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Neuroaffective reactivity profiles are associated with vulnerability to e-cigarette use

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Abstract

Background—We tested whether neuroaffective responses to motivationally salient stimuli are associated with vulnerability to cue-induced e-cigarette use in e-cigarette naïve adults who smoke daily. We hypothesized that individuals with stronger neuroaffective responses to nicotine-related cues than to pleasant stimuli (the C>P reactivity profile) would be more vulnerable to cue-induced nicotine self-administration than individuals with stronger neuroaffective responses to pleasant stimuli than to nicotine-related cues (the P>C reactivity profile).

Methods—We used event-related potentials (ERPs, a direct measure of cortical activity) to measure neuroaffective reactivity to pleasant, unpleasant, neutral, and nicotine-related cues indicating the opportunity to use an e-cigarette in 36 participants. For each picture category, we computed the amplitude of the late positive potential (LPP), a robust index of motivational salience. To identify each individual's neuroaffective reactivity profile we applied *k*-means cluster analysis on the LPP responses. We compared the e-cigarette use frequency across profiles using quantile regression for counts.

Results—K-means cluster analysis assigned 18 participants to the C>P profile and 18 participants to the P>C profile. Individuals with the C>P neuroaffective profile used the e-cigarette significantly more often than those with the P>C profile. Significant differences in the number of puffs persisted across different quantiles.

Conclusions—These results support the hypothesis that individual differences in the tendency to attribute motivational salience to drug-related cues underlie vulnerability to cue-induced drug

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Contributors FV was responsible for study concept and design. GK, DP, and FV conducted the data analyses and interpreted the results. FV drafted the manuscript. GK, DP, and FV revised the manuscript, critically reviewed its contents, and approved the final version for publication.

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self-administration. Targeting the neuroaffective profiles that we identified with tailored treatments could improve clinical outcomes.

Keywords

Drug-related cues; Nicotine self-administration; Event-Related Potentials; Late Positive Potential; Motivational Salience; Quantile Regression

1. Introduction

Neurobiological models of addiction posit that individuals with substance use disorders are prone to compulsive drug use because they attribute high levels of incentive salience to drug-related cues (i.e., stimuli that are associated with a drug and its effects) (Robinson et al., 2013; Volkow et al., 2019). Incentive salience refers to the motivational properties that make rewards (e.g., water, food, sex, or drugs) and reward-related cues attractive (Berridge, 2012). Results from animal models show that individuals that attribute high incentive salience to reward-related cues are more vulnerable to cue-induced compulsive reward seeking behaviors, including drug self-administration (Flagel et al., 2009). We proposed that humans also vary in their tendency to attribute incentive salience to reward-related cues and that those attributing high levels of incentive salience to drug-related cues would be more prone to cue-induced drug seeking (Versace et al., 2017). Identifying a biomarker of the tendency to attribute high incentive salience to drug-related cues could have significant clinical implications because it will give clinicians a new treatment target and could foster the development of personalized treatments aimed at reducing vulnerability to cue-induced compulsive substance use.

The amplitude of the late positive potential (LPP) has been proposed as an index of incentive salience attributed to drug-related and other motivationally salient stimuli (Webber et al., 2022). The LPP is a robust component of the event-related potentials (ERPs, a direct measure of cortical activity) that peaks over central scalp sites approximately 600 ms after the presentation of a stimulus and its amplitude increases as a function of a stimulus' motivational relevance, irrespective of its hedonic value (Lang and Bradley, 2010; Minnix et al., 2013; Schupp et al., 2000; Weinberg and Hajcak, 2010). Even though drug-related cues tend to evoke larger LPP responses in individuals with substance use disorders than in controls (Littel et al., 2012; Robinson et al., 2015), there are large individual differences in the neurophysiological responses evoked by drug-related cues. Applying multivariate classification algorithms to the LPP responses evoked by drug-related and non-drug-related motivationally relevant stimuli, we identified two replicable neuroaffective reactivity profiles: one characterized by larger LPPs to drug-related cues than to pleasant stimuli (C>P), the other by larger LPPs to pleasant stimuli than drug-related cues (P>C) (Kypriotakis et al., 2020; Versace et al., 2023, 2017; Webber et al., 2021). We also showed that these two neuroaffective reactivity profiles are associated with different drug-related behaviors: among people with cocaine use disorder, individuals characterized by the C>P profile have a stronger attentional bias towards drug-related cues than individuals characterized by the P>C profiles (Webber et al., 2021), and among adults who smoke, those

characterized by the C>P profile are more likely to resume smoking than those with the P>C profile (Frank et al., 2020; Versace et al., 2012).

