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Abstract

There is an ongoing public debate about the new graphic warning labels (GWLs) that the Food and Drug Administration (FDA) proposes to place on cigarette packs. Tobacco companies argued that the strongly emotional images FDA proposed to include in the GWLs encroached on their constitutional rights. The court ruled that FDA did not provide sufficient scientific evidence of compelling public interest in such encroachment. This study's objectives were to examine the effects of the GWLs on the electrophysiological and behavioral correlates of smoking addiction and to determine whether labels rated higher on the emotional reaction (ER) scale are associated with greater effects. We studied 25 non-treatment-seeking smokers. Event-related potentials (ERPs) were recorded while participants viewed a random sequence of paired images, in which visual smoking (Cues) or non-smoking (non-Cues) images were preceded by GWLs or neutral images. Participants reported their cigarette craving after viewing each pair. Dependent variables were magnitude of P300 ERPs and self-reported cigarette craving in response to Cues. We found that subjective craving response to Cues was significantly reduced by preceding GWLs, whereas the P300 amplitude response to Cues was reduced only by preceding GWLs rated high on the ER scale. In conclusion, our study provides experimental neuroscience evidence that weighs in on the ongoing public and legal debate about how to balance the constitutional and public health aspects of the FDA-proposed GWLs. The high toll of smoking-related illness and death adds urgency to the debate and prompts consideration of our findings while longitudinal studies of GWLs are underway.

Keywords

attentional bias, cigarette craving, event-related potentials, graphic cigarette warning labels, P300, tobacco control policy

Disciplines

Bioethics and Medical Ethics | Food and Drug Law | Neuroscience and Neurobiology | Neurosciences | Substance Abuse and Addiction

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Emotional graphic cigarette warning labels reduce the electrophysiological brain response to smoking cues

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Abstract

There is an ongoing public debate about the new graphic warning labels (GWLs) that the Food and Drug Administration (FDA) proposes to place on cigarette packs. Tobacco companies argued that the strongly emotional images FDA proposed to include in the GWLs encroached on their constitutional rights. The court ruled that FDA did not provide sufficient scientific evidence of compelling public interest in such encroachment. This study's objectives were to examine the effects of the GWLs on the electrophysiological and behavioral correlates of smoking addiction and to determine whether labels rated higher on the emotional reaction (ER) scale are associated with greater effects. We studied 25 non-treatment-seeking smokers. Event-related potentials (ERPs) were recorded while participants viewed a random sequence of paired images, in which visual smoking (Cues) or non-smoking (non-Cues) images were preceded by GWLs or neutral images. Participants reported their cigarette craving after viewing each pair. Dependent variables were magnitude of P300 ERPs and self-reported cigarette craving in response to Cues. We found that subjective craving response to Cues was significantly reduced by preceding GWLs, whereas the P300 amplitude response to Cues was reduced only by preceding GWLs rated high on the ER scale. In conclusion, our study provides experimental neuroscience evidence that weighs in on the ongoing public and legal debate about how to balance the constitutional and public health aspects of the FDA-proposed GWLs. The high toll of smoking-related illness and death adds urgency to the debate and prompts consideration of our findings while longitudinal studies of GWLs are underway.

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Authors Contribution

ALW, DR and DDL designed the study. ALW collected and analyzed the data. ALW, DDL, DR, IE, BIT and RCG critically reviewed and interpreted the findings and wrote the manuscript. All authors critically reviewed content and approved final version for publication.

Keywords

Attentional bias; cigarette craving; event-related potentials; graphic cigarette warning labels; P300; tobacco control policy

