Addictive Behaviors Reports 3 (2016) 28–32

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

Short communication

Young adult smokers' neural response to graphic cigarette warning labels

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ARTICLE INFO

Article history:
Received 3 December 2015
Received in revised form 9 February 2016
Accepted 10 February 2016
Available online 13 February 2016

Keywords:
Graphic warning label
Cigarettes
Neuroimaging
Young adults

ABSTRACT

Introduction: The study examined young adult smokers' neural response to graphic warning labels (GWLs) on cigarette packs using functional magnetic resonance imaging (fMRI).

Methods: Nineteen young adult smokers (*M* age 22.9, 52.6% male, 68.4% non-white, *M* 4.3 cigarettes/day) completed pre-scan, self-report measures of demographics, cigarette smoking behavior, and nicotine dependence, and an fMRI scanning session. During the scanning session participants viewed cigarette pack images (total 64 stimuli, viewed 4 s each) that varied based on the warning label (graphic or visually occluded control) and pack branding (branded or plain packaging) in an event-related experimental design. Participants reported motivation to quit (MTQ) in response to each image using a push-button control. Whole-brain blood oxygenation level-dependent (BOLD) functional images were acquired during the task.

Results: GWLs produced significantly greater self-reported MTQ than control warnings ($p < .001$). Imaging data indicate stronger neural activation in response to GWLs than the control warnings at a cluster-corrected threshold $p < .001$ in medial prefrontal cortex, amygdala, medial temporal lobe, and occipital cortex. There were no significant differences in response to warnings on branded versus plain cigarette packages.

Conclusions: In this sample of young adult smokers, GWLs promoted neural activation in brain regions involved in cognitive and affective decision-making and memory formation and the effects of GWLs did not differ on branded or plain cigarette packaging. These findings complement other recent neuroimaging GWL studies conducted with older adult smokers and with adolescents by demonstrating similar patterns of neural activation in response to GWLs among young adult smokers.

1. Introduction

Graphic warning labels (GWLs) for cigarette packs have been implemented in more than 65 countries (Sanders-Jackson, Song, Hiilamo, & Glantz, 2013) based on evidence that they are more effective than text-only warnings for reducing smoking (Noar et al., 2015). Research can continue to inform GWL implementation in at least two important ways. Studies investigating optimal approaches to designing GWL messages can inform changes to GWLs to ensure sustained effectiveness. In contexts such as the U.S. where law requires GWLs (U.S. Congress, 2009) but lawsuits have delayed their implementation, research addressing concerns raised by the courts can support implementation (Kraemer & Baig, 2013).

Studies investigating GWLs have relied largely on self-report methods, demonstrating that GWLs generate stronger cognitive and emotional responses, are better recalled, and produce stronger motivation to quit smoking than text-only warnings (Azagba & Sharaf, 2013; Borland, Wilson, Fong, et al., 2009; Emery, Romer, Sheerin, Jamieson, & Peters, 2014; Hammond, Fong, McNeill, Borland, & Cummings, 2006; Nonnemaker, Choiniere, Farrelly, Kamyab, & Davis, 2015; Peters, Romer, Slovic, et al., 2007). However, self-report measures of such constructs do not fully predict future behavior, and biobehavioral methods may help better understand GWL impact (Armitage, Norman, Alganem, & Conner, 2015; Falk, Berkman, Whalen, & Lieberman, 2011; Webb & Sheeran, 2006).

Functional magnetic resonance imaging (fMRI) can ascertain information on smokers' responses to GWLs that is not readily captured by self-report (Falk, 2010). fMRI-measured neural activity in brain regions

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http://dx.doi.org/10.1016/j.abrep.2016.02.001

involved in emotional (i.e., amygdala) and cognitive (i.e., medial prefrontal cortex) processing of antismoking messages predicts cessation outcomes, explaining ≥20% additional variance in cessation behavior than self-report responses to messages (Chua, Ho, Jasinska, et al., 2011; Falk, Berkman, Mann, Harrison, & Lieberman, 2010; Falk et al., 2011; Jasinska et al., 2012; Wang, Ruparel, Loughead, et al., 2013). Two studies also showed that GWLs produce activation in brain regions involved with emotion, cognition, and memory formation among current smokers (Newman-Norlund, Thrasher, Fridriksson, et al., 2014; Wang, Lowen, Romer, Giorno, & Langleben, 2015). Other research links frontoinsular neural activity to craving reduction in response to GWLs (Do & Galvan, 2015) and demonstrates that neural responses in similar brain systems implicated in motivation, cognition, and memory are associated with population-level success of GWL-type messages for promoting cessation (Falk, O'Donnell, Tompson, et al., 2016).

