., 2012), showing a strong association with quitting smoking after using ECIGs for at least 1 month in a longitudinal study of adult smokers (Biener & Hargraves, 2015). Additionally, such individuals consider electronic cigarettes a healthier way of nicotine consumption (Baweja et al., 2016). Being one of the most promising products for tobacco harm reduction (Polosa et al., 2013), electronic cigarettes nonetheless still have a potential for addictiveness (Berry et al., 2017). ECIGs have the potential to be addictive like regular tobacco cigarettes, with the amount of nicotine delivery variable depending on the liquid composition and puff duration (some ECIGs are much less efficient in nicotine delivery, which is especially common for the older generation of ECIGs, some have liquids with much smaller amounts of

nicotine) (Voos et al., 2019), and with the nicotine retention from ECIGs higher than tobacco

cigarettes in the respiratory tract (Wagener et al., 2017; Zuo et al., 2022). Additionally, electronic

cigarette users have reported using ECIGs on more sessions per day compared to regular

cigarettes but mentioned taking fewer puffs per occasion and less inhalation during each puff

(Farsalinos et al., 2013). This suggests that ECIGs may have a similar or even higher potential

for addiction compared to combustible cigarettes, especially in younger people (Jankowski et al.,

2019). This is important to note as ECIGs are largely marketed towards tobacco naïve youth and

young adults, which predicts subsequent ECIG experimentation (Chen-Sankey et al., 2019). It is

important to study the mechanism of ECIG addiction to aid in harm and addiction prevention.

Less work has examined cue reactivity in electronic cigarette users compared to smokers.

The existing evidence suggests that, like cigarettes, ECIG cues can elicit cravings to vape

(Blackwell et al., 2020). This is observed to be consistent throughout cues of different ECIG

device types and generations (Keijsers et al., 2022). In individuals who use both cigarettes and

ECIGs (dual users), ECIG cue reactivity is more prominent when compared to smokers who do

not use ECIGs, regardless of the type of ECIG cue (King et al., 2021). Additionally, dual

cigarette and ECIG users exhibit more craving and attribute more value to tobacco cigarette puffs

compared to ECIG puffs (Dowd & Tiffany, 2018). To date, no work is available that addresses

cue reactivity and ST/GT in samples of addicted users. Here we will use the ECIG use as a

model for examining the relationship between sign- / goal-tracking and cue reactivity.

Electroencephalography as a Measure of Cue Reactivity

Electroencephalography (EEG) is a widely used non-invasive method of measuring

cortical brain activity. EEG relies on event-related potentials ((ERPs) – electrical potentials

(impulses) generated by the brain) to record brain activity in response to stimuli (Luck, 2012).

ERPs occur in response to specific internal or external events (e.g., auditory stimuli, pictures, motor responses, decisions) and reflect mainly postsynaptic potentials, which occur during the change of the flow of ions across cell membranes during neurotransmission. ERPs can have multiple components based on a negative-going wave, which typically peaks around a certain timeframe (measured in milliseconds) after the presentation of the stimulus (Luck, 2012). ERP components are also identified by their negative or positive direction, scalp location, and timing (Woodman, 2010). EEG cue reactivity research has mostly focused on tracking the Slow Positive Waves (SPWs), which are believed to reflect the activation motivational and arousal brain systems (Cuthbert et al., 2000). Another marker of motivational systems activation is the P300 component (Lv et al., 2016), which is visible at around 300 ms after stimulus presentation (Zhao et al., 2017), preceding the SPWs. This component is considered to reflect decision-making, early attention, and stimulus detection (Picton, 1992). Additionally, another way of looking at how the brain processes visual stimuli is looking at the late-positive potential component of the ERPs . The late-positive potential (LPP) is a component that occurs in the midline around 400-2000 ms after stimulus presentation (Minnix et al., 2013; Moeller et al., 2012). LPP reflects motivational attention to emotional stimuli, which includes drug-related cues (T. A. Dennis & Hajcak, 2009; Parvaz et al., 2021)

EEG in Smoking/ ECIG Cue Reactivity

EEG signatures of smoking cue reactivity have included various frequency characteristics (alpha event-related desynchronization (ERD), and time characteristics (P300 component, slow positive waves) (Bu et al., 2019; Cui et al., 2013). Similar to increased P300 amplitudes in response to drug cues reported in individuals with substance use disorders (Horrell et al., 2010), the P300 component and slow positive wave (SPW) amplitudes show significantly larger

activation in smokers versus non-smokers when exposed to smoking cues, which is thought to reflect an attentional bias for smoking cues in addicted individuals (Lv et al., 2016). The N200 and P300 component amplitudes were significantly higher in response to smoking-related stimuli in cigarette smokers, compared to nonsmoking control participants (Herrmann et al., 2001). Finally, greater alpha desynchronization (indication of top-down processing) was observed in smokers when they were presented with smoking-related stimuli compared to neutral stimuli (Cui et al., 2013; Tamburin et al., 2021). This recorded activity was similar to the alpha desynchronization activity elicited during exposure to other highly arousing stimuli such as erotica and mutilations (Cui et al., 2013). Regarding LPPs, drug-related stimuli have been reported to elicit greater activity compared to neutral cues in cocaine-addicted individuals (Parvaz et al., 2021), which is taken to indicate attentional bias to drug-related cues. Additionally, smokers exhibited a higher LPPs when presented with cigarette cues compared to never-smokers (Minnix et al., 2013).

Statement of the Problem

Individual differences in addiction vulnerability, maintenance and treatment response remain poorly understood. Individual differences in cue reactivity predict addiction course and relapse, but it can only be observed after an addiction develops. Hence, it is unclear to what degree cue reactivity represents a state stemming from the addiction process versus a trait-like propensity towards developing particularly strong cue-reward associations. The latter would have implications for individualized treatment and prevention approaches. Animal models point to the existence of individual differences in trait-like cue reactivity in the form of a propensity to attribute incentive salience to reward cues: sign-tracking and goal-tracking. However, the translational validity of these phenotypes has been little studied. This research, for the first time

examined ECIG cue reactivity in human sign-trackers versus goal-trackers. Our specific aims were 1) to identify sign- and goal-tracking phenotypes in regular ECIG users; and 2) to examine whether these phenotypes differed in the strength of cue reactivity when exposed to ECIG-related cues.

Study Hypotheses

For the <u>primary outcomes</u>, we hypothesized that*:*

1. Relative to exposure to neutral cues, exposure to ECIG cues will significantly increase self-reported desire/craving for an ECIG measured by the QSU-Brief Factor 1.

2. ERP responses to ECIG-related cues will be enhanced relative to neutral cues in the P300 component.

3. Based on prior work in humans, compared to participants with a tendency to goal-track, those with a tendency to sign-track will exhibit a stronger PIT effect.

4. Relative to participants with a tendency to goal-track, those with a tendency to sign-track will a report greater desire to vape following exposure to ECIG cues.

5. There will be enhanced ERP P300 activity in response to ECIG cues relative to neutral cues.

6. There will be enhanced ERP P300 activity in those with a tendency to sign-track compared to those with a tendency to goal-track in response to ECIG cues relative to neutral cues.

For the <u>secondary outcomes</u>, we hypothesized that*:*

1.Relative to exposure to neutral cues, exposure to ECIG cues will significantly increase self-reported anticipated relief from withdrawal measured by the QSU-Brief Factor 2 and craving measured by the Schuh-Stitzer scale.

2. Relative to participants with a tendency to goal-track, those with a tendency to sign-track will a report greater relief from withdrawal measured by the QSU-Brief Factor 2 and craving

measured by the Schuh-Stitzer scale following exposure to ECIG cues (relative to neutral cues).

3. ERP responses to ECIG-related cues will be enhanced relative to neutral cues in the LPP

component.

4. There will be enhanced ERP LPP activity in those with a tendency to sign-track compared to

those with a tendency to goal-track in response to ECIG cues relative to neutral cues.

METHODS

Participants

Participants were 34 ECIG users. The participants were recruited from the community

using word-of-mouth referrals, flyers posted around WVU and the general Morgantown area, and

emails through WVU e-news. We also recruited via Craigslist, Facebook, and WVU Mix. Study

enrollment was open to anyone who responded to one of these advertisements and was eligible

based on the screening procedures described below.

Inclusion / Exclusion Criteria

To be eligible, the participants had to be at least 18 years of age and had to report using

ECIGs at least 4 days a week in the past 4 months. It must be noted that several changes were

made to the inclusion/exclusion criteria during the beginning stages of the study (refer to the

section on "Protocol Modifications" for comprehensive details). Specifically, changes were made

to criteria related to smoking: for a subset of participants (n=24) smoking was an exclusion

criterion: to be eligible, participants had to have smoked ≤ 100 cigarettes in their lifetime. The

entry criteria were subsequently modified as one of this study's components was completed (not

reported here). For the criteria of cigarette smoking history, initially participants (n=24) were not

allowed to be dual users, however, this was later modified to allow for smoking of regular

tobacco cigarettes (n=8 participants were dual users), as it has been shown that ECIG-related

cue-elicited cravings are observed regardless of smoking status (Keijsers et al., 2022), and this study focuses on individual differences in cue-elicited cravings rather than a specific product. For the initial 6 participants, current nicotine consumption was verified by a positive urinary cotinine result, which tests for nicotine presence, with the aim of excluding those negative for cotinine. However, this criterion was eliminated due to a protocol change (see Protocol changes). Individuals were excluded if they reported any ongoing psychiatric conditions, if they had used marijuana or alcohol more than 15 times in the past month, if they had used any illicit substances (e.g., cocaine, heroin, methamphetamine) in the past month, if they were currently taking psychoactive medication (such as SSRIs) (the criterion was added along with the EEG procedure (see Protocol changes) as research shows that psychoactive medication can potentially affect brainwave activity (Hyun et al., 2011; Saletu et al., 1983)), and if they were pregnant/breastfeeding. The absence of pregnancy was verified via a urine test. At the beginning of the first in-person visit and during the sign-/goal-tracking PIT task of the experiment in Dr. Cherkasova's lab, participants were informed of all procedures by a member of the research team. Research staff answered any questions that participants had about the study procedures and consent process.

Procedures

REDCap Screening

Individuals that responded to the advertisements completed an online REDCap questionnaire with questions about demographics, health, and tobacco/alcohol/drug use. Eligible individuals, based on the REDCap questionnaire screener, were then invited to the laboratory for an in-person screening procedure.

Informed Consent & In-Person Screening Procedures

In the first, in-person session, participants were explained the study procedures, the study purpose, and the potential benefits and risks of participating in the study as described in the consent form. Those who were qualified and consented to participate were then asked the same questions to the REDCap pre-screening questionnaire, also including more details about the participants' demographics information, ECIG type, and questions about their ECIG use. This overlap in items asked allowed the researchers to verify the reliability of participants' responses. Individuals whose responses differed from their initial pre-screening questionnaire answers were excluded from participation. After questionnaire completion, female participants' urine samples were tested to exclude pregnancy. For the first 6 participants, a cotinine urine analysis was performed. These participants also engaged in a ECIG vaping bout session prior to the start of the experiment. This vaping bout was subsequently removed (see Protocol Changes below), and a mandatory 8-hour abstinence period from vaping was introduced prior to the start of the sessions. A total of 28 participants were a part of the modified protocol that included abstinence from vaping. These 28 participants were additionally exposed to the bogus procedure of saliva collection to control for vaping abstinence (see below). Volunteers who qualified based on the screening began the first study session right away.

Study Design

Eligible participants took part in two within-subjects study visits on separate days – one with ECIG cue exposure and the other one with neutral (water) cue exposure (Fig. 1 A, B). Condition order was counterbalanced across participants (ECIG session first vs neutral session first).

Cue exposure was accompanied by EEG recordings for 12 participants. Following exposure to neutral cues, participants completed the Pavlovian to Instrumental Transfer paradigm determine their gaze index and their propensity to either sign- or goal-track.

A   B

Fig. 1. A, B. Examples of ECIG and Neutral (water) cue images utilized as stimuli for the session.

Protocol Modifications

As mentioned earlier, the study protocol underwent several changes. Six participants were tested under the initial version of the protocol, which included a vaping bout at the start of both testing sessions (to maximize consistency across participants and sessions in terms of craving and withdrawal), a urine cotinine test, no EEG recording, cue exposure taking place in the Blank lab. The first set of changes to the study protocol included 1) the removal of pre-session vape bout, 2) changes to the ECIG cues (removing vape pen devices and adding more

pod and mod devices), 3) introduction of the mandatory 8-hour abstinence period (to maximize

cravings), 4) introduction of the bogus saliva test (to test for abstinence), and 5) removal of the

current nicotine consumption verification with a positive urinary cotinine result, which tests for

nicotine presence (13 participants were tested in this version of the study). The protocol was then

changed again to add the EEG component, which also introduced an additional exclusion

criterion of SSRI use (a total of 3 participants were a part of this protocol). Finally, the last study

protocol change was to move all the procedures to Dr. Cherkasova's lab and change the

exclusion criteria to allow for dual users (allowing for >100 cigarettes / lifetime) (a total of 12

participants were tested on this protocol).

Cue Reactivity

Cue reactivity sessions were separated by a minimum of 48 hours to exclude carryover

effects. At the start of each cue reactivity visit, a subset of participants who underwent EEG were

fitted with a 32-electrode cap connected to a NeuroScan system for electroencephalography

(EEG) (Lubman et al., 2008). Electroencephalogram (EEG) recordings were taken from 32

active electrodes arranged in a modified 10-20 system (see Fig. 2).
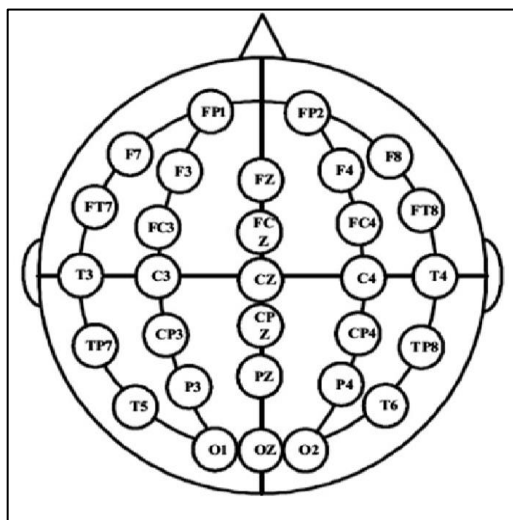
Fig.2. *The EEG Montage Used in This Study based on the modified 10-20 system (Allison et al., 2014).*

Additional electrode was placed below the left eye to monitor for blinks (artifact filtering is described in the analysis section). Using saline gel, all electrode impedances were maintained below 10 kΩ (Górecka & Makiewicz, 2019). A GRAEL EEG V2 amplifier was used to amplify the analog electrical signals from the EEG sensor and convert them into a digital signal that can be processed by the computer for further analysis. EEG recordings were taken from the 6-minute cue exposure sessions only and were not used to monitor any brain activity during the questionnaire portions of the study or during the assessments related to nicotine/tobacco use and impulsivity (see below). Signal sampling rate was set at 2048.0 Hz.

Participants first completed assessments related to nicotine/tobacco use and impulsivity (not analyzed for the purposes of the current study). Next, participants completed self-report measures of craving and then viewed a cue exposure slideshow on a computer. The slideshow presented a series of images (cues), 6 seconds each, for a total of 5 minutes of cue exposure. During the ECIG cues session, the images depicted various ECIG devices, ECIG paraphernalia, and individuals or groups or individuals using ECIGs (Fig. 1.A). During the neutral cues session, images depicted water and individuals drinking water (Fig. 1.B). The order of ECIG vs neutral cue sessions was counterbalanced across participants. Following cue exposure, participants completed the self-report questionnaires again, followed by three behavioral economic tasks (not analyzed for the purposes of the current study, see Appendix for detailed description). After 20 minutes of free time, participants viewed the same picture slideshow again, accompanied by EEG recordings and followed by self-report questionnaires and behavioral economics tasks (not analyzed). The second bout of cues was presented based on findings that repeated cue presentation produces stronger cravings in cigarette smokers (Betts et al., 2021).

The second session was identical to the first in all respects except featuring the cue type the participant had not already been exposed to in the first session (ECIG or water). See Fig. 3 for a visual layout of the study procedures. The participants were compensated a variable amount at the end of each session (there was variable compensation for the behavioral component since the compensation depended on the task performance: $50 each behavioral cue session, $15-19 for one session of the eye-tracking part of the study, and $20 for EEG).
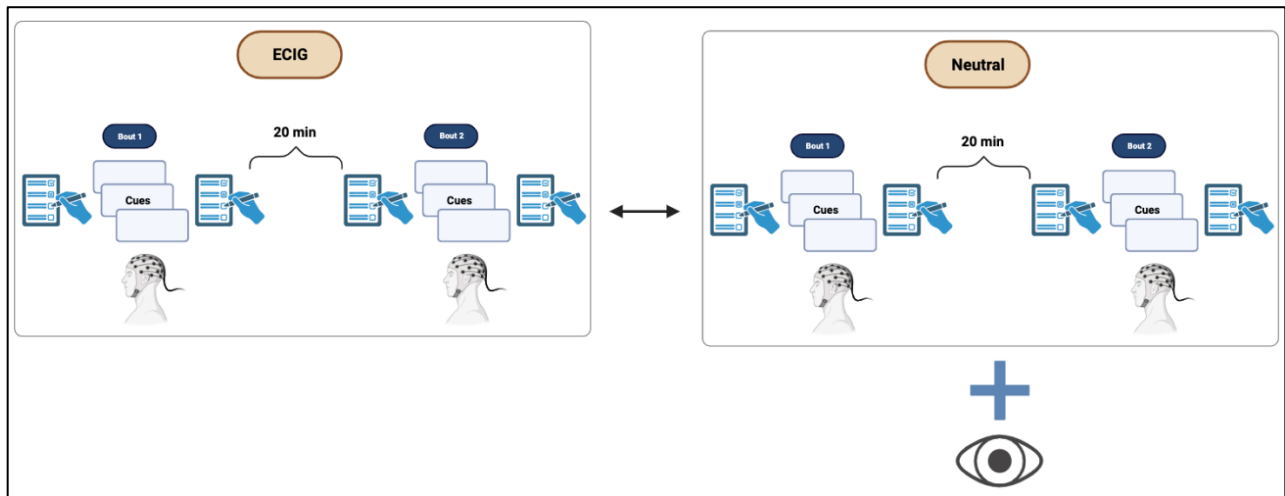
Fig.3. *Study Procedure / Session flow.*

Self-Report Craving Questionnaires

The Questionnaire of Smoking Urges-Brief (the QSU-Brief) and the Schuh-Stitzer scale were used to assess self-reported cravings. The QSU-Brief questionnaire contains 10 statements assessing how the respondent feels and thinks about their desire to smoke while they are completing the questionnaire (Herbst, 2022). For the purposes of this study, the QSU-Brief was adapted for vaping, as done previously (Blackwell et al., 2020). For each item, participants indicate how much they agree or disagree with each of the statements on a Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The QSU-Brief has a two-factor structure: factor 1 items reflect a strong desire to smoke and factor 2 items reflect anticipation of relief from

withdrawal symptoms (Cox et al., 2001). The Schuh-Stitzer scale is a visual analogue scale that measures smoking desire and cravings adapted for vaping for the purposes of the current study. Individual items are expressed as a percentage of the distance from the left anchor (i.e., 0, 0-100 range) to the point selected. To score the scale, the four items are averaged, which then creates a score with higher values indicating higher levels of craving (Schuh & Stitzer, 1995).

Pavlovian-to-Instrumental Transfer and Sign-Tracking

After the neutral cues session, the participants completed the PIT procedure, in which sign-tracking and goal-tracking tendencies were assessed. The procedure took place following the neutral cues session to ensure that the classification of participants as ST and GT was not influenced by the state of craving and reflected trait individual differences. Participants were also offered an opportunity to take a vape break prior to starting the PIT protocol.

For the PIT paradigm, participants were seated in a dimmed room with their chin positioned in a chinrest such that their eyes were at the distance of 57 cm from the computer screen (this distance permits 1cm of the computer screen to equal 1° of visual angle). Participants completed the Pavlovian Instrumental Transfer paradigm consisting of 3 tasks adapted from Garofalo & Di Pellegrino, 2015, with instructions explained by the researcher at the onset of each.

The PIT paradigm was comprised of 3 consecutive tasks: 1) Instrumental Conditioning task, in which participants learned an operant response to obtain a contingent reward (25 cent coin); 2) Pavlovian Conditioning task, in which participants learned to associate a visual cue (fractal) and a contingent reward (25 cent coin), and ST and GT conditioned responses were measured via eye-tracking; and 3) Pavlovian Instrumental Transfer (PIT) task, in which the influence of irrelevant Pavlovian cues on instrumental responding was tested.