Introduction

Warning labels on cigarette packages are a potentially important venue for communicating the health risks of smoking (Hammond *et al.* 2006). Text-only warning labels, such as those required in the United States, seem to be ineffective at fulfilling this purpose, prompting calls for alternatives, such as graphic warning labels (GWLs) (Robinson & Killen 1997; Hammond *et al.* 2006). However, studies disagree about the comparative efficacy of GWLs and their effectiveness across different target populations (CDC 2013; Moodie, Mackintosh & Hastings 2013). GWLs on cigarette packages, which are composed of textual warnings and images depicting the negative health consequences of smoking, have several hypothetical advantages as a population-based smoking prevention strategy. First, GWLs are less invasive than smoking cessation pharmacotherapies. Second, the effects of GWLs are independent of smokers' treatment compliance (or lack of thereof). Third, their placement on cigarette packs provides users with information about the product at point of purchase and at each usage occasion. Moreover, if smoking behavior reflects a primary deficit in decision-making processes (Heyman 2013), e.g. discounting of the delayed health consequences (Stillwell & Tunney 2012), a message highlighting the risk of smoking, immediately prior to lighting up, is a more direct remedy for this neuropsychological deficit than an intervention at a more distant timepoint. These theoretical advantages notwithstanding, implementation of GWLs in the United States was delayed by tobacco industry legal action. Out of the nine GWLs selected by the Food and Drug Administration (FDA) for implementation, eight were rated highest on an 'emotional reaction' (ER) scale in a large-scale FDA-commissioned survey of 36 candidate GWLs (Nonnemaker *et al.* 2010). The plaintiffs argued that these GWLs were selected to indiscriminately deter the public from buying a legal product rather than persuade them to make an informed choice. This, in plaintiffs' opinion, exceeded the government's power to regulate commercial speech and violated their First Amendment rights. This appeal was upheld by the District of Columbia Circuit Court of Appeals (FDA 2011) mainly on the grounds of the paucity of objective scientific evidence pertaining to the effectiveness of GWLs in general and of the high ER GWLs in particular, in deterring or reducing smoking [RJ Reynolds Tobacco Co. v. FDA, 696 F.3d 1205 (D.C. Cir. 2012); Moodie *et al.* 2013]. In the Courts' opinion, such evidence was essential to determine whether public interest outweighed the potential encroachment on the tobacco companies' First Amendment rights. This case unmasked the fact that despite a plethora of suggestive large-scale observational surveys and epidemiological studies (Peters *et al.* 2007; Bansal-Travers *et al.* 2011; Thrasher *et al.* 2011; Azagba & Sharaf 2013; Wakefield *et al.* 2012), convincing empirical evidence of GWLs' effectiveness for smoking behavior was lacking.

The neuropsychological rationale for introducing GWLs is indeed unclear. One potential mechanism of their action could be reducing the incentive salience and attentional bias

diverted toward smoking and conditioned cues, thus attenuating the motivational appeal of smoking (Wilson, Sayette & Fiez 2004; Robinson & Berridge 2008; Engelmann *et al.* 2012; Littel *et al.* 2012; Tang *et al.* 2012; Feltenstein & See 2013). The P300 component of event-related potentials (ERPs) has been extensively used to study attentional bias in smokers (Warren & McDonough 1999; McDonough & Warren 2001; Littel & Franken 2007, 2011; Versace *et al.* 2011; Engelmann *et al.* 2012) because the amplitude of P300 elicited by smoking cues is modulated by motivated attention and activation of brain arousal systems (Cuthbert *et al.* 2000). Increased P300 in response to smoking cues is thought to reflect the heightened incentive value of such cues in addicted smokers (Littel *et al.* 2012). Indeed, Littel & Franken (2011) showed that the amplitude of P300 declined in former smokers after prolonged abstinence and was absent in non-smokers. Similar to P300, subjective craving is also used as proxy for smoking dependence (Carpenter *et al.* 2009; Vollstadt-Klein *et al.* 2011).

To evaluate the clinical effects of GWLs on smoking addiction, we compared P300 amplitude and self-reported craving response to smoking cues preceded by GWLs with those preceded by neutral images. In addition, we examined whether the emotional intensity of GWLs modulated these responses. We hypothesized that exposure to GWLs will reduce P300 amplitude and the cigarette craving response to a smoking cue that followed it. Furthermore, we hypothesized that the effect will be greater in response to a cue preceded by high ER GWLs compared to a cue preceded by low ER GWLs.

Materials and Methods

Participants

Twenty-five non-treatment-seeking smokers (9 females, 15 Caucasian, 7 African American, 2 Asian and 1 Hispanic) were recruited through advertising and gave an informed consent to participate in this Institutional Review Board-approved study. Participants were 33.0 Å } 7.0 years old, who reported smoking an average of 14.0 Å } 4.0 cigarettes/day and had a score of 3.6 Å } 1.9 on the Fagerstrom Test for Nicotine Dependence (FTND). Exclusion criteria were (1) positive urine drug screen (UDS) for opioids, benzodiazepines, cocaine, oxycodone, Δ9-tetrahydrocannabinol or methamphetamine; (2) negative semi-quantitative urinary cotinine test; (3) current treatment or plans to seek treatment for smoking cessation in the next 2 months; (4) current use of any nicotine replacement and/or containing products other than cigarettes (e.g. nicotine patch or gum, smokeless tobacco) and/or current smoking cessation pharmacotherapy; (5) current diagnosis of or treatment for any psychiatric or neurological disorder; (6) potentially confounding medical conditions, such as such as chronic obstructive pulmonary disease, coronary artery disease, diabetes, congestive heart failure, hypertension, renal insufficiency and cirrhosis of the liver; and (7) physical or visual impairment interfering with viewing the computer screen and/or using a keyboard/mouse.

