Emotional reaction facilitates the brain and behavioral impact of graphic cigarette warning labels in smokers

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Abstract

Background—Warning labels on cigarette packages are an important venue for information about the hazards of smoking. The 2009 US Family Smoking Prevention and Tobacco Control Act mandated replacing the current text-only labels with graphic warning labels. However, labels proposed by the Food and Drug Administration (FDA) were challenged in court by the tobacco companies, who argued successfully that the proposed labels needlessly encroached on their right to free speech, in part because they included images of high emotional salience that indiscriminately frightened rather than informed consumers.

Methods—We used functional MRI to examine the effects of graphic warning labels' emotional salience on smokers' brain activity and cognition. Twenty-four smokers viewed a random sequence of blocks of graphic warning labels that have been rated high or low on an 'emotional reaction' scale in previous research.

Results—We found that labels rated high on emotional reaction were better remembered, associated with reduction in the urge to smoke, and produced greater brain response in the amygdala, hippocampi, inferior frontal gyri and the insulae.

Conclusions—Recognition memory and craving are, respectively, correlates of effectiveness of addiction related public health communications and interventions, and amygdala activation facilitates the encoding of emotional memories. Thus, our results suggest that emotional reaction to graphic warning labels contributes to their public health impact and may be an integral part of the neural mechanisms underlying their effectiveness. Given the urgency of the debate about the

constitutional risks and public health benefits of graphic warning labels, these preliminary findings warrant consideration while longitudinal clinical studies are underway

Keywords

Packaging and Labeling; Prevention; Public Policy; Litigation; Advertising and Promotion

Introduction

Warning labels on cigarette packages have long been considered an important venue for communicating the health risks of smoking.[1, 2] In 2009, the US Congress mandated graphic warning labels on cigarette packs to contain both textual warnings and color images depicting the negative health consequences of smoking.[3] The law specified the textual messages and charged the US Food and Drug Administration (FDA) with selecting the images to accompany them. For this purpose, FDA conducted an online survey of 36 candidate labels and selected nine of them based on survey results.[4] However, the anticipated implementation of the new labels was postponed by the legal action of five US tobacco companies who argued that the proposed highly emotional graphic labels were unconstitutional, in part because they 'were chosen not to convey information, but to evoke negative emotions and thereby discourage smoking'.[5] The US District Court for the District of Columbia ruled for the plaintiffs, opining that evidence of the graphic labels effectiveness presented by the FDA was insufficient to justify an encroachment on tobacco companies' right to free commercial speech.[6] In plaintiff's opinion, the images on the labels exceeded FDA's mission to inform the consumer. Indeed, eight out of nine labels selected by the FDA scored highest on a scale of emotional reaction (ER) in an Internet survey of 9474 adult smokers commissioned by the FDA.[3, 4] The survey asked participants to rate their ER to a cigarette pack they had just viewed online in regard to seven dimensions, such as 'depressed', 'worried' and 'disgusted'. The District of Columbia Circuit Court of Appeals affirmed the District Court ruling.[5]

This case brought to the fore the fact that despite a growing number of observational and behavioral studies showing positive effects of warning labels[1] and a broad international support for the inclusion of strong, negatively valenced images on cigarette warning labels,[7–19] the neurobiological mechanisms of their action remain unclear. Determining whether a strong ER enhances label effectiveness would help settle the debate on whether their public health benefit outweighs the potential encroachment on the tobacco companies' First Amendment rights.[20]

Functional magnetic resonance imaging (fMRI) in conjunction with formal behavioral paradigms has been used successfully to elucidate the neuroanatomical, cognitive and emotional mechanisms underlying basic processes, such as memory encoding and retrieval, applied to persuasive health communications. [21, 22] Recognition accuracy is commonly used to evaluate learning and is a surrogate outcome measure of the effectiveness of public health communications.[23–25] Studies show that emotion affects remembering learned material, a process involving an interaction between the amygdala and hippocampus-based memory systems.[26–28] While a majority of studies suggest that emotion facilitates memory

formation, the relationship is complex and the subject of active research.[29–32] In the present study, we used fMRI, recognition memory and cigarette craving to compare the functional neuroanatomical, cognitive and motivational impact of the labels rated high and low on the ER scale.[4] We hypothesized that the greater emotional response evoked by High ER labels will facilitate the processing of the information they contain; this will be reflected in greater activation of the amygdala, hippocampus and insula and result in better recognition and greater acute reduction in cigarette craving compared to the Low ER labels.

