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A fMRI study on the impact of advertising for flavored e-cigarettes on susceptible college-age youth*

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Abstract

Background—E-cigarettes are sold in flavors such as "Skittles," "strawberrylicious," and "juicy fruit," and no restrictions are in place on marketing e-cigarettes to youth. Sweets/fruits depicted in e-cigarette advertisements may increase their appeal to youth and interfere with health warnings. This study tested a brain biomarker of product preference for sweet/fruit versus tobacco flavor e-cigarettes, and whether advertising for flavors interfered with warning labels.

Methods—Participants (*N*=26) were college-age youth who had tried an e-cigarette and were susceptible to future e-cigarette use. They viewed advertisements in fMRI for sweet/fruit and tobacco flavor e-cigarettes, menthol and regular cigarettes, and control images of fruits/sweets/mints with no tobacco product. Cue-reactivity was measured in the nucleus accumbens, a brain biomarker of product preference. Advertisements randomly contained warning labels, and recognition of health warnings was tested post-scan. Visual attention was measured using eye-tracking.

Results—There was a significant effect of e-cigarette condition (sweet/tobacco/control) on nucleus accumbens activity, that was not found for cigarette condition (menthol/regular/control). Nucleus accumbens activity was greater for sweet/fruit versus tobacco flavor e-cigarette advertisements and did not differ compared with control images of sweets and fruits. Greater nucleus accumbens activity was correlated with poorer memory for health warnings.

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Contributors

KAG, SSO and SK were responsible for the study concept and design; KAG acquired the data; KAG and RG were responsible for data analysis; KAG, SSO and SK interpreted the data; KAG drafted the manuscript; KAG, SSO and SK provided critical revision of the manuscript for important intellectual content; all authors critically reviewed content and approved final version for publication.

Author Disclosures

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Conflict of Interest

SO is a member of the American Society of Clinical Psychopharmacology Alcohol Clinical Trials Initiative supported by Alkermes, Amygdala, Arbor Pharma, Ethypharm, Indivior, Lundbeck, Otsuka; has received donated study medications from AstraZeneca, Pfizer; and has been a consultant/advisory member to Alkermes, Amygdala, Cerecor, Mitsubishi Tanabe, Opiant.

Conclusions—These and exploratory eye-tracking findings suggest that advertising for sweet/fruit flavors may increase positive associations with e-cigarettes and/or override negative associations with tobacco, and interfere with health warnings, suggesting that one way to reduce the appeal of e-cigarettes to youth and educate youth about e-cigarette health risks is to regulate advertising for flavors.

Keywords

Advertising; E-Cigarette; fMRI; Health Warning; Nucleus Accumbens; Tobacco Flavors

1. Introduction

Nearly 99% of smokers initiate by age 26 (U.S. Department of Health and Human Services, 2012), and those who do not start as a youth or young adults are unlikely ever to smoke (Mayhew et al., 2000). When tobacco use persists into adulthood, the risk of severe health consequences increases with duration of use (HHS, 2012). Youth are particularly susceptible to initiation and use of flavored tobacco products (Ambrose et al., 2015). Younger age predicts flavored tobacco product use (Rath et al., 2016), and use of flavored cigarettes was higher among smokers ages 17–19 than those over age 25 (Klein et al., 2008). Although cigarettes with characterizing flavors other than menthol are banned by the United States (U.S.) Food and Drug Administration (FDA), no such ban exists for e-cigarettes, sold in a variety of appealing flavors.

The tobacco industry has targeted young people by developing and marketing flavors (Carpenter et al., 2005) such as "cola," "apple" and "sweet flavor" cigarettes (Memo to Brown & Williamson, 1972). Youth have high rates of exposure to flavored tobacco advertising (Shibuya et al., 2003), and exposure to tobacco advertising has been causally related to youth smoking (Dube et al., 2013; Hanewinkel et al., 2011). Under the Family Smoking Prevention and Tobacco Control Act (2009), cigarettes with characterizing flavors other than menthol are banned, and restrictions were put in place on marketing tobacco products to youth. However, no such ban exists for e-cigarettes, currently marketed in such flavors as "cola," "green apple" and "bubblegum," which may be especially attractive to young people, including college-age youth, for whom e-cigarettes as an emerging product are novel. Nearly half of Connecticut youth surveyed reported flavors as their primary reason for having tried e-cigarettes (Kong et al., 2015), and most college-age youth in Texas (95%) and nationwide (71%) reported first using a flavored e-cigarette compared with 44% of older adults nationwide (Harrell et al., 2017). Flavors, therefore, appear to contribute to the rapid uptake of e-cigarettes seen in young people. From 2013–14, use of electronic nicotine delivery systems including e-cigarettes doubled among college-age youth (HHS, 2016), and mounting evidence suggests that use is occurring in youth who would not otherwise smoke (Barrington-Trimis et al., 2016). There is growing concern that advertising for flavors may make e-cigarettes more attractive to susceptible nonsmoking youth and increase initiation.

Young people additionally have insufficient knowledge about the health risks of tobacco products, and this promotes initiation (Sanders-Jackson et al., 2015b; HHS, 2012). Tobacco health warnings can effectively provide this information (MacKinnon and Fenaughty, 1993). Health warnings are required for cigarettes, and FDA has recently established a required warning for e-cigarettes, “WARNING: This product contains nicotine derived from tobacco. Nicotine is an addictive chemical” (FDA, 2016a). Beginning work suggests that e-cigarette health warnings can influence risk perceptions (Lee et al., 2017; Sanders-Jackson et al., 2015a). However, images of flavors on advertisements may interfere with health warning labels. Plain packaging has been found to increase visual attention to warning labels and recall of health information (Maynard et al., 2013; Munafo et al., 2011). No study has tested the impact of specific tobacco advertising content such as images of sweet/fruit flavors on the effective communication of health warnings.

Previous studies have used self-report to evaluate the effects of persuasive messaging such as advertising on behavior. Yet self-reported responses to persuasive messages predict only some variability in future behavior (Webb and Sheeran, 2006). Additional variability in behavior might be explained by implicit processes that are inaccessible to conscious awareness and conscious processes that are not captured by self-report (Falk et al., 2010). Importantly, advertising is a pervasive environmental cue that consumers attend to both consciously and non-consciously. An objective measure of the response to tobacco advertising in nonsmoking youth would help to develop a complete understanding of the factors that contribute to a young person's decision to use tobacco products.

Functional magnetic resonance imaging (fMRI) can be used to objectively measure the effects of advertising beyond self-report, by testing whether the neural signal in response to advertisements can predict product preferences and purchasing. fMRI studies implicate the mesolimbic dopaminergic reward system in the representation of product preference. During a simulated shopping task in fMRI, increases in nucleus accumbens (NAc) activity when college students viewed a variety of products predicted subsequent purchasing beyond self-report (Knutson et al., 2007). Another study found that increased NAc activity in response to pop songs predicted the number of units sold over the next three years, whereas sales were not related to subjective likeability (Berns and Moore, 2012). A meta-analysis of fMRI studies found that NAc activation increased the probability of a reward-related process taking place by a Bayes factor of 9, or moderate-to-strong evidence for a causal relationship (Ariely and Berns, 2010). These studies demonstrate an objective measure of product preference in NAc response to advertisements.

Tobacco advertisements are additionally smoking-related cues and have been found to elicit neural cue-reactivity even in never-smokers. In one study (Vollstadt-Klein et al., 2011), smokers and never-smokers showed comparable neural cue-reactivity to cigarette advertisements. This cue reactivity was correlated with better recognition of the advertisements in a subsequent memory test, suggesting cue-reactivity may be a biomarker for susceptibility to tobacco advertising even in nonsmokers, yet cue-reactivity was not correlated with subjective craving, suggesting that the reward response may be subconscious. Cue-reactivity in the NAc has been found in response to drug cues in several meta-analyses of fMRI studies (Chase et al., 2011; Kuhn and Gallinat, 2011).