Stimuli

Thirty GWLs were selected from the 36 labels evaluated by the FDA-commissioned 'Experimental Study of Graphic Cigarette Warning Labels'. This study provided the ER scale score for each of the 36 GWL considered by the FDA for placement on cigarette packs

(Nonnemaker *et al.* 2010). Briefly, the FDA study surveyed 4500 adult (>25 years old) smokers through a commercial Internet panel. Participants viewed one randomly selected GWL, which combined one of the nine warning statements mandated by the 2010 law (e.g. 'Smoking Causes Cancer') with an image selected by FDA. Participants rated 1 of 36 GWLs on several dimensions (Nonnemaker *et al.* 2010). The ER scale was constructed from the 'emotional reactions to labels' section of the survey (Nonnemaker *et al.* 2010). In this section, participants rated, on a scale of 1 (i.e. *not at all*) to 5 (i.e. *completely*), how the pack made them feel on one of seven highly correlated parameters: 'Depressed'; 'Worried'; 'Disgusted or grossed out'; 'Guilty'; 'Sad'; 'Discouraged'; 'Uneasy'. The ER score was an arithmetic sum of ratings on each of the seven items, by each rater. An overall ER score for each GWL was the mean of approximately 100 individual ER scores for that GWL. Higher ER score indicates greater emotional reaction produced by the GWL. For the present study, we selected 15 GWLs rated highest and 15 rated lowest on the ER scale. The mean of the high ER GWLs (18.37 Å 0.62) differed significantly from the low ER ones (15.71 Å 0.88) [$t(28) = 9.55, P < 0.001$]. The high ER GWL included pictures with the following FDA descriptions: 'Cancerous lesion on the lip', 'Man w/ chest staples', 'Healthy/diseased lungs', 'Deathly ill woman', 'Girl in oxygen mask', 'A hole in throat', 'Smoke at toddler', 'Sick baby in an incubator', 'An oxygen mask on man's face', 'Smoke at baby', 'Lungs full of cigarettes', 'Girl crying', 'White cigarette burning Smoke approach baby' and 'Woman crying'. The 15 lowER labels included 'Woman blowing bubble', 'Man in a "I quit" t-shirt', 'Cigarette in a toilet bowl', 'Woman in the rain', 'Pacifier & ashtray', 'Man hands up & smoke', 'Man in pain with hand on chest', 'Red puppet on strings', 'Man blowing smoke at a woman', 'Toe with a morgue tag', 'Grave yard', 'Hand with an oxygen mask', 'Red cigarette burning', 'Warning in child lettering' and 'Dead man in a casket'. Thirty neutral images serving as controls for GWLs were selected from the International Affective Picture System (Cuthbert *et al.* 2000), including images numbered 2383/ 2480/ 7234/ 2580/ 7700/ 5471/ 5740/ 7100/ 7026/ 7000/ 7010/ 7950/ 7025/ 7050/ 7060/ 7061/ 7090/ 7140/ 7150/ 7175/ 7186/ 7235/ 7242/ 7491/ 7500/ 7546/ 7595/ 7705/ 8312/ 9210, based on their low arousal rating (2.89 Å 1.94). The smoking cues and the matched non-smoking cues were adapted from our previous cue-reactivity studies in smokers (Langleben *et al.* 2008; Strasser *et al.* 2012).

There were 30 individual stimuli in each category: GWLs, neutral images (Neu), smoking cues (Cue) and nonsmoking cues (non-Cue). Target events (Cue or non-Cue) were randomly preceded by GWLs or Neutral images (Neu), yielding four possible combinations (conditions): [GWL]Cue, [Neu]Cue, [GWL]non-Cue and [Neu]non-Cue (Fig. 1). Each condition comprising 30 randomly paired stimuli was presented twice during the experimental session, resulting in a total of 240 trials (30 pairs Å 2 presentations Å 4 conditions).