Materials and Methods

Participants

Twenty-four (8 female) non-treatment seeking, right-handed smokers, 28.13±7.84 (mean ±SD) years old, with 14.00±1.87 years of education, were recruited through advertisement and gave written consent to participate in the study approved by the University of Pennsylvania Institutional Review Board. Participants smoked 13.85±6.45 cigarettes per day in the previous 30 days and had Fagerström Test for Nicotine Dependence (FTND) scores[33] of 3.63±2.72. Exclusion criteria were (1) Current Diagnostic and Statistical Manual Fourth Edition Text Revision (DSM-IV-TR) Anxiety, Mood, Cognitive or Psychotic Disorder;[34] (2) medical or neurological disorder or treatment that may affect the cerebrovascular system; (3) urine drug screen (UDS, Reditest Panel-Dip Drug Screen, Redwood Toxicology Labs, Santa Rosa, California, USA) positive for illicit opioids, benzodiazepines, cocaine or methamphetamines; (4) non-detectable urine cotinine by qualitative urinary test (Reditest Smoke Cassette, Redwood Toxicology Labs, Santa Rosa, California, USA); (5) currently receiving treatment for addiction of any kind; (6) currently using nicotine-containing products or treatments other than cigarettes (eg, nicotine patch, smokeless tobacco); (7) currently seeking or planning to seek treatment for smoking cessation in the next 2 months; and (8) medical contraindications for MRI scanning.

Stimuli

From the 36 warning labels that were previously evaluated by adult smokers in an FDA-commissioned Internet survey,[4] we selected the 12 labels that were rated the highest and the 12 labels that were rated the lowest on the ER scale (1=Not at all, 5=completely). High ER labels (18.55±0.55, range 17.8–19.4) differed significantly from Low ER labels (15.48±0.83, range 14–16.5; independent sample t test, p<0.001). In addition, we created 'scrambled' images to be used as controls, by dividing graphic warning labels into 1 cm2 and rearranging them randomly within each label.[35] We compared participants' responses to 12 of these control images to responses to High ER and Low ER labels. Figure 1 shows an example from the three stimuli categories.

Tasks—Graphic labels fMRI task: The labels were presented in a block design paradigm[36] with six different blocks for each of three stimulus types: HIGH (ie, High ER graphic warning labels), LOW (ie, Low ER graphic warning labels) and CONTROL (ie, scrambled graphic warning labels). Each block contained a sequence of six images, randomly selected from the appropriate set of 12 (HIGH, LOW or CONTROL), and each image appeared for two seconds. Throughout the fMRI task, each image was presented three times. Before and

after each block, participants were prompted to answer the question "How much do you want to smoke a cigarette right now?" They used a single axis scroll wheel (FORP; Current Designs Inc, Philadelphia) to indicate their ratings on a visual analogue scale (VAS) with a range from 'not at all' (left=0) to 'extremely' (right=10). The inter-block-intervals were between 10 and 13 s long, with a white crosshair shown in the middle of the screen against a black background. Participants were instructed to attend to each image presented. All stimuli were delivered using the Presentation stimulus presentation package (Neurobehavioral System Inc, Albany, California, USA) and presented through a rear projector system (Epson America) that was viewed through a mirror mounted on the MRI scanner head coil. The duration of the graphic labels fMRI task was 9.3 min.

Recognition task: This task assessed memorability of the graphic warning labels 20 min after completion of the graphic labels fMRI task. Participants completed the task outside the scanner, using a Lenovo ThinkPad T420s laptop with a 14" HD display running MediaLab software (MediaLab Inc, Georgia, USA). This was modeled after a previously reported paradigm used to test the memorability of smoking-cessation ads.[23–25] The task contained a total of 48 labels: 24 targets (12 High ER and 12 Low ER warning labels) that participants were shown in the fMRI task, and 24 comparable warning labels that were not shown (foils). Participants were asked to respond with a 'Yes' or 'No' to the question 'Have you seen this label in the scanner?' displayed on top of each image.