Instrumental Conditioning Task

Participants were instructed to choose between two squares (colored in white during the instrumental task) located on the left and right sides of the screen to gain a reward (Fig. 4). A mouse click response inside one square yielded a monetary win (Rewarded Choice = 25 cents coin), a response within the other will yielded no reward (Unrewarded Choice = no coin). Rewarded square click yielded the reward on a variable interval schedule, with a variable interval of 4-12 seconds always being associated with no-reward. The response in the unrewarded square never yielded rewards. After each choice, a no-reward image (an empty circle of the same hue and luminance as the reward image) or reward image (25 cents coin) appeared for 1 second in the bottom square of the screen, depending on the outcome (Fig. 4). Participants were informed that they will receive an actual payment equal to the number of coins won during this task. The association between square position and outcome (right square rewarded vs left square rewarded) was counterbalanced across participants. The task lasted around 6 minutes, and participants were instructed to make as many choices as they wish, with no time pressure.
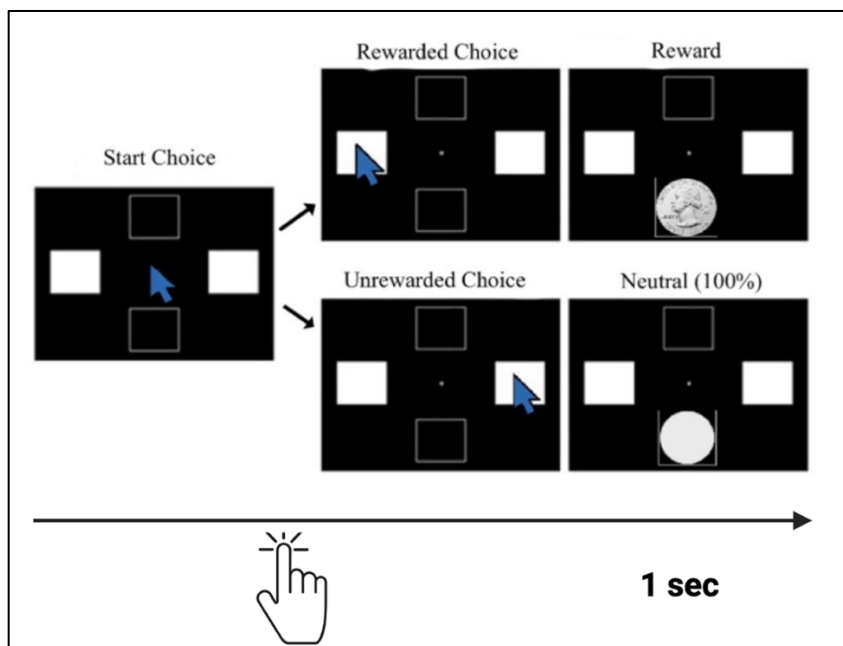
Fig.4. *Instrumental conditioning task of the PIT paradigm (adapted from Garofalo & Di Pellegrino, 2015).*

Pavlovian Conditioning Task

This experimental session was accompanied by eye-tracking to measure ST and GT conditioned responses (see below) and began with an eye tracker calibration. In each trial, one of two fractals appeared for 5 seconds in the top square of the screen. One fractal predicted the subsequent delivery of a reward (25 cent coin) on 80% of trials (CS+), while the other fractal (CS-) never predicted reward delivery. The CS phase was followed by a response phase, during which participants were presented with a white patch within the bottom square (in the absence of a CS in the top square). They were required to mouse-click on the patch as quickly as possible to remove it and discover the outcome of the trial hidden underneath: a reward signified by the image of a 25-cent coin, or a non-reward signified by the image of an empty circle of the same hue, luminance, and size. The outcome was presented for 1 second. The task included 40 trials (20 CS+ and 20 CS-) each followed by a variable intertrial interval of 0.5 – 4 seconds. Participants were instructed that they will receive an actual payment matching the number of coins collected during the task. Task outcome (coin/no coin) and the visual cue (fractal identity associated with the reward/no-reward) were counterbalanced across participants (Fig.5). The task lasted around 6 min. At the end of the task, participants were asked to rate how much they liked each of the CSs on a 5-point Likert scale. Additionally, they were asked to rate the likelihood of reward delivery for each of CSs on a scale from 0-100.
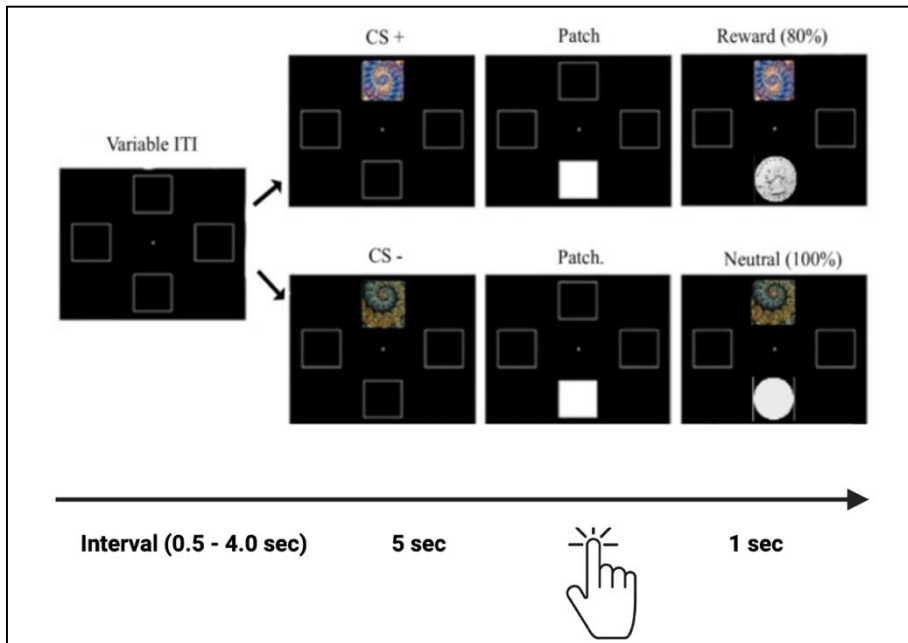
Fig.5. *Pavlovian conditioning task of the PIT paradigm (adapted from Garofalo & Di Pellegrino, 2015).*

To track participants' eye movements, we used the Tobii Pro Nano eye-tracker running the Tobii Pro software. The eye-tracker uses near-infrared illumination which creates reflection patterns on the cornea and the pupil (Smith et al., 2018). It then utilizes a physiological 3D eye model to estimate the eye position in space and identify the gaze point of the participant (*How Do Tobii Eye Trackers Work?*, 2015).

PIT Task

The Pavlovian to Instrumental Transfer (PIT) phase was identical to the Instrumental Conditioning task (choice between the left or right square to receive a coin), except for the following. In the PIT phase, task-irrelevant Pavlovian-conditioned CS was sequentially presented in the top square, alternating between CS+ and CS- every 30 seconds. Additionally, the PIT task was performed in extinction, such that participants' choices always led to a no-reward outcome. Extinction allows us to test how Pavlovian cues influence instrumental responding without the

confounding effects of ongoing rewards. The PIT task lasted around 6 min, during which

subjects were instructed to make as many choices as they want (Fig. 6).
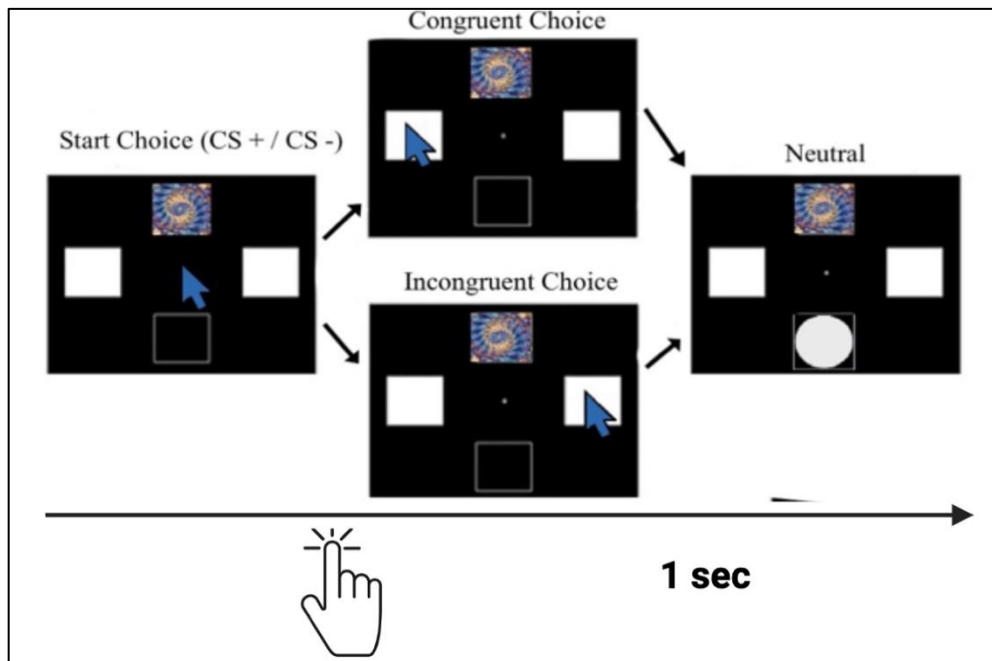
Fig.6. *Pavlovian to Instrumental Transfer (PIT) phase of the PIT paradigm (adapted from Garofalo & Di Pellegrino, 2015).*

Participant Safety and Rights

Participants' safety and rights were guaranteed through IRB-approved protocols enacted

by laboratory staff. Participants were informed that they had full right to contact the Office of

Research Integrity and Compliance with any questions/concerns about their role as participants.

We did not observe any adverse events associated with using the EEG system or the Tobii eye-

tracker on the participants. Confidentiality was ensured by using only numeric IDs to label

participant data participant data. Data was stored in locked rooms and on password-protected

computers in Dr. Cherkasova's and Dr. Blank's labs.

Data Preparation and Analysis

Data Preparation/Preprocessing

Before conducting data analyses, the data collected from surveys and self-report questionnaires was cleaned and scored according to the scoring instructions for each of the questionnaires. Additionally, each self-reported outcome (desire to vape, anticipated relief from withdrawal, and craving) was averaged across the two bouts to create a single pre- and post- cue exposure score. Participant's ECIG use duration was self-reported in months and was later converted to years for ease of interpretation. ECIG liquid nicotine concentration information was collected in percentages and was later converted into mg/mL.

Eye-tracking data was exported from the Tobii Pro software as spreadsheets for further analysis. We exported the total duration of fixations on the two predetermined areas of interest (AOIs) during the CS presentation phase: "Sign" (18.49 cm^2 square at the top of the screen), and "Goal", (18.49 sm^2 at the bottom of the screen). Only the last 4 seconds of the 5-second CS presentation phase were considered, excluding the first 1 second of CS presentation to eliminate fixations belonging to the 'orienting response'. Orienting response is involuntary and evoked by environmental stimuli, specifically if such stimuli are novel (Friedman et al., 2008). It can include things like head and eye movements (Sokolov, 1990), but can include other components such as the ERP P300. Excluding the orienting response was important for the purposes of our study to make sure that the participants' gaze index was not driven by stimulus arrival and novelty and primarily reflects their attribution of incentive salience to the stimulus.

Participants were characterized in terms of their propensity to sign-track based on the oculomotor CR recorded during the Pavlovian Conditioning task, as was done in earlier studies (Garofalo & di Pellegrino, 2015; Schad et al., 2020). The degree of sign- or goal-tracking was determined based on a *gaze index* computed as the difference between fixation durations on the sign and goal AOIs: (Sign – Goal)/(Sign + Goal), so that a higher value corresponded to looking

more at the Sign (Sign-Tracking behavior) and a lower value corresponds to looking more at the

Goal (Goal-Tracking behavior). Due to our sample's gaze index data not being bimodally

distributed (Fig. 8) (which has also been observed in previous research utilizing this measure of

the sign- / goal-tracking in humans (Cherkasova et al., 2023; Schad et al., 2020b)), we decided to

employ the gaze index as a dimensional measure of sign-tracking in subsequent analyses. Gaze

index signifying the degree of sign- / goal-tracking and was, therefore, used as a continuous

regressor in the models, as was done in a previous report (Cherkasova et al., 2023), rather than

being used to classify participants as ST or GT.

Additionally, the Pavlovian task self-report data (mouse click responses on a scale) was

preprocessed to quantify participants' liking of the CS (CS+ or CS-) on a 5-point Likert scale,

and their impression of the likelihood of reward delivery for each fractal (CS+ or CS-) on a 0-

100 scale. Based on the initial preprocessing, four participants did not learn the association

between the CS and the reward, assessed by the "likelihood of reward delivery" question, i.e.

they did not rate the CS+ as more likely to yield rewards than the CS- (see Fig. 7.B). We

analyzed the data both including and excluding these 4 participants and report both sets of

findings. Full sample results are reported first, followed by results excluding the 4 participants.

The IC task was preprocessed by first separating trials into two hemiblocks: hemiblock 1

included the first 20 trials, hemiblock 2 included the remaining 20 trials. We then calculated the

proportion of mouse click responses on the "correct" (rewarded) stimulus (a square that yielded a

monetary reward on most of the trials) for each hemiblock (Figure 9). Six participants displayed

performance that suggested inadequate operant learning, with performance of ≤50% correct in

the 2nd hemiblock. These participants were, excluded from the PIT analysis, as the PIT effect

relies on the previously learned operant response.

A total of 24 participants' data were included in the PIT analysis, as the PIT task data (final task of the three for this experiment) were lost for additional 2 participants because of equipment failure. Four participants were excluded for not showing clear evidence of learning the Pavlovian association (one of whom also did not learn the operant response). PIT data was preprocessed by calculating a 'response index' by subtracting the incongruent (unrewarded during the IC task) choice selection rate from congruent (rewarded during the IC task) choice selection rate. Higher values of the response index indicated higher rate of congruent choices (i.e. choice of the rewarded operant response in the presence of the CS+); lower values of the response index indicated higher probability of incongruent choices.

EEG data was preprocessed for further analysis using the Neuroscan CURRY 8 software. We utilized a 1.0 to 30.0 Hz bandpass filter and a Hann Fast Fourier Transform filter to process the brainwave recordings. These filters helped to identify physiological artifacts which may include events such as pulse, breathing, eye movements (blinks, lateral eye movement spikes), and muscle and movement artifacts (Louis et al., 2016). These artifacts result in low-frequency waves that can be confused with delta and theta bands. Eye blink artifacts were identified and removed by referencing the VEOG (Vertical ElectroOculoGraphy) eye-electrode channel to $0/+150 \mu V$, and global covariance reduction using all detected blinks. Early attention-related P300 component (~300–700 ms) was measured during cue exposure. This component was reported to be evoked in addicted individuals when they were exposed to drug-related cues (Bu et al., 2019). Eight electrodes in the posterior midline were used in the analysis, including CPz, CP3, CP4, Pz, P7, P4, P3, and P8 (Zorjan et al., 2021) along with a time window of 300–700 ms post-stimulus presentation (Horrell et al., 2010). Other electrode recordings were excluded and not considered in the analysis. For each participant, the voltage data for each of the specified

channels was averaged across all trials and bouts (bout 1 and bout 2) of a given type of cue (neutral cues, ECIG cues) for the specified P300 time window. To perform statistical analysis, we derived an average P300 amplitude, which was achieved by averaging voltage across the specified P300 window (300-700 ms after stimulus presentation). Attention-related LPP component (~400–2000 ms) was measured during cue exposure as a secondary outcome. This component was reported to be evoked in addicted individuals when they are exposed to drug-related cues (Parvaz et al., 2021). Eight electrodes in the posterior midline were used in the analysis, including CPz, CP3, CP4, Pz, P7, P4, P3, and P8 (Zorjan et al., 2021) along with a time window of 400–2000 ms post-stimulus presentation (Horrell et al., 2010). Other electrode recordings were excluded and not considered in the analysis. For each participant, the voltage data for each of the specified channels was averaged across all trials and bouts (bout 1 and bout 2) of a given type of cue (neutral cues, ECIG cues) for the specified LPP time window. To perform statistical analysis, we created an average LPP amplitude, which was achieved by averaging voltage across the specified LPP window (400-2000 ms after stimulus presentation).

The Brief Questionnaire of Smoking Urges (QSU-Brief) was scored for Factor 1 – Intention/Desire to Vape and Factor 2 – Relief of Negative Affect & Urgent Desire to Vape to determine each participant's pre- and post- cue exposure score for each exposure. Items from the Schuh–Stitzer scale were averaged to create a composite score, with higher values indicating higher cravings (Schuh & Stitzer, 1995). Bout 1 and bout 2 pre- and post- scores were averaged together to create a single pre- and post- score for neutral and ECIG cues. These scores were then used to calculate difference scores between pre- and post-cue exposure as an index of change in craving, desire to vape, and anticipated relief from vaping as a function of cue exposure. We obtained difference (delta) values for each of the three outcomes to use as dependent variables

the linear mixed effects models by subtracting the pre-exposure values from the post-exposure values. The primary outcome for evaluating cravings was the QSU-Brief Factor 1; the QSU-Brief Factor 2 and the Schuh-Stitzer scale were exploratory secondary outcomes. Factor 1 was chosen as a primary outcome because it measures desire/craving, whereas Factor 2 measures the anticipation of relief from withdrawal-related negative affect. We expected cue exposure to have a more pronounced effect on Factor 1, as Factor 1 is a commonly utilized measure of appetitive craving in previous literature (Shiffman et al., 2013, 2015). Another measure of craving/desire, the Schuh-Stitzer scale, was used as an additional secondary outcome. Statistical significance was set at the uncorrected $\alpha = 0.05$.

Statistical Analysis

RStudio (RStudio, PBC, Boston, MA) with R version 4.3.1 was used for fitting the linear mixed effects models, generating plots, and verifying assumptions. To create the linear mixed effects models, we utilized the lme4 package in R (Bates et al., 2015). Raincloud plots for data visualization were created by using the raincloud plots package in R (Allen, M. et al., 2021). 95% Confidence Intervals (CIs) and p-values were computed using a Wald t-distribution approximation. Linear mixed effects models were estimated using restricted maximum likelihood (REML).

Additionally, data were examined to ensure the statistical models' assumptions were met. First, we used the "check_model" function from the "performance" package (Lüdecke et al., 2021) in R to run initial model diagnostics (outliers, normality of residuals, homogeneity of variance). We used boxplots to detect potential outliers, while histograms were utilized to visualize the distribution of each dependent variable. Random effects were calculated and plotted using the "ranef" function from the "plm" package (Croissant & Millo, 2008) in R. We assessed

the normality of residuals in each model by looking at the Q-Q plots and by using the Shapiro-Wilks test (Shapiro & Wilk, 1965). Finally, we tested the assumption of homogeneity of variance by using scatterplots of residual by predicted values. Cook's distances were used to identify influential outliers. We used a cutoff criterion of Cook's distance being greater than 4 times the mean to identify influential outliers (*Outlier Treatment With R | Multivariate Outliers*; Prabhakaran, 2023).

Questionnaire & Gaze Index Analyses

We used a linear mixed effects model to predict the QSU-Brief Factor 1 (desire to vape) from gaze index in interaction with cue type (ECIG (reference category) vs neutral) with random intercepts modelled for participants, and cue session order (neutral first (ref.) vs ECIG first) and the presence or absence of the vaping session before the experiment (pre-vape: yes (ref.) vs no) as a covariate. The gaze index variable was scaled in all models specifying it as a regressor using the 'scale' function in R. The model formula was as follows:

*Desire to vape ~ scale (Gaze Index) * Cue Type + Session Order + Pre-vape + (1 |participant)*

Analogous linear mixed effects models were used to predict the QSU-Brief Factor 2 (anticipated relief from withdrawal) and the Schuh-Stitzer Scale (craving to vape) variables.

Pavlovian Learning

As an index of Pavlovian learning of stimulus-reward (CS-US) associations, we analyzed the subjective ratings of the CS+ and CS- (liking of the CS, likelihood of reward delivery for each CS). We used a linear mixed effects model to predict liking rating from CS type (CS+ (ref.) vs. CS-) in interaction with gaze index, with random intercepts modelled for participants. The presence or absence of the vaping bout before the experiment (yes (ref.) vs. no) was used as a covariate. The version of the experiment (Pavlovian 1 (CS+: blue fractal; CS-: green fractal) vs.

Pavlovian 2 (CS+: green fractal; CS-: blue fractal) (yes (ref.) vs. no) was used as a covariate. The

model formula was as follows:

 Liking Rating ~ CS Type* scale (Gaze index) + Pre-vape + Task Version + (1 |participant)

Same linear mixed effects model was used to predict the likelihood of reward delivery variable.

Instrumental Learning

We used a linear mixed effects model to predict proportion of correct responses (mouse

clicks on the "correct" rewarded stimuli) as a function of hemiblock (1 (ref.) vs. 2) in interaction

with gaze index, with random intercepts modelled for participants, and task version (version 1

(right square rewarded) (ref.), version 2 (left square rewarded) and the presence or absence of the

vaping session before the experiment (yes vs. no (no - ref.)) as a covariate. The model formula

was as follows:

Proportion ~ Hemiblock* scale (Gaze index) + Task Version + Pre-vape + (1 |participant)

As mentioned earlier, a successful acquisition of an operant response was considered as

performance of >50% correct responses in the 2nd hemiblock.

PIT Data Analysis

PIT data analysis was modeled on the Garofalo & di Pellegrino, 2015 (Garofalo & di

Pellegrino, 2015). We compared the propensity to make congruent choices (choice that was

rewarded during the instrumental conditioning part of the task) versus incongruent choices

(choice unrewarded during the instrumental conditioning part of the task) during the CS+ versus

CS- presentation as a function of gaze index.

We used a linear mixed effects model to predict response index from CS type (CS+ (ref.)

vs. CS-) in interaction with gaze index, with random intercepts modelled for participants and task

version (rewarded CS identity (blue vs green fractal) crossed with rewarded side (left vs right) in

operant conditioning; task version 1 (blue and right) (ref.)) and the presence or absence of the vaping session before the experiment (yes (ref.) vs. no) as a covariate. The model formula was as follows:

Response index ~ CS Type* scale (Gaze index) + Task Version + Pre-vape + (1 |participant)

Based on previous findings (Garofalo & di Pellegrino, 2015), we hypothesized that more ST-like participants (higher gaze index) will be more likely to choose the congruent option (higher response index) when presented with the task-irrelevant CS+ compared to when they see the CS− .

EEG Data Analysis

We used a linear mixed effects model to predict the P300 mean amplitude from stimulus type (neutral (ref.) vs. ECIG) in interaction with gaze index, with random intercepts modelled for participants, and cue session order (neutral first (ref.) vs. ECIG first) as a covariate. The model formula was as follows:

Mean amplitude ~ Stim type * scale (Gaze index) + Session Order + (1 |participant)

An analogous model was used to analyze the LPP component. We expected elevated ERP P300 and LPP component responses to ECIG-related cues relative to neutral cues, especially in participants with a tendency to sign-track.

RESULTS

Full Sample

Participant Demographics

A total number of participants that completed the study was N=34. Detailed demographic characteristics for this sample are shown in Table 1. Mean age of the sample was 22.26 (*SD* = 3.94) years. Slightly over half of the participants were female (52.94 %). The majority of the participants identified as white (67.65%). Of the 32.35% of participants who identified as other than white, the races reported included 14.71% Asian, 11.76% Native Hawaiian or other Pacific Islander, 2.94% Black, and 2.94% Multiracial. Average use of ECIGs was reported as 6.47 (*SD* = 0.86) days per week for an average of 2.33 (*SD* =1.45) years. The mean ECIG liquid nicotine concentration across all devices was 48.88 (*SD* = 6.83) mg/mL based on self-report. All participants reported using pod-style devices. Out of these device types, 25 (73.53%) were fully disposable (e.g., ELFBAR Hyde, Airis, Vaporesso) and 9 (26.47%) were rechargeable (e.g., Juul, Vuse). Out of the total number of participants, 26 (76.47%) were ECIG-only users and 8 (23.53%) were dual ECIG-cigarette users. All ECIG-only users reported smoking $\leq$ 100 cigarettes in their lifetime (*M* = 15.85, *SD* = 21.88). Dual users reported smoking an average of 1.18 (*SD* = 1.22) cigarettes per day. The average Penn State Electronic Cigarette Dependence Index (PSECDI) score (range 0-20) for all participants was 10.88 (*SD* = 3.64), which indicated medium dependence. For ECIG-only users, the PSECDI score was 11.08 (*SD* = 3.68), which indicated medium dependence. For dual users, the PSECDI score was 10.25 (*SD* = 3.69), which also indicated medium dependence. For dual users (n=8), the mean score on the Fagerstrom Test For Nicotine Dependence (FTND) was 4.75 (*SD* = 1.91) (a score of 5 indicates moderate dependence) (Heatherton et al., 1991).

