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Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect

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Recent studies have identified a distributed network of brain regions thought to support cognitive reappraisal processes underlying emotion regulation in response to affective images, including parieto-temporal regions and lateral/medial regions of prefrontal cortex (PFC). A number of these commonly activated regions are also known to underlie visuospatial attention and oculomotor control, which raises the possibility that people use attentional redeployment rather than, or in addition to, reappraisal as a strategy to regulate emotion. We predicted that a significant portion of the observed variance in brain activation during emotion regulation tasks would be associated with differences in how participants visually scan the images while regulating their emotions. We recorded brain activation using fMRI and quantified patterns of gaze fixation while participants increased or decreased their affective response to a set of affective images. fMRI results replicated previous findings on emotion regulation with regulation differences reflected in regions of PFC and the amygdala. In addition, our gaze fixation data revealed that when regulating, individuals changed their gaze patterns relative to a control condition. Furthermore, this variation in gaze fixation accounted for substantial amounts of variance in brain activation. These data point to the importance of controlling for gaze fixation in studies of emotion regulation that use visual stimuli.

Introduction

Emotion regulation can be achieved through a number of implicit and explicit processes, at early and late stages of the emotion processing stream (Frijda, 1986; Gross, 1998a,b; Thompson, 1994). Research on voluntary emotion regulation has focused on altering the expressive components of an emotional response (Demaree et al., 2006; Gross and Levenson, 1993, 1997) and on reappraising the emotion-eliciting information at hand (Gross, 1998a,b; Jackson et al., 2000) to increase or decrease the emotional response. However, people also use attentional deployment as a strategy to regulate emotion (Gross, 1998a,b; Xing and Isaacowitz, 2006). While emotionally arousing information captures and engages attention in a fairly automatic fashion (Bradley et al., 2003; Nummenmaa et al., 2006; Öhman and Mineka, 2001), people differ in gaze patterns toward emotional information depending on the individual's goal state (Isaacowitz, 2006). As has recently been demonstrated, when the goal is to decrease negative affect, one strategy that people can employ is to look away or at irrelevant information, thereby avoiding the stimuli that render a situation negative (Xing and Isaacowitz, 2006). Conversely, when the goal is to increase negative emotion, people can actively spend more time looking at aspects of the visual stimulus that prompt the negative affect (e.g., focusing on the blood in a gory image). Such different ways of scanning visual information as a means to achieve a regulatory goal are likely supported by neural circuitry that may substantially overlap with that thought to underlie voluntary emotion regulation.

Using functional brain imaging, a number of recent studies have identified a distributed network of brain regions underlying voluntary emotion regulation in response to affective images (Eippert et al., 2007; Harenski and Hamann, 2006; Ochsner et al., 2002, 2004; Ohira et al., 2006; Phan et al., 2005; Schaefer et al., 2002), film clips (Beauregard et al., 2001; Levesque et al., 2003, 2004) or the anticipation of a painful stimulus (Kalisch et al., 2005). All of these studies examined patterns of brain activation while participants decreased emotional responses through reappraisal of the eliciting stimulus (Gross, 1998a,b), and a few of these studies also examined increasing emotional responses (Ochsner et al., 2004; Urry et al., 2006). The findings of these studies reveal fairly consistent changes in activation in the amygdala, dorsal

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anterior cingulate cortex (ACC, BA32), ventrolateral (BA 44/45), dorsolateral (BA9) and dorsomedial regions of PFC (BA8/6) as a function of emotion regulation. Given the role of lateral PFC in maintaining representations and inhibitory control (Miller and Cohen, 2001; Smith and Jonides, 1998), and of dorsomedial PFC regions in representations pertaining to the self (e.g. Gusnard et al., 2001; Kelley et al., 2002; Ochsner et al., 2005), these areas are considered crucial in reducing negative emotion through reappraisal (Davidson et al., 2000; Ochsner and Gross, 2005). Activation associated with emotion regulation in other, less emphasized, regions is evident as well across those studies that reported whole-brain findings, particularly (pre)supplementary motor area (SMA), but also in (pre)cuneus and superior parietal lobule (BA7), temporal–parietal junction (TPJ, BA21/22/39) and, to a lesser extent, posterior cingulate cortex (PCC, BA23/30/31).

Several of the regions commonly activated in voluntary emotion regulation tasks, including prefrontal areas such as (pre) SMA and BA8 but also most of the posterior regions mentioned above, are thought to underlie visuospatial attention and oculomotor control (e.g. Corbetta, 1998; Grosbras et al., 2005). Thus, activation in at least some of the brain regions identified in emotion regulation tasks to be involved in cognitive reappraisal might more specifically reflect shifts in visual attention deployment when individuals are reappraising a stimulus. The focus of attention can shift covertly, without moving the eyes (Corbetta, 1998; Grosbras et al., 2005; Posner et al., 1982), thus indicating that attention and gaze fixation are dissociable. However, as underscored by Henderson (e.g. 2003), Findlay and Gilchrist (2003) and many others, shifts in gaze fixations are overt manifestations of shifts in visual attention. Indeed, cortical networks associated with oculomotor control and attentional shifts, whether overt or covert, have been found to largely overlap (Corbetta, 1998; Grosbras et al., 2005). In this view, the study of gaze fixations therefore can provide valuable insights into the operation of the attentional system.