Procedure

Participants were assessed for eligibility for MRI, demographics, the average number of cigarettes smoked per day in the preceding week, FTND and handedness.[37] On their arrival, participants provided urine samples for the urine drug screen and cotinine levels to confirm their smoking status. Between 30 and 45 min before the MRI session, participants were escorted outdoors to smoke one of their own cigarettes under observation, so as to be in a uniformly non-deprived state. All participants took the opportunity to smoke and consumed no more than one cigarette. Participants performed the graphic labels fMRI task in the scanner. The recognition task was administered outside of the scanner approximately 20 min after the end of the graphic labels fMRI task.

MRI was performed on a whole-body 3 T Siemens Tim Trio scanner (Erlangen, Germany) using a 32-channel head coil. Blood oxygenation level-dependent (BOLD) fMRI was performed with a whole-brain, single-shot gradient-echo echoplanar sequence with the following parameters: repetition time/echo time (TR/TE) =3000/32 ms, Field of view (FOV)=192x192 mm, matrix 64x64, slice thickness/gap=3.0/0 mm, 46 slices, yielding (3 mm)^3 voxels.[38, 39] Before BOLD fMRI, a 5 min Magnetization Prepared Rapid Gradient Echo (MP-RAGE) T1-weighted image (TR/TE=1810/3.51 ms, FOV=250x250 mm, matrix=192x256, yielding 0.94x0.94x1 mm voxels) was acquired for anatomic overlays of functional data and spatial normalisation.[40] (please see the Glossary of Technical Terms in the online supplementary file for an explanation of neuroimaging acronyms and technical terms).

Behavioral data analysis

Changes in self-reported craving ratings were calculated as Craving_change=After_exposure—Before_exposure for each block, averaged according to the type of stimulus block, thus generating three Craving_change scores: Craving_change_HighER, Craving_change_LowER and Craving_change_Control. A one way repeated-measures ANOVA was applied on Craving_change scores to examine the effect of label exposure on cigarette craving. Performance on the recognition task was calculated as per cent correct recognition: thus the score for either High or Low ER labels was (correct responses/12)*100. Since we were interested in how well participants could recognize the labels shown in the graphic labels fMRI task, instead of how well they could reject ones not shown, we did not include responses to foils in the calculation. A paired-sample t test was applied to examine if there was a difference in recognition accuracy between High and Low ER warning labels.

Imaging data analysis

Whole brain voxel-wise analysis: BOLD time series data were preprocessed and analyzed by standard procedures using the fMRI Expert Analysis Tool (FEAT V.5.98) of FSL (FMRIB's Software Library). Single-participant preprocessing included removal of regions outside the brain using brain extraction tool,[41] slice time correction, motion correction to the median image using the Motion Correction version of FMRIB's line image registration tool (MCFLIRT),[42] high-pass temporal filtering with a cut-off of 50s, spatial smoothing using a Gaussian kernel (5 mm full-width at half-maximum, isotropic) and mean based intensity normalization of all volumes using the same multiplicative factor. The median functional volume was co-registered to the anatomical T1-weighted structural volume, which was then registered to the standard anatomical space (Montreal Neurological Institute (MNI) T1 template). Statistical contrast maps were then transformed into standard space using one call to FMRIB's FLIRT[42, 43] per participant (ie, combine the two transformation matrices into a single matrix, and then apply that matrix to go directly from functional space to MNI space in one transformation).

Participant-level statistical analyses were performed voxel-wise using FILM (FMRIB's Improved General Linear Model) with local autocorrelation correction.[44] Three condition events (ie, HIGH, LOW and CONTROL) were modeled using a double-γ haemodynamic response function. At the group-level analysis, participant-level contrast maps were entered into single group t tests to identify brain activation for conditions and contrasts of interest. Group z (Gaussianised T) statistic images were generated for the following pairs: (1) LABEL>CONTROL; (2) HIGH>LOW. Group maps were thresholded at the voxel level of z=2.3 and cluster corrected at p<0.05 using family-wise error rate correction based on Gaussian Random Field theory.[45] Anatomic assignment of clusters was based on the peak z-score within the cluster using the Talairach Daemon Database confirmed by visual inspection.[40] Whole brain correlation analysis: To examine the relationship between brain response to graphic warning labels and smoking addiction severity, as well as the performance on the recognition task, whole brain correlation analyses were conducted. The FTND score and per cent correct recognition for each participant were entered as covariates

of interest for the LABEL> CONTROL contrast separately. The resulting positive and negative correlation maps were corrected as described above.