Table 1

Participant Demographic Characteristics

	M (SD) or N (%)
Age (years)	22.26 (3.94)
Gender	
Female	18 (52.94%)
Male	16 (47.06%)
Race	
White	23 (67.65%)
Minority	11 (32.35%)
# Cigarettes/Lifetime	1047.12 (3342.97)
# Cigarettes/Day	1.18 (1.22)
# Of dual users	8 (23.53%)
ECIG use	
Duration (years)	2.33 (1.45)
Days/week	6.47 (0.86)
FTND[1] (dual users only)	4.75 (1.91)
PSECDI[1]	10.88 (3.64)
ECIG device type[2]	
Mod	0 (0.00%)
Pod	34 (100.00%)
Individual ECIG characteristics[2]	
Flavor	
Menthol/mint	12 (35.29%)
Non-menthol/mint	22 (64.71%)
Nicotine concentration (mg/mL)	48.88 (6.83)

Note. [1] FTND = Fagerstrom Test for Nicotine Dependence (range 0-10); PSECDI = Penn State Electronic Cigarette Dependence Index (range 0-20); [2]Self-reported ECIG device types and individual characteristics

Model Diagnostics

Model diagnostics are reported below only for the models that had issues with violating assumptions and had influential outliers. If influential outliers were present in a model, we fit the model both including and excluding these influential observations. If removing the influential

observations produced a change in statistical significance, we report both the models including

and those excluding these observations. If excluding influential observations produced no change

in statistical significance, we report only the models including the full data. None of the

influential outliers based on the Cook's distances cutoffs were participants who failed to learn

the CS-US associations.

Shapiro-Wilks test was significant ($p < 0.05$) for the following models: QSU-Brief Factor

1 (Desire to Vape), QSU-Brief Factor 2 (Anticipated Relief from withdrawal), Schuh-Stitzer

Scale (Craving to Vape), CS Likings Rating, CS Reward Likelihood Rating, P300, LPP,

Instrumental Learning. Attempts were made to normalize the dependent variables in these

models using transformations (log, square root, reciprocal, depending on the dependent variable).

Such transformations were uniformly unsuccessful in normalizing the distributions, with the

original variables more closely approximating the normal distribution than their transformed

versions based on visual inspection. Also, based on visual inspection, the distributions resembled

the normal distribution more than possible alternatives (e.g. gamma distribution). Therefore, we

performed the analyses on the original variables, considering that a) regression models are

relatively robust in violations of normality and b) the current sample is incomplete, so dependent

variable distribution will likely change.

All of the above models also had influential outliers based on Cook's distances >4 times

the mean: QSU-Brief Factor 1: 3 observations (3 participants), QSU-Brief Factor 2: 5

observations (5 participants), Schuh-Stitzer Scale: 3 observations (2 participants); CS Likings

Rating: 3 observations (3 participants); CS Reward Likelihood Rating: 1 observation (1

participant); P300: 2 observations (2 participants), LPP: 2 observations (2 participants),

Instrumental Learning: 4 observations (3 participants), PIT: 1 observation (1 participant).

Overlap in the outliers was observed for: the QSU-Brief Factor 1 and the QSU-Brief Factor 2 (3 outliers overlapped); in the Pavlovian CS liking and likelihood analysis models (1 outlier overlapped); in the P300 and the LPP EEG models (2 outliers overlapped) – this could be explained by the noisiness of the collected data. Removing the influential observations from the analyses changed statistical significance in QSU-Brief Factor 2, Schuh-Stitzer Scale, EEG P300, EEG LPP, CS Reward Likelihood Rating models, for which findings both with and without the influential observations are reported in the Results (and also Table 2 below). The models excluding the influential observations are labeled as "updated model". The removal of the influential observations in these models also normalized the dependent variable distribution (Shapiro-Wilks: $p > 0.05$) for QSU-Brief Factor 1, the Schuh-Stitzer Scale, CS Likings Rating, CS Reward Likelihood Rating, P300, LPP, Instrumental Learning.

Pavlovian Conditioning (Liking, Likelihood)

For this task, a full sample of 34 participants was analyzed. Graphs on fig. 7. A, B show the data distribution for the liking and likelihood ratings. As mentioned in the data preprocessing section, 4 participants had a CS+ likelihood rating that was not higher than the CS- rating, but they were included in the analysis reported below. We ran additional statistics excluding the abovementioned 4 participants and reported them in the "RESULTS *(Excluding Participants not Learning in the Pavlovian Task)"* section.

<u>Liking Results (Original Model)</u>

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.41. There was a statistically significant main effect of CS (beta =1.79, 95% CI [3.56,10.16], t = 6.71, *SE*=0.27, p <0.001) suggesting that participants developed a preference for the CS+ (i.e. the reward-associated fractal) (Fig 7.A). There were no other significant main effects or interactions.

Likelihood Results (Original Model)

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.71. There was a statistically significant main effect of CS (beta =66.2, 95% CI [1.70×10^{24}, 1.85×10^{33}], t = 12.5, *SE*=5.30, p <0.001) suggesting that participants successfully learned CS-US reward associations (Fig 7.B). There were no other significant main effects or interactions.

Likelihood Results (Updated Model)

The updated model's explanatory power related to the fixed effects alone (marginal R^2) was 0.76. The effect of CS on reward likelihood rating remained statistically significant (beta =68.46, 95% CI [3.98×10^{25}, 7.31×10^{33}], t = 14.1, *SE*=4.85, p < 0.001) (Fig 7.B). Gaze index did not significantly affect likelihood ratings, however, there was a significant interaction between CS and gaze index (beta =-10.00, 95% CI [3.10×10^{-9}, 6.64×10^{-1}], t = -2.04, *SE*=4.89, p=0.05). Thus, while overall, participants successfully learned CS-reward associations, the effectiveness of Pavlovian conditioning (based on the updated model) differed as a function of sign-tracking propensity: participants with a stronger tendency to sign-track perceived the CS+ to be more reward-predictive relative to the CS-. Notably, based on the reward likelihood ratings, 4 individuals did not learn the CS-reward associations: 2 individuals rated CS- as more likely to yield rewards than CS+; 1 individual rated the two CS equally likely to produce rewards; 1 individual rated the likelihood of receiving rewards following CS+ as <50%. This makes Pavlovian learning and the resulting gaze index suspect in these individuals. Therefore, as mentioned earlier, we report findings both including and excluding these individuals.
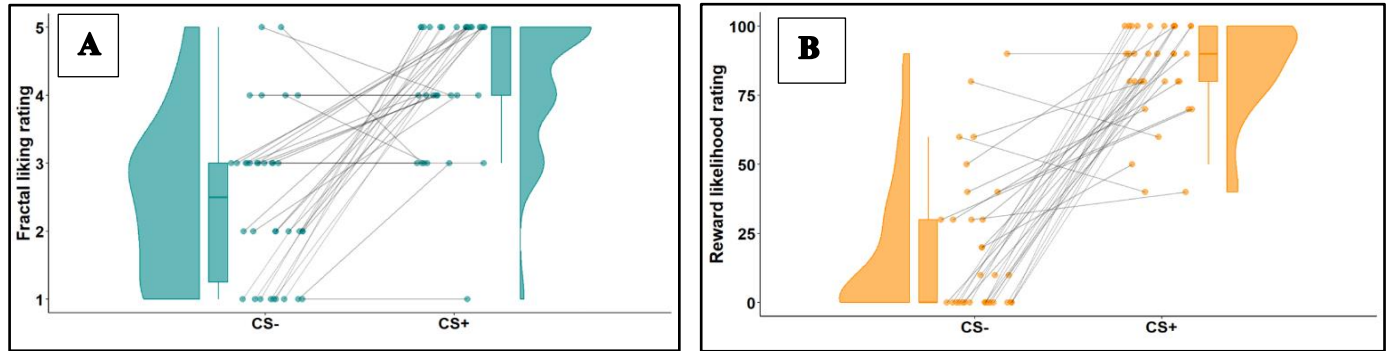
Fig.7. A. *Data visualization for the Pavlovian task demonstrating the fractal (CS+ or CS-) liking rating (1-5 on a Likert scale).* ***B.*** *Data visualization for the Pavlovian task demonstrating the rating of a likelihood of reward delivery for each fractal (CS+ or CS-).*

Sign-Tracking Propensity

As mentioned earlier, the gaze index variable in our sample was not bimodally distributed (Fig. 8). Therefore, we deemed it most appropriate to employ gaze index as a dimensional measure of the degree of sign- / goal-tracking and use it as a continuous regressor in the models below, rather than using it to classify participants as ST or GT. A total of 34 participants' data was utilized for the full sample analysis.
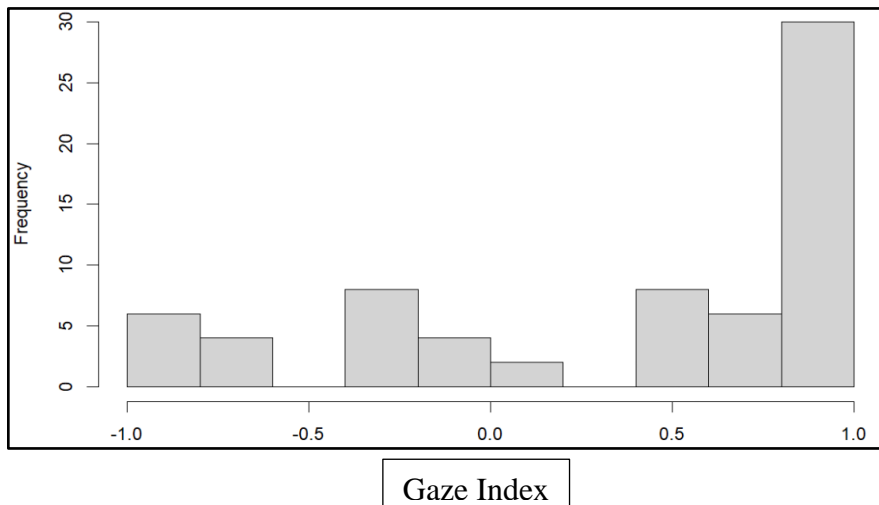
Fig.8. *Histogram of the gaze index distribution.*

Instrumental Learning

Six participants displayed performance that suggested inadequate operant learning, with performance of ≤50% correct in the 2nd hemiblock (Fig.9).
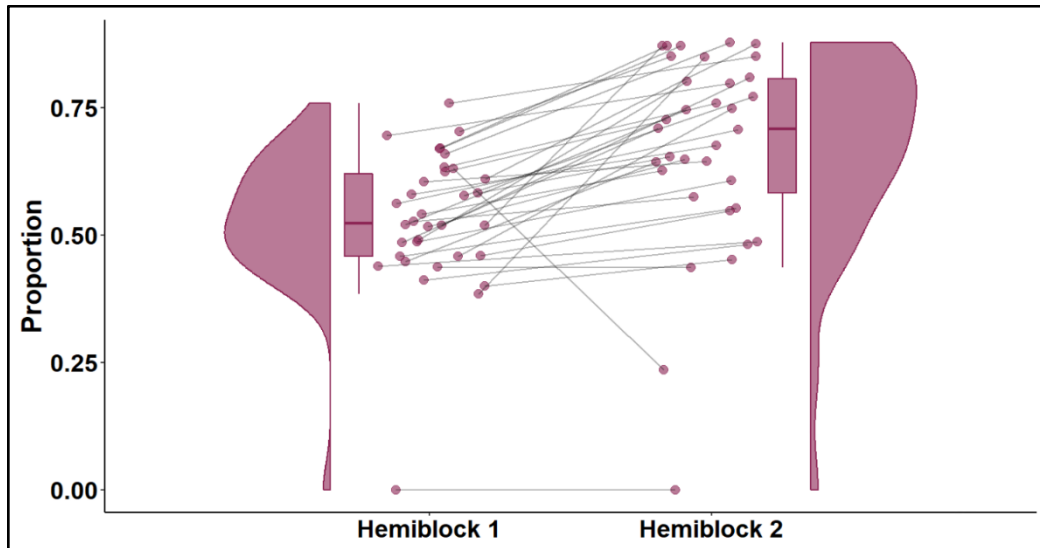
Fig.9. *Data visualization for the instrumental conditioning task demonstrating the proportion of operant responses on the rewarded side between two hemiblocks of the task (hemiblock 1 = first 20 trials; hemiblock 2 = last 20 trials).*

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.18. There was a significant main effect of hemiblock (beta =1.14, 95% CI [1.09, 1.21], t = 11.28, *SE*=0.02, p < .001), such that proportion of correct clicks increased in hemiblock 2 compared to hemiblock 1. The main effect of gaze index was not statistically significant (beta =0.18, 95% CI [0.96, 1.08], t = 0.63, *SE*=0.03, p = 0.54). The gaze index × hemiblock interaction was also not statistically significant (beta = -0.01, 95% CI [0.95,1.04], t= -0.27, *SE*=0.02, p = 0.79). Finally, there was no significant main effect of task version (p = 0.27) or pre-session vaping bout (p=0.70).

PIT Results

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.08. The main effect of CS was not significant (beta = 0.04, 95% CI [0.93, 1.17], t = 0.67, SE=0.06, p = 0.51), suggesting there is no evidence of a PIT effect overall. The main effect of gaze index (or the degree of sign-/goal-tracking) was also not significant (beta =0.01, 95% CI [0.92, 1.12], t = 0.30, SE=0.05, p = 0.77). Contrary to the prediction that the PIT effect would be more pronounced in individuals prone to sign-tracking, there was no significant gaze index x CS interaction (beta = -0.02, 95% CI [0.87, 1.10], t = -0.34, SE=0.06, p = 0.74), i.e., no evidence that the PIT effect differed as a function of sign-tracking propensity (Fig.10). Finally, there was no significant effect of task version (p_s > 0.11).
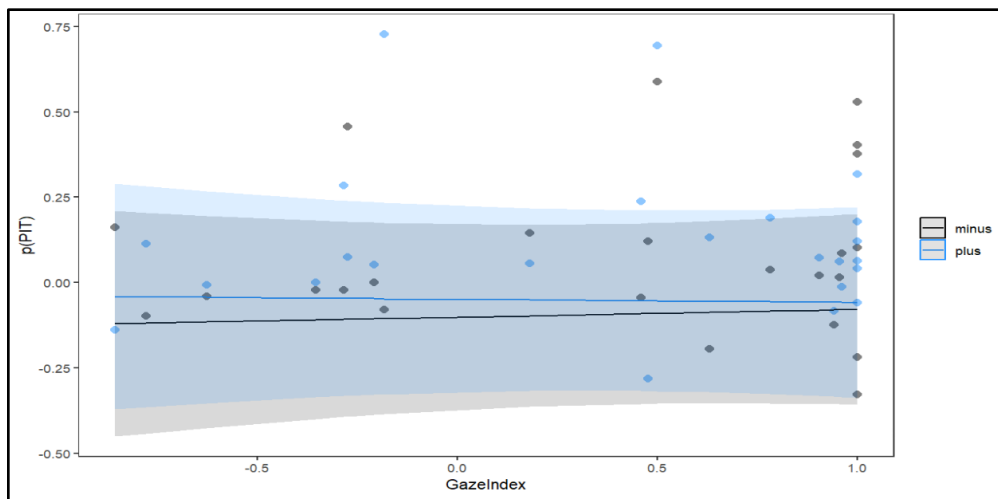
Fig.10. *Data visualization for the linear effects model demonstrating the main effect of the CS type (CS+ relative to CS-) and gaze index on response index of the PIT task (for participants learning the operant and Pavlovian associations).*

Cue-Induced Cravings

QSU-Brief Factor 1 (Desire to Vape) Results

Original Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.20. There was a significant main effect of cue type (beta =2.75, 95% CI [3.74, 65.4], t = 3.78,

SE=0.73, p < .007), such that ECIG cues increased Desire more than neutral cues (Figure 11.A). The main effect of gaze index was not statistically significant (beta =0.20, 95% CI [0.39, 3.85], t = 0.24, *SE*=0.59, p = 0.74). The gaze index × cue type interaction was also not statistically significant (beta = 0.78, 95% CI [0.52,9.22], t= 1.06, *SE*=0.74, p = 0.30). Finally, there was no significant main effect of session order (p = 0.60) or pre-session vaping bout (p=0.21) (Fig. 11.B).

QSU-Brief Factor 2 (Anticipated Relief from Vaping) Results

Original Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.15. There was a significant main effect of cue type (beta =1.63, 95% CI [1.69,15.5], t = 2.89, *SE*=0.57, p < .007), such that ECIG cues increased anticipated relief more than neutral cues (Figure 11.C). The main effect of gaze index was not statistically significant (beta =-0.48, 95% CI [0.27,1.40], t = -1.16, *SE*=0.42, p = 0.25). The gaze index × cue type interaction was a trend-level effect (beta = 1.15, 95% CI [1.04,9.67], t= 2.02, *SE*=0.57, p = 0.052) such that exposure to ECIG cues increased anticipated relief scores in individuals with the tendency to sign-track more than in individuals with the tendency to goal-track (Fig. 11.D). Finally, there was no significant main effect of session order (p = 0.51) or pre-session vaping bout (p=0.96).

Updated Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of 0.22. There was a significant main effect of cue type (beta =1.22, 95% CI [1.49,7.77], t = 2.91, *SE*=0.42, p < .005), such that ECIG cues increased Anticipated Relief more than neutral cues (Figure 11.C). The main effect of gaze index was not statistically significant (beta =-0.07, 95% CI [0.50,1.72], t = -0.23, *SE*=0.31, p = 0.82). The gaze index × cue type interaction was not

significant (beta = 0.68, 95% CI [0.86,4.55], t= 1.60, *SE*=0.43, p = 0.12). Additionally, there was

a significant main effect of session order (beta = -0.95, 95% CI [0.16,0.93], t= -2.13, *SE*=0.45, p

= 0.04), such in order of tasks of "ECIG first, neutral second" yielded more anticipated relief.

Finally, there was no significant main effect of the pre-session vaping bout (p=0.79).

Schuh-Stitzer Scale (Craving to Vape)

<u>*Original Model*</u>

The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.15.

There was a significant main effect of cue type (beta =3.94, 95% CI [1.13,2314], t = 2.02,

SE=1.95, p =0.05), such that ECIG cues increased Craving more than neutral cues (Figure 11.E).

The main effect of gaze index was not statistically significant (beta =0.29, 95% CI [0.09,20.3], t

= 0.21, *SE*=1.39, p = 0.84). The gaze index × cue type interaction was not statistically significant

(beta = 1.11, 95% CI [0.07,142.6], t= 0.57, *SE*=1.96, p = 0.57). Finally, there was no significant

main effect of session order (p = 0.44) or pre-session vaping bout (p = 0.79) (Fig. 11. F).

<u>*Updated Model*</u>

The model's explanatory power related to the fixed effects alone (marginal R^2) was of

0.15. There was a significant main effect of cue type (beta =3.05, 95% CI [1.27,351.3], t = 2.12,

SE=1.44, p =0.04), such that ECIG cues increased craving more than neutral cues. The main

effect of gaze index was not statistically significant (beta =-1.76, 95% CI [0.02,1.55], t = -1.57,

SE=1.12, p = 0.12). The gaze index × cue type interaction was statistically significant (beta =

4.27, 95% CI [4.2,1222.5], t= 2.96, *SE*=1.45, p = 0.006) such that individuals that had a higher

gaze index (and more propensity to sign-track) reported higher Craving for ECIG vs. neutral

cues compared to individuals with a lower gaze index (and more propensity to goal-track).