The goals of the current study were to test whether college-age youth showed a product preference for sweet/fruit versus tobacco flavor e-cigarettes and whether advertising for sweet/fruit flavors interfered with e-cigarette health warnings. Youth were early experimenters who had tried an e-cigarette and were susceptible to future e-cigarette use, based on findings that susceptibility predicts initiation and progression of e-cigarette use (Bold et al., 2016). fMRI was used to test the hypothesis that NAc response would be greater for sweet/fruit versus tobacco flavor e-cigarette advertisements, based on reported preferences for sweet and fruit flavor e-cigarettes as compared with other flavors of e-cigarettes, among youth (Krishnan-Sarin et al., 2015; Pepper et al., 2016; Vasiljevic et al., 2016). Menthol and regular cigarette advertisements and images of fruits and sweets with no tobacco product were used as controls. Advertisements randomly contained warning labels, and recognition of health warnings was tested after fMRI. We hypothesized that greater NAc response to e-cigarette advertisements would be associated with poorer recognition of health warnings presented on those advertisements. Finally, we explored if visual attention, measured using eye-tracking, would be greater for e-cigarette advertising content depicting sweet/fruit versus tobacco flavors and would distract the eye from warning labels.

2. Materials and methods

2.1. Participants

Twenty-six participants completed the study. One additional individual was excluded due to an incidental finding on MRI. Participants were ages 18–25, right-handed, had normal or corrected vision, and were susceptible to future e-cigarette use (Pierce et al., 1998), defined as answered anything other than “definitely not” to at least one of four items: “Do you think that you will use an e-cigarette soon?”, “Do you think that you will use an e-cigarette in the next year?”, “Do you think that in the future you might experiment with e-cigarettes?”, and “If one of your best friends were to offer you an e-cigarette, would you use it?”. They were required to have tried an e-cigarette (≥1 ≤30 lifetime e-cigarette uses) and not “extremely disliked it” (1=Extremely disliked, 7=Extremely liked). Additionally, they were required to be nonsmokers, defined according to the PhenX Toolkit (https://www.phenxtoolkit.org) protocol Tobacco - Smoking Status (#030601) by answering “yes” to the question, “Have you ever smoked part or all of a cigarette?” and “no” to the question, “Have you smoked at least 100 cigarettes in your entire life?”

Participants were excluded for any serious medical, psychiatric, cognitive or substance use disorder (*DSM-V* criteria); past month psychoactive medication use; chronic medical or psychiatric medication use; pregnancy, claustrophobia, or metal in the body incompatible with MRI.

2.2. Imaging Task

During fMRI (Vollstadt-Klein et al., 2011), participants viewed advertisements for sweet/fruit and tobacco flavor e-cigarettes, menthol and regular cigarettes, and control images depicting the same sweet/fruit/mint flavors with no tobacco product. Advertisements were taken from online media and matched within tobacco category (i.e., matched sweet/fruit and tobacco flavor e-cigarette advertisements, and matched menthol and regular cigarette advertisements) on complexity, color, and content (Vollstadt-Klein et al., 2011). All e-cigarette advertisements depicted either an e-liquid container or e-cigarette; all cigarette advertisements depicted either a cigarette pack or cigarette. E-cigarette advertisements were for sweet (i.e., candy/desserts) and fruit flavor e-cigarettes, based on evidence of the appeal of these flavors to youth compared with other flavors (Krishnan-Sarin et al., 2015; Pepper et al., 2016; Vasiljevic et al., 2016), and testing only these top flavor preferences also reduced differences in novelty between sweet/fruit and tobacco flavor e-cigarette advertisements; tobacco flavor e-cigarette advertisements depicted tobacco, tobacco plants, leaves or crops. Control images of sweets, fruits, and mint with no tobacco product were taken from online image sources to match the background images of sweet/fruit flavor e-cigarette advertisements and menthol cigarette advertisements. Sixty images in each condition (flavored/tobacco e-cigarettes, menthol/regular cigarettes, control) were presented in a blocked design with 5 images/block and 12 blocks/condition. Each image was presented for 3s followed by 500ms fixation to total 17s per block. After each block, participants pressed a button to indicate their liking ("How much do you like this product?" 1=Strongly dislike, 4=Strongly like) and intent to try ("How likely is it that you will try this product in the not too distant future?" 1=Definitely not, 4=Definitely yes). Fixation appeared upon button press or after 4s, to total 13s. The order of the categories and images were randomized in 12 blocks/run across 5 six-minute runs to total 30min.

Twenty-four advertisements in each tobacco category contained text-based health warnings about the tobacco product. Health warnings were taken from U.S. government websites (e.g., FDA, National Institutes of Health, Centers for Disease Control) and presented information about the constituents and potential risks of the tobacco product. Warnings were formatted to meet current FDA requirements (FDA, 2016b) by occupying the upper 20% of the advertisement, using black ≥12-point sans serif font, centered on a white background, with a black border of ≥3mm, capitalized, punctuated and oriented in the direction of the advertising content.

2.3. Image Acquisition

Data were acquired on a Siemens 3T Magentom Prisma Fit scanner with a 64-channel head coil at the Yale Magnetic Resonance Research Center. High-resolution T1-weighted images were acquired using a three-dimension magnetization-prepared rapid gradient-echo sequence (time to repetition [TR]=2400ms, time to echo [TE]=1.96ms, field of view[FOV]=256mm, slice thickness=1mm, 208 slices, flip angle=8°, voxel size 1x1x1mm, time to acquisition [TA]=5:45min). Functional images were acquired using a T2*-weighted multiband accelerated (simultaneous multi-slice) echo-planar imaging sequence (TR=1000ms, TE=30ms, field of view=220mm, slice thickness=2mm, 75 interleaved slices, multiband factor=5, voxel size 2.0x2.0x2.0mm, TA=6:24min per run).

2.4. Eye Tracking

Eye position was tracked using an MR-compatible EyeLink 1000 Plus system (http://www.sr-research.com/eyelink1000plus.html). Eye position was sampled at 1000Hz using default saccade detection settings. Each fMRI run began with a 9-point calibration to map right eye position to screen coordinates. Calibrations were accepted when the average error was <0.49°, and the maximum error was <0.99°. All stimuli were presented on a gray background to reduce changes in pupil dilation. Each image was followed by fixation to re-center the eye.

2.5. Post-Scan Memory Test

Immediately following scanning, participants performed an unannounced recognition memory test, in which they read 48 health messages and indicated whether they were "previously seen" or "not seen" during fMRI: 24 had been displayed on warning labels (6 each for flavored/tobacco e-cigarettes, menthol/regular cigarettes), and 24 were new, with the order randomized for each participant. The performance was measured as the number of correct responses, separately for e-cigarettes and cigarettes.

2.6. Image Preprocessing and Analysis

Image preprocessing and analysis used SPM12 in MATLAB. Functional images were realigned for motion correction. The structural image was co-registered to the mean functional image and segmented. All images were normalized to the Montreal Neurological Institute template (Mazziotta et al., 1995) and smoothed using an 8mm Gaussian kernel. Artifact Detection Tools (ART) was used to identify outliers in mean global intensity (>3 SD from the mean) and motion (>0.9mm). Any run in which ≥10% of the data were identified as outliers were excluded from the analysis (one run each from three participants was excluded). The blood oxygen level-dependent signal was modeled using regressors for each condition: flavored/tobacco e-cigarettes, menthol/regular cigarettes, control images; fixation was modeled as an implicit baseline. Regressors of no interest were included for motion parameters and outliers. Conditions were modeled using a boxcar function convolved with a canonical hemodynamic response function, and regressors were fit using SPM12's implementation of the general linear model. First-level models were specified to estimate the parameter for each condition for each subject. A second-level model was specified to compare whole brain responses between conditions.