While these findings support the hypothesis that individual differences in the tendency to attribute incentive salience to drug-related cues affect drug-related behaviors, they do not directly link the two neuroaffective profiles to differences in drug self-administration. Accordingly, we designed this study to test the hypothesis that individuals characterized by the C>P profile are more prone to cue-induced nicotine self-administration than those characterized by the P>C profile.

To test our hypothesis, we developed a new neurobehavioral assessment: the "cued nicotine availability task". During the cued nicotine availability task, we recorded ERPs while e-cigarette–naïve adults who smoked cigarettes looked at non-drug-related motivationally relevant images and at images of people using e-cigarettes. These images signaled that an electronic nicotine delivery system (ENDS) was available for use. Hence, unlike previous passive picture viewing tasks, the cued nicotine availability task allowed us to measure both the motivational relevance of drug-related cues (relative to non-drug-related motivationally relevant stimuli), and actual nicotine self-administration. We hypothesized that a) applying k-means cluster analysis to the LPP responses recorded during the cued nicotine delivery task would yield the C>P and P>C profiles and b) individuals characterized by the C>P profile would use the ENDS to self-administer nicotine significantly more often than those characterized by the P>C profile.

2. Methods

2.1 Participants

We enrolled adults who reported daily cigarette smoking and no prior use of e-cigarettes. Participants were older than 18 and did not report psychiatric disorders. We reimbursed participants with a $50 gift card at the end of the session. The original recruitment plan included 60 participants. However, owing to the COVID-19 pandemic, our laboratory shut down in March 2020. After one year of inactivity, the protocol associated with this study was closed and only 36 participants were available for the analyses. Table 1 shows the characteristics of the sample.

2.2 Procedures

The University of Texas MD Anderson Cancer Center Institutional Review Board approved all procedures. We asked participants to continue smoking at their regular rate but to refrain from using other drugs (including marijuana) in the 24 hours and caffeine in the 2 hours preceding the visit. At the visit, we explained the procedures and collected informed consent. Then, participants completed a battery of self-report questionnaires (see Supplementary Materials for details) about nicotine dependence (Fagerström Test for Cigarette Dependence, FTCD; Fagerstrom, 2012) smoking urges (Questionnaire of Smoking Urges, QSU-brief; Cox et al., 2001), impulsivity (Barratt Impulsiveness Scale, BIS; Patton et al., 1995), hedonic capacity (Snaith-Hamilton Pleasure Scale, SHAPS; Snaith et al., 1995), and mood (Positive and Negative Affect Scale, PANAS; Watson et al., 1988). We

used the responses to these questionnaires to test for differences between groups. After the questionnaire data collection, we prepared the participant for the EEG session and completed the cued nicotine availability task. At the end of the session, participants were debriefed, encouraged to quit smoking, and compensated.

2.3 Materials

2.3.1 Cued nicotine self-administration task—The task included 300 images divided into 6 equivalent blocks. The images (selected from the International Affective Picture System (Lang et al., 2008) and other picture collections; see Supplementary Table 1 for the IAPS picture numbers) belonged to 8 categories: pleasant high salience (PH, erotic scenes of naked couples), pleasant low salience (PL, romantic scenes of couples hugging or kissing), food (FD, sweet palatable foods), neutral (NE, ordinary objects and people engaged in mundane activities), unpleasant objects (UO, accidents and pollution), unpleasant low salience (UL, sadness and violence), unpleasant high salience (UH, mutilations), and ENDSs (EC, images of people vaping or images of ENDSs). Figure 1 outlines the trial structure. The images (except EC) were presented for 2 seconds, followed by a 1.5- to 3-second variable inter-trial interval. EC images were presented for 1 second, and then a banner appeared at the top of the screen to indicate that it was possible to take 1 puff from the ENDS (Model: THERION-BF-DNA75C, loaded with tobacco-flavored e-liquid with 1.2% nicotine). The ENDS rested inside a receptacle within arm's reach of the participant (See Figure 1 inset and Supplementary Figure S1). A photocell in the receptacle detected when the participant picked up the ENDS and paused the task until the ENDS was placed back in the receptacle. If the participant decided not to use the ENDS, they pressed a button to advance to the next trial. Each block included 10 vaping opportunities. To familiarize participants with the ENDS, we ran a practice block of 10 trials with 2 vaping opportunities. We asked participants to take 1 puff at both practice vaping opportunities.

