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Adolescents' behavioral and neural responses to e-cigarette advertising

Yvonne Chen,

William Allen White School of Journalism and Mass Communications, University of Kansas, USA

Carina H. Fowler,

Department of Psychology and Neuroscience, University of North Carolina—Chapel Hill

Vlad B. Papa,

Hoglund Brain Imaging Center, University of Kansas Medical Center, USA

Rebecca J. Lepping,

Hoglund Brain Imaging Center, University of Kansas Medical Center, USA

Morgan G. Brucks,

Hoglund Brain Imaging Center, University of Kansas Medical Center, USA

Andrew T. Fox, and

Hoglund Brain Imaging Center, University of Kansas Medical Center, USA

Laura E. Martin

Hoglund Brain Imaging Center, University of Kansas Medical Center, USA

Abstract

Although adolescents are a group heavily targeted by the e-cigarette industry, research in cue-reactivity has not previously examined adolescents' behavioral and neural responses to e-cigarette advertising. This study addressed this gap through two experiments. In Experiment One, adult traditional cigarette smokers ($n=41$) and nonsmokers ($n=41$) answered questions about e-cigarette and neutral advertising images. The 40 e-cigarette advertising images that most increased desire to use the product were matched to 40 neutral advertising images with similar content. In Experiment Two, the 80 advertising images selected in Experiment One were presented to adolescents ($n=30$) during an fMRI brain scan. There was a range of traditional cigarette smoking across the sample with some adolescents engaging in daily smoking and others who had never smoked. Adolescents self-reported that viewing the e-cigarette advertising images increased their desire to smoke. Additionally, *all* participants regardless of smoking statuses showed significantly greater brain activation to e-cigarette advertisements in areas associated with cognitive control (left middle

Corresponding author: Yvonne Chen, William Allen White School of Journalism and Mass Communications, 1435 Jayhawk Blvd., Room 205C, University of Kansas, Lawrence, KS 66046, USA, 1-785-264-0613, y.chen@ku.edu.

Authors contribution

YC and LEM were responsible for the study concept and design. VBP, RJL, MGB, and ATF provided feedback on the study design. YC collected the behavioral data in Experiment One. CHF and VBP acquired the fMRI data in Experiment Two. YC performed data analysis for Experiment One, and CHF, VBP, and LEM performed data analysis for Experiment Two. RJL and VBP assisted with interpretation of findings for Experiment One and Experiment Two, respectively. YC, LEM, and CHF drafted the manuscript. All authors critically reviewed content and approved final version for publication.

frontal gyrus), reward (right medial frontal gyrus), visual processing/attention (left lingual gyrus/fusiform gyrus, right inferior parietal lobule, left posterior cingulate, left angular gyrus), and memory (right parahippocampus, left insula). Further, an exploratory analysis showed that compared to age-matched nonsmokers ($n=7$), adolescent smokers ($n=7$) displayed significantly greater neural activation to e-cigarette advertising images in the left inferior temporal gyrus/fusiform gyrus, compared to their responses to neutral advertising images. Overall, participants' responses to e-cigarette advertisements suggest a need to further investigate the long-run impact of e-cigarette advertising on adolescents.

Keywords

E-cigarettes; advertising; adolescents; cue reactivity; fMRI

Introduction

Cigarette smoking continues to be the leading preventable cause of disease and death in the U.S. Although the adult smoking rate of traditional cigarettes is at a 50-year low, the tobacco industry has promoted a new type of nicotine delivery product — e-cigarettes — in mass media to attract new users, specifically adolescents (American Legacy Foundation 2014). As one of the most commonly seen electronic nicotine delivery systems (ENDS), e-cigarettes are powered by small batteries and deliver an aerosol by heating a nicotine solution that users inhale. Compared to traditional cigarettes, e-cigarettes are relatively unregulated and are controversial in part because they are popular among youth. Recent evidence indicates that use of e-cigarettes is associated with adolescents' intention to use traditional tobacco products later in life (Leventhal *et al.* 2015), with some work showing that teens who used e-cigarettes were more likely to use traditional products one year later (Barrington-Trimis *et al.* 2016).

The number of adolescents using e-cigarettes in the past five years has increased rapidly; e-cigarettes are now the most popular nicotine products among middle and high school students (Arrazola *et al.* 2015). A recent survey found that, among high school students, there has been a 900 percent increase in e-cigarette use (defined as using e-cigarettes on 1 day during the past 30 days) between 2011 and 2015; in 2011, 1.5 percent of high school students reported e-cigarette use compared to 16 percent in 2015 (FDA 2016a).

