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Smokers' Neurological Responses to Imagery From Cigarette Package Warning Labels

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SMOKERS' NEUROLOGICAL RESPONSES TO IMAGERY FROM CIGARETTE PACKAGE WARNING LABELS

by

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Dedication

I would like to dedicate my thesis work to my wife, Erla and my wonderful children, especially Gudrun Elfa who has been my biggest cheerleader all through my studies abroad. A special feeling of gratitude goes out to my loving parents, Anna and Fridrik whose encouragement has brought me a long way. I will always appreciate all they have done for me. My sister Gudrun, and my brothers Georg and Julius who are the best role models a younger brother can have, get special thanks. I would also dedicate this thesis to my mentor, Chris Rorden for all his help and support. I would also like to thank my committee for their guidance through this process. Last but not least, I like to thank Emily Garnett for the many hours of proofreading and Scott Vendemia for his support during the whole research process.

ABSTRACT

Tobacco use is the leading cause of preventable death in the United States. The Family Smoking Prevention and Tobacco Control Act was signed into law in 2009 and gave the U.S. Food and Drug Administration (FDA) the authority to implement pictorial health warning labels (HWLs) on cigarette packages. Multiple studies investigating self-reported affective, cognitive and behavioral impacts of HWLs suggest that the most effective warnings include imagery that depicts physical damage to the body due to smoking. However, self-report methods of assessment used in these studies may be biased. Far less is known about how HWLs directly modulate brain activity. To address this issue, we used functional magnetic resonance imaging (fMRI) to examine cortical activity in smokers while they viewed pictorial HWLs (including both HWLs proposed by the FDA as well as more graphic HWLs implemented in other countries) and a set of scrambled images, using an event related design. Each participant underwent fMRI while viewing stimuli and performing a simple visual discrimination task. The results revealed greater activity bilaterally in the lateral occipital cortex in response to foreign images compared to the FDA images, and there was no evidence that this effect was reduced with repeated exposure. These findings suggest that more graphic HWL imagery elicits more salient cortical response, perhaps due to their more explicit emphasis on the negative consequences of smoking on

human health. These findings bring us a step closer to understanding ways to evaluate effective HWLs and may strengthen the case for implementing even more graphic HWLs in the U.S. compared to what the FDA had proposed.

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
AM	Amygdala
BA	Brodmann area
FWE	Familywise error
FDA	Food and Drug Administration
IMGS	Images greater that scrambled
IS	Insula
LOC	Lateral occipital cortex
fMRI	Functional magnetic resonance imaging
MPFC	Medial prefrontal cortex
OC	Occipital cortex
HWLs	Pictorial health warning labels
ROI	Regions of interest
SPM	Statistical Parametric Mapping
TCLC	Tobacco Control Legal Consortium

CHAPTER 1

INTRODUCTION

Even though the adverse effects of smoking have been well documented (Morbidity and Mortality Weekly Report, 2004), smoking remains the leading cause of preventable death in the Western world (MMWR, 2004; WHO, 2009). Given the current trend, tobacco-related deaths will reach eight million by the year 2030, with deaths increasingly concentrated in low- and middle-income countries (WHO, 2011). Smoking is estimated to increase the risk of coronary heart disease and stroke by two to four times (MMWR, 2004). In addition, smoking increases the risk of developing lung cancer by 23 times in men and by 13 times in women (Surgeon General, 2004). Since 2005, the World Health Organization Framework Convention on Tobacco Control has recommended including prominent, pictorial health warning labels (HWLs) on tobacco packaging. The goal is to effectively communicate the adverse effects of tobacco use to current and potential consumers of tobacco products, as well as to promote smoking cessation and prevent smoking uptake (WHO, 2009). In 2001, Canada became the first country in the world to implement pictorial HWLs. Since then, large pictorial HWLs have been adopted and implemented in over 55 countries around the world (Canadian Cancer Society Report, 2012).

THE CURRENT CONTEXT OF PICTORIAL HWLS IN THE US

In 2009, the Family Smoking Prevention and Tobacco Control Act gave the U.S. Food and Drug Administration (FDA) the authority to select pictorial HWLs for cigarette packages in the United States with the explicit aim of increasing consumer understanding of smoking-related risks (Carvajal, Clissold, & Shapiro, 2009). By amending the Comprehensive Smokeless Tobacco Health and Education Act and the Federal Cigarette Labeling and Advertising Act, and by giving the FDA power to strengthen HWLs, the act represents the most significant change in U.S. HWL policy since 1985 (Ventura, FDA, 2012). According to the act, HWLs should cover at least the top 50 percent of the front and rear of cigarette packs and replace the small text-based warnings on the side of cigarette packs. Furthermore, the law directs the FDA to ensure quarterly rotation of messages and to issue a regulation requiring color graphics on health warning labels that depict the negative health consequences of smoking (Carvajal, 2013).

In accordance with the law, the FDA proposed the content for nine new HWLs in 2012 (FDA, 2012), which address the topics of smoking-related health risks for smokers (e.g., lung disease, cancer, stroke), nonsmokers exposed to secondhand smoke, addiction, and the benefits of quitting (Hammond, Reid, Driezen, & Boudreau, 2013).

The FDA-selected HWLs have stirred a considerable controversy. In January 2011, the Tobacco Control Legal Consortium (TCLC), the United States' legal network for tobacco control policy, submitted comments to the FDA advocating for more effective cigarette HWLs than those originally selected, suggesting that the proposed FDA HWLs were less graphic than HWLs utilized in other countries. In addition, the TCLC recommended implementation of HWLs already used and tested in other countries that are supposedly more vivid and emotionally powerful than the FDA-proposed HWLs (Armstrong & Blanke, 2012).