Finally, there was no significant main effect of session order (p = 0.712) or pre-session vaping

bout (p = 0.935).
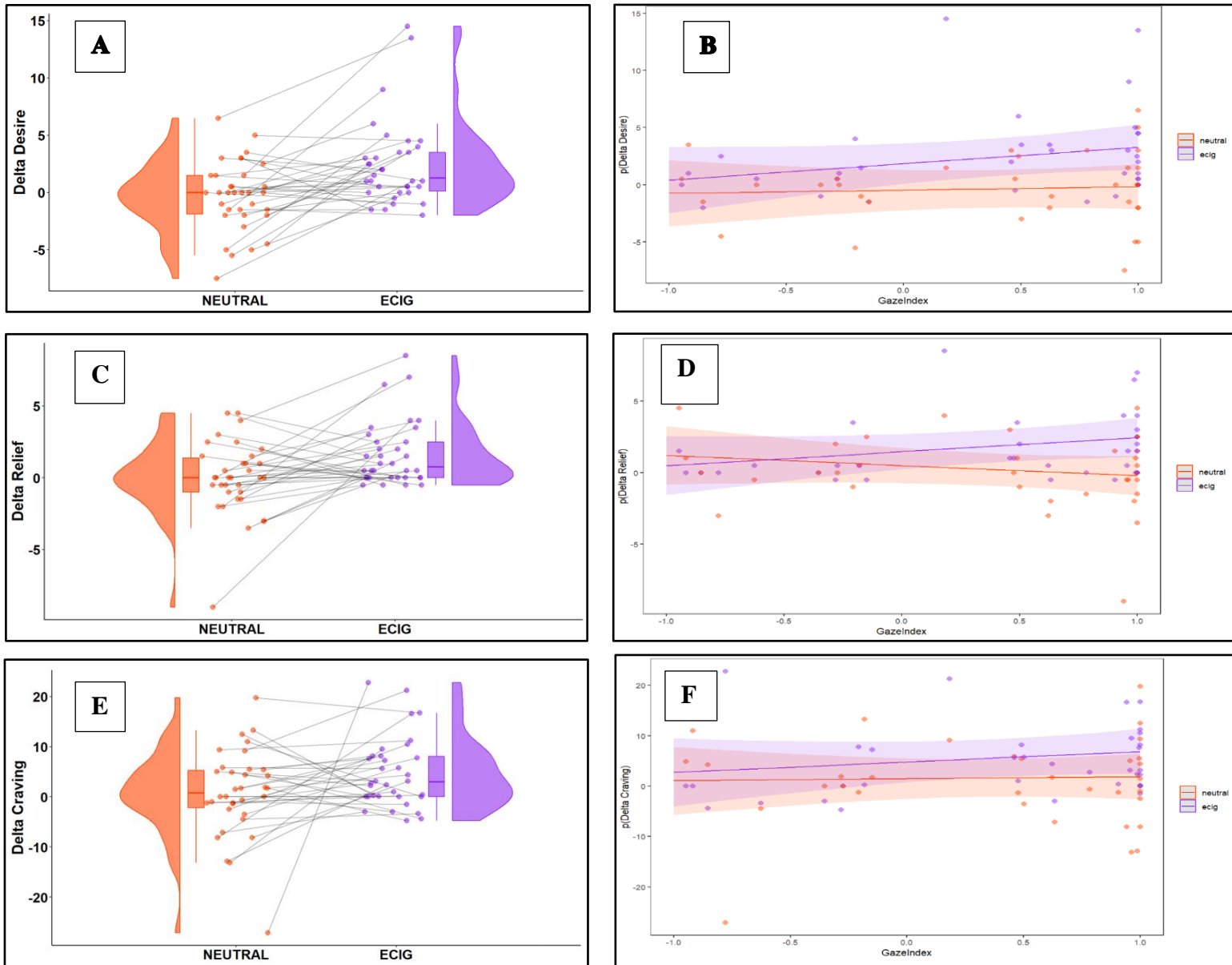
Fig.11: A, C, E. *Data visualization for all participants pre- and post-cue exposure for both ECIG and neutral cues not including gaze index for A)the QSU-Brief Factor 1 (desire to vape), B)QSU-Brief Factor 2 (anticipated relief from vaping), and C) the Schuh-Stitzer Questionnaire (craving to vape). Y-axis values represent the difference scores (delta values) calculated by subtracting the pre-cue-exposure values from post-cue-exposure values. X-axis represents cue types.* ***B, D, F.*** *Data visualization for the linear mixed effects model demonstrating gaze index x cue type interactions on B) the desire to vape, D) anticipated relief from vaping, and F) craving to vape.*

EEG Results

A total of 12 participants had EEG data. See Fig. 12 for this subsample's gaze index distribution. See Fig. 13 A, B for a visual representation of the EEG data time course including the P300 and LPP components in response to cues as a function of cue type (ECIG vs. neutral).

Gaze Index

Fig.12. Histogram of gaze index distribution for the EEG participants only (n=12).
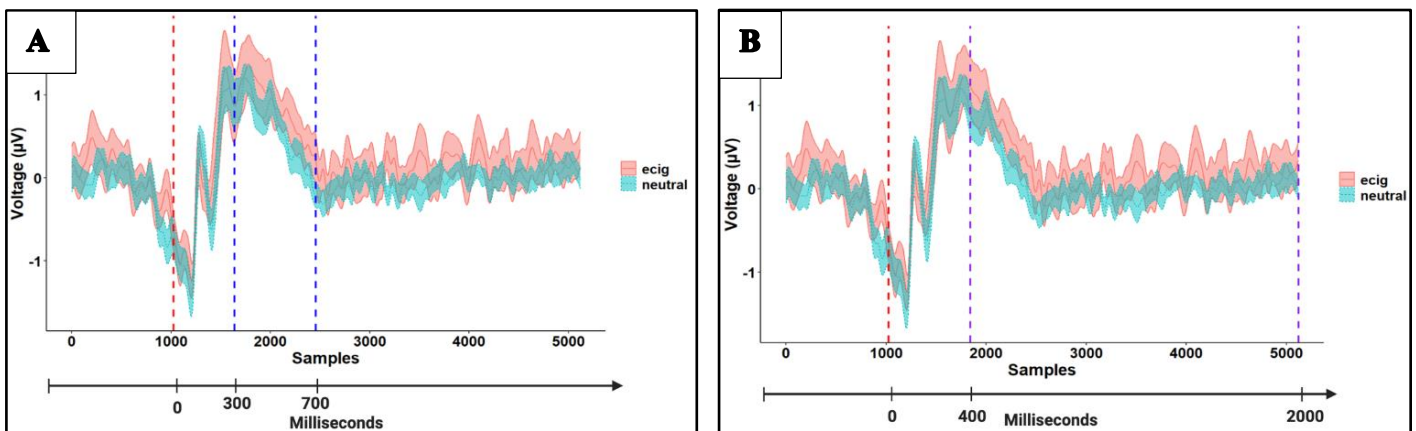
Fig.13. A, B. Cue-elicited P300 and LPP ERPs. Averaged voltage from channels (CPz, CP3, CP4, Pz, P7, P4, P3, and P8) across both bouts of cue exposure across all participants. Plots depict data from 500 ms prior to cue presentation to 2000 ms after presentation. ECIG cues timecourse depicted in pink; Neutral cues timecourse depicted in cyan. The time courses in A and B are identical, and the red vertical line represents stimulus onset. A. P300 the area between the blue lines represents the 300 ms-700 ms period of the P300 component. B. The area between the purple lines represents the 400 ms-2000 ms period of the LPP component.

P300 Component

Original Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of

0.04. There was no significant main effect of cue type (beta =-0.25, 95% CI [0.51,1.20], t = -

1.14, SE=0.22, p = 0.28). The main effect of gaze index was not statistically significant (beta

=0.01, 975% CI [0.67, 1.51], t = 0.004, SE=0.21, p = 1.0). The gaze index $\times$ cue type interaction

was also not statistically significant (beta = 0.09, 95% CI [0.70,1.69], t= 0.38, SE=0.22, p =

0.71). Finally, there was no significant main effect of session order (p = 0.77).

Updated Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of

0.09. There was no significant main effect of cue type (beta =0.05, 95% CI [0.90,1.23], t = 0.66,

SE=0.09, p = 0.53). The main effect of gaze index was not statistically significant (beta =-0.07,

95% CI [0.74, 1.18], t = -0.60, SE=0.12, p = 0.56). The gaze index $\times$ cue type interaction had a

trend towards statistical significance (beta = 0.17, 95% CI [1.02,1.38], t= 2.16, *SE*=0.08, p =

0.064) such that individuals that had a higher gaze index (and more propensity to sign-track)

exhibited enhanced EEG P300 amplitudes for neutral vs. ECIG cues compared to individuals

with a lower gaze index (and more propensity to goal-track). Finally, there was no significant

main effect of session order (p = 0.45).

LPP Component

Original Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of

0.04. There was no significant main effect of cue type (beta =-0.18, 95% CI [0.57,1.21], t = -0.98

SE=0.19, p = 0.28). The main effect of gaze index was not statistically significant (beta =0.01,

95% CI [0.67, 1.51], t = -0.98, SE=0.19, p = 0.35). The gaze index × cue type interaction was

also not statistically significant (beta = 0.06, 95% CI [0.73,1.56], t= 0.32, SE=0.29, p = 0.75).

Finally, there was no significant main effect of session order (p = 0.72).

Updated Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of

0.15. There was no significant main effect of cue type (beta =-0.07, 95% CI [0.96,1.22], t = 1.08,

SE=0.06, p = 0.31). The main effect of gaze index was not statistically significant (beta =-0.08,

95% CI [0.79,1.07], t = -1.07, SE=0.08, p = 0.30). The gaze index × cue type interaction had a

trend towards statistical significance (beta = 0.13, 95% CI [1.01,1.29], t= 2.07, *SE*=0.06, p =

0.070) such that individuals that had a higher gaze index (and more propensity to sign-track)

exhibited enhanced EEG LPP amplitudes for neutral vs. ECIG cues compared to individuals with

a lower gaze index (and more propensity to goal-track). Finally, there was no significant main

effect of session order (p = 0.37).

Table 2. *Linear Mixed-effects Models Results including the full sample of participants.*

Outcome Measure	Estimate	*SE*	*t*	*p*	*95 % CI*
QSU-Brief Factor 1 (Desire to Vape) (Original Model)					
Intercept	-0.33	0.82	-0.41	.684	[0.14,3.58]
Gaze Index	0.20	0.59	0.24	.736	[0.39,3.85]
Cue Type (ECIG) (ref. Neutral[2])	**2.75**	**0.73**	**3.78**	**.007**	**[3.74,65.4]**
Session Order (Neutral) (ref. ECIG[2])	-0.51	0.95	-0.53	.599	[0.09,3.89]
Pre-session Vape (ref. no Vape[2])	1.59	1.25	1.28	.212	[0.43,56.4]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.78	0.74	1.06	.297	[0.52,9.22]
QSU-Brief Factor 1 (Desire to Vape) (Updated Model)[1]					
Intercept	0.36	0.61	0.58	.562	[0.43,4.73]
Gaze Index	0.41	0.45	0.90	.372	[0.62,3.64]
Cue Type (ECIG) (ref. Neutral[2])	**1.81**	**0.63**	**2.85**	**.006**	**[1.76,21.1]**
Session Order (Neutral) (ref. ECIG[2])	-1.09	0.67	-1.63	.108	[0.09,1.24]
Pre-session Vape (ref. no Vape[2])	0.63	0.89	0.71	.482	[0.33,10.6]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.45	0.64	0.70	.485	[0.45,5.48]
QSU-Brief Factor 2 (Anticipated Relief from Vaping) (Original Model)					
Intercept	0.22	0.57	0.39	.697	[0.41,3.79]
Gaze Index	-0.48	0.42	-1.16	.251	[0.27,1.40]
Cue Type (ECIG) (ref. Neutral[2])	**1.63**	**0.57**	**2.89**	**.007**	**[1.69,15.5]**
Session Order (Neutral) (ref. ECIG[2])	-0.43	0.63	-0.68	.505	[0.19,2.26]
Pre-session Vape (ref. no Vape[2])	0.04	0.83	0.05	.961	[0.20,5.30]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	1.15	0.57	2.02	.052	[1.04,9.67]
QSU-Brief Factor 2 (Anticipated Relief from Vaping) (Updated Model)[1]					
Intercept	0.59	0.41	1.44	.156	[0.81,4.07]
Gaze Index	-0.07	0.31	-0.23	.820	[0.50,1.72]
Cue Type (ECIG) (ref. Neutral[2])	**1.22**	**0.42**	**2.91**	**.005**	**[1.49,7.77]**
Session Order (Neutral) (ref. ECIG[2])	**-0.95**	**0.45**	**-2.13**	**.038**	**[0.16,0.93]**
Pre-session Vape (ref. no Vape[2])	-0.45	0.58	-0.78	.440	[0.20,2.00]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.68	0.43	1.60	.115	[0.86,4.55]
Schuh-Stitzer Scale (Craving to Vape) (Original Model)					
Intercept	1.65	1.86	0.89	.379	[0.14,201.1]
Gaze Index	0.29	1.39	0.21	.835	[0.09,20.3]
Cue Type (ECIG) (ref. Neutral[2])	**3.94**	**1.95**	**2.02**	**.047**	**[1.13,2341]**
Session Order (Neutral) (ref. ECIG[2])	-1.60	2.05	-0.78	.437	[0.004,11.2]
Pre-session Vape (ref. no Vape[2])	-0.72	2.69	-0.27	.790	[0.003,94.1]

Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	1.11	1.96	0.57	.572	[0.07,142.6]
Schuh-Stitzer Scale (Craving to Vape) (Updated Model)[1]					
Intercept	1.39	1.55	0.89	.376	[0.19,84.4]
Gaze Index	-1.76	1.12	-1.57	.122	[0.02,1.55]
Cue Type (ECIG) (ref. Neutral[2])	**3.05**	**1.44**	**2.12**	**.042**	**[1.27,351.3]**
Session Order (Neutral) (ref. ECIG[2])	-0.66	1.77	-0.37	.712	[0.016,16.6]
Pre-session Vape (ref. no Vape[2])	-0.19	2.27	-0.08	.935	[0.01,70.5]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	**4.27**	**1.45**	**2.96**	**.006**	**[4.2,1222.5]**
EEG P300 (Original Model)					
Intercept	**0.79**	**0.29**	**2.74**	**.018**	**[1.25,3.86]**
Cue type (Neutral) (ref. ECIG[2])	-0.25	0.22	-1.14	.281	[0.51,1.20]
Gaze Index	0.01	0.21	0.004	.997	[0.67,1.51]
Session Order (Neutral) (ref. ECIG[2])	0.11	0.35	0.30	.769	[0.56,2.21]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.09	0.22	0.38	.709	[0.70,1.69]
EEG P300 (Updated Model)[1]					
Intercept	**0.45**	**0.17**	**2.61**	**.026**	**[1.12,2.19]**
Cue type (Neutral) (ref. ECIG[2])	0.05	0.09	0.66	.531	[0.90,1.23]
Gaze Index	-0.07	0.12	-0.60	.560	[0.74,1.18]
Session Order (Neutral) (ref. ECIG[2])	0.17	0.22	0.79	.451	[0.78,1.81]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.17	0.08	2.16	.064	[1.02,1.38]
EEG LPP (Original Model)					
Intercept	0.19	0.20	0.97	.350	[0.82,1.79]
Cue type (Neutral) (ref. ECIG[2])	-0.18	0.19	-0.98	.353	[0.57,1.21]
Gaze Index	-0.02	0.15	-0.12	.905	[0.73,1.32]
Session Order (Neutral) (ref. ECIG[2])	0.09	0.23	0.37	.720	[0.69,1.71]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.06	0.19	0.32	.752	[0.73,1.56]
EEG LPP (Updated Model)[1]					
Intercept	-0.09	0.11	-0.78	.443	[0.74,1.14]
Cue type (Neutral) (ref. ECIG[2])	0.07	0.06	1.08	.310	[0.96,1.22]
Gaze Index	-0.08	0.08	-1.07	.303	[0.79,1.07]
Session Order (Neutral) (ref. ECIG[2])	-0.13	1.35	0.95	.365	[0.87,1.48]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.13	0.06	2.07	.070	[1.01,1.29]
CS Liking (Original Model)					
Intercept	**2.60**	**0.23**	**11.1**	**<.001**	**[8.53,21.37]**
CS+ (ref. CS-[2])	**1.79**	**0.27**	**6.71**	**<.001**	**[3.56,10.16]**
Gaze Index	0.09	0.19	0.48	.630	[0.75,1.60]
Pre-session Vape (ref. no Vape[2])	-0.14	0.39	-0.36	.721	[0.41,1.86]
Task Version (Pav2) (ref. Pav1[2])	-0.27	0.28	-0.97	.337	[0.44,1.32]
CS+ (ref. CS-[2]) × Gaze Index	-0.14	0.27	-0.50	.616	[0.52,1.48]

CS Liking (Updated Model)[1]

Intercept	**2.50**	**0.20**	**12.33**	**<.001**	**[8.16,18.05]**
CS+ (ref. CS-[2])	**2.03**	**0.24**	**8.62**	**<.001**	**[4.79,12.02]**
Gaze Index	0.14	0.17	0.82	.417	[0.82,1.61]
Pre-session Vape (ref. no Vape[2])	-0.16	0.33	-0.46	.645	[0.45,1.65]
Task Version (Pav2) (ref. Pav1[2])	-0.34	0.25	-1.37	.175	[0.44,1.16]
CS+ (ref. CS-[2]) × Gaze Index	-0.36	0.24	-1.54	.130	[0.44,1.11]

CS Likelihood (Original Model)

Intercept	**18.8**	**4.68**	**4.01**	**<.001**	**[1.48×10^4, 1.35×10^{12}]**
CS+ (ref. CS-[2])	**66.2**	**5.30**	**12.5**	**<.001**	**[1.70×10^{24}, 1.85×10^{33}]**
Gaze Index	-0.68	3.82	-0.18	.860	[2.85×10^{-4}, 9.09×10^2]
Pre-session Vape (ref. no Vape[2])	-6.11	6.95	-0.88	.383	[2.68×10^{-9}, 1.83×10^3]
Task Version (Pav2) (ref. Pav1[2])	2.00	5.47	0.37	.716	[1.63×10^{-4}, 3.35×10^5]
CS+ (ref. CS-[2]) × Gaze Index	-5.29	5.33	-1.00	.323	[1.42×10^{-7}, 1.71×10^2]

CS Likelihood (Updated Model)[1]

Intercept	**16.86**	**4.26**	**3.96**	**<.001**	**[4.95×10^3, 8.82×10^{10}]**
CS+ (ref. CS-[2])	**68.46**	**4.85**	**14.1**	**<.001**	**[3.98×10^{25}, 7.31×10^{33}]**
Gaze Index	4.02	3.60	1.12	.264	[4.77×10^{-2}, 6.56×10^4]
Pre-session Vape (ref. no Vape[2])	-4.53	6.32	-0.72	.476	[4.54×10^{-8}, 2.56×10^3]
Task Version (Pav2) (ref. Pav1[2])	0.02	4.99	0.01	.996	[5.85×10^{-5}, 1.80×10^4]
CS+ (ref. CS-[2]) × Gaze Index	**-10.00**	**4.89**	**-2.04**	**.046**	**[3.10×10^{-9}, 6.64×10^{-1}]**

Instrumental Learning

Intercept	**0.51**	**0.04**	**11.83**	**<.001**	**[1.53,1.80]**
Hemiblock 2 (ref. Hemiblock 1[2])	**0.14**	**0.02**	**5.62**	**<.001**	**[1.09,1.21]**
Gaze Index	0.02	0.03	0.63	.535	[0.96,1.08]
Pre-session Vape (ref. no Vape[2])	-0.03	0.07	-0.40	.696	[0.85,1.12]
Task Version (Version 2) (ref. Version 1[2])	0.06	0.05	1.12	.271	[0.96,1.18]
Hemiblock 2 (ref. Hemiblock 1[2]) × Gaze Index	-0.01	0.02	-0.27	.788	[0.95,1.04]

Note. Uncorrected *p* values shown in table. Items significant at *p* < .05 are bolded.

[1]Updated models refer to the models with influential Cook's points removed.

[2]Ref. – Model reference group.

RESULTS

Participants Demonstrating Pavlovian Learning

Model Diagnostics

Model diagnostics are reported below only for the models that had issues with violating assumptions and had influential outliers. If influential outliers were present in a model, we fit the model both including and excluding these influential observations. If removing the influential observations produced a change in statistical significance, we report both the models including and those excluding these observations. If excluding influential observations produced no change in statistical significance, we report only the models including the full data.

Shapiro-Wilks test was significant ($p < 0.05$) for the following models: QSU-Brief Factor 1 (Desire to Vape), QSU-Brief Factor 2 (Anticipated Relief from Vaping), CS Likings Rating, P300, LPP. Attempts were made to normalize the dependent variables in these models using transformations (log, square root, reciprocal, depending on the dependent variable). Such transformations were uniformly unsuccessful in normalizing the distributions, with the original variables more closely approximating the normal distribution than their transformed versions based on visual inspection. Also, based on visual inspection, the distributions resembled the normal distribution more than possible alternatives (e.g. gamma distribution). Therefore, we performed the analyses on the original variables, considering that a) regression models are relatively robust in violations of normality and b) the current sample is incomplete, so dependent variable distribution will likely change.

Models also had influential outliers based on Cook's distances >4 times the mean: QSU-Brief Factor 1: 3 observations (3 participants), QSU-Brief Factor 2: 3 observations, Schuh-Stitzer Scale: 2 observations; CS Likings Rating: 1 observation (1 participant); P300: 2 observations (2

participants), LPP: 2 observations (2 participants), PIT: 1 observation (1 participant). Overlap in the outliers was observed for: the QSU-Brief Factor 1 and the QSU-Brief Factor 2 (3 outliers overlapped); in the P300 and the LPP EEG models (1 outlier overlapped). Removing the influential observations from the analyses changed statistical significance in QSU-Brief Factor 2, Schuh-Stitzer Scale, for which findings both with and without the influential observations are reported in the Results (and also Table 3 below). The removal of the influential observations in these models also normalized the dependent variable distribution for the QSU-Brief Factor 1, P300, and LPP (Shapiro-Wilks: $p > 0.05$).

Pavlovian Conditioning (Liking)

Liking Results (Original Model)

For this task, a sample of 30 participants was analyzed. The model's explanatory power related to the fixed effects alone (marginal R^2) was 0.48. There was a statistically significant main effect of CS (beta =2.00, 95% CI [4.29,12.72], t = 7.22, *SE*=0.28, p <0.001) suggesting that participants developed a preference for the CS+ (i.e. the reward-associated fractal) (Fig. 14). There were no other significant main effects or interactions.
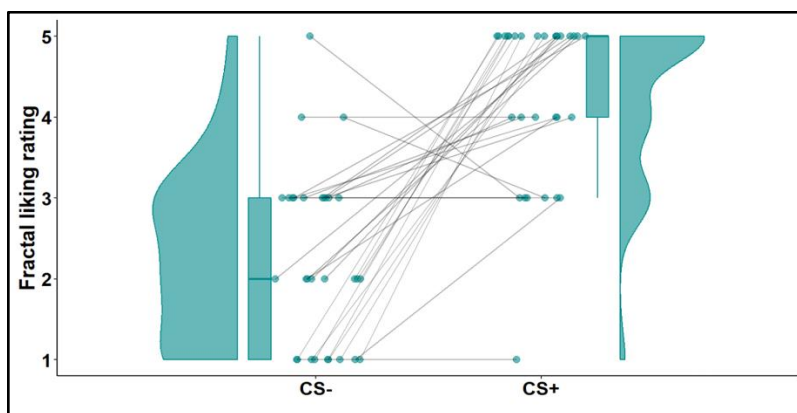
Fig.14. *Data visualization for the Pavlovian task demonstrating the fractal (CS+ or CS-) liking rating (1-5 on a Likert scale).*

Sign-Tracking Propensity

The gaze index distribution for the sample excluding the 4 participants with poor

Pavlovian learning (n=30) is shown in Fig 15.
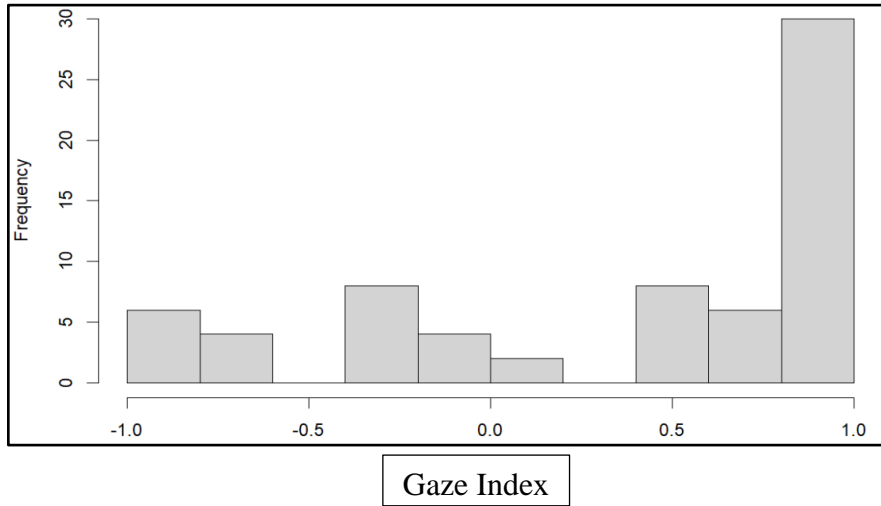
Gaze Index

Fig.15. *Histogram of the gaze index distribution for the n=30 sample.*

Cue-Induced Cravings

QSU-Brief Factor 1 (Desire to Vape) Results

<u>Original Model</u>

The model's explanatory power related to the fixed effects alone (marginal R^2) was of

0.19. There was a significant main effect of cue type (beta =2.85, 95% CI [3.47, 86.22], t = 3.48,

SE=0.82, p < .002), such that ECIG cues increased Desire more than neutral cues (Figure 16.A).