The growing popularity of e-cigarettes has brought a new level of public health concern. The main ingredient in e-cigarettes, nicotine, is a highly addictive neurotoxin that impacts adolescents' brain development (CDC 1998). Early exposure to nicotine also leads to nicotine addiction (Benowitz 2010). In addition, dual-use of cigarettes and e-cigarettes is an emerging pattern among both high school students (Anand *et al.* 2015; Dutra and Glantz 2014) and college students (American Legacy Foundation 2014; Sutfin *et al.* 2013).

E-cigarette marketing and its effects on adolescents

A probable contributing factor to the recent increase in adolescent use of e-cigarettes is the corresponding increase in e-cigarette advertising. E-cigarette advertising costs in the U.S.

have increased in recent years, from \$6.4 million in 2011 to \$115 million in 2014 (CDC 2016). In contrast to advertisements for traditional tobacco products like cigarettes, e-cigarette advertisements are relatively unregulated. Although e-cigarette regulation is a recent policy development (FDA 2016b), the current regulations limit e-cigarette advertising and promotion within the context of promotional items and sponsorship, neither of which addresses whether e-cigarettes can be freely advertised in mass media without any restrictions (FDA 2016c).

Further, e-cigarettes are often “flavored” to taste like different substances, which has been found to make them particularly appealing to youth (American Legacy Foundation 2014; Pepper *et al.* 2016). Two recent studies using nationally representative samples have found that adolescents initiate e-cigarette use with a flavored product (Ambrose *et al.* 2015; Corey *et al.* 2015). The growing fields of neuroeconomics and neuromarketing offer a new approach to understanding the impact of e-cigarette advertising. Specifically, the approach enables researchers to examine the underlying neural mechanisms involved in processing e-cigarette advertisements that are likely associated with future behaviors, such as the desire to smoke traditional cigarettes.

Cue reactivity in the context of tobacco advertising

Neuromarketing research has examined neural responses to product brands and logos (Bruce *et al.* 2014; Bruce *et al.* 2013; McClure *et al.* 2004; Schaefer 2009; Schaefer *et al.* 2006). Overall, these studies show increased brain activation in self-referential or cognitive control regions (dorsolateral prefrontal cortex, anterior cingulate cortex) and reward-processing brain regions (e.g. ventral striatum, ventromedial prefrontal cortex) as individuals evaluate the brand (Martin 2014). These results are similar to those found in fMRI studies of cue-reactivity.

Cue-reactivity describes a body of work in which individuals who engage in a particular addictive behavior are exposed to cues associated with that behavior (e.g. a smoker sees cigarette images); the individual’s responses to the cues may then be compared to their responses to neutral cues (e.g. non-smoking images such as a pack of pencils), or their peak self-reported responses to the cues may be measured (Carter and Tiffany 1999; Sayette and Tiffany 2013). Cue-reactivity is the most common approach to understanding the neural mechanisms associated with cigarette smoking (Engelmann *et al.* 2012). Previous neuroimaging work has found that smoking cues elicit greater brain activation compared to neutral cues in regions of the brain associated with reward and cognitive control among adult smokers and adolescent light smokers (David *et al.* 2005; Due *et al.* 2002; Engelmann *et al.* 2012; McClernon *et al.* 2005; Rubinstein *et al.* 2011; Wilson *et al.* 2005). This finding is consistent with the dual systems model of addiction, which posits that addiction stems from the brain’s cognitive control network failing to suppress more automatic responses from reward regions of the brain when an individual faces a desired stimulus (McClure and Bickel 2014).

Although several neuroimaging cue-reactivity studies have been conducted using smoking cues, to our knowledge only one study has used tobacco print advertisements (Vollstadt-Klein *et al.* 2010). Vollstadt-Klein *et al.* (2010) found widespread prefrontal activation to

cigarette compared to neutral advertisements; however, no differences were found between smokers and nonsmokers. Furthermore, only one study to our knowledge has examined brain responses to e-cigarette stimuli (Nichols *et al.* 2016). Nichols *et al.* (2016) focused on the development of e-cigarette and neutral video stimuli (e.g., videos of e-cigarette use versus videos of electronic toothbrush use), as opposed to the development of e-cigarette advertising stimuli.

