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Associations between Coherent Neural Activity

Abstract
Objective: Worldwide, tobacco use is the leading cause of preventable death and illness. One common strategy for reducing the prevalence of cigarette smoking and other health risk behaviors is the use of graphic warning labels (GWLs). This has led to widespread interest from the perspective of health psychology in understanding the mechanisms of GWL effectiveness. Here we investigated differences in how the brain responds to negative, graphic warning label-inspired antismoking ads and neutral control ads, and we probed how this response related to future behavior.

Method: A group of smokers ($N = 45$) viewed GWL-inspired and control antismoking ads while undergoing fMRI, and their smoking behavior was assessed before and one month after the scan. We examined neural coherence between two regions in the brain's valuation network, the medial prefrontal cortex (MPFC) and ventralstriatum (VS).

Results: We found that greater neural coherence in the brain's valuation network during GWL ads (relative to control ads) preceded later smoking reduction.

Conclusions: Our results suggest that the integration of information about message value may be key for message influence. Understanding how the brain responds to health messaging and relates to future behavior could ultimately contribute to the design of effective messaging campaigns, as well as more broadly to theories of message effects and persuasion across domains.

Keywords
behavior change, functional MRI (fMRI), neuroimaging, smoking, valuation

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Associations between coherent neural activity in the brain's value system during antismoking messages and reductions in smoking

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ABSTRACT

Objective: Worldwide, tobacco use is the leading cause of preventable death and illness. One common strategy for reducing the prevalence of cigarette smoking and other health risk behaviors is the use of graphic warning labels (GWLs). This has led to widespread interest from the perspective of health psychology in understanding the mechanisms of GWL effectiveness. Here we investigated differences in how the brain responds to negative, graphic warning label-inspired antismoking ads and neutral control ads, and we probed how this response related to future behavior. ***Methods***: A group of smokers (N = 45) viewed GWL-inspired and control antismoking ads while undergoing fMRI, and their smoking behavior was assessed before and one month after the scan. We examined neural coherence between two regions in the brain's valuation network, the medial prefrontal cortex (MPFC) and ventral striatum (VS). ***Results***: We found that greater neural coherence in the brain's valuation network during GWL ads (relative to control ads) preceded later smoking reduction. ***Conclusions***: Our results suggest that the integration of information about message value may be key for message influence. Understanding how the brain responds to health messaging and relates to future behavior could ultimately contribute to the design of effective messaging campaigns, as well as more broadly to theories of message effects and persuasion across domains.

Keywords: brain-as-predictor; behavior change; smoking; neuroimaging; functional magnetic resonance imaging (fMRI); valuation

INTRODUCTION

Tobacco use is the leading cause of preventable death worldwide, increasing the odds of developing cancer, heart disease, and other illnesses (World Health Organization, 2015b). Although the prevalence of tobacco use has dramatically decreased over the last several decades, 1.1 billion people worldwide still smoke tobacco (World Health Organization, 2015a), and more than 1 in 8 adults in the U.S. smoke tobacco cigarettes (Ward et al., 2016). The World Health Organization recommends a variety of tobacco control policies, including the addition of graphic warning labels (GWLs) to cigarette packaging (World Health Organization, 2009). Despite widespread adoption of GWLs around the world, controversies exist concerning their implementation in the U.S. (Canadian Cancer Society, 2014; *R.J. Reynolds Tobacco Co., et al v. Food & Drug Admin., et al*, 2012; *R.J. Reynolds Tobacco Co., et al v. Hamburg et al*, 2011; United States Public Laws, 2009), and the psychological and neurobiological mechanisms underlying their effects on behavior are still poorly understood. This has led to interest in understanding the effectiveness of GWLs in health messaging and the neurobiological mechanisms underlying their effects. Health warning labels are also used in a variety of other contexts, such as on alcoholic beverages and sugary drinks (Glock and Krolak-Schwerdt, 2013; Martin-Moreno et al., 2013; Pettigrew et al., 2014; Schillinger and Jacobson, 2016; VanEpps and Roberto, 2016), further increasing the need for a mechanistic understanding of their effectiveness.

