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Neural response to pictorial health warning labels can predict smoking behavioral change

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Abstract

In order to improve our understanding of how pictorial health warning labels (HWLs) influence smoking behavior, we examined whether brain activity helps to explain smoking behavior above and beyond self-reported effectiveness of HWLs. We measured the neural response in the ventromedial prefrontal cortex (vmPFC) and the amygdala while adult smokers viewed HWLs. Two weeks later, participants' self-reported smoking behavior and biomarkers of smoking behavior were reassessed. We compared multiple models predicting change in self-reported smoking behavior (cigarettes per day [CPD]) and change in a biomarkers of smoke exposure (expired carbon monoxide [CO]). Brain activity in the vmPFC and amygdala not only predicted changes in CO, but also accounted for outcome variance above and beyond self-report data. Neural data were most useful in predicting behavioral change as quantified by the objective biomarker (CO). This pattern of activity was significantly modulated by individuals' intention to quit. The finding that both cognitive (vmPFC) and affective (amygdala) brain areas contributed to these models supports the idea that smokers respond to HWLs in a cognitive-affective manner. Based on our findings, researchers may wish to consider using neural data from both cognitive and affective networks when attempting to predict behavioral change in certain populations (e.g. cigarette smokers).

Key words: smoking; fMRI; pictorial health warning labels (HWLs); amygdala; ventromedial prefrontal cortex (vmPFC)

Introduction

According to the World Health Organization (WHO), smoking remains the leading cause of preventable death in the Western world (CDC, 2004; WHO, 2009). Smoking increases the risk of many chronic, non-communicable diseases, both in smokers and in those who breathe secondhand smoke (Olasky *et al.*, 2012; Rostron *et al.*, 2014). To help reduce the broad-reaching, deadly consequences of tobacco use, the WHO's Framework Convention on Tobacco Control recommends a variety of policies and programs, including prominent pictorial health warning labels (HWLs) on tobacco packages. Regulatory decision-makers need research to inform the selection of optimal content and design for HWLs. Prior research to determine the most effective HWL content has mostly relied on self-reported responses, which may be biased (Thrasher *et al.*, 2006, 2012, 2012b; Hammond *et al.*, 2012). Falk and colleagues have suggested that functional magnetic resonance imaging (fMRI) is useful in predicting population-level responses to smoking cessation ads (Falk *et al.*, 2011). fMRI may work similarly for HWLs (Rubinstein, 2015).

Mounting evidence suggests that behavioral models based solely on self-report data are not optimal for predicting behavioral change across a wide variety of health behaviors (Berkman

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and Falk, 2013). There are many reasons why this may be the case, the first of which derives from the very nature of self-report data. Self-report measures of cognition and attitudes may not fully capture what people think and feel. This limitation could be addressed by using fMRI to add neural data to a model with self-report data. Secondarily, humans tend to under-report negative behaviors, a phenomenon known as social desirability bias (Podsakoff *et al.*, 2003). This type of bias can mask true causal relationships with health outcomes, particularly for behaviors that are stigmatized (Hammersley, 1994; Pierce, 2009; Shiffman, 2009). When reporting attitudes and feelings, a further problem appears: humans, particularly those with an addiction, are not always able to accurately identify their own internal states (Frankenstein and Wilson, 1984; Verdejo-Garcia and Perez-Garcia, 2008; Goldstein *et al.*, 2009). This is especially problematic in ambiguous situations (i.e. there are good and bad elements of a given behavior) such as those that commonly surround addiction. Taken together, these problems pose a significant hurdle to the creation of accurate predictive models of behavioral change.

Currently, approaches to evaluating and modifying public policy rely heavily on rational theories of behavioral change. Data from recent neuroimaging experiments suggest that models of behavioral change can benefit from the inclusion of fMRI data, which reflects the location and strength of brain activity elicited by specific stimuli. By directly measuring the brain's response to relevant stimuli (e.g. health messaging), this method provides a measure of response that is potentially more objective than individual self-report and that captures unique information that is not present in self-report data, thus potentially aiding in changing public policy. It is notable that a number of previous studies adopting this brain-as-predictor approach have successfully demonstrated that neural activity is a useful predictor of long-term behavioral outcomes (McClure *et al.*, 2004; Falk *et al.*, 2010, 2011; Berkman and Falk, 2013). Many studies indicate that the message-elicited activity in the ventromedial prefrontal cortex (vmPFC) predicts subsequent behavior (Knutson *et al.*, 2007; Falk *et al.*, 2010, 2011, 2012). However, these studies differ from the current study in a number of ways. Prior research examined changes in sunscreen use in response to persuasive messages (Falk *et al.*, 2010) and neural activity elicited by television campaigns promoting smoking cessation, along with a toll-free telephone number for cessation assistance (i.e. 'quit line') (Falk *et al.*, 2012). Additionally, prior fMRI studies have focused primarily on the usefulness of vmPFC activity in predicting changes in smoking behavior (Falk *et al.*, 2011). The current investigation not only adds to the literature regarding the use of fMRI to predict behavior, but specifically looks at two brain regions to predict changes in smoking behavior, one regarded as being primarily involved in cognition, and the other regarded as being primarily involved in affect.

