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Neural Correlates of Graphic Cigarette Warning Labels Predict Smoking Cessation Relapse

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Abstract

Exposure to graphic warning labels (GWLs) on cigarette packaging has been found to produce heightened activity in brain regions central to emotional processing and higher-order cognitive processes. The current study extends this literature by using functional magnetic resonance imaging (fMRI) to investigate neural activation in response to GWLs and use it to predict relapse in an evidence-based smoking cessation treatment program. Participants were 48 treatment-seeking nicotine-dependent smokers who completed an fMRI paradigm in which they were exposed to GWLs, text-only warning labels (TOLs), and matched control stimuli. Subsequently, they enrolled in smoking cessation treatment and their smoking behavior was monitored. Activation in bilateral amygdala, right dorsolateral prefrontal cortex, right inferior frontal gyrus, left medial temporal gyrus, bilateral occipital lobe, and bilateral fusiform gyrus was greater during GWLs than TOLs. Neural response in the ventromedial prefrontal cortex (vmPFC) during exposure to GWLs (relative to a visual control image) predicted relapse during treatment beyond baseline demographic and dependence severity, but response in the amygdala to GWLs did not. These findings suggest that neurocognitive processes in the vmPFC may be critical to understanding how GWL's induce behavior change and may be useful as a predictor of smoking cessation treatment prognosis.

Keywords

Nicotine Dependence; Warning Labels; Functional Magnetic Resonance Imaging; Relapse; Smoking Cessation; Medial Prefrontal Cortex

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Declaration of Interest

All authors have no conflicts of information or financial disclosures to be made.

1. Introduction

There have been efforts to reduce the health burden of smoking through a variety of approaches. One such approach has been the use of warning labels on cigarette packages as a means of encouraging smokers to quit and deterring non-smokers from beginning to smoke (see Figure 1). Epidemiological studies suggest that the introduction of these warnings was followed by reduced prevalence of smoking in Canada (Huang et al., 2014). Additionally, the Canadian graphic warning labels (GWLs) were demonstrated to decrease self-reported cigarette consumption and increase motivation to quit among smokers (Hammond et al., 2007, 2003). Studies have found that GWLs reduce overall craving (Emery et al., 2014; Wang et al., 2013) and demand for cigarettes (Thrasher et al., 2011). Furthermore, Wang and colleagues (Wang et al., 2015) found that viewing GWLs that were rated highly in emotional salience by participants reduced P300 amplitude response (a well-documented physiological marker of cigarette craving) to subsequent smoking cues. Additionally, research suggests that GWLs are more emotionally salient than text-only labels (TOLs) and may increase an individual's motivation to quit smoking (Kees et al., 2006). For example, one study found that GWLs induced greater self-reported motivation to quit smoking and higher fear intensity regarding the consequences of smoking than TOLs (Schneider et al., 2012). Another study found that GWLs elicited greater self-reported affective and cognitive reactions than TOLs (Nonnemaker et al., 2015).

Greater neural response in regions such as the amygdala, dorsolateral prefrontal cortex (dlPFC), insula, hippocampus, and inferior frontal gyrus has been specifically associated with GWLs to which participants report higher emotional reactivity (Wang et al., 2015). However, one region which seems to be especially important in understanding the neural response to GWLs is the ventromedial prefrontal cortex (vmPFC). The vmPFC is associated with many cognitive processes. It is also considered to be a part of the default network of the brain that is active during "rest", which is thought to consist primarily of mind wandering and self-directed thought (Andrews-Hanna et al., 2014, 2010). Related to this, it is considered a key region associated with self-referential thought (Denny et al., 2012; Falk et al., 2015, 2010).

The use of neuroimaging data to predict future behavior has been identified as a way that neuroscience can be applied pragmatically to improve individual outcomes (Gabrieli et al., 2015). As neuroimaging methods proliferate in medical centers around the U.S. and the world, using these methods to determine customize individual treatment plans becomes increasingly feasible (e.g., MRI and neuropsychological assessments are already comparable in price and travel distance). There are a number of ways that developing neural predictors of treatment outcome (termed "neuromarkers") may be utilized to improve quality of care. Neuromarkers may assist in customization of treatment plans in order to maximize the likelihood of patient success. For example, neural activity in the anterior cingulate cortex during a number of fMRI tasks predicts differential response to pharmacological and behavioral treatments for anxiety and depression (Ball et al., 2014). Neuromarkers may also be investigated in the context of novel neuropsychiatric treatments. For example, in depressed geriatric patients, fMRI response to a program of computerized brain training and

physical exercise designed to enhance underactive neural systems (i.e., neuromarkers) was associated with a 90% rate of recovery over 4 weeks (Morimoto et al., 2014). Furthermore, neuromarkers can provide insight into the mechanisms of treatment. For instance, it has been shown that one putative treatment mechanism of motivational interviewing, *change talk*, is associated with reduced activation in several areas associated with reward and craving, underscoring the importance of facilitating change talk in alcohol use disorder treatment (Feldstein Ewing et al., 2011). These potential benefits suggest significant value in finding neuromarkers that may incrementally predict treatment prognosis beyond existing self-report and behavioral measures.

Increased vmPFC activity during health messages has repeatedly been shown to predict positive future health behaviors consistent with the message (Falk et al., 2012, 2011, 2010). Specific to cigarette smoking, one study that found that vmPFC activity in response to GWLs predicted population-level engagement with an online smoking cessation presentation (Falk et al., 2015). Most recently, a 2016 study showed that neural activation in the vmPFC and amygdala during GWLs predicted CO verified changes in smoking behavior over a two week period (Riddle et al., 2016). These results provide reason to believe that neural response to GWLs in the vmPFC and amygdala may be useful neuromarkers of smoking cessation treatment prognosis. However, since this study examined natural variations in smoking behavior and did not include smoking cessation treatment, it is unknown whether these regions would be useful as predictors of treatment outcome. Additionally, this study only tracked smoking for two weeks.