This study extends this research by investigating young adult smokers' neural responses to GWLs and assessing whether effects differ by branded or plain cigarette packaging. Studies of neural responses to GWLs have been conducted with older adult smokers (Newman-Norlund et al., 2014; Wang et al., 2015) and adolescents (Do & Galvan, 2015). However, young adults are a priority for tobacco control due to high rates of smoking experimentation, frequent transitions to regular smoking, and the high prevalence of smoking in this group (Do & Galvan, 2015; Falk et al., 2016). Plain packaging is hypothesized to draw greater attention to and increase the effects of GWLs by eliminating tobacco industry branding, but this has not yet been tested using a neuroimaging paradigm. Examining young adult smokers' neural response to GWLs on branded and plain packaging can extend the evidence surrounding potential mechanisms of GWL action and inform future research and policy.

2. Methods

2.1. Participants and procedures

Participants were recruited through online and community-based advertisements and screened for eligibility. Eligible participants were ages 18 to 30 years, current smokers defined using validated epidemiologic measures and criteria as smoking ≥100 lifetime cigarettes and now smoking cigarettes all or some days (Agaku, King, Husten, et al., 2014). Participants also reported Camel, Marlboro, or Newport as their preferred cigarette brand. The latter criterion was imposed to tailor experimental stimuli to smokers' preferred brand, described below. All participants also met fMRI safety requirements (Kanal, Borgstede, Barkovich, et al., 2002). Eligible participants were scheduled for an in-person appointment to provide informed consent and complete a pre-scan, self-report assessment and fMRI scanning session. Prior to the appointment, participants were instructed to smoke as they normally would that day. All participants provided written informed consent, and all procedures were approved by an institutional review board.

2.2. Pre-scan measures

Pre-scan measures included demographics, cigarette smoking behaviors (Agaku et al., 2014), nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), and motivation to quit smoking (Mays, Niaura, et al., 2015; Mays, Turner, et al., 2015).

2.3. Experimental design

The study employed a two (graphic warning or control) by two (branded or plain cigarette pack) within-subjects design. Stimuli were adapted from a prior experiment (Mays, Niaura, et al., 2015; Mays, Turner, et al., 2015). GWLs tested were four of the warnings proposed for use in the U.S. by the Food and Drug Administration (FDA) communicating the smoking-associated risks of lung disease, cancer, stroke/heart attack, and mortality. These four warnings have been effective at eliciting cognitive and emotional responses in prior studies with young adults (Cameron, Pepper, & Brewer, 2015; Hammond, Reid, Driezen, & Boudreau, 2013). Similar to another recent study (Wang et al., 2015), control warnings included the same warning text as GWLs but were composed of geometric shapes overlayed on the GWLs to produce a similar appearance while visually occluding graphic content.

GWLs and control warnings were displayed on cigarette pack images sized to the dimensions of a standard cigarette pack. The pack brand (Camel, Marlboro, or Newport) was tailored to smokers' preferred brand to account for brand preferences within the design (Bansal-Travers, Hammond, Smith, & Cummings, 2011). Branded packs were created using pack images available from an online database at the time of the study (Tobacco Labelling Resource Centre, n.d.). Plain packs displayed the brand name in standard font and were brown in color and stripped of all branding (Mays, Niaura, et al., 2015; Mays, Turner, et al., 2015). Stimuli were presented in randomized order such that the same warning did not appear consecutively and there were no more than two consecutive repeats from the same condition. Example GWL and control warnings are shown in Fig. 1; complete stimuli including pack images are available from the corresponding author.

Participants viewed each pack image in the scanner for 4 s. During the scan participants used a push-button control to report how much each image motivated them to quit smoking, with response options from (1) Not At All to (4) A Lot (Mays, Niaura, et al., 2015; Mays, Turner, et al., 2015).

2.4. Imaging data acquisition

Functional data were acquired in an event-related paradigm performed using a 3-T Allegra System (Siemens, Erlangen, Germany) to collect whole-brain T2*-weighted blood oxygenation level dependent (BOLD) functional images (asymmetric spin-echo echo-planar sequence; whole-brain repetition time, TR = 2000 ms; echo time = 25 ms; field of view = 256 mm; flip angle = 80°; matrix = 64 × 64; axial slices 4 mm thick). Sequential whole-brain volumes (32 contiguous slices) were collected during one event-related functional run. Sixty-four task trials were presented in total, lasting 4 s each with “jitter” interleaved between trials across a range from 250 to 4250 ms. The scanning run began with an unanalyzed fixation period equal to 3 TRs, which allowed the scanner to reach steady state.