2.7. Region of Interest Analysis

The region of interest (ROI) activity was measured in the NAc. 10mm diameter sphere ROIs were defined functionally for the left NAc (-10, 11, 0) and right NAc (10, 12, -1) based on: (Knutson et al., 2007). MarsBar (Brett et al., 2002) was used to extract data from each functional image to a time course for each voxel in the ROI, calculate a summary time course as the mean of the voxel values in each ROI, estimate the model with the ROI data, and apply a contrast to derive effect sizes for ROIs. Unsmoothed data were used for the ROI analysis to avoid smoothing signal into nearby structures. For correlations, NAc activity was calculated across only the sweet/fruit and tobacco flavor e-cigarette trials that contained warning labels. A supplemental analysis tested a control region of interest in the auditory cortex (see supplement)[1].

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...

2.8. Eye Tracking Analysis

Eye tracking data analysis was conducted using EyeLink Data Viewer (http://www.sr-research.com/dv.html). Eye tracking data was not included from one participant due to a right eye injury. Eye movement for a given trial (image) was removed from the analysis if the total time spent looking at the image was ≤3 SD from the mean (≤1290 ms of a 3s trial, n=118 trials) or if the number of fixations was ≤3 SD from the mean (≤3 fixations, n=32 trials), indicating that the eye was closed, fixated off-screen, etc. Trials were then evaluated by eye and excluded if multiple fixations were aligned with the image along one dimension but misaligned along the other dimension, indicating drift (only trials with unambiguous drift were removed, n=30 trials). Areas of interest were defined for advertisements with warning labels to analyze separately the warning label and the advertising content. Dwell time (i.e., time spent viewing area(s) of interest) was measured and averaged across block and participant based on a prior eye-tracking study of cigarette warning labels (Strasser et al., 2012).

2.9. Statistical Analysis

Statistical analysis used SPSS 22. The primary analysis involved first comparing NAc response between conditions using 2-by-3 repeated measures analyses of variance (RM-ANOVA) with hemisphere (right/left NAc) and condition (flavored/tobacco/control) as within-subjects factors, separately for e-cigarettes and cigarettes. Next, one-tailed Spearman's correlations were tested between NAc activity during e-cigarette advertisements with warning labels and e-cigarette memory score, separately for the right and left NAc.

Exploratory analyses evaluated visual attention by comparing dwell time using 2-by-2 RM-ANOVA with interest area (advertising content/warning label) and condition (flavored/tobacco) as within-subject factors, separately for e-cigarettes and cigarettes. Next, ratings were compared using 2-by-3 RM-ANOVA with rating (liking/intent to try) and condition (flavored/tobacco/control) as within-subject factors, separately for e-cigarettes and cigarettes. Simple linear regressions were used to test whether ratings could be predicted by time spent viewing the advertising content or warning labels; each was first averaged across flavored and tobacco advertisements. Post-hoc Spearman's correlations were tested between liking or intent to try and dwell time in each area of interest.

3. Results

3.1. Demographics and Smoking Characteristics

Twelve females and 14 males took part in the study, ages 21.6±1.9, range 18–25 years; white (n=17), black (n=4), Asian (n=2), white Hispanic (n=2), black Hispanic (n=1); high school educated (n=4), some college (n=13), completed college (n=9). The Yale Human Investigations Committee approved the study. All participants provided signed informed consent.

Participants had tried an e-cigarette 2.4±1.5 times, “neither liked or disliked it” (4.0±1.2), and age of first trying an e-cigarette was 19.4±2.1 years. Only one participant had past 30-day e-cigarette use. All participants were susceptible to future e-cigarette use (Pierce et al., 1998). Ten participants were never cigarette smokers (38.5%), five participants had past 30-day cigarette use (2.0±0.7 cigarettes), and age of first trying a cigarette was 18.3±1.9 years. Only 13 participants were susceptible to future cigarette use. Participants had past 30-day alcohol use of 5.6±3.4 days, and marijuana use of 1.0±1.6 times.

3.2. Nucleus Accumbens Response to Viewing Tobacco Advertisements

For e-cigarette advertisements, there was a significant main effect of condition (flavored/tobacco/control) on NAc activity (Wilks' lambda [L]=.73, F(2,24)=4.52, p=.02), and no main effect of hemisphere (F(1,25)=1.23, p=.28) or interaction (F(2,24)=0.46, p=.64). NAc activity was greater for sweet/fruit versus tobacco flavor e-cigarette advertisements (p=.03), and greater for control images versus tobacco flavor e-cigarette advertisements (p=.03) but did not differ between sweet/fruit flavor e-cigarette advertisements and control images (p=.96). One-sample t-tests were not significant for any e-cigarette advertisement condition (mean left NAc activity: control=.40, t(25)=.89, p=.38; sweet/fruit=.43, t(25)=1.0, p=.32; tobacco=-.13, t(25)=-.30, p=.77; mean right NAc activity: control=.25, t(25)=.71, p=.49; sweet/fruit=.29, t(25)=.79, p=.44; tobacco=-.54, t(25)=-1.5, p=.12). For cigarette advertisements, tested as a control, there was no main effect of condition (menthol/regular cigarettes/control; F(2,24)=.83, p=.45), hemisphere (F(1,25)=.22, p=.64) or interaction (F(2,24)=.53, p=.6). (Figure 1).

3.3. Post-Scan Recognition of Health Warnings Presented on Tobacco Advertisements

A significant negative correlation was found between right NAc response to e-cigarette advertisements with warning labels and post-scan recognition of health information from those warning labels (r(26)=-.43, p=.03, Bonferroni-corrected for right and left NAc, Figure 2). This relationship was not found for the left NAc (r(26)=-.18, p=.38).

3.4. Whole Brain Response to Viewing Tobacco Advertisements

An exploratory whole-brain analysis demonstrated that viewing sweet/fruit versus tobacco flavor e-cigarette advertisements led to greater activity in the bilateral inferior parietal lobule, right inferior frontal gyrus, right middle temporal gyrus, inferior occipital gyrus, left lingual gyrus and fusiform gyrus (*p*<.05 family-wise error cluster-corrected, *p*<.001 cluster-forming threshold, *k*=251; Figure S1, Table S1)[2]. No brain regions showed greater activity during viewing tobacco versus sweet/fruit flavor e-cigarette advertisements. Exploratory comparisons with control conditions are provided in the supplement (Table S2)[3].

3.5. "Liking" and "Intent to Try" Ratings of Tobacco Advertisements

For e-cigarettes, there was a significant main effect of rating (L=0.53, F(1,25)=22.17, p<.001), condition (L=.10, F(2,24)=112.32, p<.001), and interaction (L=.748, F(2,24)=4.04, p=.03). The main effect of "rating" (liking/intent to try) indicates that participants reported greater liking (mean=2.4±.08 standard error) than intent to try (mean=2.1±.09) e-cigarettes, averaged over the levels of the other factors (p<.001). Liking and intent to try were greatest for control images of fruits/sweets/mint versus sweet/fruit flavor e-cigarette advertisements

[2]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...

(p<.001) and tobacco flavor e-cigarette advertisements (p<.001) and were greater for sweet/fruit flavor e-cigarette advertisements versus tobacco flavor e-cigarette advertisements (p<.001) (Figure 3A).