On the other hand, four of the five largest U.S. tobacco companies filed a lawsuit against the FDA in August 2011, claiming that HWLs violate their rights to free speech by compelling them to engage in a government campaign that is against their interests. In 2012, a federal Judge sided with the tobacco industry and blocked implementation of the HWLs proposed by the FDA, overruling at the same time an earlier federal appeals court judgment that had ruled that the warnings were constitutional (Lenzer, 2011). In March 2013 the U.S. Department of Justice and the FDA abandoned their appeal, before it reached the Supreme Court. The FDA will instead undertake further research to select a new set of HWLs although no timeline has been proposed (Davies, 2013).

HWLs

According to Fong, Hammond, & Hichmann (2009), "Health warning labels on tobacco products constitute the most cost-effective tool for educating smokers and non-smokers alike about the health risks of tobacco use" (p. 640). A systematic review of the literature suggests that HWLs promote smoking cessation and prevent smoking initiation (Hammond, 2011). A smoker who smokes one pack a day is potentially exposed to HWLs over 7000 times per year. The repeated exposure presents a successful way to influence smoking behavior (Hammond, 2009). Numerous research studies have been conducted to study the effectiveness of HWLs (Hammond, 2011).

Observational studies show that HWLs are more effective in informing people about the risks associated with smoking (Hammond, Fong, McNeill, Borland, & Cummings, 2006; Thrasher, Hammond, Fong, & Arillo-Santillán, 2007). Findings from a large survey conducted in four countries clearly show how HWLs are more likely to induce smoking cessation than text-only warnings (Borland et al., 2009a; Borland et al., 2009b; Hassan, Shiu, Thrasher, Fong, & Hastings, 2008). HWLs are also more likely to be noticed compared to their text-only counterpart (Borland et al., 2009; Hammond et al., 2007; Thrasher et al., 2010, 2007). Furthermore, studies show that text-only HWLs on cigarette packages produce minimal or no attitudinal and behavior effects (Hammond et al., 2007; Hassan et al., 2008).

Experimental studies have found that HWLs boost perceived effectiveness compared with text only warnings (Vardavas, Connolly, Karamanolis, & Kafatos, 2009). Furthermore, HWLs increase awareness of health risks to users (Fathelrahman et al., 2010) as well as enhance smoking cessation (Fathelrahman et al., 2010; Kees, Burton, Andrews, & Kozup, 2006; Schneider, Gadinger, & Fischer, 2012). In line with observational studies, experimental studies have also found HWLs to play a major role in highlighting the adverse effects of smoking (Kees et al., 2006). In addition, outcomes from a study using experimental auctions comparing different HWLs formats suggest that prominent health warnings with graphic imagery come across as less desirable to consumers while no significant differences in demand were found for packs with text warnings only, including those that were of equivalent size to the pictorial HWLs (Thrasher, Rousu, Hammond, Navarro, & Corrigan, 2011). Loeber et al. (2011) also found that smokers showed attention bias towards cigarette packages without HWLs. (Kees et al. (2011) conducted a between-subjects experimental study of 500 smokers testing the effectiveness of pictorial warnings with different levels of graphic imagery. Results indicated that the stronger the graphic pictorial warning was, the more it strengthened smokers' intentions to quit, indicating that graphic warnings evoked fear, which in turn mediated the effects of the graphic warnings cessation.

Evidence seems to be mounting to suggest that characteristics of pictorial HWLs play a major part in their effectiveness. A study evaluating different themes and content of HWLs found that warnings featuring "graphic" depictions of disease were significantly more effective than images showing experiences of human suffering or symbolic warnings. This finding are inline with a study which found graphic images depicting adverse affects of smoking as most effective (Hammond et al., 2012; Thrasher et al., 2012).

To date, HWLs have primarily been evaluated and studied using self-reported responses, which may be subject to critical biases (Raphael, 1987; Stone, 2000). Studies have shown that perceived threatening topics seem to be subject to even greater likelihood of response bias than nonthreatening issues. Furthermore, there is a tendency for this effect to increase as threat levels in questioning increase (Locander & Bradburn, 1976). Retrospective questions, which are often used in observational studies of HWLs, may be subject to telescoping and omission biases brought on by the perceived threat of the topic. Telescoping is described as the tendency of subjects to displace recent events backward in time, so that recent events appear more remote, and remote events appear more recent (Janssen, Chessa, & Murre, 2006), while omission occur when subjects leave out information intentionally (Scheffer, 2000). This can occur in experimental as well as observational studies that rely of self-report or when prospective or retrospective studies rely on recall information (Raphael, 1987; Stanton, McClelland, Elwood, Ferry, & Silva, 1996). Socially desirable responding can potentially influence participants in both experimental, as well as observational studies. In this case, socially valued attributes are exaggerated, minimized or underreported intentionally in accordance with perceived social norms (Raghubir & Menon, 1998; Scheffer, 2000).

BRAIN IMAGING methods FOR UNDERSTANDING PICTORIAL HWL EFFECTS

Given the fact that most HWL studies rely on potentially biased self-reported affective, cognitive and behavioral responses to HWLs, brain imaging may provide an additional method for determining the effectiveness of both initial and repeated viewing of HWLs, potentially acting as a biomarker of response that is independent of common self-report biases. For example, the habituation of responses to repeated viewing of images could be observed with both single-unit recordings of neurons as well as fMRI of the whole brain. Specifically, fMRI studies have shown reduced neural responses to repeated stimuli; this effect is commonly referred to as repetition suppression (Ishai, Pessoa, Bikle, & Ungerleider, 2004). Therefore, brain imaging can be used to detect both the activation elicited by an image and estimate the amount of habituation that occurs on repeated viewing (Yi & Chun, 2005).