2.5. Statistical analyses

fMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library) (FSL, n.d.). General Linear Model-based analysis in FEAT uses FSL tools including Brain Extraction Tool (BET) (Smith, 2002), an affine registration tool, FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001), and a motion-correction tool based on FLIRT (MCFLIRT) (Jenkinson et al., 2002). FEAT carries out standard-space registration after time-series statistics. FSL time-series statistics correct for temporal smoothness by applying pre-whitening (Woolrich, Ripley, Brady, & Smith, 2001). The following pre-statistics processing was applied: spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Registration to high resolution structural and, subsequently, standard space images was performed using FLIRT. At the individual subjects level, a design matrix was fitted to each subject's data as part of a general linear model with each condition modeled as events with a specified duration (i.e., the time from stimulus onset to onset of the response) convolved with a canonical hemodynamic response function. Higher-level analysis was performed using FMRIB's Local Analysis

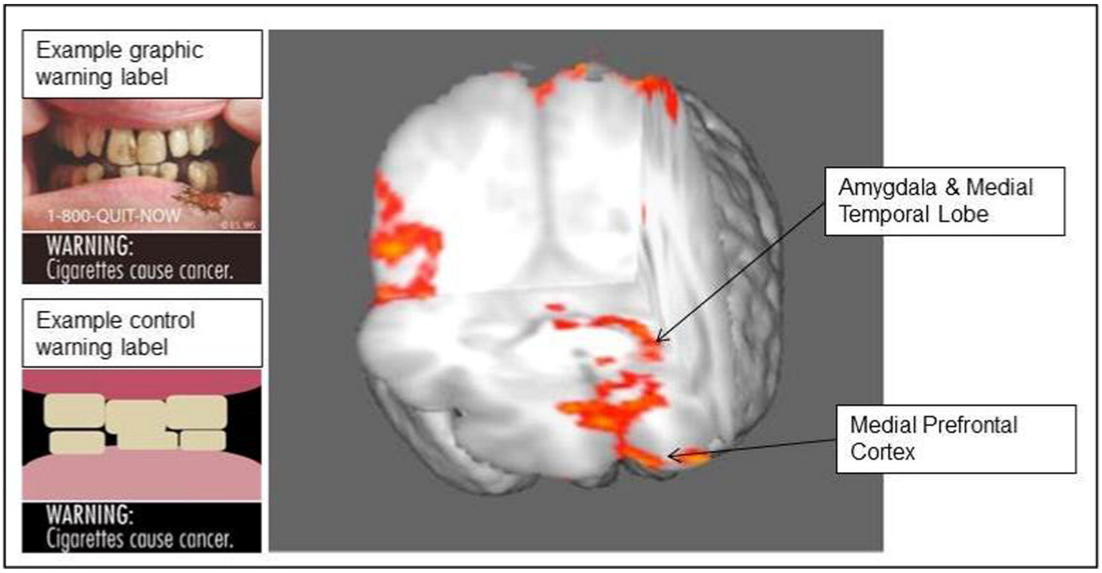

Fig. 1. Brain regions with graphic warning label activation > control at cluster corrected threshold of $p < .001$. *Note*: Brain regions based on contrast of graphic warning label > control at cluster corrected threshold of $p < .001$. Activity in medial temporal lobe, medial prefrontal cortex, amygdala, and occipital cortex was significantly greater in response to pack images displaying graphic warning labels than pack images displaying visually occluded control warnings.

of Mixed Effects (Beckmann, Jenkinson, & Smith, 2003). Z (Gaussianized T/F) statistic images were thresholded using an exploratory cluster-corrected threshold of $p < 0.001$.

3. Results

Participants ($n = 19$) averaged 22.9 years of age (*SD* 3.3), smoked on average 4.3 (*SD* 2.5, *range* 0–10) cigarettes on a typical day, averaged 3.1 (*SD 1.1*, *range* 2–6) on the FTND, and 68.4% reported using at least one other tobacco product (e.g., electronic cigarettes, hookah) in the past 30 days (Supplementary Table 1). Overall, 52.6% of participants were male, and 68.4% were non-white race/ethnicity (Supplementary Table 1). Self-report motivation to quit smoking during the imaging task was significantly greater for GWLs (*M* 3.25, *SD* 0.65) than the control warnings (*M* 1.96, *SD* 0.79, $t(18) = 8.15$, $p < .001$).