For cigarettes, there was a significant main effect of rating (L=.66, F(1,25)=13.68, p=.001) and condition (L=.11, F(2,24)=97.31, p<.001) but no interaction (L=.81, F(2,24)=2.81, p=.08). The main effect of "rating" (liking/intent to try) indicates that participants reported greater liking (mean=2.1±.09) than intent to try (mean=2.0±.1) cigarettes, averaged over the levels of the other factors (p=.001). Liking and intent to try were greatest for control images of fruits/sweets/mint versus menthol cigarette advertisements (p<.001) and regular cigarette advertisements (p<.001) but did not differ between menthol and regular cigarette advertisements (p=0.37). (Figure 3B).

3.6. Exploratory Eye Tracking Results

3.6.1. Eye tracking on tobacco advertisements—For e-cigarette advertisements, there was a significant interest area-by-condition interaction (L=0.83, F(1,24)=4.93, p=.04, Figure 4), and no main effect of condition (L=0.94, F(1,24)=1.68, p=.21) or interest area (L=.99, F(1,24)=0.30 p=.59), such that dwell time was longer on the advertising content for sweet/fruit flavor e-cigarette advertisements (p=.04), and longer on the warning label for tobacco flavor e-cigarette advertisements (p=.05).

For cigarette advertisements, there was a significant interest area-by-condition interaction (L=0.57, F(1,24)=18.05, p<.001, Figure 5), and no main effect of condition (L=0.92, F(1,24)=2.10, p=.16) or interest area (L=0.99, F(1,24)=0.27 p=.61), such that dwell time was longer on the advertising content for menthol cigarette advertisements (p<.001), and longer on the warning label for regular cigarette advertisements (p=.001).

3.6.2. Eye tracking related to ratings of tobacco advertisement—For e-cigarette advertisements, dwell time significantly predicted liking (F(2,22)=6.71, p=.005, R^2=.38) and intent to try e-cigarettes (F(2,22)=6.89, p=.005, R^2=.39). Greater time spent viewing the advertising content was positively associated with liking (r(25)=.57, p=.003) and intent to try e-cigarettes (r(25)=.54, p=.005), and greater time spent viewing warning labels was negatively associated with liking (r(25)=-.47, p=.02) and intent to try e-cigarettes (r(25)=-.49, p=.01). (Figure S2)[4].

For cigarette advertisements, dwell time significantly predicted liking (F(2,22)=5.87, p=.009, R^2=.35) and intent to try cigarettes (F(2,22)=3.99, p=.03, R^2=.27). Greater time spent viewing advertising content was positively associated with liking (r(25)=.54, p=.005) and intent to try cigarettes (r(25)=.41, p=.04), and greater time spent viewing warning labels was negatively associated with liking (r(25)=-.41, p=.05) but not with intent to try cigarettes (r(25)=-.27, p=.19). (Figure S3).

[4]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...

Mean liking was greater for e-cigarettes (1.86±.54) versus cigarettes (1.54±.61; t(25)=3.55, p=.002), and likewise, mean intent to try was greater for e-cigarettes (1.61±.49) versus cigarettes (1.44±.56; t(25)=2.48, p=.02).

4. Discussion

This study evaluated the impact of advertising for sweet/fruit versus tobacco flavor e-cigarettes in nonsmoking college-age youth who were susceptible to future e-cigarette use, including the impact of advertising for sweet/fruit flavors on the effective communication of health warnings. Our findings show a significant impact of advertising for sweet/fruit flavors on increased neural cue-reactivity relative to tobacco flavor e-cigarette advertisements, poorer memory for health warnings, increased visual attention to advertising content and decreased visual attention to warning labels, and relatively increased liking and intent to try these products. These findings suggest a potential mechanism by which advertising for sweet/fruit flavor e-cigarettes may increase the appeal of e-cigarettes to youth (who otherwise have negative associations with tobacco) and decrease knowledge of e-cigarette health risks. Increased appeal and decreased knowledge of health risks may impact e-cigarette initiation among nonsmoking youth.

Previous fMRI studies have observed neural cue-reactivity to smoking versus control cues in brain regions involved in cognitive control and reward in adult and youth smokers (Engelmann et al., 2012; Rubinstein et al., 2011). Typically, fMRI studies of smoking cue-reactivity use images of individuals smoking cigarettes or smoking-related objects such as lighters and ashtrays. Only a few fMRI studies have tested cue-reactivity to tobacco advertising. Vollstadt-Klein (2010) tested responses to cigarette advertisements and found comparable cue-reactivity to cigarette versus control advertisements in smokers and never-smokers, which was positively associated with post-scan recognition of the advertisements. Likewise, only a few fMRI studies have measured responses to e-cigarette stimuli. Nichols (2016) recently developed videos of e-cigarette use for cue-reactivity studies and pilot tested these in e-cigarette users (Nichols et al., 2016). In another fMRI study (Chen et al., 2017), adolescents with a range of regular cigarette use (never to daily) showed increased neural cue-reactivity as they viewed print e-cigarette advertisements, and reported increased craving to smoke regular cigarettes. For that study, e-cigarette advertisements were included if they had increased young adult smokers' desire to smoke regular cigarettes in an earlier behavioral study. In the current study, e-cigarette advertisements were selected for fMRI if they contained fruit/sweet or tobacco flavors and depicted either an e-cigarette or e-liquid bottle; menthol and regular cigarette advertisements contained either a cigarette or cigarette pack; and control images depicted the same sweet, fruit and mint flavors with no tobacco product.

Overall, we were interested in whether sweet/fruit flavor e-cigarette advertisements would be perceived more like sweets and fruits and less like tobacco products by nonsmoking youth, despite being equivalent products to tobacco flavor e-cigarettes. In line with this, our findings indicated no difference in NAc response to sweet/fruit flavor e-cigarette advertisements and control images of sweets and fruits and increased NAc response to sweet/fruit relative to tobacco flavor e-cigarette advertisements. One sample t-tests of NAc activity were not significant for any condition, indicating that the effect was driven by differences between conditions, including a positive NAc response to images of sweets/fruits and lack of a negative NAc response to images of tobacco. One interpretation of these results is that the very presence of images of fruits and sweets on e-cigarette advertisements leads to a positive NAc response that is comparable to images of sweets and fruits with no tobacco product. NAc activation has been shown to have a critical role in drug cue-reactivity (e.g., Chase, 2011) and addiction (Koob and Volkow, 2010). NAc response to advertisements has been shown to predict actual purchasing behavior (Knutson et al., 2007), including among youth (Berns and Moore, 2012). Although it is unlikely that a “buy button” in the brain exists, studies suggest that fMRI data including NAc activity can be combined with other measures of preference to reveal not only what people like, but also what they will buy (Ariely and Berns, 2010), or in the case of tobacco products, potentially what they will use. Although we did not test purchasing behavior, our finding of increased NAc response to sweet/fruit versus tobacco flavor e-cigarette advertisements provides evidence of a relative product preference for sweet/fruit flavor e-cigarettes in nonsmoking youth. This interpretation is substantiated by relatively increased liking and intent to try sweet/fruit as compared with tobacco flavor e-cigarettes (i.e., less disliking or lack of intent to try). Advertising is designed to create positive product associations, and positive associations with tobacco products via marketing (e.g., flavors, cartoons) attract youth to tobacco use (Wakefield et al., 2003), therefore relatively increased positive responses (NAc activity, liking and intent to try) to fruits and sweets paired with e-cigarettes may be one way in which the appeal of these products to youth is increased. For example, a recent study found that youth who viewed sweet flavor e-cigarette advertisements rated the advertisements as more appealing and reported greater interest in buying and trying e-cigarettes than youth who viewed tobacco flavor e-cigarette advertisements or control images (Vasiljevic et al., 2016).