Because smokers are repeatedly exposed to HWLs in the real world, the use of repeated exposures to assess habituation provides a potential advantage over prior experimental research, which has relied upon single exposures to HWL stimuli. Evidence suggests that processing of emotions like fear and disgust involve similar as well as distinct neural mechanisms (Stark et al., 2007). Among brain areas most consistently linked to emotional visual stimuli are the amygdala, insula, medial prefrontal cortex (MPFC) and the occipital cortex (OC) (Phan, Wager, Taylor, & Liberzon, 2002). Furthermore, research suggests that the occipital cortex might be involved with mediating and appraising visual emotional stimuli, functioning as a processing hub for visual perception (Adolphs, 2002; Beauregard et al., 1998).

Results from an fMRI meta-analysis on emotion found an overwhelming link between amygdala activation and fear-inducing stimuli (Murphy, Nimmo-Smith, & Lawrence, 2003; Phan et al., 2002). On the other hand, Stark and colleagues (2007) found that insula activation was the only region significantly correlated with subjective ratings of disgust, pointing to its specific role in response to disgust, whereas stimuli that induced both fear and disgust activated the extended occipital cortex, prefrontal cortex, and the amygdala. Research also suggests that the amygdala plays a role in processing salient visual input (Davis & Whalen, 2001).

Given the graphic nature of HWLs we focused primarily on these regions of interest (ROI). To date, no systematic study using fMRI technology has been conducted to evaluate HWLs, thus our approach was primarily exploratory. By using brain imaging to evaluate the physiological brain response to HWLs, we sought to become a step closer to understanding HWLs characteristics and their emotional impact.

Chapter 2

Materials and Methods

Sample

Nineteen neurologically healthy smokers (11 males, 8 females) with no known neurological abnormalities or diseases and with normal or corrected-to-normal vision participated in this study. One subject was excluded due to excessive head movement in the scanner. The age range was 18 to 36 years old (mean 25) and all participants reported that they were daily smokers. All subjects were right handed.

Recruitment

Flyers to recruit participants were posted around the University campus and in local coffee shops, bars, restaurants and other popular public venues. Phone screening for safety and eligibility criteria was conducted when participants contacted the study coordinator. Further safety screening was done through email, given volunteers passed the phone screening. Participants were compensated with $50 for their time, which amounted to an hour and a half experimental session. All participants gave written informed consent and provided health information required to ensure MRI safety following a protocol approved by the local Institutional Review Board. Prior to scanning, each participant completed a standardized questionnaire about his or her smoking habits. This questionnaire revealed the following details regarding this group. The mean age when participants started to smoke was 17. On average, participants had smoked on 28.9 of the past 30 days and had smoked 12.2 cigarettes a day. One participant smoked a pipe as well as cigarettes.

STUDY PROTOCOL

To examine brain activity, we asked each participant to view images presented on a computer screen. The images consisted of a subset of the proposed FDA images along with foreign HWLs images matched for health topic (Figure 2.1). Some of these images originally contained text, but were cropped to remove the text label as text in an individuals' native language might elicit reading regardless of task. All foreign images had been used on HWLs at time of the study. One of the nine FDA-proposed HWLs was excluded due to a non-removable text element.