E-cigarettes' growing popularity among adolescents, the unknown effects of long-term e-cigarette use, and the association of e-cigarette use with adolescents' later use of traditional tobacco products have raised concerns (Barrington-Trimis *et al.* 2016; CDC 2016; FDA 2016a; Leventhal *et al.* 2015; CDC 2016). Exploring adolescents' behavioral and brain responses to e-cigarette advertisements expands previous neuromarketing and smoking cue-reactivity studies and has implications for tobacco control policy and behavioral interventions. Our study is novel in that it is the first to use ecologically valid e-cigarette advertisements, which are designed to encourage product use and contain usage cues, to examine cue-reactivity in adolescents.

Given that e-cigarettes are currently more popular among adolescents than traditional tobacco products (Arrazola *et al.* 2015) and that use of e-cigarettes has been linked to later use of traditional tobacco products (Barrington-Trimis *et al.* 2016), this study sought to explore the neural and behavioral processes by which e-cigarette advertising might evoke adolescents' desire to use traditional tobacco products. To accomplish this, we examined differences in behavioral responses and brain responses to e-cigarette versus neutral advertising images in adolescents of different smoking statuses. Secondly, we conducted an exploratory analysis examining differences in behavioral and brain responses between smokers and nonsmokers of traditional cigarettes, where a smoker was defined as having smoked at least one cigarette in the past 30 days. We hypothesized that there would be greater brain activation in the reward and cognitive control networks in response to e-cigarette advertising images across all participants, and that these differences would be larger in smokers compared to nonsmokers. Two experiments were conducted to address these hypotheses. Experiment One validated advertising stimuli, and Experiment Two explored adolescents' behavioral and neural responses to these selected advertising stimuli.

Methods: Experiment One—Image Validation Study

Participants

The goal of Experiment One was to validate e-cigarette and neutral advertising images for use in a neuroimaging study (Experiment Two). Participants were recruited through an online subject panel from Qualtrics (Qualtrics, Provo, UT). An email was sent to solicit panel participants managed by Qualtrics between the ages of 18–25. A self-reported screener question “Do you currently smoke cigarettes?” was used to select smoker and nonsmoker participants.

A total of 385 participants responded to the email solicitation during a one-week period, and 82 participants (41 smokers and 41 nonsmokers, $M_{\text{age}}=22.60$) completed the validation study. The majority of the participants were female (71%; $n=58$) and white (65%, $n=53$).

One-third of the participants had completed some college (32.43%; $n=24$), one quarter were high school graduates (27.03%; $n=20$), one-fifth were college graduates (18.92%; $n=14$) and the remainder had not completed high school. Among participants who self-identified as smokers ($n=41$), 85.37% ($n=35$) had tried e-cigarettes and 56.10% ($n=23$) had used e-cigarettes more than once per day in the last 30 days.

Procedure

Image selection process—Researchers first selected 80 e-cigarette advertising images from various online resources, including the Stanford School of Medicine tobacco advertising database (SRITA, nd). During the selection process, the research team considered resolution, size, and orientation of these images for use in the MRI in Experiment Two. Neutral advertisements (non e-cigarette items, such as household, food, and cosmetic items) —also selected from various online resources (e.g., Google Images)—were chosen to match each e-cigarette advertisement on content, presence of faces, luminance, action, color, design, size, complexity, and orientation.

Participants viewed 160 images (80 e-cigarette advertisements and 80 neutral advertisements) that were randomly displayed in an online survey format. While viewing each image, participants answered three questions: (1) How likely are you going to try this product? (5-point scale from “very unlikely=5” to “very likely=1”); (2) How happy or sad does it make you feel? and (3) How excited or bored does it make you feel? Responses for the last two questions were obtained using the Self-Assessment Manikin (SAM), “a non-verbal pictorial assessment tool that measures pleasure and arousal” (Bradley and Lang, 1994), which has been widely used in validation studies of emotional stimuli.

Results from Experiment One

As the goal of the larger project was to investigate the impact of e-cigarette advertising on adolescents’ smoking behaviors, this image validation study used smokers’ responses to “how likely are you going to try this product?” as the primary selection criterion for e-cigarette advertisements. This was asked because we were interested in selecting e-cigarette advertisements that generally elicited nicotine craving, non-specific to e-cigarettes or cigarettes. The 40 e-cigarette advertisements with the highest average response to the primary question among smokers were selected. Their matching advertisements were then selected as neutral advertisements.