The main a priori region of interest (ROI) in the present study is the ventromedial prefrontal cortex (vmPFC). Past studies have shown that the vmPFC is critical in making decisions based on emotional signals (Bechara *et al.*, 1999). The vmPFC has also been shown to play a role in deciding whether to participate in or avoid risky behaviors (Bechara *et al.*, 1999), such as smoking. Recent studies have shown this area of the brain to be associated with behavioral change (Falk *et al.*, 2010, 2011). For example, Falk *et al.* (2010) showed that activity in the vmPFC was associated with smoking behavioral change beyond people's smoking-related attitudes and intentions; there was also an association between activity in the vmPFC when exposed to persuasive messages and a change in behavior from pre- to post-scan (Falk *et al.*, 2010). Based on these previous findings, there is strong reason to believe that activity elicited in the vmPFC will contribute to the predictive power of statistical models of behavioral change.

The secondary a priori ROI in this study was the amygdala. Previous studies have shown that the amygdala is involved in emotional learning and memory, particularly when fear and anxiety are aroused (Davis, 1992, 1997; Bechara *et al.*, 1999; Shin *et al.*, 2005). Additionally, studies have shown activation in the left amygdala, specifically in response to a conditioned fear stimulus (Morris *et al.*, 1998; Phelps *et al.*, 2001). Morris *et al.* (1998) showed that amygdala activation occurred when subjects were exposed to human faces with emotions such as fear or suffering. Several recent studies found that the amygdala responds robustly to the presentation of pictorial HWLs (Jasinska *et al.*, 2012; Newman-Norlund *et al.*, 2014; Wang et al., 2015). Other research suggests that the amygdala's response to emotional stimuli is predictive of a wide variety of behavioral outcomes including post-exposure memory (Canli *et al.*, 2005). What remains less clear is whether or not the amygdala's response to emotional stimuli predicts subsequent behavioral change in health-messaging models that involve emotion-laden stimuli.

Based on prior work, we hypothesized that greater neural activity elicited by pictorial HWLs in the vmPFC and amygdala would predict change in smoking behavior. We posited that neural activity when viewing graphic and suffering images would do a better job of predicting smoking cessation due to the higher rates of self-reported motivation to quit when viewing these image types compared to symbolic images. Additionally, we predicted that addition of neural data to self-report based models would significantly improve their ability to predict subsequent behavioral change. In order to test this, self-reported smoking data as well as neural response data (to visual presentation of pictorial HWLs) were obtained from a cohort of 50 current adult smokers. The models attempted to explain changes in expired carbon monoxide (CO) and cigarettes per day (CPD) controlling for (i) intention to quit and (ii) heaviness of smoking (HSI) (Heatherton *et al.*, 1989; Borland *et al.*, 2010) (both of which have been shown to predict significant variance in behavioral change and are present in several previous studies of smoking behavioral change) and (iii) the intensity of the neural response to pictorial HWLs within each of our a priori ROIs.

Material and methods

Participants

Fifty current adult smokers between the ages of 18 and 50 (24 females, 26 males, mean age = 27.56) participated in this study (Table 1). Participants were recruited from the general public in Columbia, SC and surrounding areas via advertisements in local newspapers and posted around the University of South Carolina (USC). One participant was lost to follow-up resulting in a final sample of 49 participants. All participants were either not planning to quit (in the next 6 months) or planning to quit (in the next 6 months) (Table 1). All participants were neurologically healthy with normal to corrected vision. Participants met standard criteria for fMRI scanning; phone and online screening was done to confirm qualification. Following completion of the study protocol, participants were paid $100 for transportation costs related to participation in the study. This experiment was performed according to the guidelines of the Declaration of Helsinki and approved by the IRB at USC.

Table 1. Baseline demographic and smoking behavior information

Demographic variables		N = 50, mean (s.d.) or %
Sex	% Female	48%
Age	Mean	27.56
	Range	22
Race	% White	74%
	% African American	24%
	% Other	2%
Education	High school or less	26%
	Some college/tech school	55%
	College or more	18%
Income	Low	63%
	Middle	30%
	High	7%
Smoking/consumer behavior		
CO level (ppm)		18.74 (10.57)
Days smoked (last 30 days)		28.32 (4.63)
Cigarettes (per day)		14.90 (10.09)
Intend to quit		21
Do not intend to quit		29
How worried smoking	Not at all	0%
Affects health?	A little worried	48%
	Very worried	52%
Pay attention to HWLs	Not at all	54%
	A little worried	40%
	Somewhat	4%
	A lot	2%

Stimuli development

Nineteen different sets of three pictorial HWLs with different imageries were designed to communicate the health effects of smoking, resulting in 57 total images. Each set of pictorial HWLs included the same textual warning (e.g. Smoking causes cancer), with three different types of image for each set: (i) graphic—vivid depiction of the physical effects of smoking; (ii) suffering—vivid depiction of personal experience that included faces and showed physical, social, or emotional impact of smoking-related morbidity & mortality; 3. symbolic—representation of health risks using abstract imagery or symbols (e.g. ticking time-bomb to represent impending heart attack) (Hammond *et al.*, 2012; Thrasher *et al.*, 2012a; Hammond *et al.*, 2013; Newman-Norlund *et al.*, 2014).