Results

Behavior

One-way repeated ANOVA revealed an overall effect of graphic warning labels on self-reported change in cigarette craving (F(19,2)=10.18, p<0.001). Post hoc tests indicated that although exposure to both High and Low ER labels reduced self-reported craving when compared to control images (High p=0.001; Low p=0.018), the effect of High ER labels was greater than that of Low ER labels (p=0.020). Moreover, the High ER labels were better recalled than the Low ER labels (High ER 92.80±0.02%; Low ER 80.68±0.03%, paired samples t test t=4.538, p<0.001).

Imaging

Five participants' imaging data were excluded for excessive movement in the scanner (>3 mm in any direction), leaving 19 data sets for the final analysis. Compared to control images, graphic warning labels evoked greater activation in the bilateral occipitoparietal cortex, including visual and fusiform areas, cuneus and precuneus, bilateral temporal and inferior frontal cortices, as well as the amygdala, hippocampus and parahippocampus (Table 1). Compared to Low ER labels, High ER labels were associated with greater response in the right fusiform (occipital part) gyrus, inferior frontal gyrus, thalamus, anterior insula, amygdala and hippocampus, as well as the cerebellum (Figure 2 and Table 2). Whole-brain correlation revealed that brain activation in the precuneus and the medial frontal cortex was positively correlated with performance on the recognition task (z=2.3, p<0.05; table 3 and figure 3). Brain activation in the precuneus was negatively correlated with smoking addiction severity as measured by FTND (z=2.3, p<0.05; Table 4).

Discussion

We found that the graphic warning labels associated with stronger emotional reaction (ER) had greater effects and differed from those associated with less ER on two key indicators of effectiveness: recognition memory and reduction in the immediate urge to smoke. The neuroimaging findings were congruent with recognition memory performance: High ER labels evoked greater neural activation in brain regions mediating emotional memory, such as the amygdala, hippocampi, inferior frontal gyri and insulae, than the Low ER labels.

Multiple lines of evidence indicate that amygdala activation during stimulus processing modulates the encoding and consolidation of memory,[27, 46] as well as its retrieval.[47] Neuroimaging studies show that activation of the amygdala, hippocampus and prefrontal regions during the encoding of emotional stimuli is positively correlated with delayed recognition accuracy for aversive and emotionally arousing but not neutral videos and pictures. [48–50] The amygdala mediates emotional learning and facilitates memory formation in the hippocampus and prefrontal cortex.[46, 51, 52] In line with previous studies, our brain and behavioral findings suggest that the emotional salience of graphic labels might play an important role in enhancing their impact by engaging brain regions mediating learning and

memory. Therefore, High ER warnings may owe their superior recognition to their greater emotional salience.

We also found increased anterior insula and inferior prefrontal cortex activation associated with processing of the High ER labels. The insula has traditionally considered the hub of a network that includes amygdala and prefrontal cortex responsible for conversion of sensory information into feelings, such as aversion.[53] More recently, insula involvement in addiction has been narrowed down to the recall of interoceptive drug effects when drug taking is perceived as risky or where there is a conflict between the drug taking and more adaptive goals.[54] Thus, greater activation of the anterior insula and inferior frontal gyrus associated with viewing the High ER labels is consistent with these labels conveying greater perception of the hazards of smoking. Finally, greater activation of the fusiform cortex associated with processing of the High ER labels is consistent with its role in the earlier stages of processing of emotional visual stimuli.[55]

These findings suggest that emotional imagery in graphic warning labels is an integral factor in the labels' memorability. The superior short-term memory for High ER labels suggests that stronger ERs facilitate more accurate transmission of knowledge about the risks of smoking, which is an important public health objective in its own right, as well as an important step toward a prospective evaluation of the long-term clinical outcomes of graphic warning labels. In addition, we found that greater activation of the precuneus and frontal gyri during the processing of the warning labels predicted better recognition. Both the precuneus and medial frontal cortex are involved in 'self-referential' processing.[56] Prior neuroimaging studies showed that increased response to personally relevant smoking cessation messages in these brain areas predicted better outcomes (quitting) during a 4-month follow-up.[21, 57] Thus, precuneus and medial frontal activation may indicate greater self-referential processing that facilitates remembering of the labels. If replicated, this finding may have potential application in the design of graphic warning labels. Nevertheless, the negative relationship we found between smoking addiction severity, as measured by FTND, and the precuneus response suggests that addiction severity may impair smokers' ability to relate to the warnings.[15, 58–60]