The goals of the current study were to investigate differences in neural activity in GWLs compared to TOLs and determine whether regions previously found to predict naturalistic change in smoking behavior (Falk et al., 2012; Riddle et al., 2016) predict success in a 9-week intensive smoking cessation treatment integrating pharmacological and behavioral components. Activation levels in the vmPFC and the amygdala during GWLs and TOLs (relative to a scrambled visual control image) were tested as predictors of the number of days until participants relapsed to smoking. We hypothesized that reductions in craving and increased activation in the vmPFC and amygdala during GWLs would be predictive of greater success (i.e., more days to relapse) in smoking cessation treatment.

2. Methods

2.1 Participants

Participants were recruited as part of a study on neuroimaging predictors of smoking cessation relapse. Participants all resided in the United States and as a result had limited prior exposure to GWLs since this type of warning is not currently used in the U.S. Participants were required to smoke at least 10 cigarettes per day and report a motivation to quit of at least 5 on a scale of 1 to 10. In order to avoid potentially confounding neurodevelopmental differences, participants were required to be right-handed and between 18 and 60 years of age. Participants were excluded for reporting major medical, neurological or psychiatric disorders based on a semi-structured interview administered at eligibility assessment visit. Other exclusionary criteria included reporting participation in smoking cessation treatment in the past 90 days, consumption of six or more alcoholic beverages per

day, use of marijuana more than weekly, use of any other illicit drug more than monthly, or any MRI contraindications. Additionally, participants with an estimated IQ of less than 70 were excluded based on the Wechsler Test of Adult Reading (Holdnack, 2001); participants were of average general (final sample $M = 101.12$, $SD = 14.85$). Participants were paid \$126 for participating in 5 experimental sessions and received free smoking cessation treatment. A total of 51 participants were enrolled and completed the fMRI assessment. Of these participants, 3 were excluded for excessive movement in the scanner (more than .35 millimeters moved during at least 33% of volumes collected). Thus, 48 participants were included in the final analyses. Demographic and smoking characteristics of the sample are reported in Table 1.

2.2 Measures

2.2.1 Demographics—A demographic form was administered to assess participant's age, gender, race, ethnicity, education level, income, and the number of cigarettes smoked per day.

2.2.2 Timeline follow-back—Participants completed a retrospective timeline follow-back (TLFB) calendar at every therapy session to indicate the number of cigarettes smoked each day since the previous session. The TLFB calendar is considered to be a psychometrically sound method of measuring individual smoking behavior (Robinson et al., 2014).

2.2.3 Exhaled carbon monoxide (CO)—Exhaled CO was measured at baseline and at each in-person counseling session using a PiCO+ Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) as a way to biochemically verify smoking exposure and abstinence (Deveci et al., 2004; Wald et al., 1981). Abstinence was confirmed by exhaled CO ≤ 10 parts per million (Benowitz et al., 2002).

2.3 Procedures

All procedures were approved by the University of Georgia Institutional Review Board and were in accord with the Declaration of Helsinki. Participants were screened by telephone for inclusion and exclusion criteria. Participants eligible based on initial screening were invited for an in-person assessment for the purpose of full assessment of study eligibility criteria and collection of baseline data. Subsequently, eligible participants were scheduled for an fMRI assessment session. At this session, participants completed a 90-minute MRI protocol consisting of the warning labels fMRI paradigm and a T1 anatomical scan. Additional paradigms completed during the session included a working memory task, a monetary decision making task, a cigarette cue-reactivity task, and a resting state task. All participants were administered all assessments in the same order to standardize any carryover effects that may have occurred. In order to standardize craving, participants were instructed to smoke prior to arriving at the session, which was approximately two hours prior to the administration of the warning label paradigm.

Following these assessments, participants completed a nine-week intensive smoking cessation treatment protocol that combined nicotine replacement therapy and weekly in-person counseling sessions. This treatment incorporated all elements recommended for

intensive treatments in the current guidelines for providing smoking cessation treatment (Fiore et al., 2008). Nicotine replacement was provided in the form of the nicotine patch used as directed by the manufacturer (4 weeks 21 mg, 2 weeks 14 mg, and 2 weeks 7 mg). The counseling sessions comprised a manualized motivational interviewing approach (Miller and Rollnick, 2003), with elements of cognitive-behavioral therapy (e.g., identifying antecedents of smoking; managing high-risk situations). Treatment was provided by trained masters-level clinicians who were supervised by a licensed clinical psychologist. A randomly selected sample of treatment sessions were reviewed and coded by a different therapist for adherence to the protocol and motivational interviewing spirit. Coding was accomplished using an adherence checklist developed for the treatment manual and the Global Rating of Motivational Interviewing Therapist (GROMIT; Moyers, 2004). At each treatment session, self-reported smoking and exhaled CO was assessed.