2.3.2 EEG data acquisition—During the task, we collected EEG using a 129-channel Geodesic Sensor Net, amplified with a Geodesic EEG System 400 amplifier. The sampling rate was 250 Hz, and all electrodes were referenced to Cz.

2.3.3 EEG data reduction and LPP amplitude calculation—Offline EEG data reduction followed a standard pipeline (Versace et al., 2019, 2012). It included filtering (0.1–30 Hz), EEG visual inspection and interpolation of broken channel (using spherical splines), average reference calculation, and eye movements and blink correction (as implemented in BESA 5.3). Then, data were imported into Brain Vision Analyzer 2 and divided into 1000-ms segments starting 100 ms before picture onset. After baseline correction, channels contaminated by artifacts were identified using pre-defined criteria of relative and absolute voltage amplitude. Channels contaminated by artifacts in more than 40% of the segments were interpolated using spherical splines. Segments with more than 10% of contaminated channels were discarded, and average amplitudes for each picture category were computed at each scalp site. For each participant, we calculated the mean LPP amplitude of each category as the mean voltage recorded between 400 and 800 ms after picture onset across 10 central and parietal sensors (EGI HydroCel Geodesic Sensor Net sensors: 7, 31, 37, 54, 55, 79, 80, 87, 106, 129; see Figure 1 inset). The Supplementary Results section reports the

number of channels interpolated per subject, the number of trials included in each condition, and the standardized measurement error for each condition at the end of the data reduction process (Luck et al., 2021).

2.4 Statistical Analyses

2.4.1 Event-related potentials—As a manipulation check, we analyzed the LPP responses to the 8 stimulus categories (EC, PH, PL, FD, NE, UO, UL, UH) in a repeated measures ANOVA. We expected to replicate previous findings showing that both pleasant and unpleasant images increase the LPP amplitude as a function of their motivational relevance and that nicotine cues prompt larger LPP responses than neutral stimuli.

2.4.1.1 Participant classification: To identify participants attributing high or low salience to cues, we applied *k*-means cluster analysis to the LPP responses evoked by the 8 image categories. *K*-means cluster analysis is a multivariate classification procedure that, by minimizing within-group variability and maximizing between-group variability, groups individuals according to common features. This is the same procedure used in our previous studies, and, based on those findings (Versace et al., 2019, 2012; Webber et al., 2021), we hypothesized that the 2 groups would show the following neuroaffective reactivity profiles: one group would show high reactivity to EC relative to pleasant stimuli (C>P); the other, low reactivity to EC relative to pleasant stimuli (P>C). We also expected that, irrespective of reactivity to EC, both groups would show larger LPP responses as a function of motivational relevance for both pleasant and unpleasant stimuli.

2.4.1.2 Cue-induced nicotine self-administration: We tested the relationship between group membership and number of puffs using quantile regression (QR, Koenker, 2005). Conceptually, QR is an extension of linear regression, but instead of estimating the mean of the dependent variable, it estimates the median. Hence, QR is most useful in the presence of outliers and when assumptions of the linear model are not met (including assumptions of homoscedasticity, linearity and normality). Furthermore, in addition to estimating the median (i.e., the 0.5 quantile), QR can be used to estimate any quantile (e.g., 0.25 or 0.75 quantile) of the outcome variable's distribution. Hence, by deriving regression estimates at multiple quantiles, QR provides a more comprehensive and insightful analysis than linear regression. Because our dependent variable (the number of puffs) is not continuous, we used QR for counts (Machado and Santos Silva, 2005), and for estimation we used 5,000 bootstrap samples to calculate 95% confidence intervals (CIs) around the 0.25, 0.5, and 0.75 quantile.

3. Results

3.1 Late Positive Potential

Figure 1 shows the grand-averaged ERP waveforms for neutral, pleasant, unpleasant, and nicotine-related images and the mean LPP amplitude for each category. As expected, pleasant, unpleasant, and nicotine-related stimuli prompted larger LPPs than neutral images (Bonferroni-corrected P values <0.005), and the amplitude of the LPP increased as a function of motivational relevance for both pleasant and unpleasant stimuli (polynomial

contrast for the quadratic trend including PH, PL, FD, NE, UO, UL, UH; $F(1,35)=123.3$; $p<0.001$).