A related interpretation is that advertisements for e-cigarettes paired with sweets and fruits may elicit a differential response compared with advertisements for e-cigarettes paired with images of tobacco due to negative perceptions of tobacco smoking generally held by youth in the U.S. Tobacco control efforts in the U.S. have enjoyed substantial success in associating tobacco smoking with death and dying among youth, and youth cigarette smoking has continued to fall over the last 20 years (U.S. Department of Health and Human Services, 2012). For example, adolescents in California (n = 677) now perceive cigarette smoking to be riskier and less socially acceptable, and fewer have smoked or intend to smoke cigarettes (McKelvey and Halpern-Felsher, 2017). One interpretation of our findings is that images of sweet/fruit flavors on e-cigarette advertisements reduce this bias against tobacco in nonsmoking youth, as compared with pairing e-cigarettes with images of tobacco. However, it not yet established that negative associations with cigarettes among youth extend to e-cigarettes. Youth hold more positive attitudes toward e-cigarettes (Roditis et al., 2016; Roditis and Halpern-Felsher, 2015), and are using e-cigarettes at higher rates (Centers for Disease Control and Prevention, 2015). Moreover, e-cigarette use is occurring in youth who would not otherwise have used tobacco products (Barrington-Trimis et al., 2016). Therefore, sweet/fruit flavor e-cigarette advertising may attract youth by forming new positive associations with tobacco and/or by reducing possible negative associations with tobacco.

Possibly in line with this interpretation, we found no difference in NAc responses to menthol and regular cigarette advertisements, which were significantly lower than the NAc response to control images. Cigarette advertisements were included in this study to test whether a product preference for flavors among youth generalized to menthol versus regular cigarettes. However, youth were eligible for the study if they were susceptible to future e-cigarette use, whereas only half of the subjects were susceptible to future cigarette use (n=13). Another study is needed to test whether NAc response is greater for menthol versus regular cigarette advertisements in youth who are susceptible to future menthol/regular cigarette use. A finding of no difference in NAc responses to menthol and regular cigarette advertisements, but a reduced response compared with control images, may be consistent with the findings representing negative associations with tobacco. The comparison between menthol and regular cigarette advertisements also provides additional control for some of the features that differ between sweet/fruit and tobacco flavor e-cigarette advertisements, such as colors and brightness, which may impact appeal. While not a direct test, our finding of no difference in NAc response to menthol and regular cigarette advertisements provides some preliminary evidence that a greater NAc response to sweet/fruit versus tobacco flavor e-cigarette advertisements was not due solely to differences in colors or brightness between flavor and tobacco conditions. However, this interpretation warrants direct testing in a future study, for example by comparing responses between sweet/fruit flavor e-cigarette advertisements and e-cigarette advertisements with matching bright colors and shapes but no images of sweets and fruits.

This is the first study to evaluate the impact of specific advertising content (i.e., sweet/fruit flavors) on the effective communication of health information about e-cigarettes. Previous eye-tracking studies have shown that plain packaging for regular cigarettes increased visual attention to graphic warning labels and later recall of health information (Maynard et al., 2013; Munafo et al., 2011), and that a longer time spent viewing warning labels on cigarette advertisements was associated with correct recall in adults (Strasser et al., 2012) and adolescents (Peterson et al., 2010). The current study was designed to extend this work to e-cigarette advertisements and test whether images of sweets and fruits on e-cigarette advertisements interfered with warning labels. Indeed, we found that greater NAc activity when viewing e-cigarette advertisements with warning labels was associated with poorer post-scan recognition of health information about e-cigarettes from those warning labels. For both e-cigarettes and cigarettes, participants spent more time viewing the warning label on tobacco flavor advertisements, and more time viewing the advertising content on sweet/fruit/menthol flavor advertisements, the liking and intent to try were predicted by greater time spent viewing the advertising content and less time spent viewing the warning label. For health warnings to be effective, tobacco advertisements should not have content that interferes with processing the health warning. Our data suggest that displaying fruits and sweets on e-cigarette advertisements may override the ability of the warning label to command attention and galvanize memory about health information, and this can impact a young persons' intentions to use e-cigarettes.

The relationship between greater NAc response to e-cigarette advertisements and poorer post-scan recognition of warning labels was found for the right but not left NAc. This finding is in line with a meta-analysis of fMRI drug cue-reactivity studies which found that the right but not left NAc was activated by drug cues across studies (Chase et al., 2011). However, another meta-analysis of fMRI food and smoking cue-reactivity studies found that the left ventral striatum (caudate/NAc) was activated for food cues, right NAc for smoking cues, and there was an overlap between food and smoking cues in the left ventral striatum (Tang et al., 2012). Furthermore, the NAc regions of interest tested in the current study were derived from a study of product preference in which bilateral NAc was found to predict purchasing (Knutson et al., 2007). Therefore, the apparent lateralized relationship between NAc response and memory for health warnings warrants future study, in particular in a larger group.

The current findings were demonstrated in nonsmoking college-age youth who were susceptible to future e-cigarette use. We chose to include youth who had tried an e-cigarette to ensure familiarity with this novel product. We focused on susceptibility, which has been shown to predict initiation of e-cigarette use beyond demographics or other substance use (Bold et al., 2016). Youth in the current study had tried an e-cigarette 2–3 times and not "extremely disliked it," and therefore may be particularly susceptible to the potential impact of e-cigarette advertising. Our findings provide evidence for some of the factors, including responses to tobacco advertising and risk perceptions, that may contribute to whether a susceptible young person decides to use tobacco products. The decision to use or not use a tobacco product is processed by both affective and deliberative thinking (Henningfield et al., 2011; Slovic et al., 2004). Affect is manipulated by packaging, marketing, and advertising messages such as associating tobacco with health (e.g., fruit) rather than disease and death, and reasoning is influenced by specific health risks (Henningfield et al., 2011). Our findings provide evidence that advertising for flavored e-cigarettes manipulates affect and distracts from health concerns in young early experimenters who are susceptible to future e-cigarette use. There is a critical need to identify strategies to target and prevent future e-cigarette use in susceptible youth, and our findings suggest that one such approach is the regulation of advertising for flavored e-cigarettes.

One limitation of this study is that sweet/fruit flavor e-cigarette advertisements were more novel than non-flavored (tobacco) e-cigarette advertisements. Ideally, advertisements would be matched on all features. Sweet/fruit flavor e-cigarette advertisements were limited to sweets (i.e., candy/desserts) and fruits, thereby somewhat reducing their novelty, and were matched with tobacco flavor e-cigarette advertisements in complexity and content. A variety of tobacco e-cigarette advertisements were included that depicted tobacco, tobacco plants or leaves, and were embellished with imagery (e.g., gold bars, flags, landscapes) or patterned backgrounds. Control images depicting the same sweet, fruit and mint flavors with no tobacco product were also included in the study to provide an additional measure of responses to the specific content of flavored tobacco advertisements, to help address this limitation. Moreover, the novelty of sweet/fruit flavor e-cigarette advertisements is an ecologically valid factor in their appeal to youth. A related limitation is that sweet/fruit flavor e-cigarette advertisements are typically more brightly colored than tobacco flavor e-cigarette advertisements. Our comparison of menthol and regular cigarettes advertisements, which arguably have a similar limitation, provides some evidence that the difference in responses is not due only to a difference in bright colors. However, another study is needed to compare responses to sweet/fruit flavor e-cigarette advertisements with e-cigarette advertisements with matching bright colors and shapes but no flavors. Another limitation was that, although warning labels were randomly assigned to advertisements, the pairing of warning labels and advertisements should be randomized across subjects to control for potential differences in salience between specific warning labels or advertising content. Additionally, interpretation of our findings would have been strengthened by including a neutral condition (i.e., similar to the neutral cue condition in drug cue reactivity studies) with which to compare NAc response, in order to better determine, in particular, whether the difference in NAc response found between sweet/fruit and tobacco flavor e-cigarette advertisements represents an increased reward response to flavors versus a decreased aversive response to tobacco. Finally, these findings should be replicated in a younger sample, given that 88% of smokers initiate by age 18 (HHS, 2012), and a majority of adolescents initiate e-cigarette use with a flavored product (Ambrose et al., 2015; Corey et al., 2015). Our study evaluated college-age youth for whom e-cigarettes are a relatively novel product. These findings should also be replicated in a larger sample to test for sex/gender differences, given evidence for sex/gender differences in e-cigarette susceptibility (Bold et al., 2016), use and preferences for flavored e-cigarettes (e.g., Dawkins et al., 2013), and responsiveness to tobacco advertising (Mays et al., 2014) and health warnings (O'Hegarty et al., 2006).