Procedure

Participants responding to an advertisement were screened by phone and those meeting the basic requirements were invited to attend a more thorough assessment, including demographic characteristics, clinical interview, FTND measuring smoking dependence, Attitudes Towards Quitting Smoking questionnaire (Fishbein & Ajzen 1975) and urine

toxicology (Reditest® Smoke Cassette and UDS, Redwood Toxicology Labs, Santa Rosa, CA, USA). After completion of baseline assessments, participants were asked to smoke one of their own cigarettes under observation in order to be in a uniformly non-deprived state (Langleben *et al.* 2012; Wang *et al.* 2013).

All participants took the opportunity to smoke and consumed no more than one cigarette. After smoking a cigarette, participants were seated in a comfortable chair and fitted with a 62-channel electroencephalogram (EEG) cap. They were instructed to focus on each of the two images in the pair, and to indicate their cigarette craving on a 100-mm visual analog scale (VAS) (Guthrie *et al.* 2004) with a range of 0–100, using a mouse, immediately after the target image (i.e. Cue or non-Cue picture) disappeared from the display. The VAS was labeled with ‘0’, referring to ‘do not want a cigarette at all’, and 100, referring to ‘want a cigarette extremely’.

A schematic illustration of the experiment paradigm is shown in Fig. 1. In each pair, the preceding event (GWL or Neutral) and target event (Cue or non-Cue) were displayed for 1500 milliseconds each in sequence, immediately followed by the rating screen (i.e. the question ‘How much do you want to smoke a cigarette right now?’ and the VAS). Responses to questions were logged automatically. The 240 trials were randomly distributed into 6 blocks of 40 trials each. Inter-trial intervals randomly ranged from 1000 to 2000 milliseconds, with a white crosshair appearing on a black background. The interval between blocks ranged from 3 to 5 minutes. Stimuli were delivered by Presentation (Neurobehavioral System Inc., Albany, CA, USA). All stimuli were presented at the center of the monitor, on a black background. At the end of EEG session, participants were asked again to complete the Attitudes Towards Quitting Smoking questionnaire and were debriefed. All participants denied being aware of the purpose of the study on debriefing.

EEG recording

Participants were seated at a distance of 1.8 m from a 60” liquid-crystal display monitor (Sharp PN-E601, Sharp Electronics Corp., Mahwah, NJ, USA) in a dimly lit room.

They were asked to minimize body movements and eye blinks throughout the recording. The EEG was recorded using 62 Ag–AgCl electrodes placed on the scalp according to the international 10-10 system, using the nose as the extracephalic reference. To monitor ocular movements and eye blinks, electro-oculographic (EOG) signals were recorded from two surface electrodes, one placed over the lower eyelid and the other placed 1 cm laterally to the outer corner of the orbit. Signals were amplified and digitized using a sampling rate of 1000 Hz and a precision of 32 bits (Neuroscan, Compumedics Limited, Victoria, Australia, <http://www.neuroscan.com>).

EEG data analysis

EEG data analyses were performed using EEGLAB (open source Matlab toolbox, <http://scn.ucsd.edu/eeglab/>) (Delorme & Makeig 2004). Continuous EEG recordings were bandpass filtered at 0.1–30 Hz and then segmented into epochs using a time window of 2 seconds (0.5 to +1.5 seconds relative to the onset of the Cue or non-Cue stimulus). Each epoch was baseline corrected using the time interval ranging from –0.5 to 0 second as

reference. EOG artifacts were subtracted using a validated method based on independent component analysis (Jung *et al.* 2000). In all datasets, independent components related to eye movements had a large EOG channel contribution and a frontal scalp distribution. Finally, epochs containing artifacts exceeding \hat{A} } 100 μ V were rejected. Subjects with less than 60% of epochs surviving the above procedure for each condition were excluded from further analysis. One subject satisfied this criterion and was excluded, leaving 24 subjects for the final analyses.