Recent work has demonstrated that neuroimaging can provide predictive information about the influence of health messaging, and that brain data can be a useful measurement for understanding the mechanisms of message effectiveness (Berkman and Falk, 2013; Cooper et al., 2015, 2017, Falk et al., 2015, 2016; Imhof et al., 2017; Owens et al., 2017; Riddle et al., 2016;

Schmälzle et al., 2013; Vezich et al., 2016; Wang et al., 2013, 2015; Weber et al., 2015). Average neural activity in the medial prefrontal cortex (MPFC) during messaging has been associated with future health behavior change in individuals (e.g., for smoking reduction (Chua et al., 2011; Cooper et al., 2015; Owens et al., 2017; Riddle et al., 2016; Wang et al., 2013), physical activity (Cooper et al., 2017; Falk et al., 2015), and sunscreen use (Falk et al., 2010; Vezich et al., 2016)) as well as population measures of anti-smoking campaign effectiveness (e.g., online click-through-rates (Falk et al., 2016), calls to quit lines (Falk et al., 2012)).

A current suggestion for why MPFC activity may be linked to behavior change hinges on the role of MPFC in assessing the value of ideas to oneself (Cooper et al., 2015; Falk et al., 2015; Falk and Scholz, 2018), or the integration of a message's value with one's self concept (Vezich et al., 2016). The MPFC and ventral striatum (VS) have been identified as the two regions most likely to be active during subjective valuation, or the valuation of behaviors and rewards relative to the self (Bartra et al., 2013; Levy and Glimcher, 2012). One possibility is that MPFC assesses the value or relevance of a health message to the self, and furthermore, that the extent of this process may account for the extent of future behavior change. Outside of the health domain, brain activity in the value system has also been associated with outcomes such as consumer behavior (Berns and Moore, 2012; Genevsky and Knutson, 2015; Kühn et al., 2016; Venkatraman et al., 2015) and response to social influence (Cascio et al., 2015; Klucharev et al., 2009; Mason et al., 2009; Nook and Zaki, 2015; Zaki et al., 2011).

Given the multiple psychological functions supported by MPFC (Roy et al., 2012; Vega et al., 2016), examining coherent activity, also referred to as functional connectivity, specifically within the brain's value system can provide additional information about why and how certain types of messages, like graphic warning messages, exert their effects. The meaning of activity in a particular region changes depending on its interactions with other key regions (Lindquist et al., 2012; Poldrack, 2006; Shine et al., 2016), and examining the coherence of activity between brain regions during exposure to different types of messages could provide new, complementary information about brain function (Bassett et al., 2011; Bressler and Menon, 2010; Medaglia et al., 2015; Park and Friston, 2013). In line with the importance of considering MPFC and VS together, Cooper et al. (2017) find that functional connectivity within valuation regions during exposure to physical activity health messages is linked to behavior change, independent of average neural activation. Increased functional connectivity between MPFC and VS during behaviorally relevant GWLs could indicate that an individual values the information contained in the message. This type of updating of smoking values or beliefs may, in turn, be more likely to induce later behavior change. If so, we might observe that differences in the brain's value network (MPFC and VS) during exposure to GWLs as compared to control ads in terms of overall activation, functional connectivity, or both, relate to later behavior change.

To test these possibilities, we examined neural activation within and coherent neural activity between brain regions while a group of smokers viewed antismoking ads. Some ads portrayed the negative consequences of smoking, using messaging based on the FDA's proposed GWLs for cigarette packaging (Nonnemaker et al., 2010). Others were antismoking ads with neutral control images. Smokers viewed these ads during a neuroimaging session, and their smoking behavior was assessed before and one month after the scan. We hypothesized that individuals with greater MPFC activation for GWL *versus* control ads, as well as greater coherence in activity between MPFC and VS for GWL *versus* control ads, would demonstrate larger smoking reductions. Understanding neural activation during GWLs and how this relates to future behavior change could have a large impact on the design of optimally effective GWLs and broader health interventions.

MATERIALS AND METHODS

Participants. Fifty smokers participated in this fMRI study. This sample size was based on previous studies linking brain responses to behavior change outcomes (Falk et al., 2010, 2011; Riddle et al., 2016; Vezich et al., 2016; Wang et al., 2015). All participants gave written informed consent in accordance with the procedures of the Institutional Review Board at the University of Michigan. Data were collected at the University of Michigan from February to July 2013. Two participants were excluded for missing data (one due to an error at the scanner, and another for not participating in the final session). Three participants were excluded for data quality issues (one for neurological abnormalities, one for excessive head motion, and a third for both vision problems and excessive head motion). Exclusions for excessive head motion displayed greater than 3mm total translation, 1 degree rotation, and 5 spikes of at least 1mm. This resulted in a final sample of 45 participants.