5. Conclusions

The current study is the first to provide objective fMRI evidence of a relative product preference for sweet/fruit versus tobacco flavor e-cigarette advertisements in college-age youth. Moreover, this preference was demonstrated in nonsmoking youth (early experimenters) who were susceptible to future e-cigarette use, suggesting a potential impact of advertising for flavors on youth initiation of e-cigarette use. This study is also the first to demonstrate that specific advertising content, i.e., depictions of flavors, interferes with effective communication of tobacco product health information. An effective persuasive warning must command attention, galvanize memory, evoke emotion, contain explicit instruction, and show a consequence (e.g., Bunch v. McMasker Enterprises Inc., 2004). Our evidence suggests that depictions of sweet/fruit flavors may override the ability of the warning label to command attention and galvanize memory about health information. In line with this, youth who spent more time viewing the advertising content and less time viewing the warning label reported greater liking and intentions to use e-cigarettes. This evidence suggests that regulation of advertising content is critical to prevent and reduce the use of these products by youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Ambrose BK, Day HR, Rostron B, Conway KP, Borek N, Hyland A, Villanti AC. Flavored tobacco product use among U.S. youth aged 12–17 years, 2013–2014. J Am Med Assoc. 2015; 314:1871–1873.

Ariely D, Berns GS. Neuromarketing: The hope and hype of neuroimaging in business. Nat Rev Neurosci. 2010; 11:284–292. [PubMed: 20197790]

Barrington-Trimis JL, Urman R, Leventhal AM, Gauderman WJ, Cruz TB, Gilreath TD, Howland S, Unger JB, Berhane K, Samet JM, McConnell R. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. Pediatrics. 2016:138. [PubMed: 27544347]

Berns GS, Moore SE. A neural predictor of cultural popularity. J Consum Psychol. 2012; 22:154–160.

Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. E-cigarette susceptibility as a predictor of youth initiation of e-cigarettes. Nicotine Tob Res. 2016

Brett, M., Anton, J., Valabregue, J. Region of interest analysis using an SPM toolbox. 8th International Conference on Functional Mapping of the Human Brain; Sendai, Japan. 2002. http://matthew.dynevor.org/research/abstracts/marsbar/marsbar_abstract.pdf

Bunch v. McMasker Enterprises Inc. [accessed March 2, 2018] Court of Appeal, Third District, California, No. C040177. 2004. http://appellatecases.courtinfo.ca.gov

Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: Tobacco marketing strategies. Health Aff (Millwood). 2005; 24:1601–1610. [PubMed: 16284034]

Centers for Disease Control and Prevention. Tobacco use among middle and high school students United States 2011–2014. MMWR Morb MortalWkly Rep. 2015:381–385.

Chase HW, Eickhoff SB, Laird AR, Hogarth L. The neural basis of drug stimulus processing and craving: An activation likelihood estimation meta-analysis. Biol Psychiatry. 2011; 70:785–793. [PubMed: 21757184]

Chen Y, Fowler CH, Papa VB, Lepping RJ, Brucks MG, Fox AT, Martin LE. Adolescents' behavioral and neural responses to e-cigarette advertising. Addict Biol. 2017

Corey CG, Ambrose BK, Apelberg BJ, King BA. Flavored tobacco product use among middle and high school students--United States, 2014. MMWR Morb Mortal Wkly Rep. 2015:1066–1070. [PubMed: 26421418]

Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: An online survey of electronic cigarette users. Addiction. 2013; 108:1115–1125. [PubMed: 23551515]

Dube SR, Arrazola RA, Lee J, Engstrom M, Malarcher A. Pro-tobacco influences and susceptibility to smoking cigarettes among middle and high school students--United States, 2011. J Adolesc Health. 2013; 52:S45–51. [PubMed: 23601611]

Engelmann JM, Versace F, Robinson JD, Minnix JA, Lam CY, Cui Y, Brown VL, Cinciripini PM. Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies. Neuroimage. 2012; 60:252–262. [PubMed: 22206965]

Falk EB, Berkman ET, Mann T, Harrison B, Lieberman MD. Predicting persuasion-induced behavior change from the brain. J Neurosci. 2010; 30:8421–8424. [PubMed: 20573889]

Hanewinkel R, Isensee B, Sargent JD, Morgenstern M. Cigarette advertising and teen smoking initiation. Pediatrics. 2011; 127:e271–278. [PubMed: 21242217]

Harrell MB, Weaver SR, Loukas A, Creamer M, Marti CN, Jackson CD, Heath JW, Nayak P, Perry CL, Pechacek TF, Eriksen MP. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. Prev Med Rep. 2017; 5:33–40. [PubMed: 27896041]

Henningfield JE, Hatsukami DK, Zeller M, Peters E. Conference on abuse liability and appeal of tobacco products: Conclusions and recommendations. Drug Alcohol Depend. 2011; 116:1–7. [PubMed: 21376479]

Klein SM, Giovino GA, Barker DC, Tworek C, Cummings KM, O'Connor RJ. Use of flavored cigarettes among older adolescent and adult smokers: U.S., 2004–2005. Nicotine Tob Res. 2008; 10:1209–1214. [PubMed: 18629731]

Knutson B, Rick S, Wimmer GE, Prelec D, Loewenstein G. Neural predictors of purchases. Neuron. 2007; 53:147–156. [PubMed: 17196537]

Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. Nicotine Tob Res. 2015; 17:847–854. [PubMed: 25481917]

Krishnan-Sarin S, Morean ME, Camenga DR, Cavallo DA, Kong G. E-cigarette use among high school and middle school adolescents in Connecticut. Nicotine Tob Res. 2015; 17:810–818. [PubMed: 25385873]

Kuhn S, Gallinat J. Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. Eur J Neurosci. 2011; 33:1318–1326. [PubMed: 21261758]

Lee HY, Lin HC, Seo DC, Lohrmann DK. The effect of e-cigarette warning labels on college students' perception of e-cigarettes and intention to use e-cigarettes. Addict Behav. 2017; 76:106–112. [PubMed: 28779651]

MacKinnon DP, Fenaughty AM. Substance use and memory for health warning labels. Health Psychol. 1993; 12:147–150. [PubMed: 8500442]

Mayhew KP, Flay BR, Mott JA. Stages in the development of adolescent smoking. Drug Alcohol Depend. 2000; 59:S61–81. [PubMed: 10773438]

Maynard OM, Munafo MR, Leonards U. Visual attention to health warnings on plain tobacco packaging in adolescent smokers and non-smokers. Addiction. 2013; 108:413–419. [PubMed: 22882736]

Mays D, Gilman SE, Rende R, Luta G, Tercyak KP, Niaura RS. Influences of tobacco advertising exposure and conduct problems on smoking behaviors among adolescent males and females. Nicotine Tob Res. 2014; 16:855–863. [PubMed: 24590388]

Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. A probabilistic atlas of the human brain: Theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). Neuroimage. 1995; 2:89–101. [PubMed: 9343592]

McKelvey K, Halpern-Felsher B. Adolescent cigarette smoking perceptions and behavior: Tobacco control gains and gaps amidst the rapidly expanding tobacco products market from 2001 to 2015. J Adolesc Health. 2017; 60:226–228. [PubMed: 27939880]

Memo to Brown & Williamson, 1972. Marketing innovations, “Youth Cigarette - New Concepts,” Bates No. 170042014.