For each subject, epochs in each of the four conditions (i.e. [GWL]Cue, [Neu]Cue, [GWL]non-Cue and [Neu]non-Cue) were averaged, yielding four averaged waveforms. The mean number of epochs for each condition was [GWL]Cue = 53.25 \hat{A} } 6.71, [Neu]Cue = 52.00 \hat{A} } 9.61, [GWL]non-Cue = 51.88 \hat{A} } 9.37 and [Neu]non-Cue = 50.20 \hat{A} } 9.53. One-way repeated-measures ANOVA revealed that there was no significant difference in the mean number of epochs between conditions [$F(3,69) = 2.155, P = 0.10$]. Furthermore, based on the ER of the warning labels, the [GWL]Cue condition was divided into two subgroups: [hiGWL]Cue and [loGWL]Cue; and [GWL]non-Cue condition was divided into two subgroups: [hiGWL]non-Cue and [loGWL]non-Cue.

The P300 responses to the target image (i.e. Cue or non-Cue) were identified at the medial parietal (Pz) electrode site referenced to the nose, and defined as the largest positive deflection occurring 300–800 milliseconds after stimulus onset (Hyland *et al.* 2005). For each subject and condition, the amplitude of P300 elicited by Cues and non-Cues was measured from averaged waveforms. Statistical analyses were performed using IBM SPSS Statistics (version 20, IBM Corp., Armonk, New York, USA). To test the effect of the preceding GWLs on the P300 amplitudes elicited by smoking and non-smoking cues, a one-way repeated-measures ANOVA was performed with six conditions [hiGWL]Cue, [loGWL]Cue, [Neu]Cue, [hiGWL]non-Cue, [loGWL]non-Cue and [Neu] non-Cue. *Post hoc* comparisons (two-tailed) were performed to evaluate differences between conditions using Fisher's least significant difference (LSD) correction, when there was an overall significance.

Subjective data analyses

To test the effect of the preceding GWLs on subjective craving ratings, a one-way repeated-measures ANOVA was performed with six conditions [hiGWL]Cue, [loGWL] Cue, [Neu]Cue, [hiGWL]non-Cue, [loGWL]non-Cue and [Neu]non-Cue. *Post hoc* (two-tailed) comparisons were performed to evaluate differences between conditions using Fisher's LSD correction, when there was an overall significance. Also, a paired-sample *t*-test was used to compare baseline and post-warning exposure measures of Attitudes Towards Quitting Smoking.

Results

P300 magnitude elicited by smoking cues

The one-way repeated-measures ANOVA revealed that there were significant differences between conditions [$F(5,115) = 9.02, P < 0.001$] (Fig. 2). *Post hoc* pairwise comparisons indicated that preceding high ER GWLs reduced the P300 amplitude elicited by smoking

cues, significantly more than preceding low ER GWLs ($P = 0.003$) or neutral pictures ($P = 0.007$). Preceding low ER GWLs had no effect on the P300 amplitude elicited by smoking cues ($P = 0.730$) (Fig. 3, upper panel). Furthermore, both preceding hiGWLs and loGWLs had no effect on the P300 amplitude elicited by non-smoking cues ([hiGWL] non-Cue versus [Neu]non-Cue, $P = 0.70$; [loGWL]non-Cue versus [Neu]non-Cue, $P = 0.89$).

Subjective data

The one-way repeated-measures ANOVA revealed that there were significant differences between conditions [$F(5,115) = 12.70$, $P < 0.001$]. Post hoc pairwise comparisons indicated that preceding high ER GWLs reduced the subjective craving in response to smoking cues significantly more than preceding low ER GWLs ($P < 0.001$) or neutral pictures ($P < 0.001$). Preceding low ER GWLs also significantly reduced self-reported craving ($P = 0.002$) (Fig. 3, lower panel). The latter finding was not paralleled by the effect of low ER GWL on the P300 amplitude. Finally, participants' attitudes significantly changed in favor of quitting smoking after the EEG session [pre_EEG = 3.7 Å} 1.0, post_EEG = 4.2 Å} 0.9; $t(23) = 3.953$, $P = 0.001$].

Discussion

We found that in non-treatment-seeking smokers, high ER GWLs strongly attenuated both the amplitude of P300 evoked by smoking cues and the subjective urge to smoke. The low ER warning labels also reduced the urge to smoke, but not the P300 response to smoking cues. Our findings are the first electrophysiological evidence of the superiority of GWLs with strong emotional content in reducing brain and behavioral correlates of smoking addiction.