K-means cluster analysis assigned 18 subjects to each group. As hypothesized (see Figure 2), both groups had larger LPP responses to motivationally salient images than to neutral images (the quadratic trend was significant [$p<0.001$] in both groups), but one group showed the C>P profile (i.e., larger LPP responses to EC than to pleasant images), while the other showed the P>C profile. The 2 groups did not differ according to demographic characteristics, nicotine dependence, mood, or impulsivity (see Table 1).

3.2 Cue-induced nicotine self-administration

The results of the QR analysis for counts are presented in Figure 2 and Table 2. Because the unstandardized coefficients are derived from a log-linear model and do not have an intuitive interpretation, we estimated marginal effects that have a direct interpretation. Marginal effects are the differences in the number of puffs between the groups derived from each quantile regression model. For all 3 estimated quantiles, the C>P group took a significantly higher number of puffs than the P>C group. Specifically, the differences in the estimated number of puffs were 5 (C>P = 9 vs. P>C = 4), 5 (C>P = 15 vs. P>C =10), and 8 (C>P = 35 vs. P>C = 27) puffs at the 25^{th}, 50^{th}, and 75^{th} percentiles, respectively.

4. Discussion

By applying cluster analysis to the neuroaffective responses evoked by drug-related and non-drug-related motivationally salient stimuli, among individuals who smoke cigarettes we identified those who attribute high salience to cues indicating nicotine availability (C>P), and those who do not attribute high salience to such cues (P>C). We showed that individuals characterized by the C>P neuroaffective profile are more likely to self-administer nicotine than those characterized by the P>C neuroaffective reactivity profile when given the opportunity to do so.

These results align with preclinical (Flagel et al., 2009) and clinical findings (Versace et al., 2014, 2012; Webber et al., 2021) indicating that individual differences in the tendency to attribute incentive salience to cues predicting rewards underlie vulnerability to the maladaptive cue-induced behaviors that characterize substance use disorders. The C>P profile could become a clinical target to match patient-to-treatment (Cinciripini et al., 2017; Frank et al., 2020) and to develop new personalized treatments for substance use disorders and other behavioral disorders characterized by cue-induced compulsive behaviors (Houston and Schlienz, 2018).

Notwithstanding their potential theoretical and clinical significance, these results should still be considered preliminary. The main limitation of this study is its small sample size: it has been shown that low statistical power reduces the likelihood that a nominally statistically significant finding reflects a true effect (Button et al., 2013) and the findings that we report should be replicated in a larger sample. Nevertheless, we think that the features of the cued nicotine availability task and the analytic approach that we chose allowed us to produce valid and reliable results that will likely replicate. First, because

the cued nicotine availability task includes several non-drug-related motivationally relevant conditions, it allowed us to evaluate the reliability of the results across multiple active control conditions. In line with the existing literature (Lang and Bradley, 2010; Weinberg and Hajcak, 2010), we showed that the amplitude of the LPP increases as a function of motivational salience for both pleasant and unpleasant images within both the C>P and the P>C group (Figure 3). Replicating in both groups the canonical affective modulation of the LPP for non-drug-related motivationally relevant stimuli indicates that the LPP modulation observed for drug-related cues is unlikely to be spurious. A second feature that, in our opinion, supports the claim that our findings are reliable stems from our decision to use k-means clustering to identify participants' neuroaffective profiles. K-means clustering is a data-driven multivariate classification procedure that groups individuals by minimizing the Euclidian distance of each participant to the centroid of the cluster (Pollard, 1981). While cluster analysis must yield two groups, the neuroaffective profiles of the groups identified by cluster analysis are not predetermined and are driven by the data. Yet, the profiles identified in this new sample replicate those that emerged in our previous studies (Versace et al., 2019, 2016, 2014, 2012; Webber et al., 2021), an outcome that supports our claim that the results reported are reliable, despite the small sample size. It is important to note that while the largest reactivity differences involve drug-related cues and pleasant stimuli (hence the labels that we assigned to the groups), reactivity to unpleasant and neutral stimuli somewhat contributes to the classification outcomes: the voltage differences between pleasant and drug-related cues do not predict outcomes as accurately as the results from multivariate clustering. Finally, using nicotine self-administration as the outcome measure, rather than self-reports, strengthens the validity of our conclusions. During most brain imaging studies that assess cue reactivity, participants do not have the option to self-administer nicotine, hence researchers often opt to investigate the relationship between neurophysiological responses evoked by drug-related cues and self-reported nicotine craving (Engelmann et al., 2012). While craving is considered a symptom with clinical significance (Hasin et al., 2013), empirical findings show that it is not consistently associated with smoking cessation outcomes (Wray et al., 2013). These inconsistencies suggest that self-reported craving may not be a reliable surrogate measure for validating neurophysiological markers aimed at predicting cue-induced drug use. By measuring drug self-administration rather than self-reported craving, the cued nicotine availability task allows to directly investigate the psychophysiological underpinnings of cue-induced drug use.