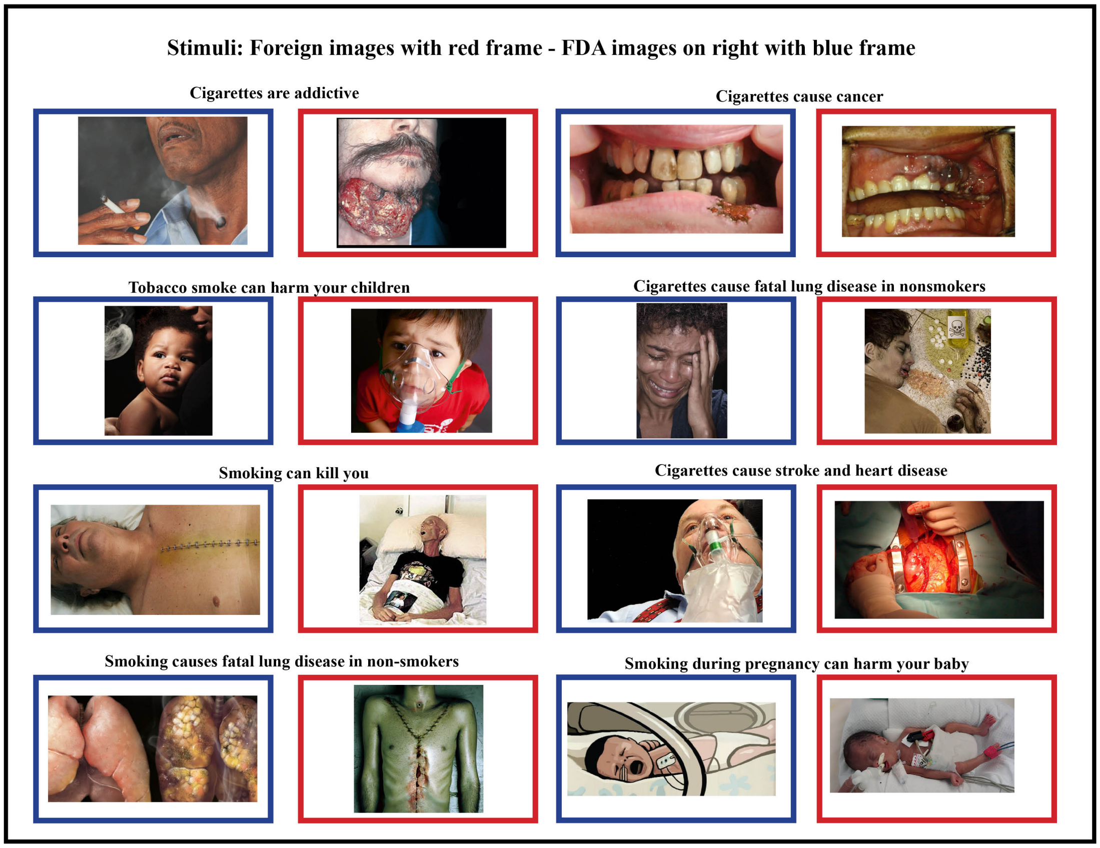

Figure 2.1 *Stimuli consisted of proposed FDA images and foreign HWLs images matched for health topic.*

All images were proportionally interpolated to fit a 1024x768 resolution screen. We also created a set of scrambled images in order to estimate the amount of brain activity generated by higher-level visual recognition versus low-level visual responses. These scrambled images were generated by Fourier transformation where the phase information was removed from the FDA and foreign HWL images. Therefore, the scrambled images had similar low-level visual properties such as colors and spatial frequency but were not recognizable (see Figure 2.1.)

In an event-related design, participants observed a pair of pictures shown in short succession followed by a pause (Yi & Chun, 2005). Most of the time the pairs were congruent (two HWLs or two phase-scrambled images). However, on a fraction of the trials (1/9) the pair was from different classes: one was a HWL and the other was a scrambled image. We asked the participants to press a button whenever they observed an incongruent pair. This task was designed to ensure that the participant was observing the stimuli, while also ensuring that the task was orthogonal to our experimental manipulations (i.e., the task was independent of whether the images were from the FDA or foreign HWLs). When HWL images were presented, both images in the pair were from either the FDA HWLs or both were from the foreign HWLs. However, in half of these trials the same HWLs were included in the pair, whereas in the other half of the trials, the two HWLs were different. This manipulation allowed us to measure the response suppression effect (e.g., the reduction in response seen to repeated exposure versus observing a novel stimulus. See Figure 2.2).

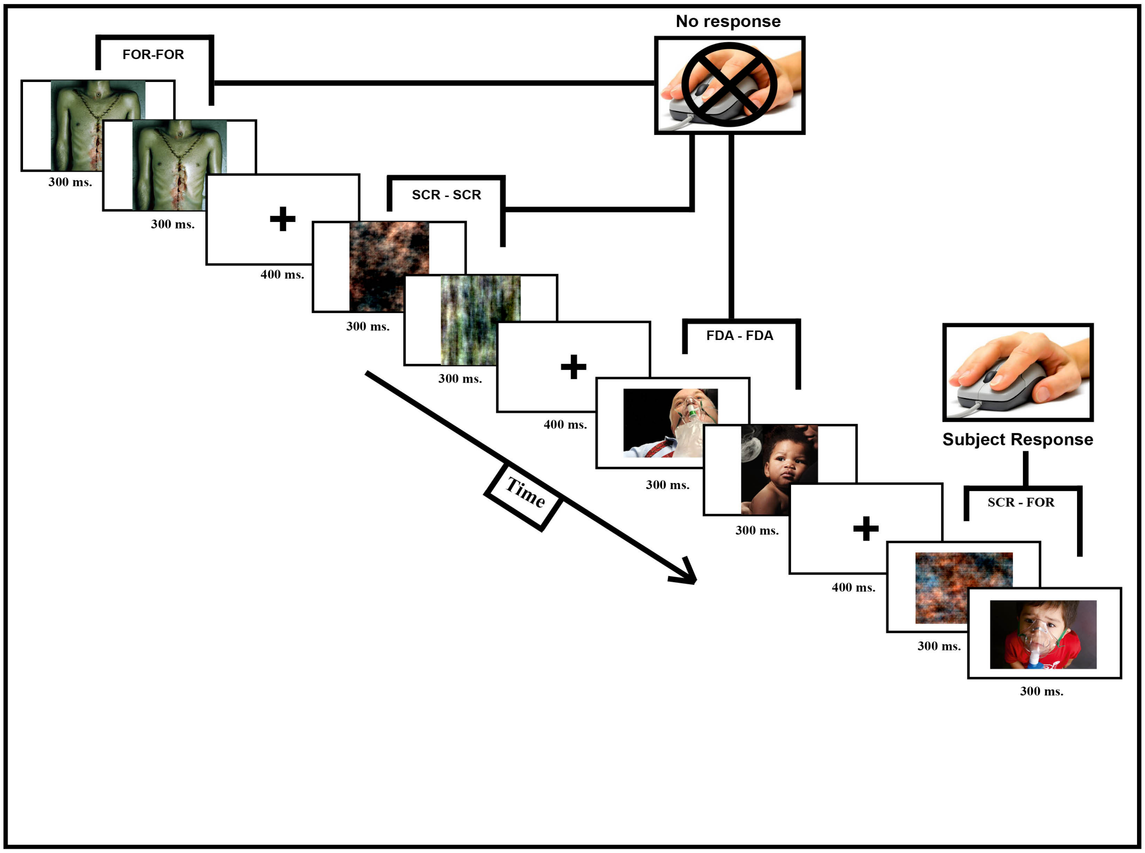

Figure 2.2 *The participants observed a pair of pictures shown in short succession followed by a pause. Pairs were typically either both real images or both scrambled images, with rare trials where the pair was from different classes (image - scrambled). The participant's task was to simply press a button whenever they observed these rare mismatch trials. Note that this task was independent of whether the images were from the FDA or foreign sets. In half of the trials the second image was identical to the first (e.g. the same scene) where in the other half of the trials the two images were different. This manipulation allows us to measure the effect of habituation to repeated stimuli.*