Participants were recruited from the general population using Craigslist and a university research website. Advertising described the study as a “research study on the neural correlates of effective health communication,” in which participants would be asked to complete surveys and evaluate health and anti-smoking messages. The university research website allowed for targeting of participants who met a particular set of health and/or demographic criteria. Wide advertising, including Craigslist, and a fixed set of recruitment questions were used to reduce bias. Interested participants completed an eligibility screening phone call. To participate in the study, participants had to report smoking at least 5 cigarettes per day for the past month, have been a smoker for at least 12 months, and be between the ages of 18 and 65. Participants also had to meet standard fMRI eligibility criteria, including having no metal in their body, no history of psychiatric or neurological disorders, and currently not taking any psychiatric or illicit drugs. See Table 1 for demographic information and Figure S1 for further details about study recruitment and retention.

Study timeline. Participants completed three appointments once enrolled in the study. The first was an intake appointment (Session 1), during which participants gave their informed consent and completed baseline self-report surveys. This session lasted approximately 1 hr. The fMRI scanning appointment (Session 2) took place an average of 6 days (SD = 4 days) after Session 1, and lasted approximately 3 hr. Participants completed both prescan and postscan self-report measures, as well as 1 hr of testing inside the MRI scanner. Participants were not instructed to abstain from cigarettes for any period prior to the scan session. The follow-up appointment (Session 3) was conducted over the phone, an average of 39 days (SD = 9 days) after Session 2.

Smoking questionnaires. Participants reported the number of cigarettes they smoked per day at every appointment. As a reference, they were told that a pack contains 20 cigarettes. In analysis, we examined the percent change in smoking from Session 2 to Session 3, because of its proximity to the scan session. Reports of daily smoking at Session 1 and Session 2 were very consistent ($r = 0.94$). Self-report measures are commonly used to track smoking behavior change (Chua et al., 2011; Jasinska et al., 2012), and have been shown to have a moderate to high correlation with physiological metrics such as expired CO (Falk et al., 2011; Jarvis et al., 1987; Middleton and Morice, 2000) and saliva and serum cotinine (Etter et al., 2000; Patrick et al., 1994; Pokorski et al., 1994; Vartiainen et al., 2002). Smoking levels were not biochemically verified. The Fagerström Test for Nicotine Dependence (FTND) was also administered at Session 1.

Finally, after reporting their daily smoking levels, participants were asked at each time point whether they were enrolled in a quit-smoking program at that time, and whether they had a planned quit date. At Session 2, one participant was enrolled in a quit-smoking program and one had a planned quit date. At Session 3, one participant had quit smoking, two participants were enrolled in quit-smoking programs and had planned quit dates, and one had a planned quit date but was not enrolled in quit-smoking program. Therefore, we infer that most of the change in participants' smoking behavior between sessions was not a result of external professional interventions.

fMRI task. Participants saw 60 images presented with the text "Stop Smoking. Start Living" (see Figure 1 for task design). Thirty were negative antismoking images, based on the FDA's proposed graphic warning labels (referred to as GWL ads). Twelve of these portrayed social consequences of smoking (e.g., exclusion from a group) and 18 portrayed non-social and health-related consequences of smoking (e.g., a tracheotomy). The remaining 30 images were neutral control images (11 social, 19 nonsocial). The negative and neutral images were matched in pairs, by content complexity, focal point, and number of people in the image.

Each trial consisted of 4s of image presentation, followed by a 3s response screen with the statement "This makes me want to quit" and a 5-point rating scale (1=definitely does not, 5=definitely does). The response period was followed by a jittered inter-trial interval, consisting of a screen with only a fixation cross (3-7.5s, mean = 4.10s, median = 3.32s, SD = 1.01s). The task also included 20 personal (Facebook) or control (NimStim) face images, which were interspersed with the other image trials but are not the focus of the current investigation.

The fMRI session consisted of four tasks, including the task that is the focus of this report. Preceding this GWL image task were a self-relevance task, in which participants made judgments about whether particular personality traits described them or close friends (Cooper et al., 2015), and a counterarguing task, in which participants were prompted to think about arguments for and against specific statements (no statements focused on smoking). Following the GWL image task, participants completed a fourth task, in which they viewed banner ads from the American Legacy Foundation's EX campaign (Cooper et al., 2015). The task reported here is also described in (Falk et al., 2016), which relates activation from single regions to measures of population-level effectiveness of the task stimuli, and also in (Pegors et al., 2017), which focuses on the relationships between multivariate measures of brain activity, social networks, and individual behavior change.