2.3.1 fMRI data acquisition—Imaging data was collected at the University of Georgia Bio-Imaging Research Center with a General Electric 16-channel fixed-site Signa HDx 3.0 Tesla MRI scanner. Structural images were acquired for anatomical reference using a high-resolution T1 SPGR sequence (voxel size = 1mm³, a field of view = 256 × 256 mm, matrix = 256 × 256, and slice thickness = 1mm, slices collected axially). Sufficient contiguous axial slices were acquired to obtain whole-brain coverage. Functional imaging used T2* echo planar imaging (EPI) with a single-shot gradient echo pulse sequence (TR = 2500 ms, TE = 25 ms, field of view = 225 × 225 mm, matrix = 64 × 64, voxel size = 3.5 mm³, slice thickness = 3.5 mm, slices collected axially). One imaging run of 108 brain volumes was acquired during the GWL paradigm.

2.3.2 fMRI warning labels paradigm—The GWLs paradigm was a block design that consisted of one imaging run lasting 270 seconds in which participants were exposed to four epochs made up of three pseudorandomly ordered 20 second blocks (eight TRs per block) of images that featured four of the eight GWLs proposed for use in the United States (Hammond et al., 2013), the text from each of these warning labels (TOLs), and scrambled images matched to color and complexity with the GWL images (e.g., Figure 1; all images in Supplemental Materials 1–3). Images and blocks were presented in immediate succession in the same order for each participant (i.e., without an interstimulus or interblock interval). Each image was displayed on the screen for 5 seconds and all eight GWLs and TOLs were presented twice over the entire paradigm. Participants were instructed to pay attention to the photographs on the screen and rate their craving for cigarettes on a visual analog scale ranging from zero (no craving) to eight (extreme craving) using a handheld device. Rating screen remained on screen for 10 seconds at the beginning, end, and midpoint of the paradigm.

2.3.3 fMRI data processing—fMRI data processing and analysis was conducted using Analysis of Functional NeuroImages software (AFNI; Cox, 1996) version 16.2.11 (updated August 19, 2016). Functional datasets were aligned to T1 anatomical datasets and volume-registered (motion-corrected for head movement). Volumes including inter-volume movement greater than .35mm along the x-, y-, or z-axes were censored and participants with greater than 33% of volumes censored were excluded from analyses. Subsequently,

datasets were transformed into Talairach space (Talairach and Tournoux, 1988) and individual volumes from each run were registered to a base volume proximal to acquisition of the T1 dataset (Saad et al., 2009). The data was spatially smoothed using a 7mm full width half-maximum Gaussian filter, masked to exclude voxels outside the brain. Raw blood oxygenation level dependent (BOLD) signal was scaled to percent signal change from mean signal intensity. For each subject, general linear modeling was completed using three regressors relating to condition (GWLs, TOLs) and six nuisance regressors to account for motion (x, y, z, roll, pitch, yaw). Additionally, the screen in which participants rated their craving to smoke was modeled so it would not be included in the baseline. The scrambled images condition was modeled as the baseline, which includes control for linear, quadratic, and cubic trends.

2.4 Data analyses

Days to relapse was based on the TLFB and exhaled CO and operationalized as the number of days from participants' quit date until they resumed smoking at least one cigarette per day for seven days (i.e., days to relapse). Smoking cessation outcome can be measured in a variety of different ways (Burns et al., 2000; Hughes et al., 2003), but this definition was selected because it uses a meaningful window of time (increasing reliability) and a continuous scaling (maximizing power), and because it provides a high-resolution measure of early treatment progress, which is in turn highly predictive of long-term post-treatment outcomes (Kenford et al., 1994). Participants who dropped out of treatment were considered to have relapsed (Francisco et al., 2002) and their days to relapse was coded as one. Four participants dropped out before treatment (prior their first session), 10 more dropped out prior to their quit date, and five more did not succeed in quitting at all. Participants who dropped out prior to quitting were coded the same as those who failed to quit. Those who dropped out after reporting they had quit successfully were coded as the number of days from their quit date to the last session they attended in which they reported not relapsing. Additionally, 22 participants completed the entire 49 day treatment program without relapsing. This led to a bimodal distribution of days to relapse ($M = 25.2$, $SD = 23.4$; median = 30.5, 33%ile = 1, 66%ile = 49). Consequently, a median split was conducted which left two groups of 24 participants: 1) those who relapsed within first 30 days of treatment (RELAPSE group) and 2) those who did not relapse in first 30 days of treatment (QUIT group).

To determine which baseline (i.e., non-imaging) variables to use as covariates, independent sample t-tests were conducted to assess for differences by relapse status in self-reported change in craving, craving after the warning label paradigm, age, sex, income, education, and baseline FTND score. To ensure that only covariates contributing unique variance were used in the final model, behavioral variables related to days to relapse were entered simultaneously into a binary logistic regression model predicting relapse group status.

To characterize differential activation during GWLs and TOLs, repeated-measures t-tests were completed comparing activation in the three regions of interest selected during GWLs relative to baseline, during TOLs relative to baseline, and between GWLs and TOLs. Then to explore the differences in other regions of the brain than those being used as predictors of

treatment outcome, voxelwise analyses were conducted using repeated-measures t-tests to compare neural responding during GWLs and during TOLs to the matched control baseline (i.e., scrambled images) and to compare activation during WLS to activation during TOLs. Voxelwise comparisons of GWLs with TOLs were corrected for familywise error using false discovery rate methods to $q = 0.05$. However, this thresholding approach was insufficiently stringent for comparing GWL and TOL to baseline (i.e., too much activation was present to interpret) and as a results these contrasts were corrected to a more stringent threshold than needed to control for familywise error, using an uncorrected alpha level of $p = 0.005$ and a cluster size of 56 to achieve a corrected alpha level of $p = 0.05$ according to the 3dClustSim program.