Results of the whole-brain functional imaging analysis contrasting neural activity in response to GWLs versus control warnings are shown in Table 1. Compared to control warnings, there was significantly greater activation in response to GWLs in the left medial frontal gyrus, right middle occipital gyrus, right orbital gyrus, left parietal precuneus, areas of left medial temporal cortex, specifically, left parahippocampal gyrus (extending to hippocampus), and left amygdala (Table 1). Activation in two of these regions (medial prefrontal cortex, and amygdala; see Fig. 1) was of a priori interest based on their respective roles in emotional and cognitive decision-making (Falk et al., 2010, 2011; Jasinska et al., 2012; Newman-Norlund et al., 2014; Wang et al., 2015). Analyses were thus conducted for these regions using a priori-defined regions of interest (ROIs) using anatomical probabilistic atlas-derived masks and images from the Harvard-Oxford cortical atlas within the FSL suite. An additional post-hoc, exploratory analysis was conducted using the same ROI approach for medial temporal activity using an atlas-defined hippocampus + parahippocampus region. Activation averaged across voxels was extracted for each ROI for the Warning Labels > Control contrast. Prior research also suggests that activity in these brain regions is associated with tobacco-related decision-making, including cessation behavior (Falk et al., 2010, 2011; Jasinska et al., 2012; Newman-Norlund et al., 2014; Wang et al., 2015). To test this possibility, we conducted exploratory analyses examining whether activity in these three ROIs was correlated with in-scanner, self-reported motivation to quit in response to the pack images during the task. A multiple regression model using extracted activation for these three ROIs as regressors indicated that differences in amygdala activity in response to GWLs versus control warnings was significantly associated with in scanner-ratings of how much the warnings motivated them to quit smoking ($\beta = .72$, $t(15) = 3.00$, $p = .009$). The medial prefrontal and medial temporal ROI regressors did not reach significance in this model.

There were no significant differences in neural activation between branded or plain packs, and the interaction between warning label (graphic or control) and pack branding (plain or branded) was not significant. In sensitivity analyses using imaging data from branded packs only (data not shown), findings reported for GWLs versus control warnings were consistent.

Table 1
Whole-brain graphic warning label > control contrast at cluster-corrected threshold of $p < .001$.

Anatomical region	Brodmann area	z	Peak Talairach coordinates x	y	z	Voxels
Left medial frontal gyrus	10	3.96	−4	54	14	43
Right middle occipital gyrus	18	3.80	30	−93	6	29
Right orbital gyrus	11	3.49	5	40	−22	52
Left parietal precuneus	31	3.43	−10	−54	30	16
Left parahippocampal gyrus	34	3.36	−26	5	−18	19
Left amygdala	NA	3.29	−24	−4	−22	11

4. Discussion

Among young adult smokers GWLs produced greater activation in brain regions involved in cognitive and emotional decision-making and memory formation compared with visually occluded control warnings. These findings are consistent with other investigations, converging on potential neurobiological mechanisms that may underlie behavioral response to graphic content in GWLs.

That GWLs produced greater amygdala activation is consistent with research with adult smokers indicating highly emotionally salient GWLs, similar to those tested, elicit the strongest amygdala response (Newman-Norlund et al., 2014; Wang et al., 2015). Similar responses to GWLs have been associated with craving reduction post-exposure (Do & Galvan, 2015), and greater amygdala activation to anti-smoking messages has predicted cessation (Jasinska et al., 2012). Our correlational analysis of ROI activity with in-scanner, self-reported motivation to quit in response to GWLs provides additional support for this idea, indicating that greater amygdala activity in response to GWLs is correlated with stronger self-reported motivation to quit smoking. The consistency of these observations with general studies of emotional response to high-arousal images (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012) also suggests that emotional content of GWLs is not being eliminated by young smokers, who may be motivated to disregard anti-smoking messages through counter-arguing or other defensive mechanisms.

That GWLs activated medial temporal regions including the hippocampus is congruent with evidence indicating that emotionally salient GWLs generate the strongest hippocampal activation and are better recalled by adult smokers (Newman-Norlund et al., 2014; Wang et al., 2015). The hippocampus plays a critical role in memory formation, and the amygdala is within a network of brain regions thought to mediate encoding of emotional stimuli (Wang et al., 2015). This suggests a cognitive-affective neurobiological pathway through which GWL messages are encoded, extending self-report evidence on GWL effects (Noar et al., 2015).