The present findings provide electrophysiological confirmation for the previous behavioral and epidemiological studies which found that exposure to GWLs had beneficial effects on smoking-related cognitions and behaviors, such as attitudes toward smoking and smoking cessation attempts (Peters et al. 2007; Bansal-Travers et al. 2011; Thrasher et al. 2011; Azagba & Sharaf 2013). Regardless of preceding events, the P300 amplitude in response to smoking cues was larger than that of non-smoking cues. This observation confirms the validity of our procedure as it is in line with previous reports of enhanced P300 response to smoking cues in smokers (Warren & McDonough 1999; McDonough & Warren 2001; Littel & Franken 2007). Similar enhancement in P300 amplitude has been reported in addiction to other substances, including alcohol, cocaine, marijuana and heroin (Herrmann et al. 2000; Namkoong et al. 2004; Lubman et al. 2007, 2008; Franken et al. 2008; Goldstein et al. 2008; Wolfling, Flor & Grusser 2008; Dunning et al. 2011).

Our data shed some light on the possible mechanism of action of the FDA- proposed GWLs, which has been at the crux of the debate about their legitimacy. The reduced brain response to smoking cues could be explained by the underlying reduction in incentive-motivational value of smoking cues (Robinson & Berridge 2008) resulting from GWL exposure. This explanation is supported by the fact that both P300 and behavioral effects of the preceding GWLs were specific to smoking cues. Indeed, while the warning labels reduced the P300 amplitude in response to smoking cues, they did not affect the response to nonsmoking cues.

Similarly, cigarette craving elicited by smoking cues that were preceded by warning labels was significantly lower than craving after cues that were preceded by neutral images. In the framework of value-based decision (Rangel, Camerer & Montague 2008), the reduction of the overall motivational appeal of smoking may be achieved through the goal-oriented decision system balancing the value of cigarettes with the value of the anticipated reward. The latter may be downgraded by the real-time warnings in the form of GWLs, resulting in diminished attentional bias to smoking cues, clinically manifested as reduced cue-induced craving and P300 amplitude. Alternatively, since P300 can also reflect aversive motivational processes triggered by cues, the reduction in P300 could have been a result of reduction in the aversiveness of the smoking cues. However, craving in response to smoking cues reported by all participants, contradicts this alternative interpretation.

Demonstration of reduced attentional bias to smoking cues in non-treatment seeking smokers following GWL exposure has practical clinical implications. Warning labels on cigarette packs are unique among tobacco control initiatives in that they are delivered immediately prior to each act of smoking. As a result, pack-a-day smokers could be exposed to the warning labels over 7000 times per year. It has been reported that cognitive training aimed at decreasing attentional bias to alcohol cues successfully reduced alcohol consumption and other drinking-related indices (e.g. drinker's readiness to change), and the effect was maintained at 3-month follow-up (Fadardi & Cox 2009). Similarly, since the high ER GWLs reduce the attentional bias to and incentive-motivational values of smoking cues in smokers, they could serve as an intervention to reduce cigarette consumption and prevent relapse.

Of all our findings, the one with perhaps most potential public policy implications is that the high ER GWLs attenuated the brain response to smoking cues whereas the low ER ones did not. This finding suggests that GWLs containing high ER images may have greater public benefits for smoking reduction than low ER GWLs. This interpretation is indirectly supported by a functional magnetic resonance imaging (fMRI) study, which found that the brain response to smoking cues predicted outcomes of smoking cessation treatment (Janes et al. 2010). Despite the lack of brain effects, the low ER GWLs reduced the subjective urge to smoke, albeit less so than the high ER GWLs (Fig. 3, lower panel). This might be explained by the fact that attentional bias to smoking cues as measured by P300 amplitude and cue-induced craving represents different stages of information processing (Littel & Franken 2007; Dittmar, Krehl & Lautenbacher 2011). Finally, our findings could serve as a template for studies evaluating labeling of other products that may pose health risks.

These results should be interpreted with a number of caveats. First, although both acute cue-induced self reported craving and P300 modulation are valid intermediate markers of smoking behaviors, a prospective study linking these intermediate markers with objective measures of smoking is required to determine which will be a better predictor of future smoking behavior. Second, while most P300 studies of smoking cue-reactivity used linked mastoids, we used the nose as reference. Although the nose is a valid reference in P300 research (Faux et al. 1990), this methodological difference might limit our ability to compare our results with some other studies of smoking cue-reactivity. Finally, further

studies employing images with comparative valence as controls, or using fMRI, could help clarify the mechanisms underlying the effect of GWLs on smoking cues.