To examine neural activation during GWLs and during TOLs as predictors of smoking cessation relapse, three regions of interest (ROIs) were selected from recent study on GWLs (Riddle et al., 2016), the vmPFC and the right and left amygdala. Then, a mask was made in which a four millimeter sphere was drawn at the coordinates for reach region indicated in that paper (illustrated in Figure 2). Average beta values were extracted from each of these regions for each individual to serve as the dependent measure in subsequent ROI analyses. To test activation in the regions of interest as a predictor of relapse, binary logistic regression analyses were conducted. First, to determine if activation during GWLs predicted relapse, average beta values for each of the three regions during GWLs were entered into a separate regression models predicting relapse group status (RELAPSE or QUIT). Then, to determine if neural activation predicted relapse group status beyond other measures available, regions that significantly predicted relapse group were entered into an additional regression model simultaneously with behavioral variables that uniquely predicted relapse status. Lastly, as an exploratory analysis we tested activation in the three regions of interest during TOLs and the difference between GWLs and TOLs in each region as predictors of relapse group status. To do this, we calculated a difference score (activation during GWLs – activation during TOLs) for reach region. We then entered the activation of each region during TOLs and the differences score associated with each region into separate regression models predicting days to relapse.

3. Results

3.1 Behavioral analyses

92% of participants attended at least one treatment session post-scan and participants averaged 25.23 days until relapsing to daily smoking ($SD = 23.42$), with 22 participants (46%) completing the 49 days of treatment without relapsing. Most of the first and second therapy sessions (74% and 73%, respectively) were coded for adherence to the treatment protocol and basic motivational interviewing principles and over half (60%) of sessions 3–9 were coded for adherence to motivational interviewing principles. Therapist adherence to the treatment protocol was 98% and adherence to motivational interviewing spirit was 95%.

On average participants rated their craving to smoke as 5.18 ($SE = .38$) out of 8 prior to the warning labels paradigm, 4.74 ($SE = .36$), half way through the paradigm, and 4.47 ($SE = .36$) following the paradigm. This change in craving was significant when tested in a one-way ANOVA ($F = 8.74$, $df = 2/84$, $p < 0.01$) and post-hoc t-tests indicate that both the

second ($t = 2.52, p = 0.02$) and third ($t = 3.65, p < 0.01$) rating were significantly lower than the initial rating. Neither participant's level of craving following the warning labels paradigm (Wald = 2.83, $p = 0.09$) nor their change in craving from before the paradigm to after (Wald = 2.01, $p = 0.16$) was predictive of days to relapse.

Independent sample t-tests indicated that income, age, education, and baseline FTND differed significantly based on relapse group status ($p < 0.05$). However, in logistic regression analyses the Wald criterion indicated that only FTND made a significant contribution to prediction (Wald = 5.35, $p = 0.02$). As a result, FTND alone was used in the integrative model (that included imaging and non-imaging variables).

3.2 Differences among conditions

Region of interest analyses indicated significant activation in the vmPFC ($t = 3.39, p = .001$) and the right ($t = 3.61, p = .001$) and left amygdala ($t = 4.54, p < .001$) during exposure to GWLs relative to scrambled control images (baseline). There was also significant activation in the vmPFC ($t = 2.07, p = .04$) and the right ($t = 2.31, p = .03$) and left amygdala ($t = 2.19, p = .04$) during TOLs relative to control images. Greater activation was found in the left amygdala during GWLs than during TOLs ($t = 3.01, p = 0.004$) and a trend toward greater activation in the vmPFC was found during GWLs than during TOLs ($t = 1.756, p = 0.086$). The right amygdala did not significantly differ between GWLs and TOLs ($t = 1.61, p = 0.12$).

Maps of voxelwise contrasts are displayed in Figure 3. Specifically, response to exposure to GWLs compared to control images are displayed in Figure 3A, regions active during exposure to TOLs compared to control images are displayed in Figure 3B, and regions active during GWLs compared to TOLs are displayed in Figure 3C. Coordinates of peak regional activity in the contrast of GWLs and TOLs are in Table 2. Coordinates of regions active during GWLs and TOLs compared to control images are provided in Supplemental Materials 4. In addition to the specified regions of interest, clusters that were more responsive to GWLs than TOLs included bilateral occipital lobe, bilateral fusiform gyrus, left medial temporal, and right inferior frontal gyrus. A table of regional activity and contrasts maps of the voxelwise comparison of GWLs to rest and TOLs to rest are in Supplemental Materials 5.

3.3 Neural prediction of relapse

Binary logistic regression analyses indicated that greater activation in the vmPFC during GWLs relative to control images was predictive of membership in the RELAPSE group. Specifically, this model reliably distinguished between RELAPSE and QUIT groups (chi square = 5.17, $p = 0.023$) with Nagelkerke R^2 of 0.14 and 62.5% prediction success. Results of ROI regression analyses are displayed in Table 3 and average activation in RELAPSE and QUIT participants are displayed in Figure 4. Additionally, binary logistic regression analyses indicated that a model including activation in the vmPFC during GWLs and FTND better predicted relapse group membership than either model alone. Specifically, this model reliably distinguished between RELAPSE and QUIT group members ($\chi^2 = 18.68, p < 0.001$) with Nagelkerke R^2 of 0.43 and prediction success of 81.3%. Separate models using

the right and left amygdala were not significantly predictive of relapse group membership. Follow-up logistic regression analyses indicated that neither activation during TOLs nor the difference between GWLs and TOLs predicted relapse group status (p s > 0.05).