Baseline assessments

Prior to arriving at the study site, participants viewed and rated all 57 pictorial HWLs images online in random order. Ratings were for fear (i.e. 'How much does this warning make you feel afraid?') and effectiveness (i.e. 'How effective is it?'), using a scale of 1–9 (i.e. 1 = not at all, 9 = extremely), as in prior studies (Hammond *et al.*, 2012; Thrasher *et al.*, 2012). Upon arrival to the study site and before participation in the fMRI protocol, participants self-reported their smoking behavior, including number of days smoked in the past 30 days, number of cigarettes per day, the time since last cigarette, time to first cigarette after waking, plans to quit in the next 6 months, and recent quit attempts. To measure extent of addiction—the most consistent predictor of smoking cessation—cigarettes per day and time to first cigarette were combined to calculate the heaviness of smoking index (HSI) (Heatherton *et al.*, 1989). At baseline and at two weeks follow-up, CO measurements were made using a piCO+ Smokerlyzer (Bedfont Scientific, Harrietsham, England), a portable CO monitor. Participants who reported having smoked at least 100 cigarettes in their lifetime and expired carbon monoxide (CO) of at least 5.0 parts per million (ppm) qualified for study inclusion (Low *et al.*, 2004).

fMRI procedure

During 50 min of fMRI scanning, each participant completed four functional MRI runs and a single, high resolution structural scan. Each functional run lasted 10 min and 24 s. Over the course of four functional runs, each of the 57 images (19 graphic images, 19 suffering images, and 19 symbolic images) was presented 10 times (i.e. 570 total HWLs). The images were presented using a block design format. Each block of stimuli was 10 s in duration (2 s per image) and consisted of the serial presentation of five images from the relevant condition (or fixation cross for rest), with each 10 s block separated by 1 s of fixation. A total of 40 blocks (10 graphic, 10 suffering, 10 symbolic and 10 rest) were presented during each of the four functional runs (i.e. 30 blocks with HWLs × 5 HWLs per block = 150 HWLs). Thus, 600 HWLs (150 HWLs per run × 4 runs) were presented with the remaining 30 chosen randomly (10 pseudorandom choices from each category with no repeats from each subset). The order of presentation of the blocks within a given functional run was chosen from one of the eight pseudo-randomly generated trial orders. These orders were constrained such that (i) each condition was equally likely to follow any other condition within a certain functional run and (ii) blocks of the same trial type never occurred more than three times in a row. Images were programmed to appear back-to-back five to six times during each functional run. When an image appeared back-to-back, the participant pushed a button on the response glove to ensure participant alertness (Newman-Norlund *et al.*, 2014). Each of the four functional runs was identical in duration and content with the exception of the random assignment of images from each condition to its corresponding block. Importantly, the total time (and thus total number of brain images recorded) spent showing blocks of each HWL type was identical to the total time spent showing rest blocks.

fMRI data acquisition

All fMRI data were collected on a 3T Siemens Trio system with a 12-element head coil. The fMRI (T_2^* echo planar imaging) imaging sequence included the following parameters: 320 full brain volumes collected in each of the four 10-minute and 24-second sessions; 75° flip angle; time repetition (TR) = 1.95 s; time echo (TE) = 30 ms; in-plane resolution = 3.30 × 3.30 mm; slice thickness = 3.0 mm (no gap); 36 axial slices collected in planes aligned parallel to the anterior commissure–posterior commissure line. To improve coregistration of images, all participants were scanned with a high-resolution T_1 MRI, which yielded a 1 mm isotropic image. This sequence had the following parameters: field of view (FOV) = 256 mm × 256 mm; 192 sagittal slices; 9° flip angle; TR = 2250 ms; TE = 4.15 ms.

Follow-up assessment

Two weeks following the fMRI scan, an in-person follow up was conducted at the scanning site. Expired CO, a quantifiable biomarker of smoking behavior, was measured and participants completed a follow-up survey similar to the baseline survey

(Benowitz et al., 2002). At this stage, one participant was unable to be reached.

fMRI data analysis

All fMRI data were analyzed using SPM (Welcome Department of Cognitive Neurology, London), version 8. For analysis of individual participant data, the following pre-statistics processing was applied: motion correction, co-registration, normalization, and spatial smoothing. Motion correction employed SPM8's fourth Degree B-Spline interpolation. For co-registration, we first calculated the appropriate transformation to bring each individual's mean echo-planar image (EPI) into the alignment with his or her structural image. Then this information was applied to the realigned EPI images. Normalization involved warping each individual's structural image onto the standard T1 weighted structural template and then applying this operation on the co-registered EPI images. As a final step in processing, all EPI images were spatially smoothed using a Gaussian kernel of full width at half maximum 8.0 mm. At the first level, we used SPM's general linear modeling approach to compute contrasts representing the main effect of each stimulus type (graphic, suffering, symbolic). The onsets and durations of each of the conditions of interest were modeled according to the block design described in the protocol. Functional data were modeled using the canonical hemodynamic response function (HRF) with no derivatives. For all group analyses reported below, a series of contrast images were first generated for each individual participant (first level models) and then entered these into random effects models in order to allow for meaningful population-level inference.

A priori ROI

Given the nature of our HWLs, a robust activation was expected to be found in a priori ROIs of the vmPFC (Bechara et al., 1999; Falk et al., 2010, 2011, 2012) and amygdala (Davis, 1992, 1997; Morris et al., 1998; Bechara et al., 1999; Phelps et al., 2001; Canli et al., 2005; Shin et al., 2005; Kensinger and Schacter, 2006; Adolphs, 2008; Newman-Norlund et al., 2014) when the participants view the HWLs (Figure 1). A whole brain search was conducted in addition to these a priori ROI.