A t -test comparing traditional cigarette smokers’ and nonsmokers’ responses to these top 40 e-cigarette advertisements found that smokers reported that they were more likely to try the product after viewing the advertisements ($M=2.43$, $SD=0.89$) than nonsmokers ($M=3.76$, $SD=0.98$), $t(80)=-6.45$, $P<.001$). Lower numbers on this scale represent a greater likelihood of trying the product. Smokers also rated these e-cigarette advertisements as more pleasurable ($M=2.53$, $SD=0.81$) than nonsmokers ($M=3.49$, $SD=0.85$), $t(80)=-5.23$, $P<.001$). Additionally, smokers rated these e-cigarette advertisements as more arousing ($M=2.75$, $SD=0.89$) than nonsmokers ($M=3.73$, $SD=0.82$), $t(80)=-5.21$, $P<.001$). No differences between smokers and nonsmokers’ responses to neutral advertisements were found across these three measures (i.e., likelihood of trying, pleasure, and arousal).

Methods: Experiment Two—Neuroimaging Study

Participants

Participants were 30 adolescents, aged 14–21 ($M_{\text{age}}=16.96$, $SD=2.39$). Twelve participants were over 18. Close to half of the participants were female (43.3%) and self-categorized as Caucasian (56.7%). One participant was excluded due to an incidental finding on the anatomical MRI, leaving 29 participants in the fMRI analyses. All participants were included in the behavioral analysis. Participants were a community sample recruited from a mid-western city and a large mid-western town using fliers, internet advertisements, and word-of-mouth. Eligible participants were contacted by phone to schedule a study visit.

To be classified as a smoker, a participant must have smoked at least one cigarette in the last 30 days. Using this criterion, 24% of participants were smokers ($n=7$). Nonsmokers were defined as individuals who had smoked fewer than 10 cigarettes in their lifetime. Because of difficulties recruiting smokers under 18, all smokers were aged 18–21. Nonsmokers were aged 14–21. Information about participants' prior e-cigarette use was also collected. Eight participants — five smokers and three nonsmokers — reported previously using e-cigarettes. For further information on our sample's experience with e-cigarettes and traditional cigarettes, as well as their frequency of use, see Tables 1–3.

Exclusion criteria for study participation were MRI contraindication (e.g., metal implants), claustrophobia, history of seizures or head trauma, current psychiatric diagnosis and treatment, and left-handedness. The University's Human Subjects Committee approved the current study. Informed consent was obtained from all participants. For participants under 18, both parental consent and child assent were acquired.

Procedures

The study visit began with an informed consent and safety screening process in a private consult room. Participants under 18 were accompanied by a parent for this portion of the experiment. After safety screening and consent, parents of children under 18 left the room, and participants completed a brief one-on-one pre-scan interview with the researcher. In the interview, participants were asked about their education, substance use, and cigarette use. Female participants were also asked to confirm the date of last menstrual period and that they were neither pregnant nor had an intrauterine device. Participants then finished a pre-scan questionnaire on RedCap (Harris *et al.* 2009) using an iPad Mini, a practice session of the fMRI task (described below), and a 50-minute MRI. After the MRI, participants were provided with a \$75 gift card as compensation. The entire visit lasted approximately two hours.

Pre-Scan Measures

Drug use—Data on participants' drug use were obtained through the pre-scan questionnaire and the pre-scan interview with the researcher. See Appendix 1 for more details about those questions.

fMRI task

In the scanner, participants viewed 40 e-cigarette and 40 neutral advertising images. The images were selected based on the results of Experiment One, and were presented in an event-related design, with the order of the advertising images randomized for each participant. Each advertising image displayed was part of a matched pair: for every e-cigarette advertising image, there was a neutral advertising image matched on pleasure and arousal ratings given by the participants, as well as other matching criteria described in Experiment One. After every image—e-cigarette or neutral—participants were asked to respond to the question: “How much does this make you want to smoke?” on a scale ranging from 1 (Not at all) to 9 (Extremely). This question, which reflects the purpose of the study, explicitly referenced participants’ desire to smoke traditional cigarettes, not vape e-cigarettes. Participants used a joystick in the scanner to make their selection.

The experiment consisted of four runs. Each run displayed 20 images — 10 e-cigarette and 10 neutral images. At the start of each run, a black fixation cross appeared on a grey background for 10–13 seconds. Then, an advertising image was displayed for 5 seconds. A fixation cross then appeared for 2.5–12.0 s. Next, the rating scale and corresponding question about desire to smoke appeared on the screen until participants responded. For an additional 0.5 seconds, the participant’s choice was highlighted on the screen. A fixation cross appeared at the end of each trial for 2.5–17.0 s. The duration of each fixation cross on the screen was jittered to allow for the separation of the hemodynamic response to the advertisements versus to the rating scales. The mean length of each run was 6.39 minutes ($SD = 0.45$ minutes). Because the scale appeared on the screen until participants responded, the duration of the task varied from run to run and participant to participant ranging from 5.62 to 8.21 minutes. An example trial is shown in Figure 1.