The main effect of gaze index was not statistically significant (beta =0.34, 95% CI [0.38, 5.16], t

= 0.52, *SE*=0.66, p = 0.61). The gaze index $\times$ cue type interaction was also not statistically

significant (beta = 0.57, 95% CI [0.35,8.90], t= 0.68, *SE*=0.83, p = 0.50). Finally, there was no

significant main effect of session order (p = 0.744) or pre-session vaping bout (p=0.25) (Figure

16.B).

QSU-Brief Factor 2 (Anticipated Relief from Vaping) Results

Original Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of 0.16. There was a significant main effect of cue type (beta =1.78, 95% CI [1.78,19.93], t = 2.89, *SE*=0.62, p < .007), such that ECIG cues increased Anticipated Relief more than neutral cues (Figure 16.C). The main effect of gaze index was not statistically significant (beta =-0.08, 95% CI [0.38,2.24], t = -1.17, *SE*=0.45, p = 0.87). The gaze index × cue type was not statistically significant (beta = 0.78, 95% CI [0.64,7.37], t= 1.25, *SE*=0.62, p = 0.22) (Fig. 16.D). Finally, there was no significant main effect of session order (p = 0.41) or pre-session vaping bout (p=0.93).

Updated Model

The model's power related to the fixed effects alone (marginal R^2) was of 0.22. There was a significant main effect of cue type (beta =1.00, 95% CI [1.12,6.58], t = 2.22, *SE*=0.45, p = 0.03), such that ECIG cues increased Anticipated Relief more than neutral cues (Figure 16.C). The main effect of gaze index was not statistically significant (beta =0.22, 95% CI [0.66,2.34], t = 0.67, *SE*=0.32, p = 0.51). The gaze index × cue type was not statistically significant (beta = 0.47, 95% CI [0.66,3.91], t= 1.03, *SE*=0.46, p = 0.31). There was a significant main effect of session order (beta =-1.20, 95% CI [0.12,0.76], t = -2.54, *SE*=0.46, p = 0.01) such as ECIG exposure first, neutral second yielded more anticipated relief. Finally, there was no significant main effect of pre-session vaping bout (p=0.34).

Schuh-Stitzer Scale (Craving to Vape)

Original Model

The model's power related to the fixed effects alone (marginal R2) was of 0.09. There was a significant main effect of cue type (beta =4.43, 95% CI [1.11,6192.8], t = 2.02, *SE*=2.19, p

=0.05), such that ECIG cues increased Craving more than neutral cues (Figure 11.E). The main effect of gaze index was not statistically significant (beta =0.62, 95% CI [0.09,40.6], t = 0.40, *SE*=1.57, p = 0.70). The gaze index × cue type interaction was not statistically significant (beta = 0.92, 95% CI [0.03,191.6], t= 0.41, *SE*=2.21, p = 0.68). Finally, there was no significant main effect of session order (p = 0.359) or pre-session vaping bout (p = 0.84) (Figure 16. F).

Updated Model

The model's explanatory power related to the fixed effects alone (marginal R^2) was of 0.13. There was no significant main effect of cue type (beta =2.86, 95% CI [10.81,377.7], t = 1.83, *SE*=1.57, p =0.08) The main effect of gaze index was not statistically significant (beta =-1.17, 95% CI [0.02,4.39], t = -0.87, *SE*=1.35, p = 0.39). The gaze index × cue type interaction was statistically significant (beta = 4.13, 95% CI [2.8,1375.7], t= 2.61, *SE*=1.58, p = 0.02) such that individuals that had a higher gaze index (and more propensity to sign-track) reported higher Craving for ECIG vs. neutral cues compared to individuals with a lower gaze index (and more propensity to goal-track). Finally, there was no significant main effect of session order (p = 0.40) or pre-session vaping bout (p = 0.82).
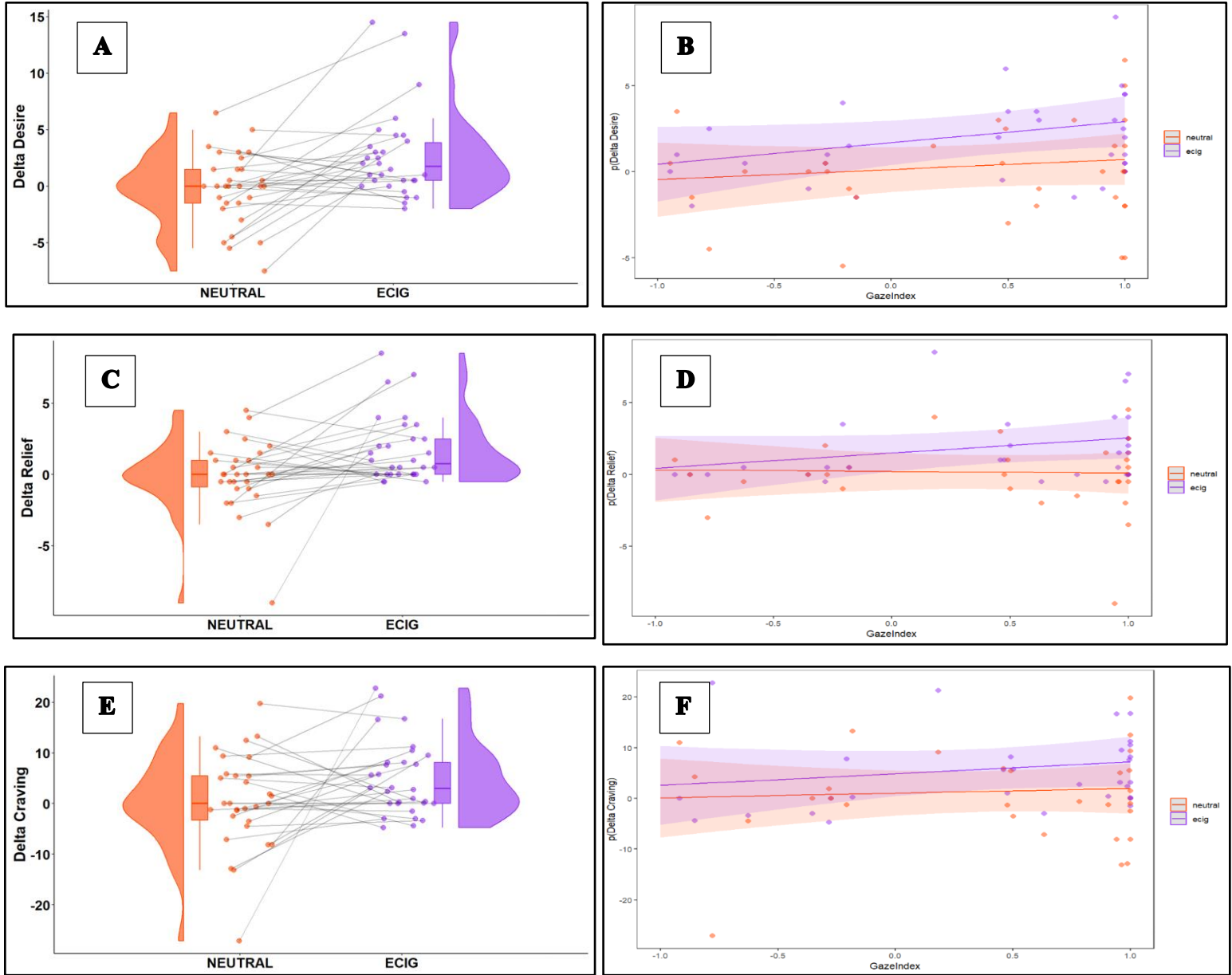
Fig.16: A, C, E. *Data visualization for all participants pre- and post-cue exposure for both ECIG and neutral cues not including gaze index for the QSU-Brief Factor 1 (desire to vape), QSU-Brief Factor 2 (anticipated relief from vaping), and the Schuh-Stitzer Questionnaire (craving to vape). Y-axis values represent the delta desire values calculated by subtracting the pre-cue-exposure values from post-cue-exposure values. X-axis represents cue types. **B, D, F.** Data visualization for the linear effects model demonstrating the main effect of gaze index and cue type on the desire to vape, anticipated relief from vaping, and craving to vape.*

EEG Results

A total of 10 participants' data was utilized for this analysis. See Fig. 17 for the sample's gaze index distribution. See Fig. 13 A, B for a visual representation of the EEG data time course including the P300 and LPP components in response to cues as a function of cue type (ECIG vs. neutral).

Gaze Index

Fig.17. *Histogram visualization of gaze index distribution for the EEG participants only (N=10).*

P300 Component

<u>*Original Model*</u>

The model's explanatory power related to the fixed effects alone (marginal R^2) was of 0.06. There was no significant main effect of cue type (beta =-0.12, 95% CI [0.57,1.38], t = -0.53 SE=0.23, p = 0.61). The main effect of gaze index was not statistically significant (beta =0.16, 95% CI [0.62, 1.18], t = -0.96, SE=0.17, p = 0.36). The gaze index $\times$ cue type interaction was also not statistically significant (beta = 0.12, 95% CI [0.72,1.77], t= 0.51, SE=0.23, p = 0.62). Finally, there was no significant main effect of session order (p = 0.79).

LPP Component

<u>*Original Model*</u>

The model's explanatory power related to the fixed effects alone (marginal R^2) was of 0.03. There was no significant main effect of cue type (beta =-0.07, 95% CI [0.65,1.35], t = -0.36, SE=0.19, p = 0.73). The main effect of gaze index was not statistically significant (beta =-0.10, 95% CI [0.69,1.19], t = -0.69, SE=0.14, p = 0.50). The gaze index $\times$ cue type interaction was also not statistically significant (beta = 0.10, 95% CI [0.76,1.61], t= 0.53, SE=0.19, p = 0.61). Finally, there was no significant main effect of session order (p = 0.88).

Table 3. *Linear Mixed-effects Models Results including the adjusted sample of participants*

(n=30).

Outcome Measure	Estimate	*SE*	*t*	*p*	*95 % CI*
QSU-Brief Factor 1 (Desire to Vape) (Original Model)					
Intercept	-0.34	0.88	-0.39	.702	[0.13,4.01]
Gaze Index	0.34	0.66	0.52	.609	[0.38,5.16]
Cue Type (ECIG) (ref. Neutral[2])	**2.85**	**0.82**	**3.48**	**.002**	**[3.47,86.22]**
Session Order (Neutral) (ref. ECIG[2])	-0.36	1.07	-0.33	.744	[0.09,5.76]
Pre-session Vape (ref. no Vape[2])	1.56	1.32	1.18	.250	[0.35,63.26]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.57	0.83	0.68	.500	[0.35,8.90]
QSU-Brief Factor 1 (Desire to Vape) (Updated Model)[1]					
Intercept	0.42	0.65	0.64	.525	[0.42,5.48]
Gaze Index	0.59	0.51	1.16	.250	[0.67,4.89]
Cue Type (ECIG) (ref. Neutral[2])	**1.78**	**0.71**	**2.51**	**.016**	**[1.47,23.8]**
Session Order (Neutral) (ref. ECIG[2])	-1.06	0.75	-1.41	.164	[0.08,1.50]
Pre-session Vape (ref. no Vape[2])	0.61	0.93	0.66	.515	[0.30,11.44]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.23	0.72	0.31	.755	[0.31,5.10]
QSU-Brief Factor 2 (Anticipated Relief from Vaping) (Original Model)					
Intercept	0.16	0.58	0.28	.778	[0.38,3.69]
Gaze Index	-0.08	0.45	-1.17	.866	[0.38,2.24]
Cue Type (ECIG) (ref. Neutral[2])	**1.78**	**0.62**	**2.89**	**.007**	**[1.78,19.93]**
Session Order (Neutral) (ref. ECIG[2])	-0.57	0.68	-0.84	.407	[0.15,2.13]
Pre-session Vape (ref. no Vape[2])	0.08	0.83	0.10	.925	[0.21,5.55]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.78	0.62	1.25	.221	[0.64,7.37]
QSU-Brief Factor 2 (Anticipated Relief from Vaping) (Updated Model)[1]					
Intercept	**0.90**	**0.42**	**2.17**	**.035**	**[1.09,5.56]**
Gaze Index	0.22	0.32	0.67	.506	[0.66,2.34]
Cue Type (ECIG) (ref. Neutral[2])	**1.00**	**0.45**	**2.22**	**.031**	**[1.12,6.58]**
Session Order (Neutral) (ref. ECIG[2])	**-1.20**	**0.48**	**-2.54**	**.014**	**[0.12,0.76]**
Pre-session Vape (ref. no Vape[2])	-0.58	0.59	-0.97	.335	[0.18,1.80]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.47	0.46	1.03	.306	[0.66,3.91]
Schuh-Stitzer Scale (Craving to Vape) (Original Model)					
Intercept	1.44	2.01	0.72	.476	[0.08,217.5]
Gaze Index	0.62	1.57	0.40	.694	[0.09,40.6]
Cue Type (ECIG) (ref. Neutral[2])	**4.43**	**2.19**	**2.02**	**.049**	**[1.1,6192.8]**

Session Order (Neutral) (ref. ECIG[2])	-2.14	2.32	-0.93	.359	[0.001,11.0]
Pre-session Vape (ref. no Vape[2])	-0.59	2.85	-0.21	.838	[0.002,148]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	0.92	2.21	0.41	.680	[0.03,191.6]
Schuh-Stitzer Scale (Craving to Vape) (Updated Model)[1]					
Intercept	2.28	1.79	1.28	.210	[0.29,326.1]
Gaze Index	-1.17	1.35	-0.87	.391	[0.02,4.39]
Cue Type (ECIG) (ref. Neutral[2])	2.86	1.57	1.83	.079	[0.81,377.7]
Session Order (Neutral) (ref. ECIG[2])	-1.94	2.28	-0.85	.401	[0.002,12.4]
Pre-session Vape (ref. no Vape[2])	-0.64	2.71	-0.24	.817	[0.003,108]
Gaze Index × Cue Type (ECIG) (ref. Neutral[2])	**4.13**	**1.58**	**2.61**	**.015**	**[2.8,1375.7]**
EEG P300 (Original Model)					
Intercept	**0.74**	**0.20**	**3.73**	**.002**	**[1.42,3.08]**
Cue type (Neutral) (ref. ECIG[2])	-0.12	0.23	-0.53	.608	[0.57,1.38]
Gaze Index	0.16	0.17	-0.96	.355	[0.62,1.18]
Session Order (Neutral) (ref. ECIG[2])	0.06	0.23	-0.28	.787	[0.60,1.47]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.12	0.23	0.51	.624	[0.72,1.77]
EEG P300 (Updated Model)[1]					
Intercept	**0.49**	**0.14**	**3.43**	**.006**	**[1.23,2.15]**
Cue type (Neutral) (ref. ECIG[2])	0.05	0.09	0.55	.598	[0.88,1.26]
Gaze Index	-0.21	0.11	-1.91	.079	[0.65,1.01]
Session Order (Neutral) (ref. ECIG[2])	0.08	0.18	0.48	.645	[0.77,1.54]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.18	0.10	1.76	.122	[0.98,1.46]
EEG LPP (Original Model)					
Intercept	0.14	0.17	0.83	.424	[0.83,1.60]
Cue type (Neutral) (ref. ECIG[2])	-0.07	0.19	-0.36	.728	[0.65,1.35]
Gaze Index	-0.10	0.14	-0.69	.500	[0.69,1.19]
Session Order (Neutral) (ref. ECIG[2])	0.03	0.20	-0.16	.877	[0.66,1.43]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.10	0.19	0.53	.614	[0.76,1.61]
EEG LPP (Updated Model)[1]					
Intercept	0.01	0.10	0.12	.904	[0.74,1.14]
Cue type (Neutral) (ref. ECIG[2])	0.02	0.08	0.20	.854	[0.96,1.22]
Gaze Index	-0.06	0.07	-0.84	.419	[0.79,1.07]
Session Order (Neutral) (ref. ECIG[2])	0.06	0.11	0.51	.637	[0.87,1.48]
Cue Type (Neutral) (ref. ECIG[2]) × Gaze Index	0.07	0.08	0.82	.460	[1.01,1.29]
CS Liking (Original Model)					
Intercept	**2.34**	**0.25**	**9.43**	**<.001**	**[6.39,16.92]**
CS+ (ref. CS-[2])	**2.00**	**0.28**	**7.22**	**<.001**	**[4.29,12.72]**
Gaze Index	0.18	0.20	0.93	.358	[0.81,1.78]
Pre-session Vape (ref. no Vape[2])	0.02	0.39	0.06	.956	[0.48,2.17]
Task Version (Pav2) (ref. Pav1[2])	-0.18	0.29	-0.63	.530	[0.47,1.47]

CS+ (ref. CS-[2]) × Gaze Index	-0.20	0.28	-0.71	.482	[0.48,1.42]
CS Liking (Updated Model)[1]					
Intercept	**2.26**	**0.21**	**10.78**	**<.001**	**[6.37,14.51]**
CS+ (ref. CS-[2])	**2.21**	**0.24**	**9.31**	**<.001**	**[5.74,14.58]**
Gaze Index	0.10	0.17	0.61	.546	[0.80,1.54]
Pre-session Vape (ref. no Vape[2])	-0.06	0.33	-0.18	.861	[0.50,1.79]
Task Version (Pav2) (ref. Pav1[2])	-0.18	0.25	-0.75	.459	[0.51,1.35]
CS+ (ref. CS-[2]) × Gaze Index	-0.35	0.24	-1.44	.157	[0.44,1.13]
PIT					
Intercept	-0.09	0.13	-0.71	.487	[0.71,1.18]
CS Type (CS+) (ref. CS-[2])	0.04	0.06	0.67	.511	[0.93,1.17]
Gaze Index	0.01	0.05	0.30	.770	[0.92,1.12]
Task Version 2 (ref. Version 1[2])	0.21	0.14	1.53	.143	[0.94,1.61]
Task Version 3 (ref. Version 1[2])	0.20	0.13	1.50	.151	[0.94,1.58]
Task Version 4 (ref. Version 1[2])	0.11	0.17	0.63	.538	[0.80,1.55]
Pre-session Vape (ref. no Vape[2])	0.02	0.10	0.25	.808	[0.85,1.24]
CS type (CS+) (ref. CS-[2]) × Gaze Index	-0.02	0.06	-0.34	.736	[0.87,1.10]

Note. Uncorrected *p* values shown in table. Items significant at *p* < .05 are bolded.

[1]Updated models refer to the models with influential Cook's points removed.

[2]Ref. – Model reference group.

DISCUSSION

This study is the first to examine the relationship between sign- and goal-tracking phenotypes and cue reactivity in a sample of ECIG users. The design of the study consisted of two separate cue exposure sessions (ECIG or neutral), during which participants' EEG brainwaves were recorded. The neutral cue exposure session was followed by the Pavlovian to Instrumental task (PIT) paradigm, the second part of which (the Pavlovian task) included eye tracking to determine each participant's propensity to sign- or goal-track. To measure cue reactivity, we used questionnaires (the QSU-Brief Factor and the Schuh-Stitzer Questionnaires) and EEG (P300 and LPP components). Sign- or goal-tracking propensity was determined by eye tracking during Pavlovian conditioning performed as part of the Pavlovian-to-Instrumental Transfer paradigm. Our primary aims were to examine the effect of the propensity to sign- or goal-track on a) the desire to vape (measured by QSU-Brief Factor 1) following cue exposure, b) the cue-evoked EEG ERP P300 component, and c) the Pavlovian-to-Instrumental transfer effect (replication). Our secondary aims included examining the effect of propensity to sign- or goal-track on a) anticipated relief from withdrawal (measured by QSU-Brief Factor 2) and craving to vape (measured by the Schuh-Stitzer Questionnaire) following cue exposure, and b) the EEG LPP component.

Sign-Tracking Propensity

Our determination of sign-tracking propensity was based on the duration of gaze fixations on conditioned stimuli following 20 trials of Pavlovian conditioning (measured during the second 20 trials of the Pavlovian conditioning task). Based on self-reported liking of the CS+ and the CS- and estimates of likelihood of these stimuli predicting rewards, Pavlovian learning was successful. Overall, participants reported liking the CS+ more and rated it as more predictive of rewards. However, 4 participants did not demonstrate evidence of Pavlovian learning, so we

performed the analyses both including and excluding these participants, as their gaze index may be suspect.

Because our sample's gaze index distribution data did not exhibit a clear bimodal pattern (as discussed previously), which aligns with findings from previous studies using this measure to assess sign- and goal-tracking in humans (Schad et al., 2020b), we opted to treat the gaze index as a continuous variable in our subsequent analyses. In this approach, we used the gaze index as a measure of the extent of sign- and goal-tracking and employed it as a continuous predictor in our models, as was done in a prior publication (Cherkasova et al., 2023), instead of using it to categorize participants as either sign-trackers or goal-trackers. This approach was taken because it was unclear how to best split the sample into sign- and goal-trackers with many participants not clearly belonging to either phenotype. There are other ways to measure sign-tracking that have been developed that more closely resemble the rodent paradigm used to classify the animals into sign- and goal-trackers (making use of an operant chamber-like set up) (Colaizzi et al., 2020; Cope et al., 2023), however these also do not yield clearly bimodal distribution of sign- and goal-tracking CRs in humans.