4. Discussion

The aims of this study were to characterize differences in neural responding to GWLs and TOLs and to investigate whether neural activity during exposure to GWLs in regions salient to processing health warnings was predictive of relapse during smoking cessation. Significant differences between GWLs and TOLs were found in a number of emotional and visual attentional regions of the brain. Although regions of interest located in the vmPFC and amygdala both significantly activated during GWLs relative to scrambled control images, only vmPFC response amplitude predicted participant relapse beyond baseline level of nicotine dependence severity.

The importance of vmPFC activity in predicting treatment outcome is consistent with a previous study that reported a relationship between activity in the vmPFC during exposure to GWLs and observed changes in naturalistic smoking behavior following a GWL fMRI paradigm (Riddle et al., 2016), as well as several other studies which demonstrate association between vmPFC activity during other health warnings both written and graphic (e.g., warnings about sunscreen use) and changes in associated health behaviors (Falk et al., 2015, 2012, 2011, 2010). The current study extends prior findings by providing evidence that vmPFC activation also predicts relapse during an intensive smoking cessation treatment program, and that this relationship is significant beyond severity of nicotine dependence. Prior literature has interpreted heightened vmPFC activity during warning messages as an indication of greater internalization of the message's relevance to an individual's own life (often termed "self-related processing"; Falk et al., 2015, 2012, 2011). However, given the large number of behaviors and mental processes that have been associated with the vmPFC, it is possible that the vmPFC's relationship with health behavior may be due to its role in other processes such as interpretation of emotional experience (Roy et al., 2012), emotion regulation (Motzkin et al., 2015), reward valuation (Strait et al., 2014), or imagining/simulating the future (Benoit et al., 2014; Levens et al., 2014).

Amygdala activation during GWLs did not predict treatment outcome, as might be expected based on Riddle and colleagues' (2016) findings. Given the current findings, it is possible that amygdala reactivity to GWLs predicts short-term reductions in smoking while vmPFC activity uniquely predicts long-term cessation during a formal smoking cessation intervention. Given the amygdala's established role in emotional processing (Phelps and LeDoux, 2005), these results may indicate that the emotional response to GWLs is less important to predicting future behavior change than the mental processes occurring in the vmPFC. Prior studies have found that activation in the vmPFC during written warnings also predicts change in certain behaviors, such as sunscreen use (Falk et al., 2010). This was not the case in the current study as vmPFC activity during TOLs did not predict treatment outcome. There are several possible explanations for this. It is possible that vmPFC response to TOLs is a less effective marker of relapse than GWLs, but with a larger sample they too may have significantly predicted relapse. Alternatively, it may suggest that vmPFC activity

during TOLs is not related to treatment outcomes in the same way that it is related to other behavioral changes. Another possibility is that vmPFC activity during TOLs did not predict treatment outcome in this study because the ROIs selected were based on prior literature using GWLs to predict smoking reductions (Riddle et al., 2016). Therefore, if ROIs based on TOLs were used they may have predicted treatment outcome.

These findings are consistent with the hypothesis that vmPFC activity during exposure to GWLs may be useful as a neuromarker of prognosis for intensive smoking cessation treatment. Future studies are needed to determine if this finding extends to other types of smoking cessation treatments or if it is unique to what would be considered intensive treatment (combined pharmacological and psychological treatment). Given the number of non-treatment studies demonstrating the vmPFC's relationship to different kinds of behavior change such as sunscreen use and cigarette smoking, it seems likely that this effect is not specific to treatment type. Addressing this question this could provide important information to clinicians on understanding of treatment mechanisms and improving treatment planning. Similarly, future studies might also provide greater clarity regarding cognitive mechanisms linking the vmPFC to treatment outcome by exploring the relationships between convergent measures of specific cognitive functions (such as specific tests of planning, future thinking, or cognitive control) to vmPFC activity during GWLs and how they both relate to treatment outcome.

In addition to the primary finding that activity during GWLs is associated with relapse in smoking cessation treatment, voxelwise analysis found a robust pattern of differences in neural response between GWLs and TOLs, with greater response to GWLs found in the occipital lobe, fusiform gyrus, amygdala, lateral temporal lobe, and inferior and dorsolateral prefrontal cortex. These are key regions involved in visual identification, emotion, and selective attention processes (Sabatinelli et al., 2014, 2009) and their greater relative activation during GWLs likely reflects greater salience to smokers viewing these emotional scenes. This pattern of activation is consistent with the results found by a prior study which compared response to GWLs with response to TOL warning associated with a non-graphic image, which found the difference between the two warnings to be localized in the occipital lobe, fusiform gyrus, amygdala, hippocampus, insula, and inferior frontal cortex (Wang et al., 2015). That this study and the current study found such similar regions to differentiate graphic and non-graphic warnings provides strong evidence that brain response in regions associate with visual attention to emotional stimuli is heightened by GWLs relative to other kinds of warnings. This provides another line of evidence suggesting the GWLs may have unique public health benefits compared to other types of cigarette warnings, doing this by their ability to draw smokers' attention and elicit an emotional response which may enhance their memorability and emotional impact.

This is the first study to examine whether neural responses to GWLs predict cessation as a part of treatment among treatment-seeking smokers. Other strengths include use of a paradigm in which participants view matched GWLs and TOLs during the same fMRI paradigm, providing biochemical verification of smoking abstinence, and use of a standardized, intensive cessation treatment protocol that incorporates evidence-based psychological and pharmacological components. Implications of these findings suggest

avenues of future research. For example, since participants' exposure to GWLs outside the laboratory was not manipulated, it cannot necessarily be concluded that the same neural processes occurs when smokers are exposed to GWLs in daily life. Future studies could address this issue by utilizing participant samples in locations with different laws surrounding GWLs and using novel study designs that include manipulation or measurement of daily exposure to GWLS. Additionally, despite providing strong evidence for vmPFC activity during GWLs as a neuromarker of treatment prognosis, the study may have been somewhat underpowered for detecting associations of change in self-reported craving following exposure to GWLs, which did not predict relapse. There was considerably greater restriction of range for the craving measure compared to the stimulus-elicited BOLD signal. Nonetheless, findings suggest that fMRI neuromarkers of smoking cessation are stronger predictors than self-reported craving.