Behavioral analysis

Behavioral data were analyzed using R 3.3.1. To accompany our neuroimaging analysis of e-cigarette versus neutral advertising images for all participants, a t -test was conducted to assess whether or not all participants’ joystick ratings for the question, “How much does this make you want to smoke?” differed significantly for the e-cigarette versus neutral advertising images. T -tests were also conducted to examine whether or not smokers of traditional cigarettes and a subset of the nonsmokers (matched with smokers on age range) differed in their ratings of e-cigarette and neutral images (i.e., differed in self-report of how much the images made them want to smoke). Paired t -tests also compared nonsmokers’ ratings of e-cigarette versus neutral images as well as smokers’ ratings of e-cigarette versus neutral images.

fMRI acquisition and analysis

Scanning was performed on a 3-Tesla full body Siemens Skyra scanner (Siemens, Erlangen, Germany) fitted with a 20-channel head coil. We acquired one anatomical scan and four functional scans. T1-weighted 3D MPRAGE anatomic images were obtained (TR/TE 23/2ms, flip angle 9°, FOV = 256 mm, matrix = 256×176 , slice thickness = 1 mm). These images provided slice localization for functional scans, Talairach transformation (Talairach and Tournoux 1988), and coregistration with fMRI data. Gradient echo blood oxygen level

dependent (BOLD) scans were acquired in 43 interleaved slices at a 40° angle to the AC/PC line (TR/TE = 2300/2.01ms, flip angle = 90°, matrix = 80 × 80, slice thickness = 3 mm, in-plane resolution = 2.9 mm, for 198 volumes). All functional scans were acquired at a 40° angle to the AC-PC line to optimize orbitofrontal cortex (OFC) signal by minimizing susceptibility artifact and all participants were positioned in the scanner so that the angle of the AC-PC plane was between 7.8° and 22°. Because one participant was small, we had to adjust the head angle to 7.8°. Otherwise, the angle range was between 15°–22°.

Data pre-processing and statistical analyses were performed in AFNI (Medical College of Wisconsin) (Cox 1996). Preprocessing steps included motion correction, alignment, spatial smoothing and spatial normalization. The fMRI images were realigned to the third slice collected in each run to correct for motion. The images were spatially smoothed with a 4 mm FWHM Gaussian kernel. Anatomic images were aligned to functional images and spatially normalized to Talairach stereotaxic space (Talairach and Tournoux 1988) using AFNI's automated algorithm. Statistical contrasts were conducted using multiple regression analysis with motion parameters included as nuisance regressors. Regressors representing the experimental conditions (e.g., e-cigarette advertising images and neutral advertising images) were entered into the multiple-regression analysis using a random-effects model. The duration modulated block basis function in AFNI was used so that experimental conditions and time to response were taken into account.

The primary data analysis focused on a whole-brain voxelwise *t*-test to determine brain activation (i.e., percent signal change from baseline) differences between e-cigarette and neutral advertising images. Secondary analyses examined group differences between smokers and nonsmokers for the e-cigarette vs. neutral contrast. The exploratory fMRI analysis of smokers' versus nonsmokers' differential activations to e-cigarette and neutral advertising images was conducted by contrasting the seven smokers to seven age-matched nonsmokers to account for the sample's imbalance in age and smoking status. To correct for multiple comparisons, the spatial autocorrelation function (acf) option was used in AFNI's 3dFWHMx to estimate intrinsic smoothness and 3dClustSim to estimate probability of false positives using the corrected approach recommended by Eklund *et al.* (2015). Cluster size corrections for multiple comparisons at $\alpha < 0.05$ over the whole-brain were achieved with voxel-wise $P < .005$ and a minimum cluster volume of 656 mm³.

Finally, to improve understanding of the significance of the regions activated by the fMRI task, a quantitative reverse inference was also conducted. ROI maps of each of the surviving clusters were uploaded into the NeuroSynth decoder (<http://www.neurosynth.org>), a component of an online platform that contains interactive meta-analyses of 3,107 search terms. The NeuroSynth decoder computed the voxel-wise Pearson correlation between the uploaded cluster image file and the meta-analytical image file linked to each of the 3,107 terms. For each surviving cluster, the top ten functional terms were reported, following the example set in Yang *et al.* (2016). Words that were generic in meaning (e.g., presumably, substantially), terms that referred to biological regions (e.g., hippocampus), and/or terms that referred to specific tasks (e.g., fixation, task-based), were not included. Redundant terms were also removed (e.g., mind tom, theory of mind, tom, etc.).