Stimuli presentation and data collection was done using E-Prime software (Psychology Software Tools, Pittsburgh, PA). Each participant briefly practiced the task outside the scanner suite to familiarize them with the procedure and task. The participants were then tested inside the scanner where they observed a digital projector screen that was located outside the scanner via a mirror mounted on the scanners' head coil. Manual responses (i.e., button pressing) were made using a MRI compatible response glove. Each image was shown 13-

16 times. The duration of presentation for each image was 300 milliseconds (ms), after showing a fixation cross for 400 milliseconds. Time between trials varied from 1800 ms to 3000 ms (see Figure 2.2).

All fMRI data were collected on a Siemens 3T Trio scanner at the McCausland Center for Brain Imaging, fitted with a 12-channel receiver head coil. During the first part of the scanning, the participants underwent a localizer and a structural scan. Next, the participants completed the two sessions of the tasks during continuous fMRI acquisition. Each session lasted 12 min, with a T2* echo planar imaging pulse sequence using the following parameters: repetition time, 2.130ms; echo time, 35 ms; flip angle, 90°; 64 × 64 matrix; 192 × 192 mm field of view; 36 ascending 3.6-mm-thick slices with 20% slice gap, resulting in voxels with an effective distance of 3.25 × 3.25 × 3.6 mm between voxel centers with 344 volumes per session.

Image data were converted from DICOM format which is the native scanner format to NIfTI format using a software called dcm2nii with subsequent processing performed using Statistical Parametric Mapping (SPM) 8 (http://www.fil.ion.ucl.ac.uk/). Data preprocessing included motion correction, spatial normalization and spatial smoothing using an 8 mm full-width half-maximum Gaussian kernel. Voxelwise analysis was computed for 18 participants, excluding one subject due to numerous large head movements observed as more that 5mm translation jumps between successive volumes (e.g., coughing). The subsequent statistical maps were thresholded at $p < 0.05$ adjusted for familywise error (FWR) as estimated with random field theory. We then conducted region of interest analysis (ROI) using the MarsBaR toolbox (http://marsbar.sourceforge.net). *A priori* regions of interest included the amygdala and insula brain regions. We also created a custom ROI based on the voxelwise analysis for regions that responded more to recognizable versus phase-scrambled images (identifying regions of the brain involved with higher level visual processing), images greater that scrambled (IMGS) (see Figure 2.3). Note that the selection of this region is orthogonal to the contrasts where it was applied, contrasting FDA HWLs versus foreign HWLs and contrasting repeated versus different stimuli.

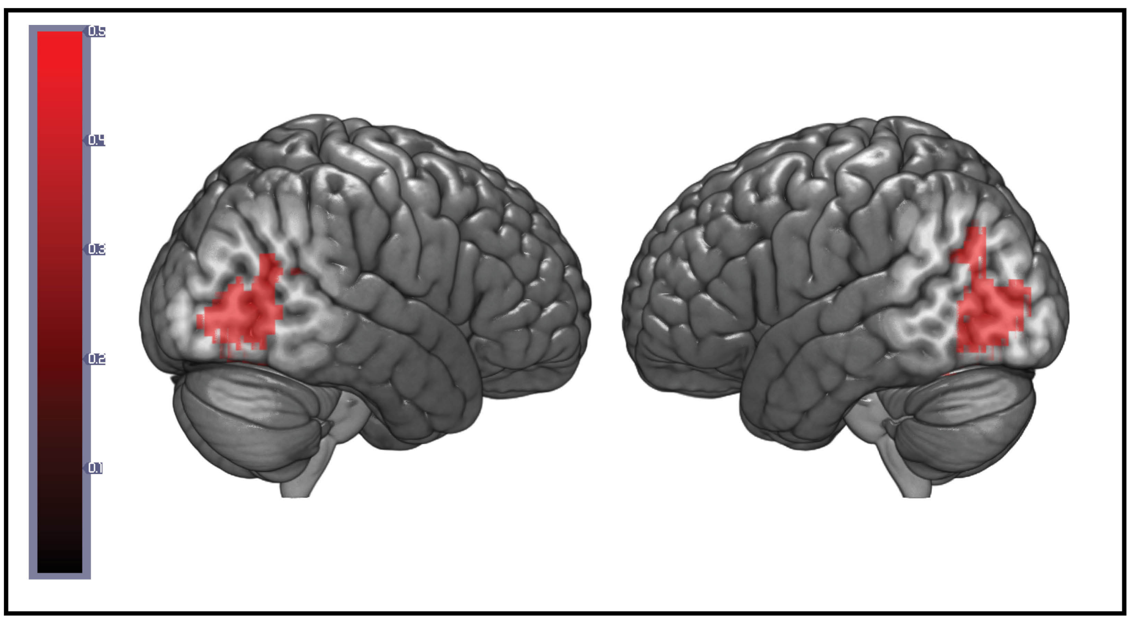

Figure 2.3 *Regions where more activity was observed for real images than phase-scrambled images (p <0.05 corrected for multiple comparisons). These regions served as our regions of interest for subsequent analyses between different types of real images (foreign versus FDA image; repeated versus different images).*