The left and right amygdala locations (Figure 1) were identified in a prior study that localized brain activity associated with pictorial HWLs (Newman-Norlund et al., 2014). The ventromedial prefrontal site (Figure 1) was found to be related to behavioral changes in prior MRI studies by Falk and colleagues (Falk et al., 2010, 2011).

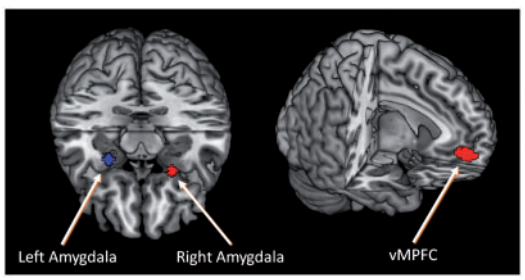

Fig. 1. A priori regions of interest. Left amygdala radius = 4 mm spherical ROI centered at XYZmni = −26, −2, −17, Right amygdala radius = 4 mm spherical ROI centered at XYZmni = 23, 7, −17, vmPFC centered at XYZ = 0, 60, −9 (Falk et al., 2011).

Associations between neural activity during HWL exposure and changes in CO

Changes in expired CO and self-reported CPD from baseline to follow-up were used as our primary measures of behavioral change. Change was calculated as the difference between baseline and follow-up assessments (baseline minus follow-up equals difference; positive values indicate reduction in smoking). To assess whether neural activity in the a priori ROI was associated with behavioral change, hierarchical multiple regression models were ran using IBM SPSS Statistics Version 22 (SPSS) with change in expired CO and with change in CPD as dependent variables. In the models, HSI and quit intention, two factors associated with reducing smoking behavior (Newman-Norlund et al., 2014), were controlled (first block). The second block of the model included self-reported ratings of the HWLs (How effective is it?). The third block included one brain area per model (i.e. vmPFC, left amygdala, right amygdala). Brain areas were searched at the group level looking for significant variance ($P < 0.05$) in smoking behavior (change in expired CO, change in CPD) resulting from the combination of neural activity and self-reported ratings of HWLs.

Results

Self-reported responses to HWLs

Mean self-reported ratings of effectiveness for each type of HWL on a scale of 1 (not effective) to 9 (very effective) were calculated suggesting graphic were most effective ($M = 5.47$, s.d = 1.88), followed by suffering ($M = 4.32$, s.d. = 1.73) and symbolic ($M = 2.66$, s.d. = 1.46).

Self-reported smoking behavior data

All participants were current smokers at baseline and reported smoking an average of 14.90 CPD (s.d. = 10.09), with an average expired CO of 18.74 ppm (s.d. = 10.57). At follow-up, participants reported smoking an average of 8.74 CPD (s.d. = 4.59), with an average expired CO of 18.02 ppm (s.d. = 11.30). Based on prior research indicating that smokers who intend to quit have stronger responses to HWLs (Falk et al., 2011; Hammond et al., 2012; Thrasher et al., 2012), we stratified participants based on intention to quit. The change in CPD from baseline to follow-up among those who intended to quit was significant: $M = 8.43$ (s.d. =12.37), $T(20) = 3.12$, $P = 0.005$. The change in CPD from baseline to follow-up among those who did not intend to quit was also significant: $M = 4.75$ (s.d. = 5.99), $T(27) = 4.20$, $P < 0.001$. No significant difference was found in expired CO for either those who intended to quit ($M = 2.00$ [s.d =8.09], $T[20] = 1.13$, $P = 0.270$) or who did not intend to quit ($M = -0.71$ [s.d = 7.51], $T[27] = -0.503$, $P = 0.619$). The correlation between self-reported smoking behavior (CPD) and our biological measure of smoking (expired CO) among those who intended to quit was not significant at baseline ($R = 0.390$, $N = 21$, $P = 0.074$) but was significant at follow-up ($R = 0.549$, $N = 21$, $P = 0.010$). The correlation between self-reported CPD and CO among those who did not intend to quit was significant at baseline ($R = 0.807$, $N = 29$, $P < 0.001$) and at follow-up ($R = 0.591$, $N = 28$, $P = 0.001$).

Associations between Self-reported intentions, HSI, and expired CO

No significant correlation was found between self-reported intention to quit and HSI ($R = -0.005$, $P = 0.972$) nor between

intention to quit and self-reported effectiveness for any HWL type ($R_{quitintent\_graphic} = -0.221$, $P = 0.122$; $R_{quitintent\_suffering} = -0.135$, $P = 0.350$; $R_{quitintent\_symbolic} = -0.151$, $P = 0.296$). However, there was a significant, positive association between HSI and effectiveness of graphic ($R_{HSI\_graphic} = 0.358$, $P = 0.011$) and suffering ($R_{HSI\_suffering} = 0.310$, $P = 0.29$) but not for symbolic HWLs ($R_{HSI\_symbolic} = 0.209$, $P = 0.146$). This suggests that the heavier the smoker, the more likely the graphic and suffering HWLs are reported to be effective.