MRI image acquisition. Neuroimaging data were acquired using a 3 Tesla GE Signa MRI scanner. Two functional runs of the task (454 volumes total) were acquired. Functional images were recorded using a reverse spiral sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, 43 axial slices, FOV = 220 mm, slice thickness = 3mm; voxel size = 3.44 x 3.44 x 3.0 mm). We also acquired in-plane T1-weighted images (43 slices; slice thickness = 3 mm; voxel size = .86 x .86 x 3.0mm) and high-resolution T1-weighted images (SPGR; 124 slices; slice thickness = 1.02 x 1.02 x 1.2 mm) for use in coregistration and normalization.

fMRI pre-processing. Functional data were pre-processed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). To allow for the stabilization of the BOLD signal, the first five volumes (10s) of each run were discarded prior to analysis. Functional images were despiked using the 3dDespike program (AFNI (Cox, 1996)). Data were next corrected for differences in the time of slice acquisition using sinc interpolation; the first slice served as the reference slice. Data were then spatially realigned to the first functional image. We then co-registered the functional and structural images using a two-stage procedure. First, in-plane T1 images were registered to the mean functional image. Next, high-resolution T1 images were registered to the in-plane image. After coregistration, high-resolution structural images were skull-stripped using the VBM8 toolbox for SPM (http://dbm.neuro.uni-jena.de/vbm), and then normalized to the skull-stripped MNI template provided by FSL. Finally, functional images were smoothed using a Gaussian kernel (8 mm FWHM).

Activation analysis. The fMRI data were modeled for each participant using fixed effects models within the general linear model as implemented in SPM8. The six rigid-body translation and rotation parameters derived from spatial realignment were included as nuisance regressors in the first level model. Data were high-pass filtered with a cutoff of 128 s. Ad presentations were modeled as four regressors, one for each trial type (GWL social, GWL nonsocial, control social, control nonsocial). The contrast of interest was GWL (social and nonsocial) minus control (social and nonsocial) image trials. We modeled the 20 face trials in one nuisance regressor, and the response period for all trials as an additional nuisance regressor. Fixation rest-periods constituted an implicit baseline. The resulting contrast images were combined using a random effects model in SPM8. From the *a priori* region of interest (ROI), average parameter estimates were extracted at the group level using MarsBaR (Brett et al., 2002) and converted to percent signal change.

Regions of interest (ROIs). The *a priori* ROIs in medial prefrontal cortex (MPFC) and ventral striatum (VS) were defined based on a quantitative meta-analysis of 206 studies that reported subjective value-related neural signals during decision-making (Bartra et al., 2013).

This meta-analysis identified a subregion of MPFC (volume=3.58 cm^3) and the VS (volume=4.00 cm^3) as most likely to be active during personal value-related decision-making. The study authors provided masks of the meta-analysis results.

Psychophysiological interactions. To assess functional connectivity, we estimated psychophysiological interactions (PPIs) utilizing the SPM generalized PPI toolbox (McLaren et al., 2012). PPI examines whether the coherence of neural activation in two brain regions is stronger in one task condition than another task condition (Friston et al., 1996). We used the MPFC region described above as the seed region. First-level PPI models included four PPI regressors – GWL social, GWL nonsocial, control social, and control nonsocial ad trials. As covariates of no interest, the PPI models included the time series of the seed region, the onsets of each trial type, as well as the face trials, response periods, and 6 motion parameters. The contrast of interest was GWL (social and nonsocial) minus control (social and nonsocial) image trials. This results in a GLM for each voxel in the brain, for each individual, which contains information about the extent to which activity in that voxel is differentially correlated with average activity in the seed region during GWL and control images. To investigate group-level PPI effects, the first-level contrast images were combined using a random effects model in SPM8. Average parameter estimates of functional connectivity were extracted from MPFC and VS ROIs at the group level using MarsBaR. Supplemental, exploratory analyses examining a broader network of regions defined by the whole brain PPI analysis are reported in Supplemental Materials.