Results: Experiment two

Joystick ratings for all participants in response to the question “How much does this make you want to smoke?” differed between the e-cigarette ($M=2.45$, $SD=1.82$) versus neutral advertising images ($M=1.45$, $SD=.62$), $t(29)=3.95$, $P<.001$. The same trend also applies to smokers. Smokers of traditional cigarettes and matched nonsmokers differed in their ratings of e-cigarette versus neutral advertising images, with smokers giving higher ratings to the e-cigarette images ($M=5.39$, $SD=1.12$) than nonsmokers ($M=1.64$, $SD=0.64$), $t(12)=7.68$, $P<.001$. Within the smokers, a paired t -test revealed that smokers also gave higher ratings to the e-cigarette advertising images than to the neutral advertising images, $t(6)=7.52$, $P<.001$. Within the nonsmokers, a paired t -test also revealed differences in their ratings of the e-cigarette ($M=1.55$, $SD=.65$) versus neutral advertising images ($M=1.21$, $SD=.31$), $t(22)=3.15$, $P<.01$.

Across all participants of different smoking statuses, significantly greater brain activation to e-cigarette versus neutral advertising images was found in the left middle frontal gyrus, right medial frontal gyrus, left posterior cingulate, left lingual gyrus, right parahippocampal gyrus, left angular gyrus, and right inferior parietal lobule at $\alpha < 0.05$. See Table 4 and Figure 2. Also, see the supplemental table for a complete list of results from the quantitative reverse inference analysis, which displays the correlations between each reported region and the top ten functional search terms with which it is associated.

No significant differences were found between smokers of traditional cigarettes and nonsmokers in response to e-cigarette compared to neutral advertising images at the neural level. In addition, we explored within group differences and found that within smokers, greater activation to e-cigarette advertising images was observed in the left inferior temporal gyrus/fusiform gyrus at $\alpha < 0.05$. Within the nonsmokers, there were no statistically significant differences in neural response to the different types of advertising images. See Table 5 for within smoker analysis results.

Discussion

Expanding on prior cue reactivity and tobacco advertising research with adults (Vollstadt-Klein *et al.* 2010), the current study is the first, to our knowledge, that has validated e-cigarette advertising stimuli and explored adolescents’ behavioral and neural responses to e-cigarette advertising. Experiment One validated a set of 40 e-cigarette and matched neutral advertisements based on young adult smokers’ self-reported rating. Young adult smokers responded highly to e-cigarette advertisements, expressing more desire to try advertised e-cigarette products than nonsmokers.

Experiment Two extends Experiment One by measuring adolescents’ behavioral and brain responses to e-cigarette advertising. In this study, adolescents of varying smoking statuses responded more to e-cigarette advertisements than neutral advertisements in terms of whether the advertisements made them want to smoke traditional cigarettes. This behavioral result is consistent with the fMRI outcomes. Our fMRI analysis revealed greater brain activation among *all* participants in response to the e-cigarette versus neutral advertising

images. Our analysis displayed increased activation in response to areas associated with cognitive control (left middle frontal gyrus), reward (right medial frontal gyrus), visual processing/attention (left lingual gyrus/fusiform gyrus, right inferior parietal lobule, left posterior cingulate, left angular gyrus), and memory (right parahippocampus) (Engelmann *et al.* 2012; Kober *et al.* 2010; Tang *et al.* 2012).

These results overlap with regions found in smoking cue reactivity studies as shown in a meta-analysis by Engelmann *et al.* (2012). Notably, the Talairach coordinates of the peak activations within the left posterior cingulate, right medial frontal gyrus, and left angular gyrus are spatially proximate to the suprathreshold clusters of smoking > neutral cue fMRI activation reported in Engelmann *et al.*'s 2012 meta-analysis. Further, the quantitative reverse inference analysis indicated that the observed regions also correlated with the extended visual system, an area that Engelmann *et al.* (2012) found to be more reactive to smoking cues than neutral cues. These findings also suggest that participants of different smoking statuses may consider e-cigarette stimuli to be more arousing than neutral images. This is important given that we carefully matched neutral advertisements with e-cigarette stimuli and is significant given that the e-cigarette industry specifically targets adolescents (American Legacy Foundation 2014; CDC 2016).