Neural activity during HWL exposure predicts subsequent changes in expired CO

To determine whether neural activity in a priori ROIs was associated with a change in smoking behavior, change in expired CO from baseline to two-week follow-up was regressed onto parameter estimates of activity during viewing of HWLs compared with rest (Middleton and Morice, 2000; Deveciet *et al.*, 2004; Kumar *et al.*, 2007; Falk *et al.*, 2011; Overeem *et al.*, 2012). Neural activity in the left amygdala suggested that activity when viewing the suffering HWLs significantly predicted CO change both before and after controlling for HSI and intention to quit (Table 2). Activity in the vmPFC was significant for all HWL types both before and after controlling for HSI and intention to quit (Table 2). When the participants were stratified into groups based on intention to quit, those who intended to quit (Table 3) had significant neural activity in the vmPFC when viewing all HWL types similar to Table 2. The same group did not have any significant neural activity in the left or right amygdala. Participants who did not intend to quit (Table 4) had significant neural activity in the left amygdala when viewing human suffering HWLs, but no significant neural activity in the right amygdala or vmPFC. Stratifying by quit intent is a post hoc exploratory analysis of the relationship between quit intentions and observed reduction in smoking via expired CO.

Hierarchical multiple regression models were run to determine the amount of variance in biomarkers of behavioral change that could be explained above and beyond self-reported responses to our HWLs (i.e. 'How effective is it?'). The models in Table 5 followed the same pattern of significance as Table 2. Neural activity in the left amygdala was a significant predictor of CO change when averaged across all image types, with the relationship driven primarily by suffering HWLs. The *P* value for the vmPFC model with all HWL types ($P = 0.052$) was marginally significant. When stratified by intention to quit (Table 6), neural activity in the vmPFC for each image type was a significant

Table 2. Predicting change in expired CO among all participants

	Before controlling for HSI & quit intent				After controlling for HSI & quit intent			
	B (95% *CI*)	ß	*t*(48)	*P*	*B* (95% *CI*)	ß	*t*(48)	*P*
Left Amygdala								
Graphic	−1.077 (−2.670, 0.515)	−0.195	−1.361	0.180	−1.157 (−2.777, 0.464)	−0.209	−1.438	0.157
Suffering	−2.308 (−3.944, −0.672)	−0.383	−2.838	**0.007**	−2.264 (−3.931, −0.596)	−0.375	−2.734	**0.009**
Symbolic	−1.313 (−3.104, 0.477)	−0.210	−1.476	0.147	−1.470 (−3.294, 0.354)	−0.236	−1.632	0.112
Right Amygdala								
Graphic	−1.209 (−2.884, 0.467)	−0.207	−1.451	0.153	−1.252 (−2.963, 0.458)	−0.215	−1.475	0.147
Suffering	−1.705 (−3.574, 0.164)	−0.259	−1.835	0.073	−1.650 (−3.576, 0.276)	−0.250	−1.725	0.091
Symbolic	−1.627 (−3.637, 0.384)	−0.231	−1.627	0.110	−1.748 (−3.791, 0.295)	−0.248	−1.723	0.092
vmPFC								
Graphic	−1.259 (−2.129, −0.389)	−0.391	−2.910	**0.006**	−1.255 (−2.137, −0.372)	−0.389	−2.863	**0.006**
Suffering	−1.328 (−2.304, −0.351)	−0.371	−2.736	**0.009**	−1.373 (−2.362, −0.385)	−0.383	−2.799	**0.008**
Symbolic	−1.182 (−2.059, −0.304)	−0.367	−2.709	**0.009**	−1.227 (−2.115, −0.339)	−0.382	−2.783	**0.008**

This table shows neural activity in our ROIs predicting changes in expired CO among all participants ($N = 49$). Bold numerals indicate statistical significance ($P < 0.05$).

Table 3. Predicting change in expired CO among those who intended to quit

	Before controlling for HSI				After controlling for HSI			
	B (95% *CI*)	ß	*t*(20)	*P*	*B* (95% CI)	ß	*t*(20)	*P*
Left Amygdala								
Graphic	−1.495 (−3.906, 0.915)	−0.285	−1.298	0.210	−1.665 (−3.971, 0.641)	−0.318	−1.517	0.147
Suffering	−2.156 (−4.539, 0.226)	−0.399	−1.894	0.074	−2.094 (−4.392, 0.205)	−0.387	−1.914	0.072
Symbolic	−1.528 (−3.968, 0.912)	−0.288	−1.311	0.206	−1.790 (−4.119, 0.539)	−0.337	−1.615	0.124
Right Amygdala								
Graphic	−1.688 (−4.593, 1.217)	−0.269	−1.216	0.239	−1.878 (−4.663, 0.906)	−0.299	−1.417	0.173
Suffering	−2.121 (−4.991, 0.749)	−0.334	−1.547	0.138	−1.947 (−4.751, 0.858)	−0.307	−1.458	0.162
Symbolic	−1.310 (−4.104, 1.484)	−0.220	−0.981	0.339	−1.626 (−4.313, 1.062)	−0.273	−1.271	0.220
vmPFC								
Graphic	−1.877 (−3.148, −0.606)	−0.578	−3.090	**0.006**	−1.891 (−3.078, −0.705)	−0.583	−3.348	**0.004**
Suffering	−1.571 (−2.995, −0.147)	−0.468	−2.308	**0.032**	−1.721 (−3.044, −0.399)	−0.513	−2.734	**0.014**
Symbolic	−1.521 (−2.914, −0.127)	−0.464	−2.283	**0.034**	−1.625 (−2.928, −0.322)	−0.496	−2.620	**0.017**

This table shows neural activity in our ROIs predicting changes in expired CO among those who intended to quit ($N = 21$). Bold numerals indicate statistical significance ($P < 0.05$).