Our study included predominantly loss-framed labels and excluded non-daily smokers and non-smokers. The latter include important populations, such as youth at risk of becoming addicted smokers.[61] In population-level studies, loss-framed labels, that is, carrying images and text emphasizing the negative health consequence of smoking, have been generally found to be more effective than gain-framed labels.[18, 62–64] However, since processing in 'uninvolved' (eg, not addicted) audiences may differ from 'involved' (ie, addicted) smokers, further studies evaluating gain and loss-framed labels in potential smokers would be required to extend our findings to this important target audience.[18, 62, 65–68] Finally, although better recognition and greater reduction in craving suggest greater efficacy of the High ER labels in reducing smoking, longitudinal studies are required to determine whether our findings translate to clinical outcomes, expressed by quantitative biomarkers, such as nicotine metabolite levels.

Taken together, our findings provide the first neuroimaging data showing that graphic warning labels that evoke greater ER also produce greater activation of the brain regions mediating emotional memory, and are associated with better label recognition and greater reduction in the urge to smoke. These results suggest that the ER elicited by graphic labels contributes to their behavioral impact. Controlled longitudinal studies are required to determine whether our findings are maintained over time and translate from the cognitive, motivational and neurophysiological correlates of effectiveness to the clinical outcomes. In addition to directly contributing to the current regulatory and legal debate about the implementation of graphic warning labels in the USA, the study provides a blueprint for future applications of neuroimaging to evaluate the labeling and packaging of tobacco products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What this paper adds

What is already known on this subject

- Despite broad consensus about the benefits of using strong, negatively valenced images in cigarette warning labels, their neurobehavioral mechanisms of action and effectiveness in changing behaviour remained unclear.

- Existing data are largely derived from cross-sectional studies that relied on self reported measures. Neuroimaging is more sensitive to the neurophysiological mechanisms underlying effectiveness, than self-report.

What important gaps in knowledge exist on this topic

- The question of whether emotional salience is essential to graphic warning label effectiveness has been at the core of the legal and public debate on whether the labels' public health benefit outweighs the potential encroachment on the tobacco companies' First Amendment rights. Evidence of graphic labels' neurophysiological impact measured by objective neuroimaging probes such as functional MRI could help settle this debate.

What this study adds

- This study provides the first functional MRI data showing that graphic warning labels that evoke stronger emotional reaction produce greater activation of the brain regions mediating emotional memory, and are associated with better recognition and greater reduction in the urge to smoke. These findings suggest that stronger emotional arousal elicited by graphic labels is important for their behavioural impact.

Figure 1.
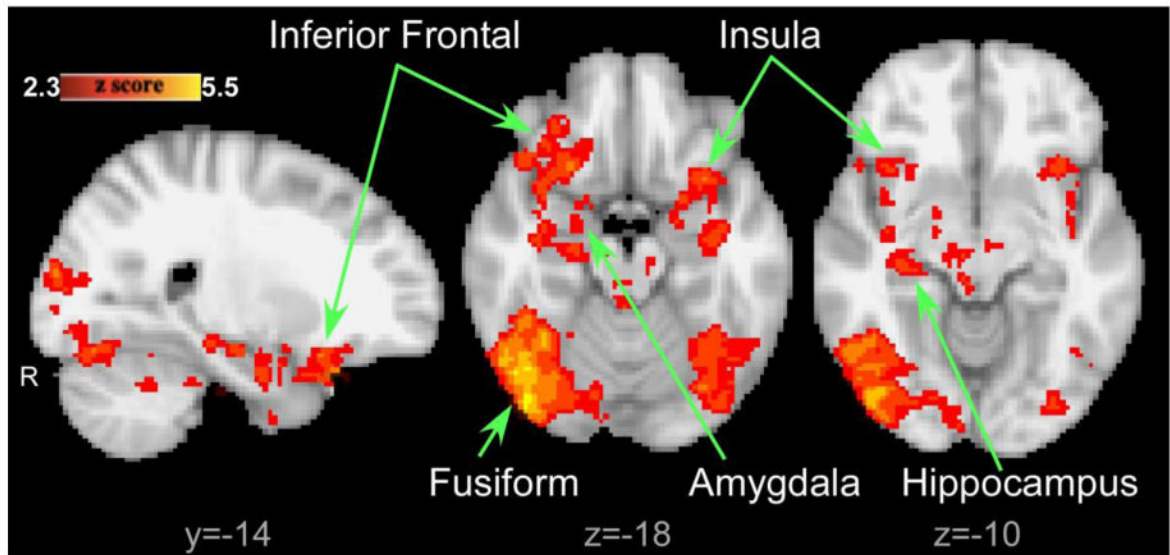Examples of stimuli used in the graphic labels functional MRI (fMRI) task.