We also found greater activation in response to GWLs in areas of the medial prefrontal cortex that are involved in self-related processing and positive valuation of external stimuli (Bartra, McGuire, & Kable, 2013; Denny, Kober, Wager, & Ochsner, 2012). In prior studies, medial prefrontal activation in response to smoking cessation messages is a stronger predictor of future cessation behavior than self-report responses to such messages (Chua et al., 2011; Falk et al., 2011). Similarly, research also indicates that medial prefrontal activation in response to GWL-type images on public health messages is a stronger predictor of population-level effects of these messages for promoting cessation (Falk et al., 2016) than self-report responses. Although activity in the medial prefrontal and medial temporal ROIs was not significantly correlated with in-scanner, self-reported motivation to quit, this may not necessarily be a strong indication that activity in these regions in response to GWLs is not associated with future behavior change. In previous studies neural activity in response to similar cessation messages, particularly in the medial prefrontal region, is a stronger predictor of future quitting behavior than self-report measures (Falk et al., 2010, 2011). Overall, our findings are consistent with the idea that GWLs may motivate cessation among young smokers by integrating affective salience and self-related processing.

We did not observe differences in neural activation to GWLs based on branded versus plain cigarette packaging. One hypothesis proposed previously is that removing branding may reduce the degree to which packs stimulate anticipated reward among smokers, decreasing neural activation in brain regions involved in reward anticipation (e.g., ventral striatum) (Martin, 2014). The lack of differences could be due to the modest sample size and insufficient statistical power to detect subtle effects, or the low levels of nicotine dependence in the sample (i.e., less craving in response to pack images to produce a clear contrast) (Munafo, Roberts, Bauld, & Leonards, 2011). These issues should be examined in future studies.

This study has important limitations. The sample included young adults who smoked on average about 5 cigarettes per day and with relatively low levels of nicotine dependence. The findings observed within this relatively heterogeneous sample of young smokers may not generalize to older, heavier smoking populations. However, as noted the results are generally consistent with recent neuroimaging GWL studies conducted with older, heavier smoking adults and adolescents, suggesting that these studies may converge on similar findings. We did not gather additional information on the sample that may have affected our findings, such as psychiatric comorbidities and detailed information on use of tobacco products other than cigarettes. The contrast of primary interest in the present study was between GWLs and visually occluded control warnings. Given our results and the related literature described herein, it appears likely that the intended featural differences between GWLs and control warnings (e.g., emotional salience, self-relevance) rather than incidental features (e.g., color or luminance) are primarily responsible for the observed regional effects. However, the possibility that non-identical incidental visual features in control vs. GWL images had some effect on our data cannot be ruled out. Finally, we did not investigate other questions germane to policy that will be important to examine in the future, such as whether varying GWL message design (e.g., level of graphicness, message content) or size (e.g., 30% of pack surface versus 50%) impacts observed neural activation. Future research that directly links such neural activation to downstream, smoking-relevant cognitions and behaviors is also important.

Despite these limitations, our findings contribute to an apparent convergence of evidence on neurobiological mechanisms involving emotional cognitive decision-making and memory formation in response to GWLs among smokers. Our study uniquely adds to this evidence by demonstrating that even in a sample of young adult smokers that may be motivated to disregard GWL messages, their effects are consistent with broader research on emotionally salient, aversive images and are evident with plain and branded packaging. These data begin to delineate a neural underlay for recent self-report investigations indicating that GWLs are an important intervention for motivating young adult smokers to quit (Cameron et al., 2015; Magnan & Cameron, 2015; Mays, Turner, et al., 2015; Villanti, Pearson, Cantrell, Vallone, & Rath, 2015). Future studies can advance this area of research by prospectively examining whether neural activation in response to GWLs predicts future quitting behavior and examining differences based on aspects of warning message content relevant to policy decision-making (Newman-Norlund et al., 2014; Wang et al., 2015).

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.abrep.2016.02.001.

Role of funding sources

Data collection for this study was supported in part through a contract from the Truth Initiative (formerly Legacy). Manuscript preparation was supported in part by the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) Center for Tobacco Products (CTP) under NIH grant number CA172217 (D. Mays). This work was also supported in part by the Georgetown Lombardi Comprehensive Cancer Center Support Grant under NIH grant number P30CA051008. The study sponsors had no role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA.

Contributors

Authors Adam E. Green and Darren Mays designed the study, led data collection and analysis, and led writing of the manuscript. Authors Emily Falk, Natalie Gallagher, Amanda Richardson, and Raymond Niaura contributed to the study design, interpretation of the findings, and manuscript preparation. Authors Donna Vallone, Kenneth P. Tercyak, and David B. Abrams contributed to the study design and manuscript preparation. All authors have approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

Acknowledgments

Findings of this research were presented in part at the 2014 Annual Meeting of the Society for Research on Nicotine and Tobacco, Philadelphia, PA. The authors thank Andrea Johnson and Sarah Murphy for their assistance with data collection.

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