Table 4. Predicting change in expired CO among those who did not intend to quit

	Before controlling for HSI				After controlling for HSI			
	B (95% *CI*)	ß	*t*(27)	*P*	*B* (95% *CI*)	ß	*t*(27)	*P*
Left Amygdala								
Graphic	−0.970 (−3.263, 1.323)	−0.168	−0.870	0.393	−0.959 (−3.300, 1.383)	−0.166	−0.843	0.407
Suffering	−2.542 (−4.965, −0.119)	−0.389	−2.156	**0.041**	−2.635 (−5.114, −0.155)	−0.404	−2.189	**0.038**
Symbolic	−1.248 (−4.169, 1.674)	−0.170	−0.878	0.388	−1.211 (−4.233, 1.812)	−0.165	−0.825	0.417
Right Amygdala								
Graphic	−1.347 (−3.545, 0.851)	−0.240	−1.260	0.219	−1.378 (−3.623, 0.867)	−0.245	−1.264	0.218
Suffering	−1.684 (−4.316, 0.948)	−0.250	−1.315	0.200	−1.824 (−4.547, 0.899)	−0.271	−1.380	0.180
Symbolic	−2.636 (−5.864, 0.591)	−0.313	−1.679	0.105	−2.631 (−5.924, −0.662)	−0.312	−1.645	0.112
vmPFC								
Graphic	−0.691 (−1.928, 0.546)	−0.220	−1.148	0.262	−0.696 (−1.957, 0.566)	−0.221	−1.136	0.267
Suffering	−0.936 (−2.411, 0.539)	−0.248	−1.304	0.204	−0.928 (−2.435, 0.579)	−0.246	−1.268	0.216
Symbolic	−0.843 (−2.052, 0.366)	−0.270	−1.433	0.164	−0.833 (−2.073, 0.407)	−0.267	−1.384	0.179

This table shows neural activity in our ROIs predicting changes in expired CO among those who did not intend to quit ($N = 28$). Bold numerals indicate statistical significance ($P < 0.05$).

Table 5. Variance in expired CO among all participants

	$R^2_{\text{self-report}}$	$R^2_{\text{self-report + neural activity}}$	R^2_{change}	*P*
Left amygdala				
All types	0.066	0.250	0.184	**0.031**
Graphic	0.053	0.089	0.036	0.191
Suffering	0.040	0.184	0.144	**0.008**
Symbolic	0.019	0.073	0.054	0.117
Right amygdala				
All types	0.066	0.157	0.091	0.244
Graphic	0.053	0.092	0.039	0.177
Suffering	0.040	0.103	0.063	0.086
Symbolic	0.019	0.080	0.061	0.096
vmPFC				
All types	0.066	0.228	0.163	0.052
Graphic	0.053	0.196	0.144	**0.007**
Suffering	0.040	0.192	0.152	**0.006**
Symbolic	0.019	0.163	0.144	**0.009**

This table shows the variance in expired CO explained by self-reported responses to our HWLs and self-reported responses to our HWLs combined with neural activity among all participants ($N = 49$). Bold numerals indicate statistical significance ($P < 0.05$).

Table 6. Variance in expired CO among those who intended to quit

	$R^2_{\text{self-report}}$	$R^2_{\text{self-report + neural activity}}$	R^2_{change}	*P*
Left amygdala				
All types	0.159	0.402	0.243	0.204
Graphic	0.130	0.218	0.087	0.186
Suffering	0.119	0.266	0.147	0.082
Symbolic	0.119	0.250	0.132	0.102
Right Amygdala				
All types	0.159	0.375	0.216	0.261
Graphic	0.130	0.206	0.076	0.220
Suffering	0.119	0.209	0.090	0.182
Symbolic	0.119	0.210	0.091	0.179
vmPFC				
All types	0.159	0.481	0.323	0.089
Graphic	0.130	0.456	0.326	**0.005**
Suffering	0.119	0.379	0.260	**0.016**
Symbolic	0.119	0.365	0.246	**0.020**

This table shows the variance in expired CO explained by self-reported responses to our HWLs and self-reported responses to our HWLs combined with neural activity among participants who intended to quit ($N = 21$). Bold numerals indicate statistical significance ($P < 0.05$).

predictor of change in expired CO. No significant activity was observed in the left or right amygdala in participants who intended to quit. Those who did not intend to quit (Table 7) had significant activity in the left amygdala when viewing HWLs depicting human suffering and in the right amygdala when viewing symbolic HWLs. There was no statistically significant association with activity in the right amygdala or vmPFC among participants who did not intend on quitting.

Using neural activity to predict change in self-reported cigarettes per day

To determine whether change in cigarettes per day (CPD) could also be explained by neural activity, the same analyses reported above for CO, were conducted with change in CPD from baseline to follow-up as the dependent variable. Neural activity was not a statistically significant correlate of change in CPD for any HWL type. Stratifying participants by intention to quit and controlling for HSI and quit intent also did not yield any significant results. BOLD signal observed in the left amygdala in response to graphic HWLs provided a statistically significant explanation of variance in CPD (R^2 change = 0.028). This was true regardless of participants' intention to quit.

Discussion

The main purpose of this study was to examine the hypothesis that neural activity elicited by pictorial HWLs in the vmPFC and amygdala would predict change in smoking behavior. We expected that inclusion of vmPFC and amygdala activity would improve the predictive power of our models. While the results of this study should be interpreted with some caution due to the large number of analyses conducted, they are generally consistent with these predictions, and provide novel data regarding the relationship between behavioral change and neural measures. Furthermore, this study makes a unique contribution by showing that smokers respond to HWLs in a cognitive-affective manner (i.e. the link between warnings and behavioral change is driven by both emotional and cognitive factors).