We encourage addiction neuroscientists to adapt the cued nicotine availability task to other drugs and other environments: following our recommendations of measuring reactivity to non-drug-related motivationally relevant stimuli and making rewards immediately available during the task (Versace et al., 2023) is likely to foster the discovery of new biomarkers and treatment targets for substance use disorders.

5. Conclusions

Our results show that neuroaffective responses to motivationally salient stimuli are associated with vulnerability to cue-induced nicotine self-administration: when individuals who smoke combustible cigarettes are given the opportunity to use an e-cigarette, those with stronger neuroaffective responses to nicotine-related cues than to pleasant stimuli

(C>P) used the device more often than those with stronger neuroaffective responses to pleasant stimuli than to nicotine-related cues (P>C). Determining the extent to which the neurobehavioral outcomes that we obtained using this laboratory task predict real-world vulnerability to cue-induced compulsive smoking following an attempt to quit, the next step in our research agenda, will contribute to the development and optimization of new targeted clinical interventions for substance use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Highlights

- We used ERPs to measure neuroaffective reactivity to emotional and drug-related cues
- Drug-related cues signaled the opportunity to puff from an e-cigarette
- We identified neuroaffective reactivity profiles associated with e-cigarette use
- Smokers reacting more to drug-related than pleasant cues vaped more
- Targeting this neuroaffective biomarker could foster personalized treatments

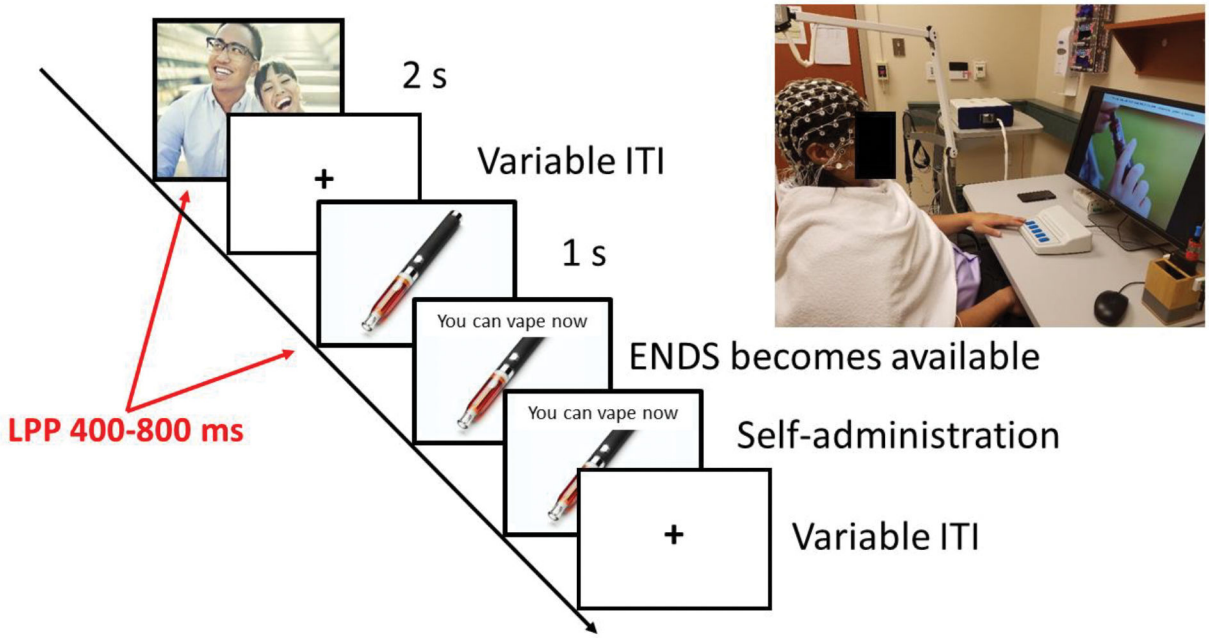

Figure 1. Schematic sequence of events during the cued nicotine availability task.