Importantly, this study does not speak directly to the efficacy of GWLs at a population level, but instead informs the understanding of the person-level characteristics regarding response to GWLs that are associated with subsequent treatment success and highlights enhancement of visual attention and emotional processing in response to GWLs relative to other types of visual warnings. Future studies may expand this scope using brain-as-predictor frameworks, such as Falk et al., 2012. Furthermore, the current results also suggest avenues for improvement of warning label development in the future, with results indicating that GWLs are more salient than TOLs and that warnings that elicit vmPFC activity (possibly indicative of self-related processing) may be more effective at encouraging long-term behavior change.

In sum, this study is the first to predict the outcome of intensive smoking cessation treatment based on neural responding during GWLs. This is an important finding given current the potential benefits of neuromarkers of treatment prognosis to understanding mechanisms of treatment, improving individualized treatment planning, and advancing treatment efficacy. Findings support previously proposed models that cognitive processes specific to the vmPFC are instrumental in individuals changing their behavior in response to health messages (Falk et al., 2012; Riddle et al., 2016) and suggest widespread increases in neural activation in response to GWLs compared to TOLs. Broadly, the results of this study reveal the ways that GWLs and TOLs differ from each other, provide support for theoretical models proposing that processes occurring in the vmPFC are especially salient to behavior change, and suggest that activity in the vmPFC may be useful as a neuromarker of prognosis in smoking cessation treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron*. 2010; 65:550–562. DOI: 10.1016/j.neuron.2010.02.005 [PubMed: 20188659]
- Andrews-Hanna JR, Smallwood J, Spreng RN. The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Ann N Y Acad Sci*. 2014; 1316:29–52. DOI: 10.1111/nyas.12360 [PubMed: 24502540]
- Ball TM, Stein MB, Paulus MP. Toward the application of functional neuroimaging to individualized treatment for anxiety and depression. *Depress Anxiety*. 2014; doi: 10.1002/da.22299
- Benoit RG, Szpunar KK, Schacter DL. Ventromedial prefrontal cortex supports affective future simulation by integrating distributed knowledge. *Proc Natl Acad Sci*. 2014; 111:16550–16555. DOI: 10.1073/pnas.1419274111 [PubMed: 25368170]
- Benowitz NL, Jacob P, Ahijevych K, Jarvis MJ, Hall S, LeHouezec J, et al. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. 2002; 4:149–159. DOI: 10.1080/14622200210123581 [PubMed: 12028847]
- Burns, DM., Anderson, CM., Johnson, M., Major, JM., Biener, L., Vaughn, J., et al. Population Based Smoking Cessation: Proceedings of a Conference on What Works to Influence Cessation in the General Population Smoking and Tobacco Control. U.S. Department of Health and Human Services; Bethesda, MD: 2000. Cessation and Cessation Measures among Adult Daily Smokers: National and State-Specific Data.
- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996; 29:162–73. [PubMed: 8812068]
- Denny B, Kober H, Wager T, Ochsner K. A meta-analysis of functional neuroimaging studies of self and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *J Cogn Neurosci*. 2012; 24:1742–1752. DOI: 10.1162/jocn [PubMed: 22452556]
- Deveci SE, Deveci F, Açıık Y, Ozan AT. The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. *Respir Med*. 2004; 98:551–556. DOI: 10.1016/j.rmed.2003.11.018 [PubMed: 15191041]
- Emery LF, Romer D, Sheerin KM, Jamieson KH, Peters E. Affective and cognitive mediators of the impact of cigarette warning labels. *Nicotine Tob Res*. 2014; 16:263–9. DOI: 10.1093/ntr/ntt124 [PubMed: 23946325]
- Falk EB, Berkman ET, Lieberman MD. From neural responses to population behavior: Neural focus group predicts population-level media effects. *Psychol Sci*. 2012; 23:439–445. DOI: 10.1177/0956797611434964 [PubMed: 22510393]
- Falk EB, Berkman ET, Mann T, Harrison B, Lieberman MD. Predicting persuasion-induced behavior change from the brain. *J Neurosci*. 2010; 30:8421–8424. DOI: 10.1523/JNEUROSCI.0063-10.2010 [PubMed: 20573889]
- Falk EB, Berkman ET, Whalen D, Lieberman MD. Neural activity during health messaging predicts reductions in smoking above and beyond self-report. *Heal Psychol*. 2011; 30:177–185. DOI: 10.1037/a0022259
- Falk EB, O'Donnell MB, Thompson S, Gonzalez R, Cin S, Strecher V, et al. Functional brain imaging predicts public health campaign success. *Soc Cogn Affect Neurosci*. 2015; :1–11. DOI: 10.1093/scan/nsv108
- Feldstein Ewing SW, Filbey FM, Sabbineni A, Chandler LD, Hutchison KE. How psychosocial alcohol interventions work: A preliminary look at what fMRI can tell us. *Alcohol Clin Exp Res*. 2011; 35:643–651. DOI: 10.1111/j.1530-0277.2010.01382.x [PubMed: 21223301]
- Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry S, et al. Treating Tobacco Use and Dependence: 2008 Update Guideline Panel. 2008
- Francisco S, Francisco S, Jarvis MJ, Hall S, Francisco S, Consumer P, et al. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. 2002; 4:149–159. DOI: 10.1080/14622200210123581 [PubMed: 12028847]