Primary Outcomes

QSU-Brief Factor 1 (Desire to Vape)

We hypothesized that, relative to exposure to neutral cues, exposure to ECIG cues would significantly increase self-reported desire for an ECIG, as measured by the QSU-Brief Factor 1. Additionally, we hypothesized that participants with a higher gaze index (indicating a greater propensity to sign-track) would report a higher self-reported desire for an ECIG on this factor compared to participants with a lower gaze index (indicating a greater propensity to goal-track). ECIG cues evoked a significantly greater self-reported desire to vape than neutral cues.

However, this effect was not significantly modulated by gaze index, i.e. there was no significant cue type x gaze index interaction on the QSU-Brief Factor 1. The absence of a statistically significant interaction may be explained by the study being underpowered due to not having a full sample of participants collected. The outcomes may change once the full sample has been obtained.

EEG P300

We hypothesized that, relative to exposure to neutral cues, exposure to ECIG cues would significantly increase P300 ERP responses. Additionally, we hypothesized that participants with a higher gaze index (indicating a greater propensity to sign-track) would exhibit a higher P300 ERP brainwave response when exposed to ECIG cues compared to participants with a lower gaze index (indicating a greater propensity to goal-track). No significant difference in the P300 ERP responses was observed between cue types (ECIG vs. neutral). After 2 influential observations based on Cook's distances, there was a trend-level interaction of gaze index and cue type (ECIG or neutral) on the P300 ERP brainwave component. This trend indicates that individuals with higher gaze index show more of an increase in amplitude in response to <u>neutral</u> vs. ECIG cues, which is the opposite from what we hypothesized. This trend currently goes counter to our hypothesis that individuals with a greater propensity to sign-track have a higher ERP P300 brainwave response when exposed to ECIG cues compared to individuals with a greater propensity to goal-track. It must be noted that this pattern of results is inconclusive and may change once we obtain a full sample of participants.

PIT

Based on prior work (Garofalo & di Pellegrino, 2015), we hypothesized that, individuals with a stronger sign-tracking propensity would exhibit a more pronounced PIT effect. No

significant PIT effect was observed, and there was no significant modulation of PIT by sign-tracking propensity. Notably, an earlier study employing the same PIT paradigm adapted from Garofalo & Di Pellegrino, 2015 had also failed to find a significant PIT effect or a significant modulation of the PIT effect by sign-tracking in a sample of nearly 200 participants (Cherkasova et al., 2023). Another extant human PIT paradigm produces the PIT effect more robustly, based on the published literature (Garbusow et al., 2014; Schad et al., 2020b), and future studies may consider using that paradigm. As mentioned earlier, the sample is incomplete, and results may change.

Secondary Outcomes

QSU-Brief Factor 2 (Anticipated Relief from Vaping)

We hypothesized that, relative to exposure to neutral cues, exposure to ECIG cues would significantly increase self-reported anticipated relief from withdrawal, as measured by the QSU-Brief Factor 2. Additionally, we hypothesized that participants with a higher gaze index would report a higher self-reported anticipated relief from vaping on this factor compared to participants with a lower gaze index. There was a significant difference in the self-reported score of anticipated relief between cue types (ECIG vs. neutral). Additionally, there was a trend (p=0.052) for a gaze index by cue type interaction on the QSU-Brief Factor 2: participants with a greater propensity to sign-track tended to report anticipating greater relief from vaping following exposure to ECIG relative to neutral cues. Although this suggests some initial support for our hypothesis that greater propensity to sign-track would be associated with greater ECIG cue-reactivity, this preliminary finding is inconclusive a) because it is a non-significant trend and b) because removing influential observations changed the p-value to clearly non-significant (p = 0.12). Also, the findings may change once we obtain a full sample of participants.

Schuh-Stitzer Questionnaire (Craving to Vape)

We hypothesized that, relative to exposure to neutral cues, exposure to ECIG cues would significantly increase self-reported craving for an ECIG, as measured by the Schuh-Stitzer Questionnaire. Additionally, we hypothesized that participants with a higher gaze index (indicating a greater propensity to sign-track) would report a higher self-reported craving for an ECIG on this factor compared to participants with a lower gaze index (indicating a greater propensity to goal-track). There was a significant difference in the self-reported score of craving to vape between cue types (ECIG vs. neutral). After adjusting for influential Cook's values, there was a significant effect for a gaze index by cue type interaction on the Schuh-Stitzer Questionnaire: participants with a greater propensity to sign-track tended to report higher craving to vape following exposure to ECIG relative to neutral cues. Although this suggests some initial support for our hypothesis that greater propensity to sign-track would be associated with greater ECIG cue-reactivity, this preliminary finding is inconclusive and may change once we obtain a full sample of participants.

EEG LPP

We hypothesized that, relative to exposure to neutral cues, exposure to ECIG cues would significantly increase LPP EEG responses. Whereas the P300 component which is observed around 300-500 ms after stimulus presentation and known to reflect early attention to stimuli and stimuli categorization (Picton, 1992), the LPP component is observed between 400-2000 ms after stimulus onset (Moeller et al., 2012) and reflects motivational attention to emotional stimuli, which also includes drug-related cues (Parvaz et al., 2021). Additionally, we hypothesized that participants with a higher gaze index (indicating a greater propensity to sign-track) would exhibit a higher LPP EEG brainwave response when exposed to ECIG cues compared to participants

with a lower gaze index (indicating a greater propensity to goal-track). No significant difference in the LPP EEG responses was observed between cue types (ECIG vs. neutral). After adjusting for influential Cook's values, there was a non-significant trend toward (p=0.07) for an interaction of gaze index and cue type (neutral or ECIG) on the LPP EEG brainwave component. This trend indicates that individuals with higher gaze index show more of an increase in LPP amplitude in response to neutral vs. ECIG cues, which is the opposite from what we hypothesized. However, this finding is inconclusive and may change once we obtain a full sample of participants. Additionally, it must be noted that the LPP amplitudes overlap with the P300 amplitudes in our analysis.

Strengths and Limitations

The conducted study has several strengths. First, the use of multiple measures to evaluate different craving-related factors evoked by cues (desire to vape, expected relief from vaping, craving to vape) provided a multidimensional understanding of cue reactivity effects as a function of the propensity to sign- or goal-track. Additionally, including an EEG measure of cue reactivity added another dimension of cue-reactivity beyond self-reported craving.

The study also had a number of limitations. First, the current study sample is incomplete, and, therefore, the study is currently underpowered to detect the hypothesized effects (34 participants out of 64 needed; only 12 participants for the EEG components). The results are, therefore, inconclusive and preliminary. Another limitation is that some participants did not learn the operant response in the instrumental conditioning task of the PIT paradigm, and some did not learn the Pavlovian associations in the Pavlovian task. This is potential evidence of task disengagement and raises questions regarding data quality. To mitigate this issue, we excluded participants that were not learning the operant response from the PIT data analysis. Additionally,

we conducted a second round of analyses for a sample of participants excluding the ones that did not learn the Pavlovian associations (Table 3). However, this approach decreases our sample size and power. Another limitation is that the experimental paradigm underwent several changes in the course of data collection. We expanded our inclusion criteria to allow for dual ECIG and cigarette users, which could introduce potential noise to the data related to nicotine dependence from cigarettes, not just from ECIGs. We also removed the pre-session vaping bout and added a period of 8-hour vaping abstinence. Moreover, we updated the ECIG cue stimuli to reflect more modern devices by removing the older models (e.g. vape pen devices) and adding more modern ECIGs (e.g. pod- and mod-styles). A related limitation is that while some of the ECIG cues were pictures of mod-style devices, none of our completed participants were users of these device types. The presence of mods may have diluted the effect of the cues, although we did observe higher cravings for ECIG than neutral cues across all our measures. Finally, we added EEG to our experiment midway through the testing. All of these changes could contribute to noise in the data. Additionally, we did not use an actual biochemical test to verify abstinence for the 8 hours prior to the session, relying instead on a bogus pipeline procedure, which raises uncertainty about whether participants actually abstained from vaping as instructed by the research staff. While each participant had a 30-minute abstinence period at the beginning of the session in the presence of research personnel, future studies may opt to biochemically verify the period of abstinence. Another limitation of the study is that it was conducted in a non-naturalistic research laboratory environment, which could potentially impact cue reactivity in the sample. As noted in previous research in rodent models, sign- and goal-trackers are influenced differently by various cue types – sign-trackers are more influenced by discrete cues, while goal-trackers are more influenced by contextual cues (Robinson et al., 2014), which was not considered in the current

study. Additionally, the limitations of measuring sign-tracking the way we did was that the "Sign" and "Goal" locations were shown in two separate locations on the screen, which were the same on every trial for all participants. Therefore, gaze index could have reflected a spatial bias unrelated to the attribution of incentive salience (e.g. if participants with a more sign-tracking like CR had a tendency to gaze downward). Finally, the sample of participants was recruited from a population of college students in a predominantly white area, which could potentially limit generalizability. Despite this, the current sample was fairly ethnically diverse (of the 32.35% of participants identified as other than white, races reported included 14.71% Asian, 11.76% Native Hawaiian or other Pacific Islander, 2.94% Black, and 2.94% Multiracial).

Conclusions and Future Directions

The results of this study help us understand the relationship between cue reactivity and the propensity to sign- or goal-track in ECIG users. Although the study is incomplete and its results are currently inconclusive, a significant association between sign-tracking and cue-induced craving was observed on one of the secondary outcomes, in addition to a trend on another secondary outcome (anticipated relief) in the same direction. If this pattern of findings persists when the study is completed, this would make a valuable contribution to the literature. Some previous studies have relied on a mechanical measure of sign-tracking, which is more aligned with animal models but can be both burdensome and costly when applied in a laboratory setting (Colaizzi et al., 2020; Cope et al., 2023). These studies did not examine sign-tracking in relation to addictive disorders. To our knowledge, the only studies that have attempted to look at sign-tracking in the context of addictive disorders in humans are those that have employed a measure called value-modulated attentional capture (VMAC), which measures a capture of attention during the performance of a singleton task by task-irrelevant reward-related stimuli

(Albertella et al., 2019). VMAC has been likened to sign-tracking by the authors. This work reported that greater attentional capture (sign-tracking) was associated with risky alcohol use behaviors and with less probability of remaining abstinent during an alcohol abstinence challenge (Albertella et al., 2019, 2021). Our work extends this line of research to nicotine use and shows initial trends in the same direction. It is worth emphasizing the importance of future research to cross-validate different measures of sign-/goal-tracking (eye-tracking based measures, mechanical tasks, and VMAC).

Subsequent work could also expand on the types of cues presented to participants by including both discrete and contextual cues to comprehensively assess the relationship between cue reactivity and the sign- or goal-tracking tendencies. Furthermore, the selected ECIG cues included both pod and mod ECIG devices, which may not be ideal for the current sample given that the majority of participants used pod or disposable devices. Future research may benefit from tailoring cue presentations based on the type of device used by each participant. Understanding how environmental cues influence each of these phenotypes may have potential implications for preventing relapse and improving treatment outcomes, potentially informing patients and providers about the risks of relapse associated with cues. However, further research is needed to expand on the relationship between sign- and goal-tracking and cue reactivity in the context of other types of drugs of abuse.

REFERENCES

Ahrens, A. M., Singer, B. F., Fitzpatrick, C. J., Morrow, J. D., & Robinson, T. E. (2016). Rats that sign-track are resistant to Pavlovian but not instrumental extinction. *Behavioural Brain Research*, *296*, 418–430. https://doi.org/10.1016/j.bbr.2015.07.055

Albertella, L., Vd Hooven, J., Bovens, R., & Wiers, R. W. (2021). Reward-related attentional capture predicts non-abstinence during a one-month abstinence challenge. *Addictive Behaviors*, *114*, 106745. https://doi.org/10.1016/j.addbeh.2020.106745

Albertella, L., Watson, P., Yücel, M., & Le Pelley, M. E. (2019). Persistence of value-modulated attentional capture is associated with risky alcohol use. *Addictive Behaviors Reports*, *10*, 100195. https://doi.org/10.1016/j.abrep.2019.100195

Allen, M., Poggiali, D., Whitaker, K., Marshall, T. R., van Langen, J., & Kievit, R. A. (2021). Raincloud plots: A multi-platform tool for robust data visualization. *Wellcome Open Research*, *2021*. https://doi.org/10.12688/wellcomeopenres.15191.2

Allison, B., Jin, J., Zhang, Y., & Wang, X. (2014). A four-choice hybrid P300/SSVEP BCI for improved accuracy. *Brain-Computer Interfaces*, *1*. https://doi.org/10.1080/2326263X.2013.869003

Bardo, M. T., Donohew, R. L., & Harrington, N. G. (1996). Psychobiology of novelty seeking and drug seeking behavior. *Behavioural Brain Research*, *77*(1), 23–43. https://doi.org/10.1016/0166-4328(95)00203-0

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using **lme4**. *Journal of Statistical Software*, *67*(1). https://doi.org/10.18637/jss.v067.i01

Baweja, R., Curci, K. M., Yingst, J., Veldheer, S., Hrabovsky, S., Wilson, S. J., Nichols, T. T., Eissenberg, T., & Foulds, J. (2016). Views of Experienced Electronic Cigarette Users.

Addiction Research & Theory, *24*(1), 80–88.

https://doi.org/10.3109/16066359.2015.1077947

Bedi, G., Preston, K. L., Epstein, D. H., Heishman, S. J., Marrone, G. F., Shaham, Y., & de Wit, H. (2011). Incubation of Cue-Induced Cigarette Craving During Abstinence in Human Smokers. *Biological Psychiatry*, *69*(7), 708–711.

https://doi.org/10.1016/j.biopsych.2010.07.014

Berridge, K. C., & Robinson, T. E. (2016). Liking, Wanting and the Incentive-Sensitization Theory of Addiction. *The American Psychologist*, *71*(8), 670–679.

https://doi.org/10.1037/amp0000059

Berry, C., Burton, S., & Howlett, E. (2017). The Impact of E-Cigarette Addiction Warnings and Health-Related Claims on Consumers' Risk Beliefs and Use Intentions. *Journal of Public Policy & Marketing*, *36*(1), 54–69. https://doi.org/10.1509/jppm.15.024

Betts, J. M., Dowd, A. N., Forney, M., Hetelekides, E., & Tiffany, S. T. (2021). A Meta-Analysis of Cue Reactivity in Tobacco Cigarette Smokers. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco*, *23*(2), 249–258.

https://doi.org/10.1093/ntr/ntaa147

Bhatnagar, A., Benowitz, N., Bullen, C., Chaloupka, F., Goff, D., McAuley, T., Piano, M. R., Robertson, R. M., Ribisl, K. M., Whitsel, L. P., Goniewicz, M., Schroeder, S. A., Warner, K., & Widome, R. (2014). Electronic Cigarettes. *Circulation*, *130*(16), 1418–1436.

https://doi.org/10.1161/CIR.0000000000000107

Biener, L., & Hargraves, J. L. (2015). A Longitudinal Study of Electronic Cigarette Use Among a Population-Based Sample of Adult Smokers: Association With Smoking Cessation and

Motivation to Quit. *Nicotine & Tobacco Research*, *17*(2), 127–133.

https://doi.org/10.1093/ntr/ntu200

Blackwell, A. K. M., De-Loyde, K., Brocklebank, L. A., Maynard, O. M., Marteau, T. M.,

Hollands, G. J., Fletcher, P. C., Attwood, A. S., Morris, R. W., & Munafò, M. R. (2020).

Tobacco and electronic cigarette cues for smoking and vaping: An online experimental

study. *BMC Research Notes*, *13*(1), 32. https://doi.org/10.1186/s13104-020-4899-3

Bu, J., Young, K. D., Hong, W., Ma, R., Song, H., Wang, Y., Zhang, W., Hampson, M., Hendler,

T., & Zhang, X. (2019). Effect of deactivation of activity patterns related to smoking cue

reactivity on nicotine addiction. *Brain*, *142*(6), 1827–1841.

https://doi.org/10.1093/brain/awz114

Bullitt, E. (1990). Expression of c-fos-like protein as a marker for neuronal activity following

noxious stimulation in the rat. *The Journal of Comparative Neurology*, *296*(4), 517–530.

https://doi.org/10.1002/cne.902960402

Caponnetto, P., Campagna, D., Papale, G., Russo, C., & Polosa, R. (2012). The emerging

phenomenon of electronic cigarettes. *Expert Review of Respiratory Medicine*, *6*(1), 63–

74. https://doi.org/10.1586/ers.11.92

Carter, B. L., & Tiffany, S. T. (1999). Meta-analysis of cue-reactivity in addiction research.

Addiction (Abingdon, England), *94*(3), 327–340.

Casey, K. F., Benkelfat, C., Cherkasova, M. V., Baker, G. B., Dagher, A., & Leyton, M. (2014).

Reduced dopamine response to amphetamine in subjects at ultra-high risk for addiction.

Biological Psychiatry, *76*(1), 23–30. https://doi.org/10.1016/j.biopsych.2013.08.033

Chen-Sankey, J. C., Unger, J. B., Bansal-Travers, M., Niederdeppe, J., Bernat, E., & Choi, K.

(2019). E-cigarette Marketing Exposure and Subsequent Experimentation Among Youth

and Young Adults. *Pediatrics*, *144*(5), e20191119. https://doi.org/10.1542/peds.2019-1119

Cherkasova, M., Limbrick-Oldfield, E., Clark, L., Barton, J. J., Stoessl, A. J., & Winstanley, C. (2023). *Risk-Promoting Effects of Reward-Paired Cues in Human Sign- and Goal-Trackers*. PsyArXiv. https://doi.org/10.31234/osf.io/rxbpw

Colaizzi, J. M., Flagel, S. B., Joyner, M. A., Gearhardt, A. N., Stewart, J. L., & Paulus, M. P. (2020). Mapping sign-tracking and goal-tracking onto human behaviors. *Neuroscience and Biobehavioral Reviews*, *111*, 84–94. https://doi.org/10.1016/j.neubiorev.2020.01.018

Conklin, C. A., Vella, E. J., Joyce, C. J., Salkeld, R. P., Perkins, K. A., & Parzynski, C. (2015). Examining the relationship between cue-induced craving and actual smoking. *Experimental and Clinical Psychopharmacology*, *23*(2), 90–96. https://doi.org/10.1037/a0038826

Cope, L. M., Gheidi, A., Martz, M. E., Duval, E. R., Khalil, H., Allerton, T., & Morrow, J. D. (2023). A mechanical task for measuring sign- and goal-tracking in humans: A proof-of-concept study. *Behavioural Brain Research*, *436*, 114112. https://doi.org/wafaye

Cousijn, J., Goudriaan, A. E., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Wiers, R. W. (2013). Neural responses associated with cue-reactivity in frequent cannabis users. *Addiction Biology*, *18*(3), 570–580. https://doi.org/10.1111/j.1369-1600.2011.00417.x

Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco*, *3*(1), 7–16. https://doi.org/10.1080/14622200020032051

Croissant, Y., & Millo, G. (2008). Panel Data Econometrics in *R*: The **plm** Package. *Journal of Statistical Software*, *27*(2). https://doi.org/10.18637/jss.v027.i02

Cui, Y., Versace, F., Engelmann, J. M., Minnix, J. A., Robinson, J. D., Lam, C. Y., Karam-Hage, M., Brown, V. L., Wetter, D. W., Dani, J. A., Kosten, T. R., & Cinciripini, P. M. (2013). Alpha Oscillations in Response to Affective and Cigarette-Related Stimuli in Smokers. *Nicotine & Tobacco Research*, *15*(5), 917–924. https://doi.org/de

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology*, *52*(2), 95–111. https://doi.org/10.1016/S0301-0511(99)00044-7

de Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: A review of underlying processes. *Addiction Biology*, *14*(1), 22–31. https://doi.org/10.1111/j.1369-1600.2008.00129.x

Dennis, M., & Scott, C. K. (2007). Managing addiction as a chronic condition. *Addiction Science & Clinical Practice*, *4*(1), 45–55. https://doi.org/10.1151/ascp074145

Dennis, T. A., & Hajcak, G. (2009). The late positive potential: A neurophysiological marker for emotion regulation in children. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *50*(11), 1373–1383. https://doi.org/10.1111/j.1469-7610.2009.02168.x

Devoto, F., Zapparoli, L., Spinelli, G., Scotti, G., & Paulesu, E. (2020). How the harm of drugs and their availability affect brain reactions to drug cues: A meta-analysis of 64 neuroimaging activation studies. *Translational Psychiatry*, *10*(1), 429. https://doi.org/lin

Dowd, A., & Tiffany, S. (2018). Comparison of Tobacco and Electronic Cigarette Reward Value Measured During a Cue-Reactivity Task: An Extension of the Choice-Behavior-Under-

Cued-Conditions (CBUCC) Procedure. *Nicotine & Tobacco Research*, *21*.

https://doi.org/10.1093/ntr/nty143

Drummond, C., & Glautier, S. (1994). A Controlled Trial of Cue Exposure Treatment in Alcohol

Dependence. *Journal of Consulting and Clinical Psychology*, *62*, 809–817.

https://doi.org/10.1037//0022-006X.62.4.809

Due, D. L., Huettel, S. A., Hall, W. G., & Rubin, D. C. (2002). Activation in Mesolimbic and

Visuospatial Neural Circuits Elicited by Smoking Cues: Evidence From Functional

Magnetic Resonance Imaging. *American Journal of Psychiatry*, *159*(6), 954–960.

https://doi.org/10.1176/appi.ajp.159.6.954

Erblich, J., & Montgomery, G. H. (2012). Cue-Induced Cigarette Cravings and Smoking

Cessation: The Role of Expectancies. *Nicotine & Tobacco Research*, *14*(7), 809–815.

https://doi.org/10.1093/ntr/ntr288

Estes, W. K. (1948). Discriminative conditioning. II. Effects of a Pavlovian conditioned stimulus

upon a subsequently established operant response. *Journal of Experimental Psychology*,

38, 173–177. https://doi.org/10.1037/h0057525

Farsalinos, K. E., & Polosa, R. (2014). Safety evaluation and risk assessment of electronic

cigarettes as tobacco cigarette substitutes: A systematic review. *Therapeutic Advances in*