In conclusion, our study provides experimental biological evidence that weighs in on the ongoing public and legal debate about the constitutionality and the public benefit of the FDA-proposed GWLs. Since at least 400 000 people die of smoking-related illnesses each year in the United States alone and the use of these graphic labels could potentially reduce the number of smoking-related deaths, our data provide valuable guidance even before conclusive longitudinal experimental studies of GWLs are completed.

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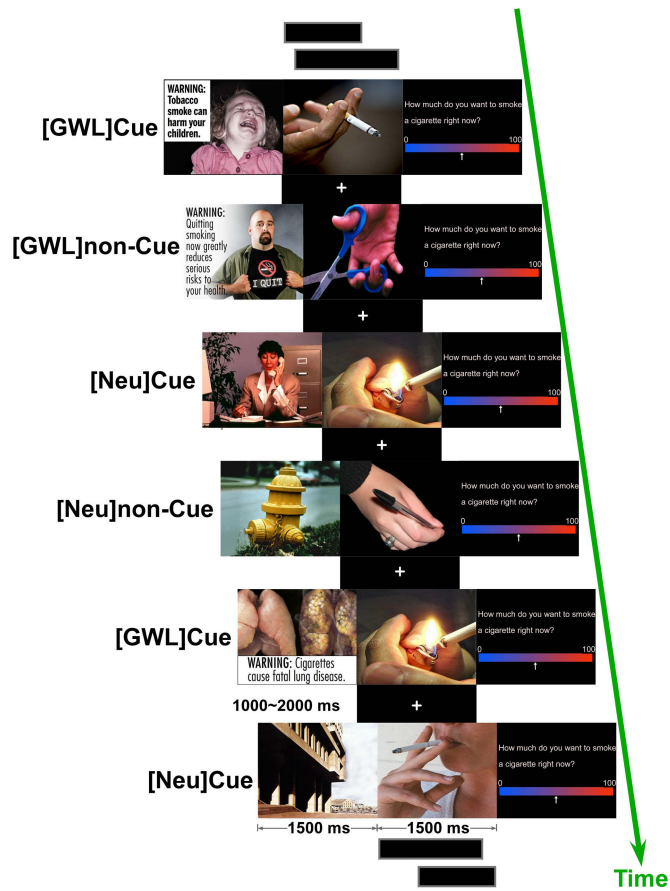


Figure 1.

The experimental paradigm. smoking cues (Cue) or non-smoking cues (non-Cue), were randomly preceded by graphic warning labels (GWL) or neutral images (Neu), yielding four conditions: [GWL]Cue, [Neu]Cue, [GWL]non-Cue and [Neu]non-Cue. Participants were asked to rate their cigarette craving on a visual analog scale immediately after each target event (Cue or non-Cue).