The current results are consistent with Vollstadt-Klein *et al.* (2010), the only other study that has examined cue-reactivity using tobacco advertisements. These authors demonstrated greater brain responses to smoking compared to neutral advertisements and no significant difference in brain responses between adult smokers and nonsmokers. To our knowledge, there is only one cue-reactivity study of e-cigarette stimuli (Nichols *et al.* 2016), which found a main effect of e-cigarette cues in the sensorimotor regions when adult e-cigarette smokers viewed videos of individuals using e-cigarettes. The difference between these findings and our own may stem from the type of stimuli used (i.e., videos versus viewing e-cigarette advertisements) between our study and this previous study on e-cigarettes.

Unlike previous cue-reactivity studies comparing smokers to nonsmokers which show significant differences between smoking and neutral cues in smokers but not in nonsmokers (David *et al.* 2005; Due *et al.* 2002; McClemon *et al.* 2005), the current study — like Vollstadt-Klein *et al.* (2010) — did not find differences in brain responses in smokers compared to nonsmokers when viewing e-cigarette/smoking vs. neutral advertisements. There are many possible reasons for this discrepancy. First, like Vollstadt-Klein *et al.* and unlike most other studies of cue-reactivity, our study used real advertisements specifically designed to increase arousal and attention. Perhaps, for an adolescent, simply seeing someone smoke an e-cigarette is not as powerful as seeing an advertisement that makes using an e-cigarette seem enticing. Second, the current study may have been underpowered to show group differences given the small sample size of smokers.

Within-group analyses, however, suggested greater activation in temporal and prefrontal regions to e-cigarette compared to neutral advertising images in smokers and no differences in nonsmokers. Additionally, in behavioral analysis, smokers rated the e-cigarette advertising images as making them want to smoke more, both compared to neutral advertisements, and compared to nonsmokers. This pattern of activation within smokers,

coupled with significant behavioral results, suggests that e-cigarette advertising images may be particularly appealing to smokers and may reinforce their current smoking behavior as well as possibly encourage future e-cigarette use among individuals who currently use traditional tobacco products.

Limitations

This study is not without limitations. First, this study has a small sample size with few participants who self-reported using traditional cigarettes or e-cigarettes. Because the goal of this study was to examine the neural and behavioral processes by which e-cigarette advertising might evoke adolescents' desire to use traditional tobacco products, our analyses focused broadly on the responses of all adolescents to e-cigarette versus neutral advertisements. Work in this paper comparing the responses of smokers and nonsmokers was limited by the small number of smokers ($n = 7$) and age-matched nonsmokers ($n = 7$) and was, for this reason, exploratory. Future work should compare the responses of equal numbers of smokers and nonsmokers.

Additionally, all of the smoker participants in this study were over 18. As cigarette use among middle and high school students is at an all-time low in the U.S., recruiting adolescent smokers is an increasingly challenging task. However, it should be noted that some studies of risk-taking behaviors consider adolescence to extend until age 21 (Steinberg 2008). Nevertheless, we were still able to recruit seven adolescent smokers of traditional cigarettes and pair them with nonsmokers for an exploratory analysis.

Finally, we cannot exclusively conclude that the observed effects only pertain to adolescents, as there was no other developmental group with whom to compare. Work comparing the responses of individuals during different developmental periods and with a larger sample of smokers would be particularly useful. This manuscript is a first step toward a more comprehensive understanding of the influences e-cigarette advertising images may have on potential users of traditional tobacco products. Future longitudinal research is necessary to empirically address the neural processes that support the connection between e-cigarette use and future traditional tobacco product use.

In addition, given that one of the few known studies on tobacco advertising only recruited male participants (Vollstadt-Klein *et al.* 2010), our study recruited female participants in an effort to balance the experimental design. Although our sample size is too small to warrant additional analyses for gender differences, future research should follow the suggestion from prior research (Field and Duka, 2004; McClernon *et al.* 2008) to investigate how gender impacts participant cue reactivity. We also noticed a pattern of poly-drug use behavior among the smokers during the initial screening. Although we were able to measure their prior drug use experience, their frequency of drug use (aside from cigarettes and e-cigarettes) was not directly measured. Future research should consider how these smokers' substance use history impacts their interactions with e-cigarette advertising stimuli. Finally, because adolescents use e-cigarettes for various reasons (e.g., multiple flavors, the "cool" factor, peer/family influences, and curiosity) (Kong *et al.* 2014), future research should explore how attitudes toward e-cigarettes moderate the way in which adolescents respond to e-cigarette advertising.