Measuring gaze fixation in the scanner, Dalton et al. (2005) demonstrate that individuals with autism, as well as their siblings (Dalton et al., 2007), visually scan images of faces differently, spending less time fixating the eyes, than non-autistic individuals, possibly so as to reduce negative emotion elicited by social stimuli. Importantly, these researchers found activation in fusiform gyrus and amygdala within individuals with autism to be strongly correlated with time spent fixating the eyes. These findings imply that patterns of brain activation underlying emotion regulation, such as that observed in amygdala, may partly reflect different ways in which the visual information is scanned when regulating negative affect.

In the present study, we sought to replicate the findings of prior brain imaging studies (Ochsner et al., 2004; Urry et al., 2006) of emotion regulation, in particular activation of prefrontal areas. As previously demonstrated, successful regulation should be reflected in differential amygdalar activation. Hence, we predicted decreasing negative affect to be associated with lower amygdalar activation, and increasing negative affect with higher amygdalar activation, relative to attending to negative stimuli. Using eye tracking data collected in the scanner while participants performed the task, we also examined the extent to which voluntary regulation would be associated with a different pattern of gaze deployment on the emotional stimuli relative to a control condition. Finally, we assessed the extent to which the patterns of brain activation underlying the voluntary regulation of negative affect might reflect differences in gaze control.

As with previous studies, individuals were trained to use cognitive strategies to increase or decrease their affective response to unpleasant images in an event-related fMRI study while their gaze fixations were recorded. They were explicitly instructed to always look at the image and not to close their eyes or avert their gaze. We predicted that the time spent fixating the image and the number and extent of gaze movements would correlate with signal differences in brain regions commonly associated with oculomotor and attentional control, including frontal and supplementary eye fields, and parietal (e.g. (pre)cuneus) and temporal–occipital regions, all regions in which prior research on emotion regulation has found main effects of regulation. Furthermore, given Dalton and colleagues' data on the amygdala and gaze fixations, we expected that gaze fixations in our study would predict a significant amount of variance in amygdalar activation, putatively reflecting overt attentional control as a successful regulatory strategy.

A complication with studies on voluntary emotion regulation is the lack of control over whether participants actually perform the task while in the scanner. Prior studies have used self-report assessments of valence and/or arousal ratings after each trial or block of trials in the scanner (Ochsner et al., 2002, 2004; Phan et al., 2005). The problem with such self-reported assessments of whether participants performed the task as intended is the fallibility of such reports, which are subject to demand characteristics, and reliance on memory (see also Quirk and Beer, 2006). Measures of peripheral psychophysiology which have been repeatedly demonstrated to reflect arousal and expended effort, such as heart rate, skin conductance and pupil dilation, would provide an online measure of at least cognitive involvement and levels of bodily arousal during the task. Indeed, Ohira et al. (2006) collected skin conductance and heart rate while participants regulated emotion in the PET scanner, and found increased phasic skin conductance activity when decreasing negative affect, relative to the attend condition. Pupil dilation is under sympathetic control and has proven to be a sensitive index of cognitive processing demands (Kahneman and Beatty, 1966). Measuring pupil dilation and the BOLD response concurrently, Siegle et al. (2003) demonstrated larger pupil diameters with increasing task demands in a digit-sorting task and pupil dilation was associated with greater activation in the left middle frontal gyrus. In a prior study, we (Urry et al., 2006) demonstrated stronger pupil dilation for the emotion regulation conditions, in particular the increase condition, relative to the control condition, suggesting that attempts to voluntarily regulate negative emotional responses require more cognitive processing demands than simply attending to the negative information. In this study, we used pupil dilation as an index of arousal expended due to cognitive effort as a manipulation check of resource allocation for the increase and decrease conditions.

Method

Participants

Twenty-nine participants (18 females, ages 61–65 years) were recruited by placing advertisements in a local newspaper. In addition to serving the scientific aims described above, this effort also served as a feasibility study for recruiting participants from the Wisconsin Longitudinal Study, a larger longitudinal study of older adults in which the aim was to investigate the neural bases of

voluntary emotion regulation (see Urry et al., 2006). As a result, we recruited participants of the same age. All participants were right-handed, and none had a history of or currently had a neurological illness. None of the participants suffered from claustrophobia or had any muscular or back problems that would prevent them from lying in the scanner for more than 1 h. Participants received $70 for their participation in the MRI session, and all participants gave informed consent prior to the administration of any of the procedures. All procedures were approved by the University of Wisconsin-Madison Health Sciences IRB. Useable eyetracking data were obtained from 21 of the 29 participants.