During the cued nicotine availability task, non-drug-related cues are presented for two seconds and are followed by a blank screen. Nicotine-related cues (images of people vaping or images of e-cigarettes) are presented for 1 second, then a banner appears on the top of the screen to let the participant know that the electronic nicotine delivery system (ENDS) is ready for use. The participant decides whether to take one puff from the ENDS or to push a button to move to the next trial (See inset and Supplementary Figure 1 for details about the nicotine self-administration apparatus). During the task, EEG is continuously recorded and the amplitude of the late positive potential (LPP) is computed offline for every picture category presented during the study. Supplementary Figure S1 details the elements of the apparatus depicted in the right panel.

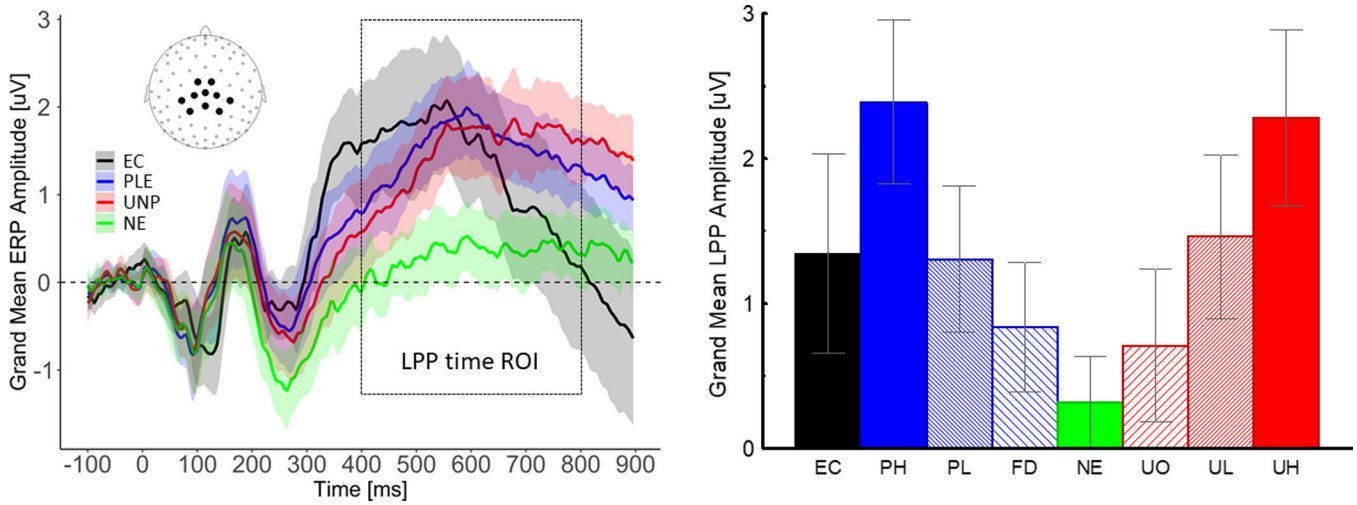

Figure 2.

Left: Motivationally salient images (including EC) prompted larger LPPs than neutral images. **Right**: The LPP amplitude increased as a function of motivational salience for both pleasant and unpleasant contents. **Note**: LPP=late positive potential, ROI=region of interest, EC=E-cigarettes, PLE=pleasant (PH, PL, FD averaged), UNP=unpleasant (UH, UL, UO averaged), NE=neutral, PH=pleasant high motivational salience (erotica), PL=pleasant low motivational salience (romantic), FD=food (appetizing sweet food), UO=unpleasant objects (accidents, pollution), UL=unpleasant low motivational salience (violence), UH=unpleasant high motivational salience (mutilations). The values are calculated averaging the voltage across the 10 sensors shown in the inset on the left panel. The shaded areas in the left panel and the error in the right panel represent ±95% confidence intervals around the means.