Chapter 3

Results

SPM 8 group analysis for the whole brain revealed significantly greater activation for foreign HWLs compared to FDA HWLs in the right lateral occipital cortex, (p<0.05, corrected for familywise error (FWE), p< 0.002, t= 9.05 *Z=5.40, (X 15, Y -97, Z 4),* Brodmann's area (BA) 17 (see Table 3.1 and Figure 3.1). The whole brain analysis (FWE<0.05) also revealed a statistical difference between foreign repeated HWLs and different foreign HWLs in the bilateral occipital cortex, BAs 18 and 19, (Table 3.1). In contrast, this effect was not revealed for comparisons across FDA HWLs. To compare activation across the foreign and FDA HWLs within a *priori* ROIs, we performed an analysis of variance (ANOVA). Results from a *priori* ROI analysis for left and right amygdala and insula were not statistically significant (Table 3.2) while the *priori* ROI established by contrasting HWLs vs. scrambled images (IMGS) revealed greater activation in the bilateral occipital cortex (Table 3.2, Figure 3.2). This analysis revealed robust differences between foreign and FDA images where foreign HWLs evoked significantly greater neural modulation $F(1,17) = 6.79$, p<0.018 (Figure 3.2).

Presentation of two different HWLs evoked greater response compared to exposure to two repeated HWLs for both foreign and FDA HWLs bilaterally, *F*(1,17) = 16 *p*=0.0009, while interaction between foreign repeated HWLs and FDA repeated HWLs did not reach statistical significance $F(1,17) = 0.210$ $p<0.65$ (Table 3.2, Figure 3.2). A left-right hemisphere comparison revealed greater activation in the right ROI, $F(1,17) = 32.5$ $p<0.00003$, which was consistent with the whole brain analysis (Table 3.2).

Table 3.1 Whole brain analyses

Contrast	***Cluster -level***	***Threshold***	***FWE corr. 0.05. P>***	***Peak-level***	***Z***	***MNI coordinates mm.***	***BM area***
Foreign vs. FDA images	11	6.87	0.002	9.5	5.40	X 15 Y -97 Z 4.	17
FOR different vs. FOR repeated.	3	7.01	0.008	7.45	4.90	X -15 Y -91 Z 22	18
FOR different vs. FOR repeated.	3	7.01	0.016	7.15	4.80	X 36 Y -76 Z 10	19
FOR different vs. FOR repeated.	3	7.01	0.016	7.09	4.77	X -21 Y -91 Z 22	19

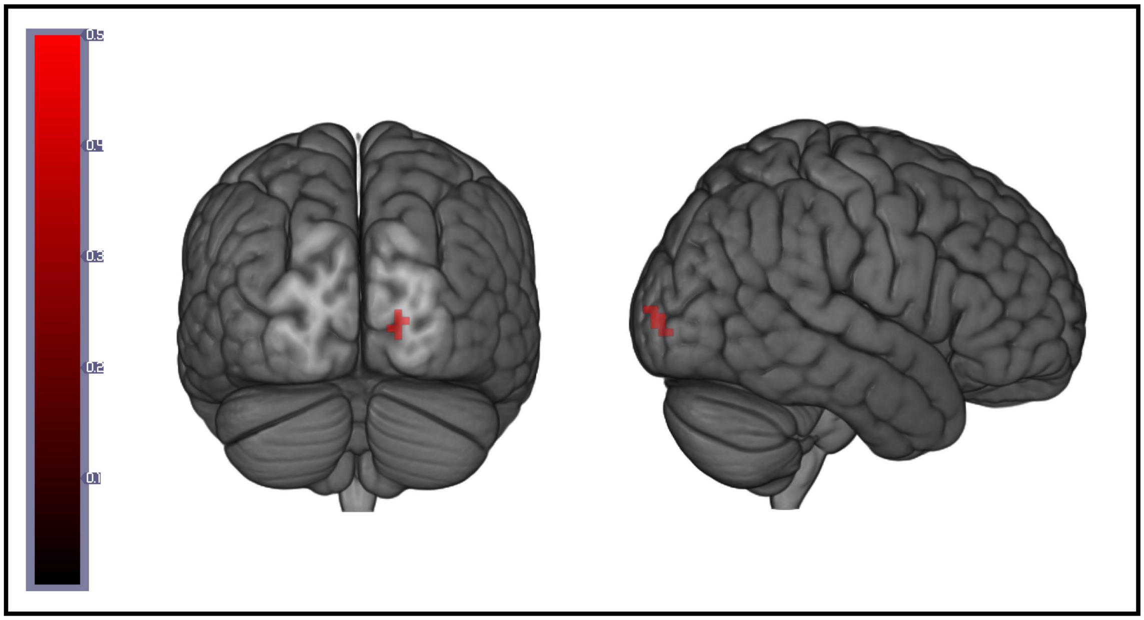

Figure 3.1 *Activation (shown in red) for foreign images with greater activation then FDA images in the right lateral occipital cortex, corrected for familywise error, (FWE<0.05) p< 0.002 Z 5.40, (X 15, Y, -97, Z 4), Brodmann area 17. Image shown on the left shows back of the brain. Image on the right shows activation from a right side view of the brain.*