Relating neural measures to smoking behavior. We used the robust linear model (RLM) function in R's (version 3.2.4) MASS library to relate neural activation and functional connectivity measures to behavior change. Behavior change is primarily reported as the percent change in smoking from Session 2 to Session 3. We also constructed a normalized score by normalizing cigarettes smoked per day across participants and taking the difference in these scores between Session 2 and Session 3. The Wald test was used to assess significance of RLM coefficients (robtest, R's sfsmisc package). All models controlled for gender, centered age, ethnicity (white *versus* other), and FTND score. Robust linear models are less sensitive to outliers and high leverage data points, allowing the inclusion of all data points.

RESULTS

In this study, we examined the effectiveness of GWL-inspired messaging on promoting smoking cessation behaviors. Each subject participated over a 6 week period, reporting smoking behavior before and approximately one month after completing an fMRI scanning session involving exposure to GWL and control anti-smoking messages. We first assessed smoking behavior change and then employed a two-stage analysis approach to examine neural activity that related to future smoking behavior.

Smoking behavior change. Participants reported the number of cigarettes they smoked on a typical day at each appointment. At the scanning appointment (Session 2), participants smoked an average of 13.2 ($SD = 6.8$) cigarettes per day. The average score on the FTND was 4.7 ($SD = 1.3$), indicating moderate addiction. At the follow-up appointment (Session 3), which took place an average of 39 days later ($SD = 9$ days), participants smoked an average of 10.2 ($SD = 7.7$) cigarettes per day. This was a significant decline in daily smoking (paired $t(44) = 3.06$, $p < 0.004$). A histogram of smoking reduction, modeled as the percent change in smoking from Session 2 to Session 3, can be found in Figure 2. During the fMRI task, participants rated whether the images made them want to quit smoking. The average of participants' quit ratings was 2.75 (on a scale from 1 to 5; SD = 0.7); quit ratings were not a significant predictor of behavior change $t(39)=-0.47$, $p<0.64$), controlling for gender, age, ethnicity (white *versus* other), and FTND score.

Associations between behavior change and neural activation. We tested whether the difference between neural responses to GWL and control images in medial prefrontal cortex (MPFC) was associated with the percent change in the number of cigarettes participants smoked per day in the month following the scan. A negative percent change in smoking corresponds to a reduction in cigarettes smoked per day. We used robust linear regression to predict behavior change from the difference in MPFC activation between ad types. Across participants, the difference in activation in our MPFC ROI during GWL and control ads (GWL > control) was not related to behavior change (percent change in smoking: $t(39) = 0.86$, $p < 0.401$; normalized change score: $t(39) = 0.81$, $p < 0.426$). This relationship was also not significant in the VS ROI (percent change in smoking: $t(39) = 1.08$, $p < 0.293$; normalized change score: $t(39) = 0.78$, $p < 0.441$). We further examined whether these activation differences were related to baseline smoking rates; cigarettes smoked per day before the scan was not significantly correlated with activation for GWL > control ads in MPFC ($r=-0.04$, $t(43)=-0.28$, $p<0.781$) or VS ($r=0.24$, $t(43)=1.62$, $p<0.113$). See Supplemental Materials for the results of an exploratory whole brain analysis examining the relationship between behavior change and activation for GWL vs control ads in other brain regions.

Associations between behavior change and functional connectivity. To complement our activation analyses, we used functional connectivity to examine whether coherent activity between brain regions is related to future behavior change. We compared functional connectivity in the valuation network (MPFC and VS) during exposure to GWL and control ads. We used robust linear regression to predict behavior change from connectivity, where a negative percent change in smoking corresponds to a reduction in cigarettes smoked per day. Functional connectivity from MPFC to VS during GWL > control ads was significantly related to behavior change (percent change in smoking: $t(39) = -2.79$, $p < 0.008$[1]; normalized change score: $t(39) = -2.63$, $p < 0.012$), such that greater connectivity during GWL ads was associated with a larger reduction in smoking in the month after the scan (see Figure 2). The difference in connectivity from MPFC to VS during GWL and control ads was not significantly correlated with participants' baseline number of cigarettes smoked per day ($r=0.13$, $t(43)=0.88$, $p<0.384$). Finally, we performed an exploratory whole-brain analysis, described in the Supplemental Materials, which identified a network of regions whose interactions with MPFC, and among one another, relate to behavior change.