Table 7. Variance in expired CO among those who did not intend to quit

	$R^2_{\text{self-report}}$	$R^2_{\text{self-report + neural activity}}$	R^2_{change}	*P*
Left amygdala				
All types	0.034	0.274	0.240	0.119
Graphic	0.030	0.058	0.028	0.407
Suffering	0.027	0.204	0.177	**0.030**
Symbolic	0.009	0.036	0.027	0.418
Right amygdala				
All types	0.034	0.176	0.142	0.355
Graphic	0.030	0.090	0.060	0.222
Suffering	0.027	0.119	0.091	0.128
Symbolic	0.009	0.105	0.097	0.120
vmPFC				
All types	0.034	0.123	0.089	0.577
Graphic	0.030	0.085	0.054	0.244
Suffering	0.027	0.115	0.087	0.137
Symbolic	0.009	0.080	0.071	0.187

This table shows the variance in expired CO explained by self-reported responses to our HWLs and self-reported responses to our HWLs combined with neural activity among participants who did not intend to quit ($N = 28$). Bold numerals indicate statistical significance ($P < 0.05$).

Predicting changes in tobacco smoke exposure (CO) with neural responses to HWLs

Neural activity in a priori ROIs was associated with a change in CO (biomarker of tobacco smoke exposure), including when key predictors of behavioral change (i.e. HSI, quit intention) were controlled for. Previous research shows that the vmPFC is involved in executive functioning and decision-making, particularly with regards to risky behavior (e.g. deciding whether to or not to purchase cigarettes) (Bechara *et al.*, 1996, 1997, 1999; Falk *et al.*, 2010). Highly relevant prior work by Falk and colleagues (2011) demonstrated a significant relationship between vmPFC activity and cessation behavior. Critically, this prior study measured vmPFC activity elicited by smoking cessation ads. The current study indicated that vmPFC activity, in response to any type of pictorial HWL (graphic, suffering, symbolic), partially explained subsequent changes in CO levels. When models were stratified by participant intention to quit, the associations between vmPFC activity and CO were limited to those who intended to quit (Table 3). These data suggest that activity in the vmPFC is particularly relevant to individuals that intend to change their behaviors, confirming work done by Falk and colleagues (2011).

Neural responses observed in the left amygdala significantly predicted CO change in our sample. Interestingly, only neural responses to suffering HWLs (not graphic or symbolic HWLs) improved predictive models based on CO. When the data were stratified by intention to quit, this relationship was statistically significant only among smokers who did not intend to quit. Emotion often enhances memory; emotional events are often easier to recall, particularly 'negative' emotional stimuli (e.g. HWLs depicting human suffering) (Mickley and Kensinger, 2008). Amygdala activation resulting from HWLs with emotional appeal has been shown to play a role in quitting and has been used as a predictor of quitting (Jasinska *et al.*, 2012). However, unlike the messages used in the current study (i.e. Smoking causes lung cancer), Jasinska and colleagues (2012) showed tailored smoking-cessation messages (i.e. You want to quit because you are tired of spending your money on cigarettes), untailored smoking cessation messages (i.e. Many people quit with another person so they can support each other), and neutral (i.e. Bali attracts more tourists than any other Indonesian island) to 91 smokers who intended to quit and had completed a smoking cessation intervention and attempted to quit. Consistent with claims made by Rubinstein (2015), our results suggest that messaging that evokes activation in emotional brain centers (i.e. the amygdala) is important to behavioral change. In addition, the results in the present study suggest that activation in emotional centers may be particularly valuable in predicting the decision to change behavior in individuals that have not yet decided to make a change.

Seen from this perspective, activation in the amygdala could constitute a key part of pre-decision cognition that is highly relevant to an individual's plans regarding subsequent behaviors. After an individual 'decides' to pursue change, it may be that activation in higher-order cognitive centers (such as the vmPFC), associated with the 'self' broadly defined, become more relevant. This possibility deserves further scrutiny. Additional studies could identify the exact time points that decisions to quit are made, and then examine the ability of brain signals recorded at these sites to predict the direction and size of behavioral change. Taken together, the present findings regarding vmPFC and amygdala activation suggest that behavioral change in response to health warnings may be best predicted by activity at specific brain sites, possibly in an attitude (i.e. intention to quit) dependent manner.

A second important finding that emerges from the current dataset is that neural responses can add unique predictive power to models of behavioral change (Tables 5–7). Neural activity explained up to 32.6% of the total amount of variance in CO change (Table 6), after accounting for the contribution of self-report measures. As in the aforementioned analyses, inclusion of neural data capturing the vmPFC's response to graphic, suffering, or symbolic stimuli, significantly improved these models. This was the case both in the overall sample and when considering smokers who intend to quit (Table 6). Amygdalar responses to HWLs depicting human suffering also explained variance in CO change, both in the sample as a whole (Table 5) and when considering just those who did not intend to quit (Table 7). Models including a combination of self-report and neural data accounted for more variability than models incorporating either one or the other. These findings are consistent with the possibility discussed above, that behavioral change is best predicted and variance is best explained by activity at different brain sites in an attitude dependent fashion.