Figure 2.
Greater brain activation associated with processing of High emotional reaction (ER) compared to Low ER warnings. Statistical map (red-yellow scale) is displayed over a standard Montreal Neurological Institute space T1-weighted average structural template image and thresholded at z=2.3 (cluster corrected for multiple comparison at p<0.05). Greater brain activation associated with processing of High ER compared to Low ER warnings. Statistical map (red yellow scale) is displayed over a standard MNI space T1-weighted average structural template image and thresholded at $z = 2.3$ (cluster corrected for multiple comparison at $p<0.05$).
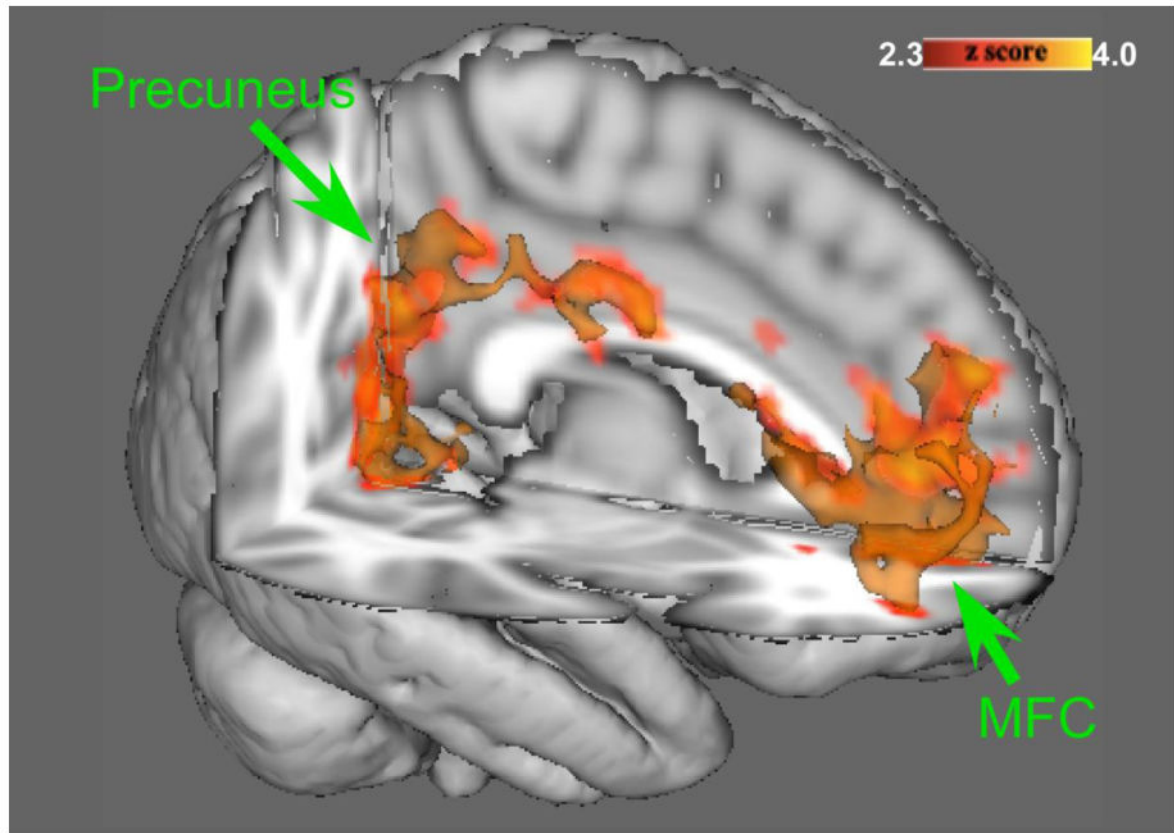
Figure 3.
Whole-brain correlation between brain response to graphic warning labels (High+Low emotional reaction (ER) together, compared to Control images) and performance in the recognition task (overall correct recognition scores). Significant positive correlations are present in the precuneus and medial frontal cortex (MFC) (z=2.3, cluster corrected for multiple comparisons at p<0.05; Table 3). There were no significant negative correlations at this threshold.