DISCUSSION

In this report, we investigate neural responses to graphic warning labels to determine how the brain may forecast future behavior change and to aid in understanding why and how graphic warnings may contribute to behavior change. We examined differences in how the brain responds to negative, graphic warning label-inspired antismoking ads and to neutral control ads. In particular, we focused here on the medial prefrontal cortex (MPFC). Across several domains of health behavior, neural activity in the MPFC during exposure to messaging has been related to subsequent message-consistent behavior change. This effect has been demonstrated in the contexts of smoking (Chua et al., 2011; Falk et al., 2011; Owens et al., 2017; Riddle et al., 2016; Wang et al., 2013), physical activity (Cooper et al., 2017; Falk et al., 2015), and sunscreen use

[1] Excluding the 4 participants who had quit smoking or were enrolled in quit programs at any time point, this result remains significant ($t(35) = -3.02$, $p < 0.005$).

(Falk et al., 2010; Vezich et al., 2016). We expanded upon this previous work by examining functional connectivity during exposure to anti-smoking messages within a system of brain regions, including MPFC, that process how valuable an idea or object is to a person. Analyses of functional connectivity, which consider interactions of neural activity between brain regions, can aid in identifying the brain networks that are engaged by messaging and precede behavior change. The neuroimaging literature identifies the MPFC as an information processing hub (Andrews-Hanna et al., 2010; Buckner et al., 2009; Tomasi and Volkow, 2011), which can connect systems throughout the brain to integrate conceptual and affective information (D'Argembeau, 2013; Roy et al., 2012). Thus, the MPFC likely integrates information from multiple brain processes in response to persuasive messaging to determine the self-relevance and value of incoming stimuli (Bartra et al., 2013; Denny et al., 2012; Levy and Glimcher, 2012; Murray et al., 2012), but this has not been considered for responses to tobacco messaging.

Building on past studies that focused on average activity in single brain regions, we first considered two core regions in the valuation network, the MPFC and ventral striatum (VS). Although the current analyses did not find significant relationships between average activity in MPFC or VS and behavior change, greater connectivity within these regions was associated with larger reductions in smoking. We found that smokers who showed more functional connectivity from MPFC to VS during exposure to GWL ads compared to control ads also decreased their smoking more in the month following the scan. Thus, greater coherence within the valuation network during GWL-inspired, behaviorally relevant ads than during control ads preceded behavior change. A similar effect was recently demonstrated in the physical activity domain (Cooper et al., 2017), adding confidence in the robustness of this effect. This finding is also in line with work in the neuroeconomics literature demonstrating both that value-related activity in these regions can reflect changes in preferences (for example, following exposure to others' opinions (Berns et al., 2010; Klucharev et al., 2009; Mason et al., 2009; Zaki et al., 2011)) and that functional connectivity between these regions increases during learning (Camara et al., 2009; van den Bos et al., 2013).

An interpretation consistent with our data is that the MPFC serves as a region that integrates information about the significance of a concept or a health message, and indexes the extent to which an individual may use that information to change their behavior (Falk and Scholz, 2018; Vezich et al., 2016). This is consistent with the idea that the MPFC functions as the "final common pathway" for representing subjective value (Kable and Glimcher, 2009; Levy and Glimcher, 2012; Rangel and Hare, 2010); we propose broadening the application of subjective value from tangible goods to abstract ideas and behaviors, as in health warning labels whose goal is to change the value that smokers place on smoking *versus* quitting. During exposure to behaviorally relevant health messaging, individuals may increase the value that they place on message-related behaviors, such as quitting smoking to avoid its negative consequences, which is then associated with a reduction in that behavior. A similar interpretation is that MPFC activity could index the integration of message value into one's self-concept, increasing the likelihood of message-consistent behavior (Vezich et al., 2016).

Our data are further consistent with the possibility that the subjectively-assessed value, or relative importance, of the content in a health message is a component of how persuasive the message is to an individual, and that persuasion involves updating one's values. Several prominent health behavior theories, such as the health belief model (Rosenstock et al., 1988; Strecher and Rosenstock, 1997) and social cognitive theory (Bandura, 1977, 1986), emphasize the importance of the personal relevance of the costs and benefits of health behavior change;

personal relevance also plays a role in the elaboration likelihood model of persuasion (Petty and Brinol, 2012; Petty and Cacioppo, 1986). Learning, both through experience and observation of others, is a key component of updating self-efficacy in social cognitive theory. Likewise, reasoned action models (Fishbein et al., 2001; Fishbein and Ajzen, 2011) include elements of expected value of outcomes. One possibility is that message value and personal relevance may be responsible for the relationship between MFPC activity and behavior change, and may be critical components to emphasize in the design of tobacco control and other health intervention materials.