- Gabrieli JDE, Ghosh SS, Whitfield-Gabrieli S. Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. *Neuron*. 2015; doi: 10.1016/j.neuron.2014.10.047
- Hammond D, Fong G, McDonald P, Cameron R, Brown K. Impact of the graphic Canadian warning labels on adult smoking behaviour. *Tob Control*. 2003; 12:391–395. [PubMed: 14660774]
- Hammond D, Fong GT, Borland R, Cummings KM, McNeill A, Driezen P. Text and graphic warnings on cigarette packages: Findings from the international tobacco control four country study. *Am J Prev Med*. 2007; 32:202–209. DOI: 10.1016/j.amepre.2006.11.011 [PubMed: 17296472]
- Hammond D, Reid JL, Driezen P, Boudreau C. Pictorial health warnings on cigarette packs in the united states: An experimental evaluation of the proposed FDA warnings. *Nicotine Tob Res*. 2013; 15:93–102. DOI: 10.1093/ntr/nts094 [PubMed: 22505660]
- Holdnack, HA. Wechsler Test of Adult Reading: WTAR. The Psychological Corporation; San Antonio: 2001.
- Huang J, Chaloupka FJ, Fong GT. Cigarette graphic warning labels and smoking prevalence in Canada: a critical examination and reformulation of the FDA regulatory impact analysis. *Tob Control*. 2014; 23(Suppl 1):i7–12. DOI: 10.1136/tobaccocontrol-2013-051170 [PubMed: 24218057]
- Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res*. 2003; 5:13–25. DOI: 10.1080/1462220031000070552 [PubMed: 12745503]
- Kees J, Burton S, Andrews JC, Kozup J. Tests of graphic visuals and cigarette package warning combinations: Implications for the framework convention on tobacco control. *J Public Policy Mark*. 2006; 25:212–223. DOI: 10.1509/jppm.25.2.212
- Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation. Who will quit with and without the nicotine patch. *J Am Med Assoc*. 1994; 271:589–594. DOI: 10.1001/jama.271.8.589
- Levens S, Larsen J, Bruss J, Tranel D, Bechara A, Mellers B. What might have been? The role of the ventromedial prefrontal cortex and lateral orbitofrontal cortex in counterfactual emotions and choice. *Neuropsychologia*. 2014; 54:77–86. DOI: 10.1016/j.pestbp.2011.02.012. Investigations [PubMed: 24333168]
- Miller WR, Rollnick S. Motivational Interviewing: Preparing for change. *Am J Forensic Psychol*. 2003; 21:83–85.
- Morimoto SS, Wexler BE, Liu J, Hu W, Seirup J, Alexopoulos GS. Neuroplasticity-based computerized cognitive remediation for treatment-resistant geriatric depression. *Nat Commun*. 2014; 5:4579. doi: 10.1038/ncomms5579 [PubMed: 25093396]
- Motzkin JC, Philippi CL, Wolf RC, Baskaya MK, Koenigs M. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biol Psychiatry*. 2015; 77:276–284. DOI: 10.1016/j.biopsych.2014.02.014 [PubMed: 24673881]
- Moyers T. The Global Rating of Motivational Interviewing Therapists. 2004
- Nonnemaker JM, Choiniere CJ, Farrelly MC, Kamyab K, Davis KC. Reactions to graphic health warnings in the United States. *Health Educ Res*. 2015; 30:46–56. DOI: 10.1093/her/cyu036 [PubMed: 24974219]
- Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*. 2005; doi: 10.1016/j.neuron.2005.09.025
- Riddle PJ, Newman-norlund RD, Baer J, Thrasher JF. Neural response to pictorial health warning labels can predict smoking behavior change. *Soc Cogn Affect Neurosci*. 2016; :1–35. DOI: 10.1093/scan/nsw087 [PubMed: 26141925]
- Robinson SM, Sobell LC, Sobell MB, Leo GI. Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychol Addict Behav*. 2014; 28:154–62. DOI: 10.1037/a0030992 [PubMed: 23276315]
- Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci*. 2012; doi: 10.1016/j.tics.2012.01.005