Munafo MR, Roberts N, Bauld L, Leonards U. Plain packaging increases visual attention to health warnings on cigarette packs in non-smokers and weekly smokers but not daily smokers. Addiction. 2011; 106:1505–1510. [PubMed: 21401767]

Nichols TT, Foulds J, Yingst JM, Veldheer S, Hrabovsky S, Richie J, Eissenberg T, Wilson SJ. Cue-reactivity in experienced electronic cigarette users: Novel stimulus videos and a pilot fMRI study. Brain Res Bull. 2016; 123:23–32. [PubMed: 26478134]

O'Hegarty M, Pederson LL, Nelson DE, Mowery P, Gable JM, Wortley P. Reactions of young adult smokers to warning labels on cigarette packages. Am J Prev Med. 2006; 30:467–473. [PubMed: 16704939]

Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. Tob Control. 2016; 25:ii62–ii66. [PubMed: 27633762]

Peterson EB, Thomsen S, Lindsay G, John K. Adolescents' attention to traditional and graphic tobacco warning labels: An eye-tracking approach. J Drug Educ. 2010; 40:227–244. [PubMed: 21313984]

Pierce JP, Choi WS, Gilpin EA, Farkas AJ, Berry CC. Tobacco industry promotion of cigarettes and adolescent smoking. J Am Med Assoc. 1998; 279:511–515.

Rath JM, Villanti AC, Williams VF, Richardson A, Pearson JL, Vallone DM. Correlates of current menthol cigarette and flavored other tobacco product use among U.S. young adults. Addict Behav. 2016; 62:35–41. [PubMed: 27310032]

Roditis M, Delucchi K, Cash D, Halpern-Felsher B. Adolescents' perceptions of health risks, social risks, and benefits differ across tobacco products. J Adolesc Health. 2016; 58:558–566. [PubMed: 27107909]

Roditis ML, Halpern-Felsher B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes, and marijuana: A qualitative analysis. J Adolesc Health. 2015; 57:179–185. [PubMed: 26115908]

Rubinstein ML, Luks TL, Moscicki AB, Dryden W, Rait MA, Simpson GV. Smoking-related cue-induced brain activation in adolescent light smokers. J Adolesc Health. 2011; 48:7–12. [PubMed: 21185518]

Sanders-Jackson A, Schleicher NC, Fortmann SP, Henriksen L. Effect of warning statements in e-cigarette advertisements: An experiment with young adults in the United States. Addiction. 2015a; 110:2015–2024. [PubMed: 25557128]

Sanders-Jackson AN, Tan AS, Bigman CA, Henriksen L. Knowledge about e-cigarette constituents and regulation: Results from a national survey of U.S. young adults. Nicotine Tob Res. 2015b; 17:1247–1254. [PubMed: 25542915]

Shibuya K, Ciecierski C, Guindon E, Bettcher DW, Evans DB, Murray CJ. WHO framework convention on tobacco control: Development of an evidence based global public health treaty. BMJ. 2003; 327:154–157. [PubMed: 12869461]

Slovic P, Finucane ML, Peters E, MacGregor DG. Risk as analysis and risk as feelings: Some thoughts about affect, reason, risk, and rationality. Risk Anal. 2004; 24:311–322. [PubMed: 15078302]

Strasser AA, Tang KZ, Romer D, Jepson C, Cappella JN. Graphic warning labels in cigarette advertisements: Recall and viewing patterns. Am J Prev Med. 2012; 43:41–47. [PubMed: 22704744]

Tang DW, Fellows LK, Small DM, Dagher A. Food and drug cues activate similar brain regions: A meta-analysis of functional MRI studies. Physiol Behav. 2012; 106:317–324. [PubMed: 22450260]

U.S. Department of Health and Human Services. A report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Atlanta, GA: 2012. Preventing tobacco use among youth and young adults. https://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/full-report.pdf [accessed March 2, 2018]

U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: A report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Atlanta, GA: 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf [accessed March 2, 2018]

U.S. Food and Drug Administration. [accessed March 2, 2018] Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products; Final Rule; Fed Regist. 2016a. p. 81https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm500254.pdf

U.S. Food and Drug Administration. Guidance for Industry, Small Entity Compliance Guide. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products; 2016b. FDA deems certain tobacco products subject to FDA authority, sales and distribution restrictions, and health warning requirements for packages and advertisements (revised)*. https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM499354.pdf [accessed March 2, 2018]

Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. Tob Control. 2016; 25:e107–e112. [PubMed: 26781305]

Vollstadt-Klein S, Kobiella A, Buhler M, Graf C, Fehr C, Mann K, Smolka MN. Severity of dependence modulates smokers' neuronal cue reactivity and cigarette craving elicited by tobacco advertisement. Addict Biol. 2011; 16:166–175. [PubMed: 20331560]

Wakefield M, Flay B, Nichter M, Giovino G. Role of the media in influencing trajectories of youth smoking. Addiction. 2003; 98(Suppl 1):79–103. [PubMed: 12752363]

Webb TL, Sheeran P. Does changing behavioral intentions engender behavior change? A meta-analysis of the experimental evidence. Psychol Bull. 2006; 132:249–268. [PubMed: 16536643]

Highlights

- College age early experimenters show a product preference for flavored e-cigarettes.
- Neural cue-reactivity was greater for flavored than tobacco e-cigarette advertisements.
- Greater cue-reactivity to ads related to poorer recognition of health warnings.
- Eye-tracking indicated that fruit/sweet flavors on ads interfere with warning labels.
- Nonsmoking youth reported greater liking and intent to try flavored e-cigarettes.

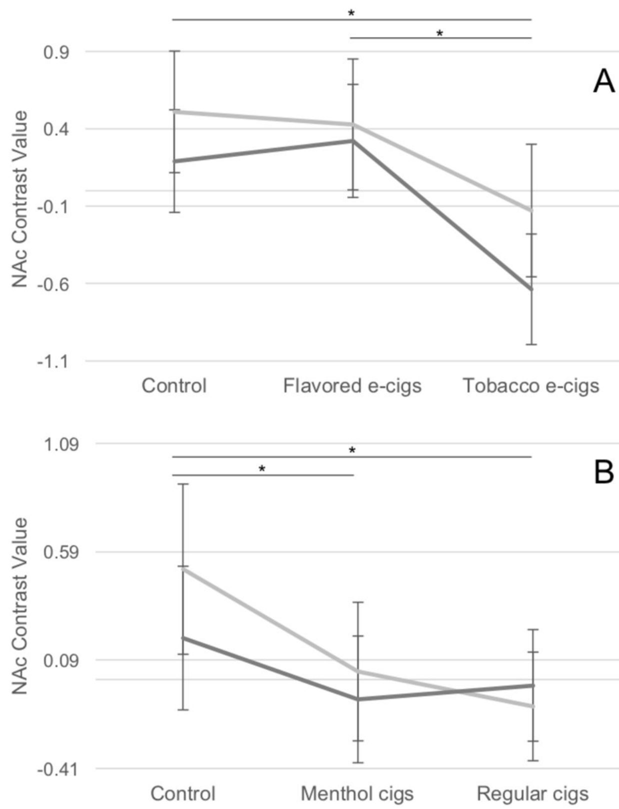

Figure 1.