Predicting changes in cigarettes smoked per day (CPD) with neural responses to HWLs

Self-reported CPD decreased from baseline to follow-up, but neither neural data recorded in the vmPFC nor the amygdala captured these changes. It is worth noting that a statistically significant association was observed between CPD change and activity in the left amygdala in response to graphic HWLs when assessing all participants ($R^2_{\text{self-report}} = 0.675$, $R^2_{\text{self-report + neural activity}} = 0.703$, $R^2_{\text{change}} = 0.028$, $P = 0.049$) and those who intended to quit ($R^2_{\text{self-report}} = 0.853$, $R^2_{\text{self-report + neural activity}} = 0.888$, $R^2_{\text{change}} = 0.035$, $P = 0.034$). The generally weaker predictive power of neural data with regards to changes in CPD, as opposed to change in CO, is interesting to consider. Traditional methods used to quantify CPD are prone to multiple forms of bias, including social desirability and memory biases. Expired CO may be a more reliable and objective marker of exposure to cigarette smoke, particularly if participants perceived participation in the study as an attempt to convince them to quit—even though our

recruitment and consent materials communicated that this was not our aim. Mean CPD levels decreased from baseline to follow-up, a fact that is at least consistent with potential biases in CPD measurement. Future investigations should continue to evaluate the utility of multiple measures of behavioral change in order to maximize experimental sensitivity and validity.

Limitations and future directions

Results from the current study are subject to a few caveats. First, the models contained relatively few self-report measures (i.e. HSI, intention to quit) to predict changes in smoking behavior; however, the measures we included are the most consistent predictors of smoking cessation (Vangeli *et al*, 2011). Future studies should nevertheless integrate more detailed self-report and behavioral measures. Even so, the neural data in our models accounted for a significant amount of variation (up to $R^2_{change} = 0.326$), suggesting that the inclusion of additional self-report measures is unlikely to explain all of these variations.

A second limitation concerns the disjoint between what the ROIs were thought to detect (cognitive and emotional processing) and what was captured in self-report (perceived effectiveness of warnings, which is more cognitive). We would expect the ROIs to be a stronger predictor of change in smoking since they captured different cognitive and affective processes than what the self-report data captured. Future studies should be conducted to further explore this.

A third limitation concerns the outcomes that were assessed. Smoking cessation was also not assessed, which would likely require larger sample sizes and longer follow-up than 2 weeks. Larger samples may not be feasible for fMRI studies, due to the high cost of MRI scanning, which typically ranges from $500 to $1000 per hour. In light of this fact, it is suggested that future research considers longer follow-up periods, perhaps focusing on smokers who are ready to quit and therefore more likely to change their behavior, as in prior research (Falk *et al*., 2011). Our biomarker of tobacco smoke exposure, CO, has a short half-life of approximately 1 — 4 h (Scherer, 2006), reflects more recent exposure to smoking, and is dependent on the time since the last cigarette. Several prior studies have confirmed the utility of both CPD and CO levels to verify self-reported cigarette consumption, with correlation coefficients ranging from 0.3 — 0.8 (Perez-Stable *et al*., 1995; Domino and Ni, 2002; Mustonen *et al*., 2005; Scherer, 2006). The correlation is generally stronger for people with higher CPD (Perez-Stable *et al*., 1995; Domino and Ni, 2002; Mustonen *et al*., 2005), which applies to the majority of our sample. Due to CO's relatively short half-life, other biomarkers with longer half-lives (e.g. cotinine) may be considered for better assessment of tobacco smoke exposure (Perez-Stable *et al*., 1995; Ho *et al*., 2009).

Fourth, over the course of the study, participants showed decreases in both expired CO and the number of cigarettes they smoked per day. The neural response to HWLs was more associated with CO change than with CPD change. Admittedly, expired CO is an imperfect measure of recent exposure to cigarette smoke. Future research should consider collecting additional biomarkers of exposure, such as cotinine (a nicotine metabolite) and 3-hydroxycotinine, which are more valid than expired CO (Benowitz, 1983; Benowitz and Jacob, 2001; Benowitz *et al*., 2002).

General conclusion

The present study examined the hypothesis that neural responses to emotion-laden pictorial HWLs can predict subsequent behavioral change. Public policy is changed based behavioral science, which often relies on self-report models. The question is whether or not these models benefit from the inclusion of neural data. If so, what types of neural data are of particular value? Our findings suggest that these models do benefit from the inclusion of neural data, and that activation at both cognitive and affective sites should be considered as valuable. Not only did neural responses predict change, they did so above and beyond self-report measures, in some cases accounting for as much as 32.6% of additional variance. Interestingly, activation in the vmPFC was most useful when predicting change in individuals who intended to quit smoking, whereas activation in the amygdala was most useful in models designed to predict change in individuals that did not intend to quit. Critically, this is one of the first papers to find that neural activation in emotion-processing areas (i.e. the amygdala) can be useful in modeling subsequent behavioral change. This may be due to the highly emotionally charged nature of the messaging stimuli used in the current study. It was also found that models designed to capture changes in CO benefited from inclusion of different neural data than models designed to capture change in CPD. This suggests that models of behavioral change based on different types of outcome data could be differentially informed by specific neural data. Overall, these findings suggest that, in addition to traditional self-report data, the responses of specific brain areas (specifically the vmPFC and amygdala) to different types of health messaging stimuli are useful to consider when attempting to develop HWLs and in similar studies that aim to understand how health messaging can influence behavioral change.

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