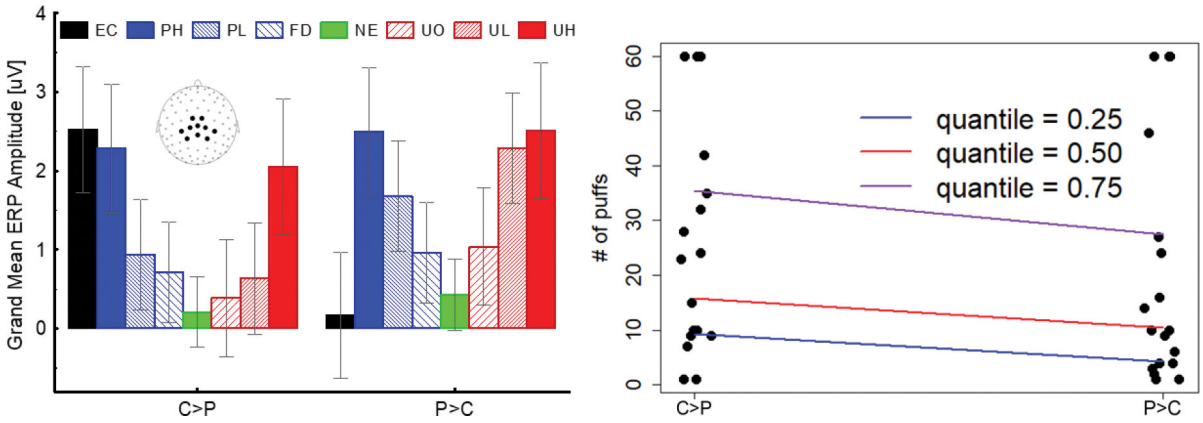

Figure 3.

Left: The cluster analysis identified two groups of individuals with the hypothesized characteristics: one group (C>P) had larger late positive potential (LPP) responses to EC than to pleasant images and the other (P>C) had larger LPP responses to pleasant than to EC images. **Right**: Individuals categorized as C>P took significantly more puffs from the electronic nicotine delivery system (ENDS) than individuals categorized as P>C. The between-groups difference in number of puffs was significant ($p<.05$) at every predicted quantile (.25, .50, and .75). **Note**: The error bars represent the ±95% confidence intervals around the means. EC=images of people vaping, PH=pleasant high motivational salience, PL=pleasant low motivational salience, FD=food, NE=neutral, UO=unpleasant objects, UL=unpleasant low motivational salience, UH= unpleasant high motivational salience. The LPP values are calculated averaging the voltage across the 10 sensors shown in the inset. LPP responses from each subject for EC, PLE, NE, and UNP contents are shown in Supplement Figure S4

Table 1.

Demographic characteristics

	All (N=36)	C>P (N=18)	P>C (N=18)
Mean age (SD)	46 (11)	42 (12)	49 (10)
Females	42%	39%	44%
Race			
White	17%	22%	11%
Black	83%	78%	89%
Questionnaire scores			
FTCD	4.7 (4.7)	5.2 (1.6)	4.2 (2.1)
QSU	47.1 (29.4)	53.2 (31.9)	50.1 (30.4)
$BIS_{attention}$	14.9 (3.2)	14.4 (3.4)	15.4 (3)
BIS_{motor}	22.2 (4.7)	21.4 (4.6)	23.1 (4.8)
$BIS_{nonplanning}$	24.5 (4.3)	23.9 (3.3)	25.1 (5.1)
$PANAS_{negative}$	17.6 (5.4)	17.7 (5.2)	17.6 (5.7)
$PANAS_{positive}$	34 (8.7)	33.9 (9.2)	34 (8.5)
SHAPS	9.9 (5.5)	10.6 (5.4)	9.2 (5.6)

NOTE: FTCD = Fagerström Test for Cigarette Dependence, QSU=Questionnaire for Smoking Urges, BIS = Barratt Impulsiveness Scale, PANAS=Positive and Negative Affect Scale, SHAPS=Snaith-Hamilton Pleasure Scale.

Table 2.

Unstandardized and marginal effects of group membership on the number of puffs.

Model	Effect	CI	p-value
Unstandardized Effects			
Quantile 0.25	−0.80	(−1.29, −0.31)	0.001
Quantile 0.50	−0.41	(−0.76, −0.07)	0.018
Quantile 0.75	−0.26	(−0.43, −0.09)	0.002
Marginal effects of differences between groups			
Quantile 0.25	−5.00	(−7.61, −2.39)	< 0.001
Quantile 0.50	−5.08	(−9.66, −0.49)	0.029
Quantile 0.75	−7.99	(−12.95, −3.03)	0.002