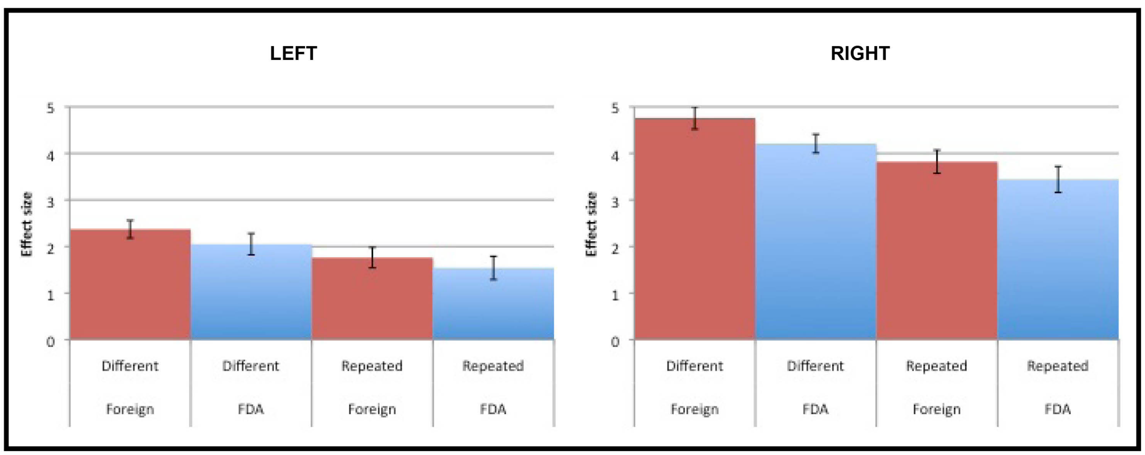

Figure 3.2 *In ROI IMGS/LOC, foreign images evoked greater neural activation bilateral for both repeated and different HWLs. Different HWLs evoked strong response than repeated for both foreign and FDA. Activation is greater in the right versus the left hemisphere.*

Table 3.2 Results for Analysis of variance (ANOVA) for regions of interest.

Factors F(1,17)	*F*	*P=*
(IMGS/LOC) Foreign/FDA	6.79	0.018*
(IMGS/LOC) Different/repeated	16.0	0.0009*
(IMGS/LOC) Right/left - hemispheres	32.5	0.00003*
(IMGS/LOC) FOR-FDA/DIFF-REP	0.21	0.652
(IMGS/LOC) FOR-FDA/RIGHT-LEFT	4.69	0.045*
(IMGS/LOC) DIFF-REP/RIGHT-LEFT	10.2	0.005*
(IMGS/LOC) FOR-FDA/DIFF-REP/R/L.	0.11	0.74
(AM) Foreign/FDA	0.002	0.96
(AM) Different/repeated	1.64	0.22
(AM) Right/left - hemispheres	2.62	0.12
(AM) FOR-FDA/DIFF-REP	0.85	0.37
(AM) FOR-FDA/RIGHT-LEFT	1.20	0.29
(AM) DIFF-REP/RIGHT-LEFT	2.70	0.12
(AM) FOR-FDA/DIFF - REP/RIGHT-LEFT	0.02	0.88
(IS) Foreign/FDA	0.37	0.55
(IS) Different/repeated	1.48	0.24
(IS) Right/left - hemispheres	1.47	0.24
(IS) FOR-FDA/DIFF-REP	0.28	0.60
(IS) FOR-FDA/RIGHT-LEFT	0.51	0.49
(IS) DIFF-REP/RIGHT-LEFT	1.53	0.23
(IS) FOR-FDA/DIFF - REP/RIGHT-LEFT	1.10	0.31

*Analysis of variance (ANOVA) within ROIs; Images greater than scrambled (IMGS/LOC), Amygdala (AM) & Insula (IS). Within Subject Factors design *(p<0.05).*

CHAPTER 4

DISCUSSION

The present study used brain imaging to investigate differences in cortical activity when adult smokers were presented with two types of visual stimuli made up of HWLs imagery, those proposed by the FDA and foreign HWLs matched for the health topic. When participants viewed the more graphic, foreign HWLs compared to the FDA HWLs, we observed significantly greater neural modulation in the lateral occipital cortex (LOC), both in a whole brain analysis in the right LOC, as well as in the region of interest defined by images greater than scrambled (IMGS/LOC). The whole brain analysis also revealed a statistical difference between foreign repeated HWLs and different foreign HWLs in the bilateral occipital cortex, while this effect was not revealed for comparisons across FDA HWLs. This activation is likely due to a greater difference between different versus repeated stimuli within foreign HWLs; however, although the difference was large enough for foreign HWLs to be detected after correction for FWR, it does not imply interaction between the two. Using fearful and neutral face stimuli Fischer and colleagues (2003) studied habituation of the blood oxygenated level dependent signal (BOLD) using repeated stimulus presentations. Similar to the current findings, their study did not reveal interaction effects between the two kinds of stimuli, suggesting similar neural attenuation rates to fearful and neutral stimuli. These results might indicate that brain regionsinvolved in processing of novel imagery (i.e. seeing the stimuli for the first time) and processing familiar stimuli (i.e. seeing the same stimuli repeated) habituate similarly regardless of stimulus type. Presentation of two different HWLs evoked greater response compared to exposure to two repeated HWLs for both foreign and FDA HWLs, bilaterally in the ROI IMGS/LOC, while interaction between foreign repeated HWLs and FDA repeated HWLs did not reach statistical significance in the same region.

For the contrast between foreign and FDA images, we found no significant difference in activation at the group level in the amygdala nor the insula, although numerous studies have observed neural modulation in both areas associated with processing emotionally charged stimuli (Murphy et al., 2003; Phan et al., 2002; Stein, Simmons, Feinstein, & Paulus, 2007). Similar to the present findings, Jehna et al. (2011) found that disgust yields significantly greater activation in the bilateral occipital cortex and did not find specific modulation in the insula or the amygdala for the same contrast.