Conclusions

The popularity of e-cigarettes among adolescents and their unknown health consequences continue to be a public health concern. This study is novel in that it demonstrates that, regardless of smoking statuses, adolescents demonstrated an elevated neural response to e-cigarette versus neutral advertisements and rated behaviorally that e-cigarette advertisements make them want to smoke more than neutral advertisements. As seen in previous meta-analysis of smoking cue-reactivity, adolescents showed increased brain activations to e-cigarette compared to neutral advertisements in prefrontal and visual processing regions. Additionally, exploratory within group analysis shows that smokers responded to e-cigarettes images significantly more than to neutral images, both behaviorally and neurally. Because e-cigarette advertising is substantially less regulated than tobacco advertising, continuing to investigate why adolescents respond more strongly to e-cigarette advertising images than to carefully matched neutral advertising images may help future tobacco control efforts address the increasing popularity of e-cigarettes among youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1. Drug Use Questions in the Pre-Scan Questionnaire

The pre-scan questionnaire asked participants how many cigarettes they had smoked in their lifetime, how many cigarettes they had smoked in the past 30 days, the age at which they first tried smoking, and if they had smoked cigarettes for longer than 6 months. The pre-scan questionnaire also asked participants how many times they had used e-cigarettes in the past 30 days, and the age at which they first tried e-cigarettes. During the confidential questions interview, participants were asked if they had ever recreationally used any type of substance, drug, or prescription medication. If yes, the participants were asked to enumerate those illegal and/or prescription drugs that they had used. Participants were only asked about frequency of use for e-cigarette and tobacco products, not for illegal or prescription drugs.

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Figure 1.
fMRI design including examples of e-cigarette and neutral advertisements

Figure 2.

Activation Maps Among Participants of Varying Degree of Smoking Statuses

Note: Activation maps showing BOLD response to e-cigarette ads compared to neutral ads in participants of varying degree of smoking statuses, $\alpha < .05$ corrected for multiple comparisons.

Table 1

Distribution of responses to the question: About how many cigarettes have you smoked in your entire life?

Option	Number of Responses
I have never smoked cigarettes, not even 1 or 2 puffs	19
1 or more puffs, but never a whole cigarette	2
1 cigarette	0
2 to 5 cigarettes	1
6 to 15 cigarettes	0
16 to 25 cigarettes	1
26 to 99 cigarettes	1
100 or more cigarettes	6

Table 2

Distribution of responses to yes-no use questions

	Yes	Yes – Smokers	Yes - Nonsmokers
Have you ever tried cigarette smoking, even 1 or 2 puffs?	11	7	4
Have you ever tried electronic cigarettes, or e-cigs, vape pens, or vapes, such as Blu, NJOY, or 21 st Century Smoke, even just one time?	8	5	3
Have you ever used any type of illegal substances (i.e. marijuana, heroin, prescription drugs not prescribed to you?)	9	6	3

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Table 3

Distribution of e-cigarette and cigarette use in the past 30 days

	0 days	1 or 2 days	3 to 5 days	6 to 9 days	10 to 19 days	27 or more days
In the past 30 days, did you use electronic cigarettes, or e-cigs, vape pens, or vapes, such as Blu, NJOY, or 21 st Century Smoke?	26	2	1	0	1	0
During the past 30 days on how many days did you smoke at least one cigarette?	23	0	1	1	2	3

Table 4

E-cigarette vs. Neutral Advertisement Activations

Region	x	y	z	Cluster Volume (mm ³)	t-score
Left Middle Frontal Gyrus	-54	21	26	1406	4.83
Right Medial Frontal Gyrus	9	56	16	750	5.82
Left Posterior Cingulate	-6	-36	26	2219	4.37
Left Lingual Gyrus/Fusiform Gyrus	-21	-69	-6	10,156	6.02
Right Parahippocampal Gyrus	26	-56	-4	1437	5.22
Left Angular Gyrus	-49	-66	34	4469	5.67
Right Inferior Parietal Lobule	61	-34	36	2641	-5.34
Right Inferior Parietal Lobule	34	-54	41	1937	4.98

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Table 5

Smoker: E-cigarette vs. Neutral Advertisement Activations

Region	x	y	z	Cluster	Volume (mm ³)	t-score
Left Inferior Temporal Gyrus/Fusiform Gyrus	-54	-46	-14		766	8.79