- Saad ZS, Glen DR, Chen G, Beauchamp MS, Desai R, Cox RW. A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage*. 2009; 44:839–848. DOI: 10.1016/j.neuroimage.2008.09.037 [PubMed: 18976717]
- Sabatinelli D, Frank DW, Wanger TJ, Dhamala M, Adhikari BM, Li X. The timing and directional connectivity of human frontoparietal and ventral visual attention networks in emotional scene perception. *Neuroscience*. 2014; 277:229–238. DOI: 10.1016/j.neuroscience.2014.07.005 [PubMed: 25018086]
- Sabatinelli D, Lang PJ, Bradley MM, Costa VD, Keil A. The timing of emotional discrimination in human amygdala and ventral visual cortex. *J Neurosci*. 2009; 29:14864–14868. DOI: 10.1523/JNEUROSCI.3278-09.2009 [PubMed: 19940182]
- Schneider S, Gadinger M, Fischer A. Does the effect go up in smoke? A randomized controlled trial of pictorial warnings on cigarette packaging. *Patient Educ Couns*. 2012; 86:77–83. DOI: 10.1016/j.pec.2011.03.005 [PubMed: 21482060]
- Strait CE, Blanchard TC, Hayden BY. Reward value comparison via mutual inhibition in ventromedial prefrontal cortex. *Neuron*. 2014; 82:1357–1366. DOI: 10.1016/j.neuron.2014.04.032 [PubMed: 24881835]
- Talairach, J., Tournoux, P. *Atlas of the Human Brain*. 1st. Thieme Medical Publishers; Stuttgart, Germany: 1988. Co-Planar Stereotaxis.
- Thrasher JF, Rousu MC, Hammond D, Navarro A, Corrigan JR. Estimating the impact of pictorial health warnings and “plain” cigarette packaging: Evidence from experimental auctions among adult smokers in the United States. *Health Policy (New York)*. 2011; 102:41–48. DOI: 10.1016/j.healthpol.2011.06.003
- Wald NJ, Idle M, Boreham J, Bailey A. Carbon monoxide in breath in relation to smoking and carboxyhaemoglobin levels. *Thorax*. 1981; 36:366–369. DOI: 10.1136/thx.36.5.366 [PubMed: 7314006]
- Wang AL, Lowen SB, Romer D, Giorno M, Langleben DD. Emotional reaction facilitates the brain and behavioural impact of graphic cigarette warning labels in smokers. *Tob Control*. 2015; 24:225–232. DOI: 10.1136/tobaccocontrol-2014-051993 [PubMed: 25564288]
- Wang AL, Romer D, Elman I, Turetsky BI, Gur RC, Langleben DD. Emotional graphic cigarette warning labels reduce the electrophysiological brain response to smoking cues. *Addict Biol*. 2013; 20:368–376. DOI: 10.1111/adb.12117 [PubMed: 24330194]

HIGHLIGHTS

- Graphic cigarette warning labels elicit greater neural response in regions associated with emotion, cognitive control, and self-referential thought than do text only warnings.
- Greater neural response in the ventromedial prefrontal cortex in response to graphic warning labels predicts greater success in smoking cessation treatment.
- Results support a previously proposed model that higher order processes specific to the ventromedial prefrontal cortex are activated by health messages and are predictive of behavior change.

C)

Figure 1. Examples of images shown in warning label paradigm. Panel A depicts a graphic warning label (GWL), panel B depicts a text only label (TOL), panel C depicts a scrambled image used as a visual control baseline.

Figure 2.

Regions of interest. Panel A depicts this in an axial view (at z coordinates of -11 and 0). Panel B depicts a sagittal view (at an x coordinate of -2). Panel C depicts a coronal view (at y coordinates of -3 and 5). Regions by color: orange = ventromedial PFC, purple = right amygdala, green = left amygdala. Images are in Talairach (RAI) space and are shown in radiological convention (i.e., left = right).

Figure 3.

Brain maps of neural activity during exposure to graphic warning labels (GWLs) and text only warning labels (TOLs). Panel A depicts GWLs compared to baseline, panel B depicts TOLs compared to baseline, Panel C depicts the contrast of GWLs to TOLs, and Panel D depicts the legend for brain map color in units of percent signal change. Z coordinates are presented below each image in Talairach (RAI) space. Images are shown in radiological convention (i.e., left = right). Regional peaks coordinates are reported in Supplemental Materials 4.

Figure 4. Activation during graphic warning labels (GWLs) in RELAPSE and QUIT groups in the three regions of interest. vmPFC = ventromedial prefrontal cortex.

Table 1Baseline participant characteristics ($N = 48$)

Variable	<i>M (SD) or %</i>
Age	39.1 (11.9)
Gender (%female)	35.4%
Race (%)	
White	68.8%
Black/African-American	29.2%
Mixed Race	2.1%
Ethnicity	
Hispanic or Latino	2.1%
Not Hispanic or Latino	97.9%
Annual Income (%)	
\$0–9,000	33.3%
\$10–19,000	33.3%
\$20–29,000	14.6%
\$30–39,000	14.6%
\$40–49,000	4.2%
Education (years)	13.5 (2.1)
Cigarettes smoked per day	23.1 (15.1)
Estimated IQ	101.1 (14.9)

Peak regional activity in exploratory voxelwise contrast of graphic warning labels and text only labels. Coordinates of differentially active regions are in Talairach (RAI) space, accompanied by the peak t value in each region and corresponding Broadman's Areas.

Table 2

Hemi	Region	BA	x	y	z	t
Frontal Lobe						
R	Inferior Frontal Gyrus	45, 46	-51	-34	10	3.1
R	Middle Frontal	9, 46	-54	-20	27	3.6
Occipital Lobe						
L	Occipital Lobe	19	47	71	6	4.7
R	Occipital Lobe	19	-40	71	-4	5.2
L	Fusiform Gyrus	37	37	46	-11	4.7
R	Fusiform Gyrus	37	-37	50	-15	5.7
Subcortical Structures						
L	Amygdala	-	16	4	-8	3.1
R	Amygdala	-	-19	1	-8	2.9
L	Medial Temporal Lobe	28	23	15	-11	2.6

Table 3

Activations in regions of interest during graphic warning labels (GWLs) relative to baseline as predictors of days to relapse. Center of mass coordinates reported in Talairach space.

Hemi	Region	X	Y	X	B	WALD	p	Odds Ratio
	FTND	-	-	-	-0.50	9.37	0.002	0.61
	Ventromedial PFC	0	-57	0	1.17	4.28	0.04	3.23
R	Amygdala	-22	-5	-11	0.13	0.04	0.84	1.14
L	Amygdala	24	3	-11	0.34	0.23	0.63	1.40
	FTND	-	-	-	-0.57	8.92	0.003	0.57
	Ventromedial PFC	0	-57	0	1.47	4.56	0.03	4.33