There are a number of potential reasons for this lack of modulation. One possibility is that the foreign and FDA stimuli were not sufficiently different to provoke selective modulation of the amygdala and insula, even though subtle differences showed clear differences in the LOC. Also, a top-down modulating activity might be involved in perception of emotional stimuli, where the occipital cortex functions as a mediator to other parts of the limbic system (e.g. amygdala, insula, MPFC etc.), which could help explain why the LOC showed greater response than more specified regions of the emotional system (Eippert et al., 2007; Ochsner, Bunge, Gross, & Gabrieli, 2002). Another possibility for the discrepant findings could relate to a potential anatomical explanation, where magnetic field inhomogeneities near the amygdala caused by air-filled bone cavities might cause different magnetic susceptibilities (Merboldt, Fransson, Bruhn, & Frahm, 2001). Findings from our study are in line with results from an fMRI study by Lang and colleagues (1998), where the functional activity of the visual cortex was studied as subjects viewed a series of pleasant, neutral, and unpleasant stimuli. Results indicated that both emotional and neutral pictures produced activation in Brodmann area 17, while only emotional stimuli evoked bilateral activation. Greater activation was also found overall in the right hemisphere, as well as significantly greater activity when processing emotional stimuli contrasted to neutral stimuli (Lang et al., 1998).

As demonstrated in previous research that examined the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1999), pictures rated for emotional responses using self-report and physiological measures, although somewhat different in perceptual differences, can provoke similar emotional effects (Bradley, Codispoti, Cuthbert, & Lang, 2001). Similarly, our results suggest that that in spite of minimal differences between foreign HWLs and proposed FDA HWLs, foreign HWLs showed greater neural response, supporting concerns that the proposed FDA HWLs are weak compared to their foreign counterparts (Armstrong & Blanke, 2012). Indeed, our results are consistent with both web-based and in-person experimental studies in which adult smokers and adolescents reported responses to FDA HWLs and generally rated them as less effective than foreign HWLs (David Hammond et al., 2013; Thrasher et al., 2012). fMRI can complement behavioral and self-report assessments. One needs to be careful not to over-interpret results. For example, in our study we saw larger responses when pairs of images showed different scenes than when the scene was repeated. This is clear evidence for some form of habituation to familiar stimuli. However, it is possible that this low-level response suppression is not directly related to an images ability to have washout over a period of months. Questioning the use of self-report methods to study mental processes is nothing new and carefully designed fMRI studies could potentially be used to cross-validate self-report measures.

Limitations

This study has several important limitations. First, brain activation could have been influenced by participants smoking prior to the scanning session leading to alteration in cerebral blood flow in different brain areas (Kumari et al., 2003). Even though this potential artifact is worth mentioning, there is no reason to think that such a biological effect would only influence one stimulus type and not the other, or have an interaction with the effects of repeated versus different images. In other words, our design interleaved the differential experimental conditions within the scanning session. It remains challenging to quantify cortical response to visual stimuli due to individual preferences and experiences. While an image of a woman holding a baby in the vicinity of white smoke (see FDA stimuli) may evoke neutral emotional response for someone that is not a parent it could very well trigger a negative reaction in a person who is a parent. Another possible limitation is the lack of text, leading to a minimal emotional association between stimuli given the fact that textual elements give HWL imagery greater context, with some studies showing how different text works better than others (Thrasher, et al., 2012). We removed text from HWLs to eliminate factors involved with text processing and thereby focus solely on responses to picture stimuli. Other studies have specifically examined the effects of text on HWLs arguing that text and graphics serve in unison to capture smokers' attention. Using a visual dot probe task Brown, Reidy, Weighall, & Arden (2012) studied graphic versus neutral HWLs with and without text captions. Reaction times towards probes replacing graphic images versus probes replacing neutral images were used to create an index of attention bias. Graphic HWLs imagery increases attention capture, but only when accompanied by a text message linked to the health risks.

Furthermore, Brown and colleagues found greater attention bias toward graphic HWLs among smokers elicited by the presence of text captions, while only a minimal bias was observed in the absence of the text. Graphic HWLs have also been shown to diminish recall of text elements compared with graphic pictures or controls. In addition, results indicate that graphic HWLs offset this diminished recall by evoking fear that increases intentions to quit, highlighting the importance of pictorial HWL content in absence of text elements (Kees et al., 2011). It should be noted here that regional brain activity may be influenced by individual differences, including personality, emotional reactions, memory and perception (Hamann & Canli, 2004). Sex differences can also effect brain regions sensitive to emotion (Canli, Desmond, Zhao, & Gabrieli, 2002).

WHERE DO WE GO FROM HERE?

This study suggests that proposed FDA HWLs activate less neural response than foreign HWLs. This effect does not diminish over time meaning that foreign HWLs cause stronger responses both on initial, as well as on subsequent viewing. No habituation interaction was observed between the two classes of HWLs, and foreign HWLs imagery consistently provoked stronger neural response in whole brain analysis as well as in LOC, but not in other ROIs (i.e. amygdala and insula). Given the exploratory nature of this study, more extensive fMRI research is needed on different types of HWLs, with different study designs, including prior exposure to HWLs as in the real world, in order to better understand their effects on neural activity and behavior. Furthermore, there is a need to explore potential effectiveness of HWLs by cross-validating smokers' self-reported responses, including a focus on regions like the medial prefrontal cortex, an area which has previously been associated with behavior change (Falk, Berkman, & Lieberman, 2012; Falk, Berkman, Whalen, & Lieberman, 2011).

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