Table 1

Location and magnitude of the brain response to graphic warning labels compared to control images.

Regions[a]	Hem	BA[b]	Size[c]	P value	z-max[d]	X[e]	Y[e]	Z[e]
Inferior Occipital Gyrus	**L**	**19**	**21807**	**4.37 E-42**	**5.97**	**-45**	**-71**	**-5**
Inferior Frontal Gyrus	L	47	-	-	-	-48	27	-15
Inferior Frontal Gyrus	R	47	-	-	-	31	8	-18
Uncus	L	38	-	-	-	-24	6	-38
Uncus	R	20, 31	-	-	-	-37	-12	-27
Parahippocampal Gyrus	L	19, 35, 36, 37	-	-	-	-24	-30	-12
Parahippocampal Gyrus	R	28, 35, 36	-	-	-	23	-27	-11
Hippocampus	L	-	-	-	-	-33	-13	-19
Hippocampus	R	-	-	-	-	29	-9	-19
Amygdala	L	-	-	-	-	-26	-7	-19
Amygdala	R	-	-	-	-	27	-6	-19
Precuneus	L	31	-	-	-	-5	-58	28
Precuneus	R	30, 31	-	-	-	2	-55	12
Cuneus	L	17, 18, 19, 30,	-	-	-	-11	-81	7
Cuneus	R	17, 18	-	-	-	8	-81	7
Lingual Gyrus	L	18, 19	-	-	-	-11	-75	4
Lingual Gyrus	R	18, 19	-	-	-	16	-68	4
Fusiform Gyrus	L	19, 37	-	-	-	-43	-74	-11
Fusiform Gyrus	R	19	-	-	-	44	-71	-10
Putamen	L	-	-	-	-	-26	-6	-6
Superior Temporal Gyrus	L	22, 38, 41, 13,	-	-	-	-58	-43	15
Superior Temporal Gyrus	R	22, 38, 39	-	-	-	39	16	-24
Middle Temporal Gyrus	L	20, 21, 37,	-	-	-	-54	-3	-17
Middle Temporal Gyrus	R	21, 37	-	-	-	52	-57	2
Inferior Temporal Gyrus	L	19, 20	-	-	-	-49	-57	-3
Substania Nigra	L	-	-	-	-	-14	-19	-13
Substania Nigra	R	-	-	-	-	10	-19	-12
Culmen	L	-	-	-	-	-39	-46	-25

Regions[a]	Hem	BA[b]	Size[c]	P value	z-max[d]	X[e]	Y[e]	Z[e]
Culmen	R	-	-	-	-	35	-40	-23
Declive (Cerebellum)	L	-	-	-	-	-37	-76	-15
Precentral Gyrus	**L**	**4, 6**	**552**	**0.0156**	**3.78**	**-52**	**-7**	**46**
Cerebellum	**L**	**-**	**481**	**0.0329**	**4.11**	**-1**	**-67**	**-31**
Uvula	L	-	-	-	-	-1	-67	-32
Nodule	R	-	-	-	-	1	-50	-33
Cerebellar Tonsil	L	-	-	-	-	-3	-52	-33
Fastigium	R	-	-	-	-	6	-58	-22

[a] z>2.3 cluster corrected at *p*<0.05. **Bold font - global peaks of activation**, *regular font italics* - local peaks.

[b] Brodmann area.

[c] Number of voxels.

[d] z-MAX values represent peak activation for the cluster.

[e] Talairach (1988) coordinates.