Region of interest activity in the left (light gray) and right (dark gray) nucleus accumbens as susceptible nonsmoking young adults viewed (A) control images of fruits, sweets and mint; fruit/sweet flavored e-cigarette advertisements; and tobacco flavor e-cigarette advertisements. Note: (main effect of condition: $F(2,24)=4.52$, $p=.02$; *$p<.05$ pairwise); and (B) the same control images; menthol cigarette advertisements; and regular cigarette advertisements ($F(2,24)=.83$, $p=.45$). Error bars indicate standard error of the mean.

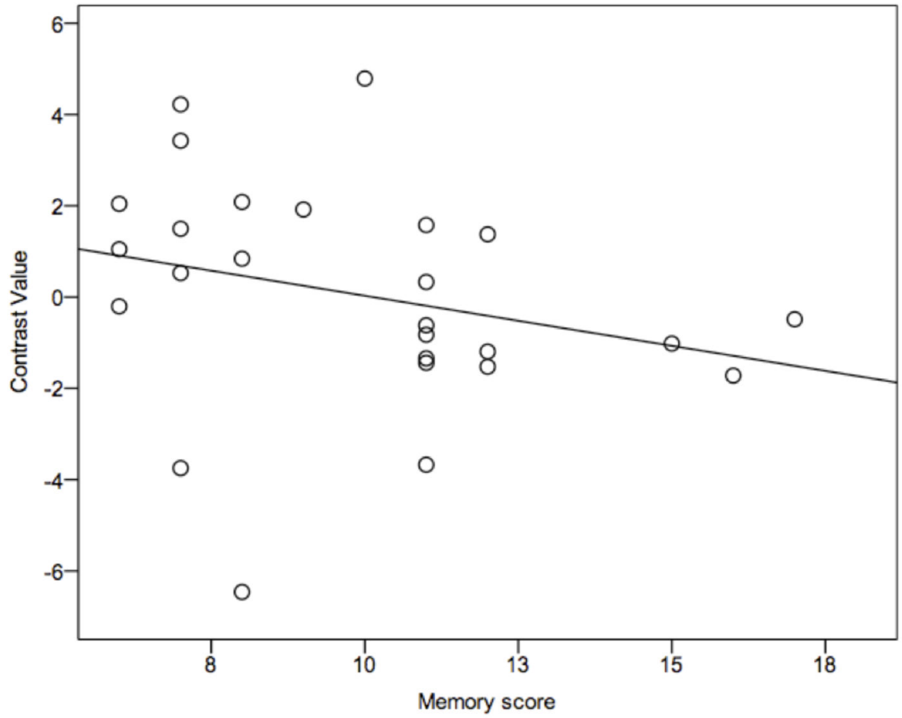

Figure 2.

Right nucleus accumbens (NAc) activity when viewing e-cigarette advertisements with warning labels. Note: (contrast value) was significantly negatively associated with recognition of those warning labels (memory score) after scanning (r(26)=-.43, p=.03).

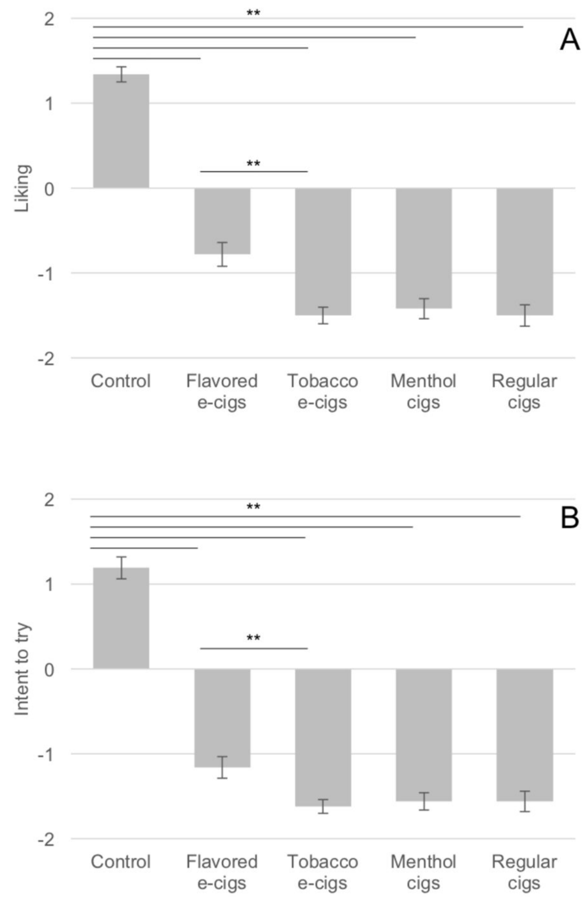

Figure 3.

(A) Liking and (B) intent to try were greatest for control images of fruits and sweets as compared with advertisements for fruit/sweet flavor e-cigarettes, tobacco flavor e-cigarettes, menthol and regular cigarettes (all p<.001). Note: Ratings were also greater for advertisements for fruit/sweet versus tobacco flavor e-cigarettes (p<.001) but did not differ between advertisements for menthol versus regular cigarettes (p=.34). Error bars indicate standard error of the mean.

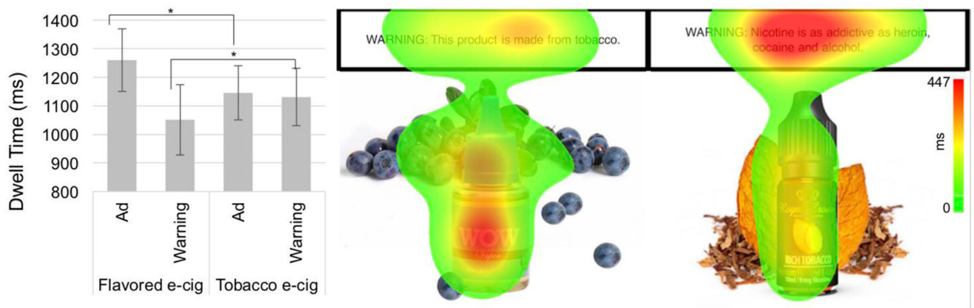

Figure 4.

Dwell time on the advertising content or the warning label for e-cigarette advertisements. Note: Dwell time (ms) was greater on the advertising content for fruit/sweet versus tobacco flavor e-cigarette advertisements, and greater on the warning label for tobacco versus fruit/sweet flavor e-cigarette advertisements ($F(1,24)=4.93$, $p=.04$, *$p<.05$ pairwise). Error bars indicate standard error of the mean. Heat maps display average dwell time (ms) across subjects for example fruit/sweet and tobacco flavor e-cigarette advertisements.

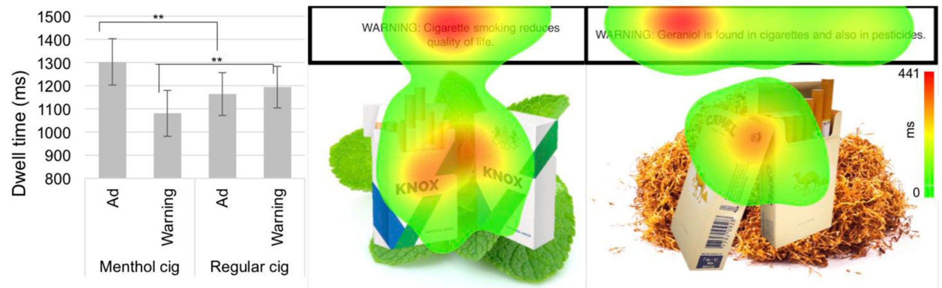

Figure 5.

Dwell time on the advertising content or the warning label for cigarette advertisements. Note: Dwell time (ms) was greater on the advertising content for menthol versus regular cigarette advertisements, and greater on the warning label for regular versus menthol cigarette advertisements (F(1,24)=18.05, p<.001, *p<.001 pairwise). Error bars indicate standard error of the mean. Heat maps display average dwell time (ms) across subjects for example menthol and regular cigarette advertisements.