To search more broadly for regions related to behavior change beyond connections between MPFC and VS, we also examined connections from the MPFC to the rest of the brain. This exploratory analysis, described in the Supplemental Materials, identified a network that showed differential connectivity between GWL and control ads, and which was related to behavior change. This network included regions implicated in the processing of salience and cognitive control (e.g., anterior and middle cingulate gyrus; Miller and Cohen, 2001; Seeley et al., 2007; Shenhav et al., 2016), mentalizing and prospection (e.g., parahippocampal gyrus, precuneus; Andrews-Hanna, 2012; Spreng et al., 2008; Yeo et al., 2011), and behavior and action planning (e.g., motor and supplementary motor areas; Desmurget and Sirigu, 2009; Kennerley et al., 2004; Nachev et al., 2008). We found that the interactions between these regions, and not only their interactions with MPFC, were associated with smoking reduction. Building on recent work in the burgeoning field of network neuroscience, this result highlights the promise in considering larger brain networks in understanding message-induced behavior change.

Future work would also benefit from several improvements in behavior measurement. For example, the addition of methods such as timeline follow-back and biochemical verification for assessing smoking could increase confidence in the accuracy of behavior outcomes (Brown et al., 1998; Perkins et al., 2013; Robinson et al., 2014). Self-report may be more susceptible than these other methods to demand effects, or the desire of participants to appear in a positive light to the experimenter (Nichols and Maner, 2008; McCambridge et al., 2014; Orne, 1962; Zizzo, 2010); it is possible that participants may report lower levels of smoking than would appear with biochemical verification. We also note that especially in the case of heavier smokers, participants could have experienced withdrawal during the course of the scanning session. Future work could investigate the possible interaction between participants' experiences of withdrawal and neural responses to messaging, particularly in relation to later behavior change.

This report provides evidence for a differential neural response to GWL-inspired messages than to control messages that is related to later behavior change. GWLs are used on cigarette packaging and in other health contexts in countries around the world, with many reports of positive effects (Brewer et al., 2016; Canadian Cancer Society, 2014; Hammond, 2011; Noar, Francis, et al., 2016; Noar, Hall, et al., 2016). From a regulatory perspective, adding to our understanding of the neurobiological mechanisms of GWLs could affect their implementation in the United States and other countries lacking expansive tobacco control policies. Further, understanding how the brain responds to different types of health messaging and how this is associated with later behavior could ultimately contribute to the efficient design of effective messaging campaigns, as well as more broadly to theories of health message effects and persuasion across domains.

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TABLES AND FIGURES

Table 1. Demographic information

Age	32 (SD=13)
Gender	28 M, 17 F
Race	30 Cau, 5 AA, 5 His, 5 Mixed
Education	10 BS+, 4 AS, 7 current college, 18 >HS, 6 <=HS

Cau, Caucasian; AA, African American; His, Hispanic/Latino

BS, Bachelor's degree or postgraduate; AS, Associate's degree; >HS, some post-high school training or college; <=HS, high school education or less

Fig 1. Task design. Participants viewed GWL-inspired images portraying the negative health and social consequences of smoking and neutral control images. After viewing each image, participants rated how much the ad made them want to quit smoking, then viewed an intertrial fixation period.

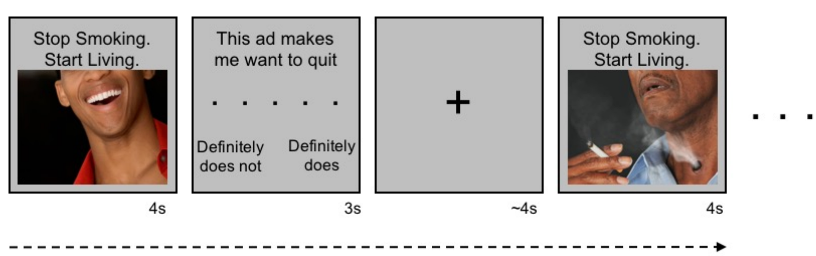

Fig 2. Analysis design and results. (A) Histogram of smoking behavior change, where a negative percent change represents a reduction in cigarettes smoked per day. (B) Functional connectivity within value regions (from MPFC to VS) was assessed for the contrast of GWL >

control ads. (C) Percent change in cigarettes smoked per day plotted against functional connectivity for each participant. Greater connectivity during GWL ads was related to a larger reduction in smoking.