Drug Safety, *5*(2), 67–86. https://doi.org/10.1177/2042098614524430

Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., & Voudris, V. (2013). Evaluation

of electronic cigarette use (vaping) topography and estimation of liquid consumption:

Implications for research protocol standards definition and for public health authorities'

regulation. *International Journal of Environmental Research and Public Health*, *10*(6),

2500–2514. https://doi.org/10.3390/ijerph10062500

Filbey, F. M., Claus, E., Audette, A. R., Niculescu, M., Banich, M. T., Tanabe, J., Du, Y. P., & Hutchison, K. E. (2008). Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *33*(6), 1391–1401. https://doi.org/10.1038/sj.npp.1301513

Flagel, S. B., Akil, H., & Robinson, T. E. (2009). Individual differences in the attribution of incentive salience to reward-related cues: Implications for addiction. *Neuropharmacology*, *56 Suppl 1*, 139–148. https://doi.org/10.1016/j.neuropharm.2008.06.027

Flagel, S. B., Cameron, C. M., Pickup, K. N., Watson, S. J., Akil, H., & Robinson, T. E. (2011). A food predictive cue must be attributed with incentive salience for it to induce c-fos mRNA expression in cortico-striatal-thalamic brain regions. *Neuroscience*, *196*, 80–96. https://doi.org/10.1016/j.neuroscience.2011.09.004

Flagel, S. B., Clark, J. J., Robinson, T. E., Mayo, L., Czuj, A., Willuhn, I., Akers, C. A., Clinton, S. M., Phillips, P. E. M., & Akil, H. (2011). A selective role for dopamine in stimulus–reward learning. *Nature*, *469*(7328), 53–57. https://doi.org/10.1038/nature09588

Flagel, S. B., Robinson, T. E., Clark, J. J., Clinton, S. M., Watson, S. J., Seeman, P., Phillips, P. E. M., & Akil, H. (2010). An Animal Model of Genetic Vulnerability to Behavioral Disinhibition and Responsiveness to Reward-Related Cues: Implications for Addiction. *Neuropsychopharmacology*, *35*(2), 388–400. https://doi.org/10.1038/npp.2009.142

Flagel, S. B., Watson, S. J., Akil, H., & Robinson, T. E. (2008). Individual differences in the attribution of incentive salience to a reward-related cue: Influence on cocaine

sensitization. *Behavioural Brain Research*, *186*(1), 48–56.

https://doi.org/10.1016/j.bbr.2007.07.022

Friedman, D., Goldman, R., Stern, Y., & Brown, T. R. (2008). The brain's orienting response:

An event-related functional magnetic resonance imaging investigation. *Human Brain*

Mapping, *30*(4), 1144–1154. https://doi.org/10.1002/hbm.20587

Garbusow, M., Schad, D. J., Sommer, C., Jünger, E., Sebold, M., Friedel, E., Wendt, J.,

Kathmann, N., Schlagenhauf, F., Zimmermann, U. S., Heinz, A., Huys, Q. J. M., & Rapp,

M. A. (2014). Pavlovian-to-instrumental transfer in alcohol dependence: A pilot study.

Neuropsychobiology, *70*(2), 111–121. https://doi.org/10.1159/000363507

Garland, E. L., Franken, I. H. A., & Howard, M. O. (2012). Cue-elicited heart rate variability and

attentional bias predict alcohol relapse following treatment. *Psychopharmacology*,

222(1), 17–26. https://doi.org/10.1007/s00213-011-2618-4

Garofalo, S., & di Pellegrino, G. (2015). Individual differences in the influence of task-irrelevant

Pavlovian cues on human behavior. *Frontiers in Behavioral Neuroscience*, *9*.

https://doi.org/10.3389/fnbeh.2015.00163

Gerdeman, G. L., Partridge, J. G., Lupica, C. R., & Lovinger, D. M. (2003). It could be habit

forming: Drugs of abuse and striatal synaptic plasticity. *Trends in Neurosciences*, *26*(4),

184–192. https://doi.org/10.1016/S0166-2236(03)00065-1

Gillis, Z. S., & Morrison, S. E. (2019). Sign Tracking and Goal Tracking Are Characterized by

Distinct Patterns of Nucleus Accumbens Activity. *eNeuro*, *6*(2), ENEURO.0414-18.2019.

https://doi.org/10.1523/ENEURO.0414-18.2019

Górecka, J., & Makiewicz, P. (2019). The Dependence of Electrode Impedance on the Number of Performed EEG Examinations. *Sensors (Basel, Switzerland)*, *19*(11), E2608. https://doi.org/10.3390/s19112608

Grant, J. E., Atmaca, M., Fineberg, N. A., Fontenelle, L. F., Matsunaga, H., Janardhan Reddy, Y., Simpson, H. B., Thomsen, P. H., van den Heuvel, O. A., Veale, D., Woods, D. W., & Stein, D. J. (2014). Impulse control disorders and "behavioural addictions" in the ICD-11. *World Psychiatry*, *13*(2), 125–127. https://doi.org/10.1002/wps.20115

Haight, J. L., Fuller, Z. L., Fraser, K. M., & Flagel, S. B. (2017). A food-predictive cue attributed with incentive salience engages subcortical afferents and efferents of the paraventricular nucleus of the thalamus. *Neuroscience*, *340*, 135–152. https://doi.org/10.1016/j.neuroscience.2016.10.043

Hansen, J., Hanewinkel, R., & Morgenstern, M. (2020). Electronic cigarette advertising and teen smoking initiation. *Addictive Behaviors*, *103*, 106243. https://doi.org/10.1016/j.addbeh.2019.106243

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*, *86*(9), 1119–1127. https://doi.org/10.1111/j.1360-0443.1991.tb01879.x

Herbst, E. (2022). *N-Acetylcysteine for Smoking Cessation in Tobacco and Cannabis Co-Use: A Randomized Controlled Trial* (Clinical Trial Registration NCT04627922). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04627922

Herrmann, M. J., Weijers, H.-G., Wiesbeck, G. A., Böning, J., & Fallgatter, A. J. (2001). Alcohol Cue-Reactivity In Heavy And Light Social Drinkers As Revealed By Event-

Related Potentials. *Alcohol and Alcoholism*, *36*(6), 588–593.

https://doi.org/10.1093/alcalc/36.6.588

Holmes, N. M., Marchand, A. R., & Coutureau, E. (2010). Pavlovian to instrumental transfer: A

neurobehavioural perspective. *Neuroscience and Biobehavioral Reviews*, *34*(8), 1277–

1295. https://doi.org/10.1016/j.neubiorev.2010.03.007

Horrell, T., El-Baz, A., Baruth, J., Tasman, A., Sokhadze, G., Stewart, C., & Sokhadze, E.

(2010). Neurofeedback Effects on Evoked and Induced EEG Gamma Band Reactivity to

Drug-related Cues in Cocaine Addiction. *Journal of Neurotherapy*, *14*(3), 195–216.

https://doi.org/10.1080/10874208.2010.501498

How do Tobii Eye Trackers work? | Learn more with Tobii Pro. (2015, August 10).

[Information]. https://www.tobiipro.com/learn-and-support/learn/eye-tracking-

essentials/how-do-tobii-eye-trackers-work/

Hyun, J., Baik, M. J., & Kang, U. G. (2011). *Effects of Psychotropic Drugs on Quantitative EEG*

among Patients with Schizophrenia-spectrum Disorders. *9*(2), 78–85.

https://doi.org/10.9758/cpn.2011.9.2.78

Jankowski, M., Krzystanek, M., Zejda, J. E., Majek, P., Lubanski, J., Lawson, J. A., & Brozek,

G. (2019). E-Cigarettes are More Addictive than Traditional Cigarettes—A Study in

Highly Educated Young People. *International Journal of Environmental Research and*

Public Health, *16*(13), Article 13. https://doi.org/10.3390/ijerph16132279

Jordan, C. J., & Andersen, S. L. (2017). Sensitive periods of substance abuse: Early risk for the

transition to dependence. *Developmental Cognitive Neuroscience*, *25*, 29–44.

https://doi.org/10.1016/j.dcn.2016.10.004

Joyner, M. A., Gearhardt, A. N., & Flagel, S. B. (2018). A Translational Model to Assess Sign-Tracking and Goal-Tracking Behavior in Children. *Neuropsychopharmacology*, *43*(1), 228–229. https://doi.org/10.1038/npp.2017.196

Keijsers, M., Vega-Corredor, M. C., Hoermann, S., & Tomintz, M. (2022). Cue Reactivity to Electronic Cigarettes: A Systematic Review. *Substance Abuse: Research and Treatment*, *16*, 11782218221114971. https://doi.org/10.1177/11782218221114971

Kim, S. (2013). Neuroscientific Model of Motivational Process. *Frontiers in Psychology*, *4*, 98. https://doi.org/10.3389/fpsyg.2013.00098

King, A., Brett, E., Vena, A., Miloslavich, K., & Cao, D. (2021). Electronic Nicotine Delivery Systems (ENDS) Cue Reactivity in Dual Users. *Drug and Alcohol Dependence*, *227*, 108909. https://doi.org/10.1016/j.drugalcdep.2021.108909

Krank, M. D. (2003). Pavlovian Conditioning With Ethanol: Sign-Tracking (Autoshaping), Conditioned Incentive, and Ethanol Self-Administration: *Alcoholism: Clinical & Experimental Research*, *27*(10), 1592–1598. https://doi.org/10.1097/01.ALC.0000092060.09228.DE

Kreek, M. J., Nielsen, D. A., Butelman, E. R., & LaForge, K. S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience*, *8*(11), Article 11. https://doi.org/10.1038/nn1583

Kuhn, B. N., Klumpner, M. S., Covelo, I. R., Campus, P., & Flagel, S. B. (2018). Transient inactivation of the paraventricular nucleus of the thalamus enhances cue-induced reinstatement in goal-trackers, but not sign-trackers. *Psychopharmacology*, *235*(4), 999–1014. https://doi.org/10.1007/s00213-017-4816-1

Kühn, S., & Gallinat, J. (2011). Common biology of craving across legal and illegal drugs – a quantitative meta-analysis of cue-reactivity brain response. *European Journal of Neuroscience*, *33*(7), 1318–1326. https://doi.org/10.1111/j.1460-9568.2010.07590.x

LaRowe, S. D., Saladin, M. E., Carpenter, M. J., & Upadhyaya, H. P. (2007). Reactivity to nicotine cues over repeated cue reactivity sessions. *Addictive Behaviors*, *32*(12), 2888–2899. https://doi.org/10.1016/j.addbeh.2007.04.025

Levenson, J., & Grady, M. (2016). Childhood adversity, substance abuse, and violence: Implications for trauma-informed social work practice. *Journal of Social Work Practice in the Addictions*, *16*, 24–45. https://doi.org/10.1080/1533256X.2016.1150853

Lin, X., Deng, J., Shi, L., Wang, Q., Li, P., Li, H., Liu, J., Que, J., Chang, S., Bao, Y., Shi, J., Weinberger, D. R., Wu, P., & Lu, L. (2020). *Translational Psychiatry*, *10*(1), 97. https://doi.org/10.1038/s41398-020-01115-7

Louis, E. K. S., Frey, L. C., Britton, J. W., Frey, L. C., Hopp, J. L., Korb, P., Koubeissi, M. Z., Lievens, W. E., Pestana-Knight, E. M., & Louis, E. K. S. (2016). Appendix 4. Common Artifacts During EEG Recording. In *Electroencephalography (EEG): An Introductory Text and Atlas of Normal and Abnormal Findings in Adults, Children, and Infants [Internet]*. American Epilepsy Society. https://www.ncbi.nlm.nih.gov/books/NBK390358/

Lovibond, P. F. (1981). Appetitive Pavlovian-instrumental interactions: Effects of inter-stimulus interval and baseline reinforcement conditions. *The Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology*, *33*(Pt 4), 257–269. https://doi.org/10.1080/14640748108400811

Lubman, D., Allen, N., Peters, L., & Deakin, J. (2008). Electrophysiological evidence that drug cues have greater salience than other affective stimuli in opiate addiction. *Journal of Psychopharmacology*, *22*(8), 836–842. https://doi.org/10.1177/0269881107083846

Luck, S. J. (2012). Event-related potentials. In *APA handbook of research methods in psychology, Vol 1: Foundations, planning, measures, and psychometrics* (pp. 523–546). American Psychological Association. https://doi.org/10.1037/13619-028

Lüdecke, D., Ben-Shachar, M., Patil, I., Waggoner, P., & Makowski, D. (2021). performance: An R Package for Assessment, Comparison and Testing of Statistical Models. *Journal of Open Source Software*, *6*(60), 3139. https://doi.org/10.21105/joss.03139

Lv, W., Wu, Q., Liu, X., Chen, Y., Song, H., Yang, L., & Zhang, X. (2016). Cue Reactivity in Nicotine and Alcohol Addiction: A Cross-Cultural View. *Frontiers in Psychology*, *7*. https://www.frontiersin.org/article/10.3389/fpsyg.2016.01335

Minnix, J. A., Versace, F., Robinson, J. D., Lam, C. Y., Engelmann, J. M., Cui, Y., Brown, V. L., & Cinciripini, P. M. (2013). The Late Positive Potential (LPP) in Response to Varying Types of Emotional and Cigarette Stimuli in Smokers: A Content Comparison. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *89*(1), 18–25. https://doi.org/10.1016/j.ijpsycho.2013.04.019

Moeller, S. J., Hajcak, G., Parvaz, M. A., Dunning, J. P., Volkow, N. D., & Goldstein, R. Z. (2012). Psychophysiological prediction of choice: Relevance to insight and drug addiction. *Brain*, *135*(11), 3481–3494. https://doi.org/10.1093/brain/aws252

Moin Afshar, N., Cinotti, F., Martin, D. A., Khamassi, M., Calu, D. J., Taylor, J. R., & Groman, S. M. (2022). Reward-mediated, model-free reinforcement-learning mechanisms in

Pavlovian and instrumental tasks are related. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, JN-RM-1113-22. https://doi.org/10.1523/JNEUROSCI.1113-22.2022

Morrow, J. D., Maren, S., & Robinson, T. E. (2011). Individual variation in the propensity to attribute incentive salience to an appetitive cue predicts the propensity to attribute motivational salience to an aversive cue. *Behavioural Brain Research*, *220*(1), 238–243.

Morrow, J., Gheidi, A., Cope, L., & Billing, S. (2019). T214. Sign-Tracking, Goal-Tracking, and Impulsivity in College-Aged Subjects. *Biological Psychiatry*, *85*(10), S212. https://doi.org/10.1016/j.biopsych.2019.03.537

Niaura, R. S., Rohsenow, D. J., Binkoff, J. A., Monti, P. M., Pedraza, M., & Abrams, D. B. (1988). Relevance of cue reactivity to understanding alcohol and smoking relapse. *Journal of Abnormal Psychology*, *97*(2), 133–152. https://doi.org/10.1037/0021-843X.97.2.133

Noori, H. R., Cosa Linan, A., & Spanagel, R. (2016). Largely overlapping neuronal substrates of reactivity to drug, gambling, food and sexual cues: A comprehensive meta-analysis. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *26*(9), 1419–1430. https://doi.org/10.1016/j.euroneuro.2016.06.013

Norberg, M. M., Kavanagh, D. J., Olivier, J., & Lyras, S. (2016). Craving cannabis: A meta-analysis of self-report and psychophysiological cue-reactivity studies. *Addiction (Abingdon, England)*, *111*(11), 1923–1934. https://doi.org/10.1111/add.13472

Outlier Treatment With R | Multivariate Outliers. (n.d.). Retrieved October 25, 2023, from https://r-statistics.co/Outlier-Treatment-With-R.html

Palazzolo, D. L. (2013). Electronic cigarettes and vaping: A new challenge in clinical medicine and public health. A literature review. *Frontiers in Public Health*, *1*, 56. https://doi.org/10.3389/fpubh.2013.00056

Parvaz, M. A., Malaker, P., Zilverstand, A., Moeller, S. J., Alia-Klein, N., & Goldstein, R. Z. (2021). Attention bias modification in drug addiction: Enhancing control of subsequent habits. *Proceedings of the National Academy of Sciences*, *118*(23), e2012941118. https://doi.org/10.1073/pnas.2012941118

Pauly, J., Li, Q., & Barry, M. B. (2007). Tobacco-free electronic cigarettes and cigars deliver nicotine and generate concern. *Tobacco Control*, *16*(5), 357. https://doi.org/10.1136/tc.2006.019687

Peciña, S., Cagniard, B., Berridge, K. C., Aldridge, J. W., & Zhuang, X. (2003). Hyperdopaminergic Mutant Mice Have Higher "Wanting" But Not "Liking" for Sweet Rewards. *The Journal of Neuroscience*, *23*(28), 9395–9402. https://doi.org/10.1523/JNEUROSCI.23-28-09395.2003

Picton, T. W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, *9*(4), 456–479. https://doi.org/10.1097/00004691-199210000-00002

Pohořalá, V., Enkel, T., Bartsch, D., Spanagel, R., & Bernardi, R. E. (2021). Sign- and goal-tracking score does not correlate with addiction-like behavior following prolonged cocaine self-administration. *Psychopharmacology*, *238*(8), 2335–2346. https://doi.org/10.1007/s00213-021-05858-z

Polosa, R., Rodu, B., Caponnetto, P., Maglia, M., & Raciti, C. (2013). A fresh look at tobacco harm reduction: The case for the electronic cigarette. *Harm Reduction Journal*, *10*(1), 19. https://doi.org/10.1186/1477-7517-10-19

Prabhakaran, S. (2023, August 9). Cook's Distance for Detecting Influential Observations. *Machine Learning Plus*. https://www.machinelearningplus.com/machine-learning/cooks-distance/

Rescorla, R. A., & Solomon, R. L. (1967). Two-process learning theory: Relationships between Pavlovian conditioning and instrumental learning. *Psychological Review*, *74*(3), 151–182. https://doi.org/10.1037/h0024475

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research. Brain Research Reviews*, *18*(3), 247–291. https://doi.org/10.1016/0165-0173(93)90013-p

Robinson, T. E., & Berridge, K. C. (2008). The incentive sensitization theory of addiction: Some current issues. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *363*(1507), 3137–3146. https://doi.org/10.1098/rstb.2008.0093

Robinson, T. E., & Flagel, S. B. (2009). Dissociating the Predictive and Incentive Motivational Properties of Reward-Related Cues Through the Study of Individual Differences. *Biological Psychiatry*, *65*(10), 869–873. https://doi.org/10.1016/j.biopsych.2008.09.006

Robinson, T. E., Yager, L. M., Cogan, E. S., & Saunders, B. T. (2014). On the motivational properties of reward cues: Individual differences. *Neuropharmacology*, *76*, 450–459. https://doi.org/10.1016/j.neuropharm.2013.05.040

Rohsenow, D. J., Niaura, R. S., Childress, A. R., Abrams, D. B., & Monti, P. M. (1990). Cue reactivity in addictive behaviors: Theoretical and treatment implications. *The*

International Journal of the Addictions, *25*(7A-8A), 957–993.

https://doi.org/10.3109/10826089109071030

RStudio, PBC, Boston, MA. (n.d.). *RStudio: Integrated Development for R.* [Computer

software]. RStudio, PBC, Boston, MA. URL http://www.rstudio.com/.

Saletu, B., Grünberger, J., & Rajna, P. (1983). Pharmaco-EEG profiles of antidepressants. *British

Journal of Clinical Pharmacology*, *15*(Suppl 3), 369S-383S.