Table 2

Location and magnitude of the brain response to High compared to Low ER graphic warning labels (Figure 1)

Regions[a]	Hem	BA[b]	Size[c]	P value	z-max[d]	X[e]	Y[e]	Z[e]
Inferior Frontal Gyrus	**R**	**44, 9**	**384**	**0.0469**	**3.48**	**52**	**13**	**22**
Insula		13	-	-	-	39	7	20
Precentral Gyrus		6	-	-	-	39	1	29
Superior Temporal Gyrus		22	-	-	-	54	8	6
Inferior Frontal Gyrus	**L**	**13, 47, 45**	**785**	**0.000445**	**3.63**	**-31**	**14**	**-12**
Insula		13	-	-	-	-41	13	0
Putamen		-	-	-	-	-28	11	2
Parahippocampus		34, 21	-	-	-	-24	4	-17
Hippocampus		-	-	-	-	-35	-11	-16
Amygdala		21	-	-	-	-20	-4	-13
Cerebellum (Uvula)	**L**		**1293**	**3.40E-06**	**3.77**	**-35**	**-69**	**-23**
Cerebellum (Declive)	**R**		**8097**	**3.96E-24**	**3.74**	**37**	**-63**	**-19**
Inferior Frontal Gyrus		47,13	-	-	-	20	21	-15
Middle Frontal Gyrus		11	-	-	-	27	32	-13
Fusiform Gyrus		37, 20, 19	-	-	-	42	-57	-18
Inferior Occipital Gyrus		18	-	-	-	35	-84	-13
Middle Occipital Gyrus		19,18	-	-	-	29	-88	12
Lingual Gyrus		17	-	-	-	14	-89	5
Insula		13	-	-	-	35	14	-3
Middle Temporal Gyrus		39, 37	-	-	-	37	-72	10
Parahippocampal Gyrus		28, 34, 35, 36	-	-	-	37	-26	-22
Amygdala		-	-	-	-	20	-6	-11
Posterior Cingulate		30	-	-	-	31	-69	13
Uncus		20, 36	-	-	-	33	-8	-33
Thalamus		-	-	-	-	14	-15	15
Striatum (Caudate Body)		-	-	-	-	14	-6	16
Striatum (Globus Pallidus)		-	-	-	-	12	-3	0
Striatum (Putamen)		-	-	-	-	24	3	-9

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[a] $z>2.3$ cluster corrected at $p<0.05$. **Bold font - global peaks of activation,** *regular font italics* - local peaks.

[b] Brodmann Area

[c] Number of voxels.

[d] z-MAX values represent peak activation for the cluster.

[e] Talairach (1988) coordinates.

Table 3

Location and magnitude of the positive correlations between the Recognition Test score and the brain response to graphic warning labels (Figure 2).

Regions[a]	Hem	BA[b]	Size[c]	P value	z-max[d]	X[e]	Y[e]	Z[e]
Precuneus	L	7	4133	3.64 E-14	3.74	-13	-66	33
Medial Frontal Cortex	L	9	2774	1.45 E-10	3.77	-9	44	17

[a] z>2.3 cluster corrected at *p<0.05*.

[b] Brodmann's area.

[c] Number of voxels.

[d] z-MAX values represent peak activation for the cluster.

[e] Talairach (1988) coordinates.

Table 4

Location and magnitude of the negative correlations between the FTND score and the brain response to graphic warning labels.

Brain Region[a]	Hem	BA[b]	Size[c]	P value	z-max[d]	X[e]	Y[e]	Z[e]
Posterior Cingulate	**R**	**29**	**540**	**0.001**	**3.18**	**4**	**-54**	**11**
Posterior Cingulate	*R*	*23,29*	*-*	*-*	*-*	*12*	*-57*	*18*
Precuneus	*R*	*31*	*-*	*-*	*-*	*8*	*-61*	*23*
Posterior Cingulate	*L*	*23*	*-*	*-*	*-*	*1*	*-59*	*12*

[a] z>2.3 cluster corrected at p<0.05. **Bold font** - global peaks of activation, *regular font italics* - local peaks.

[b] Brodmann's area.

[c] Number of voxels.

[d] z-MAX values represent peak activation for the cluster.

[e] Talairach (1988) coordinates.