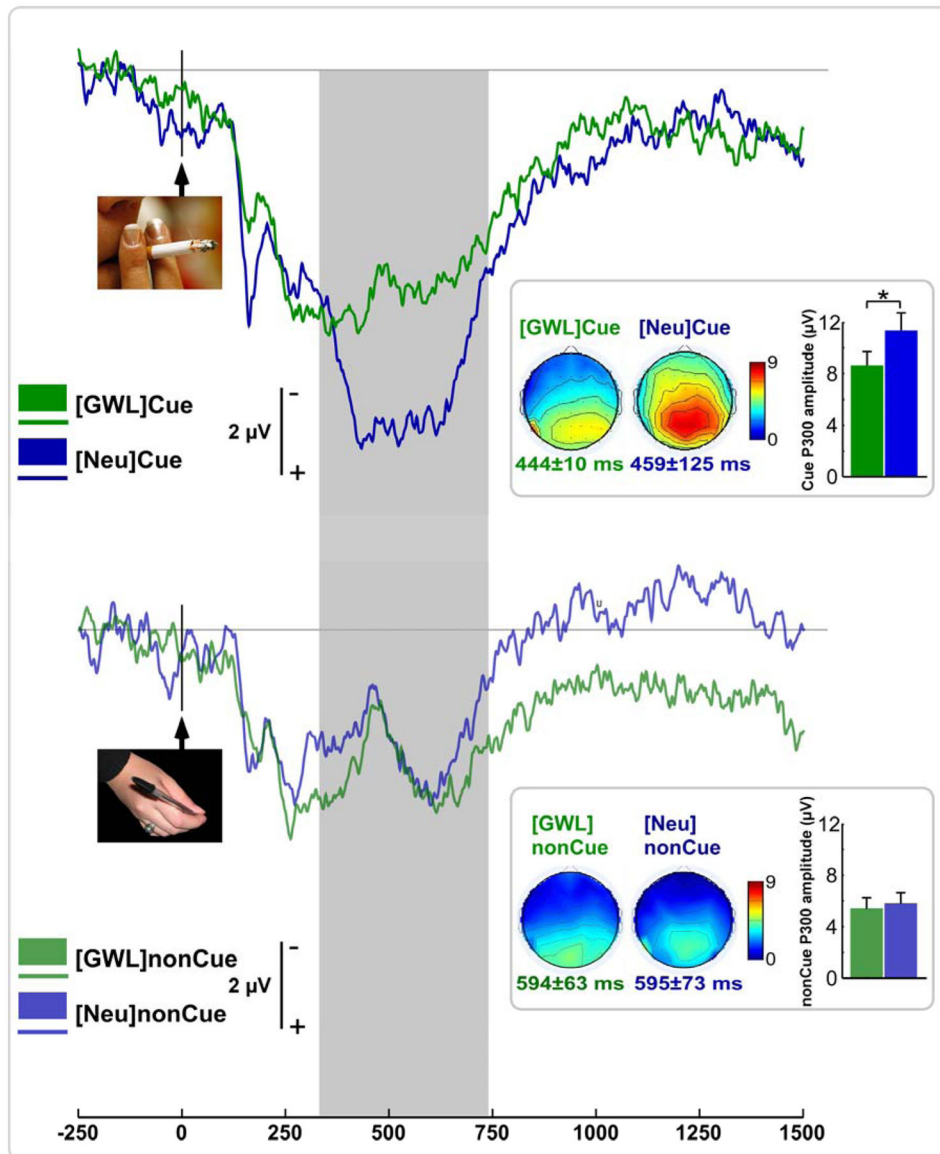


Figure 2.

Waveforms and scalp topography of P300 elicited by smoking cues (upper panel) and nonsmoking cues (lower panel) were modulated by preceding events (i.e. graphic cigarette warning labels [GWL] vs. neutral pictures [Neu]) (Pz vs. nose reference, n=24). The vertical calibration bar presents amplitude (2μV, negativity plotted upward). The color bar charts in the inserts show the P300 amplitudes (asterisk denotes significance level of $p < 0.01$, error bars present SEM). Green=Cue preceded by [GWL], Blue=Cue preceded by [Neu].

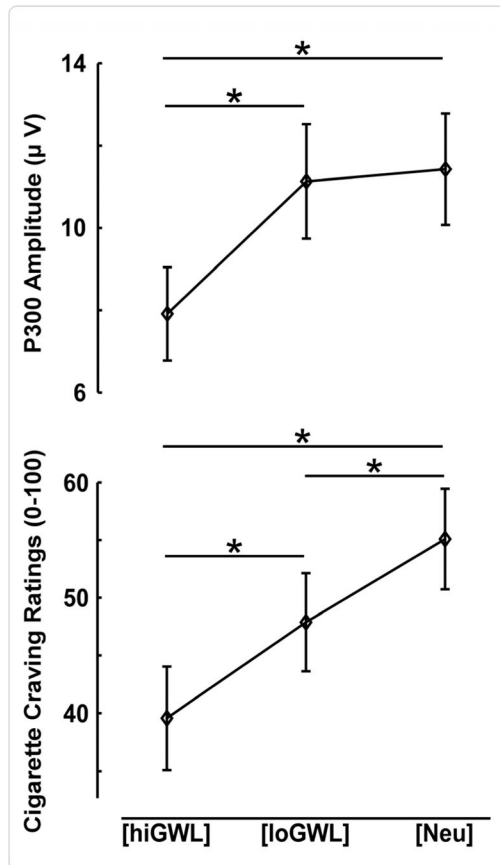


Figure 3.

Effects of preceding events (i.e. high ER graphic warning labels [hiGWL], low ER graphic warning labels [loGWL] and neutral pictures [Neu]) on brain and behavioral responses to smoking cues. *Upper panel:* preceding high ER GWLs reduced the P300 amplitude elicited by smoking cues, significantly more than preceding low ER GWLs or neutral pictures. *Lower panel:* preceding high and low ER GWLs significant reduced subjective rating for cigarette craving (range from 0–100). Asterisks denotes significance level of $p < 0.05$. Error bars present SEM.