Sarter, M., & Phillips, K. (2018). The Neuroscience of Cognitive-Motivational Styles: Sign- and

Goal-Trackers as Animal Models. *Behavioral Neuroscience*, *132*.

https://doi.org/10.1037/bne0000226

Saunders, B. T., & Robinson, T. E. (2011). Individual Variation in the Motivational Properties of

Cocaine. *Neuropsychopharmacology*, *36*(8), 1668–1676.

https://doi.org/10.1038/npp.2011.48

Saunders, B. T., & Robinson, T. E. (2012). The role of dopamine in the accumbens core in the

expression of Pavlovian-conditioned responses. *The European Journal of Neuroscience*,

36(4), 2521–2532. https://doi.org/10.1111/j.1460-9568.2012.08217.x

Saunders, B. T., & Robinson, T. E. (2013). Individual variation in resisting temptation:

Implications for addiction. *Neuroscience and Biobehavioral Reviews*, *37*(0),

10.1016/j.neubiorev.2013.02.008. https://doi.org/10.1016/j.neubiorev.2013.02.008

Saunders, B. T., Yager, L. M., & Robinson, T. E. (2013). Cue-Evoked Cocaine "Craving": Role

of Dopamine in the Accumbens Core. *The Journal of Neuroscience*, *33*(35), 13989–

14000. https://doi.org/10.1523/JNEUROSCI.0450-13.2013

Schacht, J. P., Anton, R. F., & Myrick, H. (2013). Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. *Addiction Biology*, *18*(1), 121–133. https://doi.org/10.1111/j.1369-1600.2012.00464.x

Schad, D. J., Rapp, M. A., Garbusow, M., Nebe, S., Sebold, M., Obst, E., Sommer, C., Deserno, L., Rabovsky, M., Friedel, E., Romanczuk-Seiferth, N., Wittchen, H.-U., Zimmermann, U. S., Walter, H., Sterzer, P., Smolka, M. N., Schlagenhauf, F., Heinz, A., Dayan, P., & Huys, Q. J. M. (2020a). Dissociating neural learning signals in human sign- and goal-trackers. *Nature Human Behaviour*, *4*(2), 201–214. https://doi.org/10.1038/s41562-019-0765-5

Schad, D. J., Rapp, M. A., Garbusow, M., Nebe, S., Sebold, M., Obst, E., Sommer, C., Deserno, L., Rabovsky, M., Friedel, E., Romanczuk-Seiferth, N., Wittchen, H.-U., Zimmermann, U. S., Walter, H., Sterzer, P., Smolka, M. N., Schlagenhauf, F., Heinz, A., Dayan, P., & Huys, Q. J. M. (2020b). Dissociating neural learning signals in human sign- and goal-trackers. *Nature Human Behaviour*, *4*(2), 201–214. https://doi.org/10.1038/s41562-019-0765-5

Schuh, K. J., & Stitzer, M. L. (1995). Desire to smoke during spaced smoking intervals. *Psychopharmacology*, *120*(3), 289–295. https://doi.org/10.1007/BF02311176

Shapiro, S. S., & Wilk, M. B. (1965). An analysis of variance test for normality (complete samples). *Biometrika*, *52*(3–4), 591–611. https://doi.org/10.1093/biomet/52.3-4.591

Shiffman, S., Dunbar, M., Kirchner, T., Li, X., Tindle, H., Anderson, S., & Scholl, S. (2013). Smoker Reactivity to Cues: Effects on Craving and on Smoking behavior. *Journal of Abnormal Psychology*, *122*(1), 264–280. https://doi.org/10.1037/a0028339

Shiffman, S., Li, X., Dunbar, M. S., Tindle, H. A., Scholl, S. M., & Ferguson, S. G. (2015). Does laboratory cue reactivity correlate with real-world craving and smoking responses to cues? *Drug and Alcohol Dependence*, *155*, 163–169. https://doi.org/10.1016/j.drugalcdep.2015.07.673

Sleiman, M., Logue, J. M., Montesinos, V. N., Russell, M. L., Litter, M. I., Gundel, L. A., & Destaillats, H. (2016). Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. *Environmental Science & Technology*, *50*(17), 9644–9651. https://doi.org/10.1021/acs.est.6b01741

Smith, J. K., Liss, M., Erchull, M. J., Kelly, C. M., Adragna, K., & Baines, K. (2018). The Relationship Between Sexualized Appearance and Perceptions of Women's Competence and Electability. *Sex Roles*, *79*(11), 671–682. https://doi.org/10.1007/s11199-018-0898-4

Sokolov, E. N. (1990). The orienting response, and future directions of its development. *The Pavlovian Journal of Biological Science*, *25*(3), 142–150. https://doi.org/10.1007/BF02974268

Spindle, T. R., Talih, S., Hiler, M. M., Karaoghlanian, N., Halquist, M. S., Breland, A. B., Shihadeh, A., & Eissenberg, T. (2018). Effects of electronic cigarette liquid solvents propylene glycol and vegetable glycerin on user nicotine delivery, heart rate, subjective effects, and puff topography. *Drug and Alcohol Dependence*, *188*, 193–199. https://doi.org/10.1016/j.drugalcdep.2018.03.042

Starcke, K., Antons, S., Trotzke, P., & Brand, M. (2018). Cue-reactivity in behavioral addictions: A meta-analysis and methodological considerations. *Journal of Behavioral Addictions*, *7*(2), 227–238. https://doi.org/10.1556/2006.7.2018.39

Talmi, D., Seymour, B., Dayan, P., & Dolan, R. J. (2008). Human Pavlovian–Instrumental Transfer. *Journal of Neuroscience*, *28*(2), 360–368. https://doi.org/10.1523/JNEUROSCI.4028-07.2008

Tamburin, S., Dal Lago, D., Armani, F., Turatti, M., Saccà, R., Campagnari, S., & Chiamulera, C. (2021). Smoking-related cue reactivity in a virtual reality setting: Association between craving and EEG measures. *Psychopharmacology*, *238*(5), 1363–1371. https://doi.org/10.1007/s00213-020-05733-3

Tiffany, S. (1995). Potential functions of classical conditioning in drug addiction. In *Cue Exposure: Theory and Practice* (pp. 47–71).

Tomie, A., & Morrow, J. (2018). Sign-Tracking and Drug Addiction. *Maize Books*. https://doi.org/10.3998/mpub.10215070

Tunstall, B. J., & Kearns, D. N. (2015). Sign-tracking predicts increased choice of cocaine over food in rats. *Behavioural Brain Research*, *281*, 222–228. https://doi.org/10.1016/j.bbr.2014.12.034

Vafaie, N., & Kober, H. (2022). Association of Drug Cues and Craving With Drug Use and Relapse: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *79*(7), 641–650.

van Timmeren, T., Quail, S. L., Balleine, B. W., Geurts, D. E. M., Goudriaan, A. E., & van Holst, R. J. (2020). Intact corticostriatal control of goal-directed action in Alcohol Use Disorder: A Pavlovian-to-instrumental transfer and outcome-devaluation study. *Scientific Reports*, *10*(1), Article 1. https://doi.org/10.1038/s41598-020-61892-5

Vandaele, Y., & Janak, P. H. (2018). Defining the place of habit in substance use disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *87*(Pt A), 22–32. https://doi.org/10.1016/j.pnpbp.2017.06.029

Villarroel, M. A. (2020). *Electronic Cigarette Use Among U.S. Adults, 2018*. *365*, 8.

Voos, N., Goniewicz, M. L., & Eissenberg, T. (2019). What is the nicotine delivery profile of electronic cigarettes? *Expert Opinion on Drug Delivery*, *16*(11), 1193–1203. https://doi.org/10.1080/17425247.2019.1665647

Wagener, T. L., Floyd, E. L., Stepanov, I., Driskill, L. M., Frank, S. G., Meier, E., Leavens, E. L., Tackett, A. P., Molina, N., & Queimado, L. (2017). Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tobacco Control*, *26*(e1), e23–e28. https://doi.org/10.1136/tobaccocontrol-2016-053041

White, W., & Kurtz, E. (2005). The Varieties of Recovery Experience: A Primer for Addiction Treatment Professionals and Recovery Advocates. *International Journal of Self Help and Self Care*, *3*(1–2), 21–61. https://doi.org/10.2190/911R-MTQ5-VJ1H-75CU

Williams, M., Villarreal, A., Bozhilov, K., Lin, S., & Talbot, P. (2013). Metal and Silicate Particles Including Nanoparticles Are Present in Electronic Cigarette Cartomizer Fluid and Aerosol. *PLoS ONE*, *8*(3), e57987. https://doi.org/10.1371/journal.pone.0057987

Wollscheid, K. A., & Kremzner, M. E. (2009). Electronic cigarettes: Safety concerns and regulatory issues. *American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists*, *66*(19), 1740–1742. https://doi.org/10.2146/ajhp090127

Woodman, G. F. (2010). A Brief Introduction to the Use of Event-Related Potentials (ERPs) in Studies of Perception and Attention. *Attention, Perception & Psychophysics*, *72*(8), 10.3758/APP.72.8.2031. https://doi.org/10.3758/APP.72.8.2031

Wyvell, C. L., & Berridge, K. C. (2000). Intra-Accumbens Amphetamine Increases the Conditioned Incentive Salience of Sucrose Reward: Enhancement of Reward "Wanting" without Enhanced "Liking" or Response Reinforcement. *The Journal of Neuroscience*, *20*(21), 8122–8130. https://doi.org/10.1523/JNEUROSCI.20-21-08122.2000

Yager, L. M., & Robinson, T. E. (2015). Individual variation in the motivational properties of a nicotine cue: Sign-trackers vs. goal-trackers. *Psychopharmacology*, *232*(17), 3149–3160. https://doi.org/10.1007/s00213-015-3962-6

Zhao, Q., Li, H., Hu, B., Li, Y., Gillebert, C. R., Mantini, D., & Liu, Q. (2017). Neural Correlates of Drug-Related Attentional Bias in Heroin Dependence. *Frontiers in Human Neuroscience*, *11*, 646. https://doi.org/10.3389/fnhum.2017.00646

Zorjan, S., Gremsl, A., & Schienle, A. (2021). Changing the visualization of food to reduce food cue reactivity: An event-related potential study. *Biological Psychology*, *164*, 108173. https://doi.org/10.1016/j.biopsycho.2021.108173

Zuo, Y., Mukhin, A. G., Berg, H., Morgan, J. D., Mintz, A., Rose, J. E., & Solingapuram Sai, K. K. (2022). Comparison of brain nicotine uptake from electronic cigarettes and combustible cigarettes. *Neuropsychopharmacology*, *47*(11), Article 11. https://doi.org/10.1038/s41386-022-01410-5

APPENDICES

Appendix A

A delay discounting task, a cross-commodity multiple choice procedure, and a single-commodity purchase task is assessed in Dr. Blank's lab as a part of battery of tests not analyzed for this project. Participants complete one of two versions (puffs and minutes) of these tasks at this time, and the other version is completed later in the session.

Appendix B

Screening Questions

1. What is your age in years? _____ years
2. Do you currently have any intracranial/other metal implants?
   ○ Yes   ○ No
3. Are you taking any prescription medications?
   ○ Yes   ○ No
4. Do you have any chronic health concerns or problems?
   ○ Yes   ○ No
5. Do you have any diagnosed psychiatric conditions like depression, anxiety, schizophrenia, or bipolar disorder?
   ○ Yes   ○ No
6. Have you ever tried a cigarette, even one or two puffs?
   ○ Yes   ○ No
7. Do you currently smoke cigarettes?
   ○ Yes   ○ No
8. Approximately how many cigarettes have you smoked in your lifetime? ____
9. Approximately how many cigarettes have you smoked in the past year? ____
10. Approximately how many cigarettes have you smoked in the past month? ____
11. Have you used an ECIG/vape in the past 30 days?
    ○ Yes   ○ No
12. For how many months have you used an ECIG/vape? ____
13. On average, over the past 3 months, how many days per week did you use an ECIG/vape? ____
    Does the ECIG/vape that you use most often contain nicotine?
    ○ Yes   ○ No
14. What nicotine concentration of liquid do you use most often? (please specify whether it is in % or mg/ml) _____
15. What brand and model of ECIG/vape do you use most often? ____
16. What flavor ECIG/vape liquid do you use most frequently? ____
    How many times per day do you usually use your electronic cigarette? (assume that one time consists of around 15 puffs or lasts around 10 minutes)
    ○ 0-4 ○ 5-9   ○ 10-14   ○ 15-19   ○ 20-29   ○ 30+
17. How soon after you wake up do you first use your electronic cigarette?
    ○ 0-5 min ○ 6-15 min   ○ 16-30 min   ○ 31-60 min ○ 61-120 min ○ 121+ min
18. Do you sometimes awaken at night to use your electronic cigarette?
    ○ Yes   ○ No
19. How many nights per week do you typically awaken to use your electronic cigarette?
    ○ 0-1 night ○ 2-3 nights   ○ 4+ nights
20. Do you use an electronic cigarette now because it is really hard to quit?
    ○ Yes   ○ No
21. Do you ever have strong cravings to use an electronic cigarette?
    ○ Yes   ○ No

22. Over the past week, how strong have the urges to use an electronic cigarette been?
    ○ None/slight ○ Moderate/strong ○ Very/extremely strong
23. Is it hard to keep from using an electronic cigarette in places where you're not supposed to?
    ○ Yes ○ No
24. Did you feel more irritable because you couldn't use an electronic cigarette?
    ○ Yes ○ No
25. Did you feel nervous, restless, or anxious because you couldn't use an electronic cigarette?
    ○ Yes ○ No
26. I find myself reaching for my e-cigarette without thinking about it
    ○ Never ○ Rarely ○ Sometimes ○ Often ○ Almost always
27. I vape more before going into a situation where vaping is not allowed
    ○ Never ○ Rarely ○ Sometimes ○ Often ○ Almost always
28. When I haven't been able to vape for a few hours, the craving gets intolerable
    ○ Never ○ Rarely ○ Sometimes ○ Often ○ Almost always
29. I drop everything to go out and get e-cigarettes or e-juice
    ○ Never ○ Rarely ○ Sometimes ○ Often ○ Almost always
30. Do you currently use any other nicotine or tobacco products?
    ○ Yes ○ No
31. Select all products that you have used in the past 30 days: Cigars, cigarillos, or small cigars, hookah or waterpipe, smokeless tobacco (snus, dip, chew), nicotine gum, patch, lozenge, or inhaler, cigarettes, other
32. Have you used alcohol in the past month?
    ○ Yes ○ No
33. How many days out of the last 30 have you used alcohol? _____
34. Have you ever been treated for alcohol abuse or dependence?
    ○ Yes ○ No
35. Have you used marijuana in the past month?
    ○ Yes ○ No
36. How many days out of the last 30 have you used marijuana? _____
37. Have you ever been treated for marijuana abuse or dependence?
    ○ Yes ○ No
38. Have you used any other drugs in the past month?
    ○ Yes ○ No
39. How many days out of the last 30 have you used other drugs? _____

Appendix C

Informed Consent – Dr. Blank

Introduction

You have been asked to participate in this research study, which has been explained to you by an authorized member of the research team. This study is being conducted by Melissa Blank, PhD, in the Department of Psychology at West Virginia University, along with Ashley Douglas, M.S., Margaret Childers, B.S., Andrea Milstred, M.S, Polina Krom, B.A., and Mariya Cherkasova, PhD. Funding for this research is provided by the 2020 WVU Behavioral and Biomedical Sciences Stevenson Scholarship (T32 GM132494).

Purpose

The purpose of this study is to evaluate how seeing images of electronic cigarettes (ECIGs) and people using ECIGs might impact choice behavior. Additionally, we will examine your physiological and subjective, and brain responses to viewing the images. A total of approximately 50 subjects are expected to participate in this study.

Description of Procedures

To participate in this study, you must abstain from ECIG use for 8-12 hours prior to each session. If you agree to participate in the study, you will first provide saliva and breath samples to verify nicotine use and 8-12 hour ECIG abstinence. Urine samples will be provided by females to test for pregnancy. Pregnant females will not be eligible to participate in the study. If the screening procedures show you are eligible to participate, you will be enrolled in the study, which consists of two laboratory visits. Each of these two visits will be approximately 2 hours long, for a total time commitment of 4 hours. Each of the two study visits will begin with connection to heart rate and blood pressure monitors. After that you will also be capped with an elastic electrode cap and an eye electrode which will be placed under your eye with a soft adhesive sticker. Then you will be connected to an encephalography machine that will record your brainwaves. To ensure the correct conductance of each electrode, saline gel will be used in each of the 32 channels. Next, you will wait in a study room for 30 minutes. During this 30-minute period, you will complete questionnaires on tobacco use and can use the remaining time to do homework or read. Your phone will need to be stored away during this time. You do not need to answer every question on the questionnaires. After the full 30 minutes elapses, you will complete more questionnaires. During one of the two study visits, you will then watch a 5-minute picture slideshow of ECIG products and people using ECIGs. Then, you will be asked complete questionnaires again. After about 20 minutes, you will see the picture slideshow again and complete another questionnaire. The other session will be the similar, but you will watch a 5-minute picture slideshow of water and people drinking water. At the end of the first session, you will be compensated for that session and the next session will be scheduled. After the second session, you will be compensated for that session.

Risks and Discomforts

Tobacco use may involve risk to the unborn child. For this reason, women who are pregnant will not be enrolled in this study. If you are a woman who could become pregnant, you will not be allowed to participate in this study until you have had a urine pregnancy test and the test has indicated that you are not pregnant. In addition, there is always the risk of uncommon or previously unknown side effect(s) or event. If you find any data collection procedures unacceptable, you may stop your participation at any time. There are no risks of physical injury associated with EEG. However, you may experience mild discomfort associated with wearing the EEG cap and staying still during the EEG recordings. Following EEG, there will be gel in your hair, which you may find inconvenient. After the experiment, you will be given an opportunity to either wipe the gel off with a towel or wash your hair. You may also experience some mild itching at the locations where the EEG sensors were attached.

Alternatives and Benefits

This study provides no therapeutic benefits. You do not have to participate in this study. You may or may not directly benefit from participating in this research. The knowledge gained from this study may eventually benefit others.

Financial Considerations

You will be compensated $70 for each study session: $50 for the behavioral part of the study plus $20 for EEG. Thus, you can earn up to $140 for participating in this study. If you withdraw your participation before the requirements are met, you will not be paid for requirements that you did not complete. If you decide to opt-out of the EEG procedure but complete the behavioral part of the study, you will be compensated for the behavioral part only. For information regarding the method of payment, contact the Principal Investigator. You may be asked to provide your Social Security Number and verification of U.S. Citizenship or Permanent Resident Status to receive payment. Your information may be provided to the appropriate parties for billing and/or payment purposes. Please be advised that any compensation received for participation in a research study, including a gift card, is considered taxable income and must be reported to the Internal Revenue Service (IRS). If you are a WVU employee or a WVU student-employee, you are required to report the total amount of compensation received for your participation in a research study to the WVU Tax Services Office upon receipt of payment. Your data, health information, research results, specimens, or any and all other information related to this research study used in this research study may contribute to a new discovery or treatment. In some instances, your data, your health information, your research results, your specimens, these discoveries or treatments, or any other information related to this research study, even if identifiers are removed, may be of commercial value and may be sold, patented, or licensed by the investigators and West Virginia University for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money or commercial profit that the investigators, West Virginia University, or their agents may realize.

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or

federal regulatory authorities, including the Food and Drug Administration (FDA), without your additional consent. In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases, mandatory reporting of information about behavior that is imminently dangerous to you or to others, such as suicide, child abuse, etc. All data will be kept locked up and will be destroyed as soon as possible after the research is finished. In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent.

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time. If you choose to withdraw your participation from the study, the data collected on you up until that time remains a part of the study database and may not be removed. No additional information will be added to the study database after your withdrawal. If you are a student at WVU, refusal to participate or withdraw will not affect your class standing or grades and will involve no penalty to you. If you are an employee, refusal to participate or withdraw will not affect your employee status at West Virginia University. Refusal to participate or withdraw will not affect your future care or status at West Virginia University. In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation. Individual research results and/or incidental findings will not be disclosed to subjects.

Contact Persons

If you have any questions, concerns, or complaints about this research, you can contact Dr. Melissa Blank at (304) 293-8341 or melissa.blank@mail.wvu.edu. You can also contact Ashley Douglas at aed0034@mix.wvu.edu, Margaret Childers at mgc0002@mix.wvu.edu, Andrea Milstred at arm0042@mix.wvu.edu, Polina Krom at pk00013@mix.wvu.edu or Dr. Mariya Cherkasova at mariya.cherkasova@mail.wvu.edu. If you are hurt from being in this research, you should contact Dr. Blank at (304) 293-8341. If injury occurs outside of business hours and is related to your participation in this research, please contact Dr. Blank at (304) 906-8109. For information regarding your rights as a participant in research or to talk about the research, contact the WVU Office of Human Research Protection (OHRP) at (304) 293-7073 or by email at IRB@mail.wvu.edu.

I willingly agree to participate in this study.

○ Yes   ○ No

Informed Consent – Dr. Cherkasova

Introduction

You have been asked to participate in this research study, which has been summarized above. This study is being conducted by Mariya V. Cherkasova, PhD in the Departments of Psychology and Neuroscience at West Virginia University, along with the PhD student Polina Krom and the research assistants Jamie J. Dotson, Gillian R. Kaier, Molly L.M. Summers.

Purpose

Learning about what stimuli in the environment signal or predict rewards is important for our daily functioning. This type of learning allows us to be successful in pursuing and obtaining rewards. Mechanisms that govern this type of learning have been very extensively studied in animals but less so in humans. Disruptions in this type of learning may lead to maladaptive behaviors such as addictive disorders. Hence, it is important to better understand these learning mechanisms in humans and establish solid links with the wealth of animal research on the topic. The purpose of the study is to increase our understanding of these learning mechanisms in humans. A total of 200 participants, are expected to take part in this study.

Description of Procedures

Should you agree to participate, you will complete the study in the laboratory of Dr. Mariya V. Cherkasova, Life Sciences Building, 2127. You will then complete a series of 3 computer tasks in which you will perform mouse clicks and key presses to earn money bonuses. Your eye movements will be monitored while you perform the second task using a Tobii Pro infrared eye tracker. The eye tracking is non-invasive and is not harmful to your eyes. The eye tracker sends a near infrared light towards your eyes and uses cameras to record the reflections. Each task will last approximately 6 minutes, and the total duration of the study will be around 20 minutes. If you have corrected vision, you will be asked to wear contacts to make it easier to calibrate the eye tracker. This is not a requirement: the eye tracker will work with glasses (unless they are made of a reflective type of glass) but may be more challenging to operate.

Risks and Discomforts

This is an in-person laboratory study. You will be in a building on WVU campus and in the lab together with the experimenter. This entails the risk of contracting COVID-19. The following precautions will be taken to minimize that risk. Both you and the experimenter will wear masks at all times. The experimenter will remain at the distance of ≥ 6 ft from you at all times except for brief periods of assistance with eye tracker set-up (of < 1 minute each, e.g. when it will be necessary to measure your distance from the screen, adjust your chinrest). During the testing session, the experimenter will be in an adjacent room (not in your testing cubicle) observing the session through a one-way mirror and communicating with you, when necessary via a small window next to it. All surfaces in the lab will be disinfected prior to your arrival. In addition, there is always the risk of uncommon or previously unknown side effect(s) or event.

Alternatives and Benefits

You do not have to participate in this study. You may or may not directly benefit from participating in this research. The knowledge gained from this study may eventually benefit others.

Financial Considerations

You will be compensated $5 for the 20 minutes of your time completing the experiment completing the experiment. In addition, you are likely to earn a bonus on the tasks, which could be up to $15, although for most people it will be less. If you do not complete the study, you will be compensated $0 You will receive your study compensation via an Amazon gift card. Please be advised that any compensation received for participation in a research study, including a gift card, is considered taxable income and must be reported to the Internal Revenue Service (IRS).

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or federal regulatory authorities without your additional consent. In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases, mandatory reporting of information about behavior that is imminently dangerous to you or to others, such as suicide, child abuse, etc. In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent. After the study's completion, your de-identified data (without any identifiable private information) may be used for future research studies (such as secondary analyses) without additional informed consent. You de-identified data may be also be placed in an online repository such as the Open Science Network and other researchers may be able to access these data for further analyses.

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time. If you choose to withdraw your participation from the study, the data collected on you up until that time remains a part of the study database and may not be removed. No additional information will be added to the study database after your withdrawal. Refusal to participate or withdraw will not affect your future care or status. In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation. The investigator is also free to terminate your participation if you do not complete the study's procedures as instructed.

Contact Persons

If you have any questions, concerns, or complaints about this research, you can contact Mariya V. Cherkasova at mariya.cherkasova@mail.wvu.edu. If you are hurt from being in this research, you should contact Mariya V. Cherkasova at mariya.cherkasova@mail.wvu.edu. If injury occurs outside of business hours and is related to your participation in this research, please contact Mariya V. Cherkasova at phone 304-293-4223. For information regarding your rights as a

participant in research or to talk about the research, contact the WVU Office of Human Research Protection (OHRP) at (304) 293-7073 or by email at IRB@mail.wvu.edu.

I willingly agree to participate in this study.

○ Yes   ○ No