Stimuli

We used a randomized event-related paradigm in which we presented one of two sets of digital color pictures (800×600 resolution) selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999) to each participant in the scanner. In each set, 72 negative photos were selected according to the IAPS norms to be both highly unpleasant (1=most unpleasant to 9=most pleasant), M=2.35, SD=0.65, and arousing (1=least arousing to 9=most arousing), M=5.82, SD=0.80, while 24 neutral photos were selected to be neither pleasant nor unpleasant, M=5.04, SD=0.29, and non-arousing, M=3.14, SD=0.79 (means and standard deviations represent aggregations across the two sets of images). For each session the negative pictures were randomly assigned to one of the regulation conditions. Picture presentation order was pseudorandomized with the constraint that no more than 5 pictures of the same valence were shown consecutively. Stimulus presentation was accomplished using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA), while visual stimulation was delivered via a fiber-optic goggle system (Avotec, Inc., Stuart, FL) during the scan session.

Trial structure

A white fixation cross was depicted in the center of a black screen for 1 s, coupled with a simultaneous tone to ensure attention to the upcoming trial. A picture was then presented for 8 s. An auditory cue instructing the participant which cognitive strategy to use ("enhance" for increase, "attend", or "suppress" for decrease) was delivered through headphones 4 s after picture onset. To ensure alertness during the task, participants were instructed to indicate whether they evaluated each picture as negative or neutral by pressing one of two buttons on a button box as soon as the picture appeared, and before the instruction was provided (data reported elsewhere, see van Reekum et al., 2007). Participants were instructed to continue following the task instruction, also after picture offset, until they were cued by auditory instruction to "relax". This relaxation instruction was presented 4 s after picture offset. The ensuing inter-trial interval varied from 4 to 7 s, providing sufficient variation to estimate the evoked BOLD response function.

Regulation task and procedure

In this study, we used a variant of the Jackson et al. (2000) regulation task and closely followed the procedures for the emotion regulation task described in detail in Urry et al. (2006). In summary, participants were instructed to use cognitive strategies to increase or decrease their emotional responses to negative pictures, or to maintain their attention (i.e. "attend") to the pictures without changing the affective experience elicited by the pictures. Two strategies to establish effective reappraisal were outlined, one of which focused on imagining that the person him/herself or a loved one experienced what was depicted in the picture (to increase negative affect) or, conversely, that the situation depicted was not real (to decrease negative affect). The other strategy focused on imagining a worse or better outcome than those suggested in the situations depicted in the pictures. Presentation of regulation conditions was pseudorandomized to ensure no more than 2 consecutive repetitions of the same regulation condition. Participants were further instructed to watch the pictures for the entire duration of the presentation, without closing the eyes or looking away, to avoid blinking as much as possible and to avoid head movement.

A day prior to the scanning session, participants underwent a separate simulation session to acquaint them with the scanning environment and to train on performing the task. After detailed instructions and a short practice, participants were positioned inside the bore of an inactive MRI scanner shell, complete with bed, head coil, response box, and goggles, and further practiced on a block of 24 trials of the regulation task. During a brief exit-interview, the experimenter queried the participants to ensure effective use of the regulation strategies outlined during training and proper understanding of the instructions. The real scan occurred on the morning following the simulation session. This scan session was divided into 4 blocks of 24 trials. Prior to the real scan, the experimenter presented the task instructions again to consolidate participant understanding of their duties in the scanner. Once the scan session was over, participants were led into a separate room, where they provided subjective ratings of valence (stimulus unpleasantness) and arousal on half of the set (12 per condition) of the experimental picture stimuli seen in the scanner. Each picture was presented for 6 s, after which the participant immediately provided their valence rating followed by the arousal rating.

Data acquisition and reduction

Gaze fixations and pupil diameter

Gaze fixations and horizontal pupil diameter were measured using an iView X system (v. 1.3.31) with a remote eye-tracking device (SensoMotoric Instruments, Teltow, Germany), which was interfaced with the fiber optic goggle system while participants performed the task. The iView system enables the display of tracking over time of pupil gaze position, along with the amount of time spent on any given fixation point. Prior to the start of the first scan, gaze fixations were calibrated by asking the participant to focus their attention on each of 9 dots presented in a random order in either one of the 4 corners of the display space, midway between each corner, and in the middle of the screen. Movement and diameter of the pupil were monitored at 60 Hz during the entire scan period. Fixations were pre-defined as a minimal time of 50 ms spent within a 50-pixel diameter region. These fixations were processed for a 4 second regulation period beginning at regulation instruction onset until picture offset. Four variables were quantified: (1) the amount of time a person fixated the image in total, (2) the amount of time a person fixated pre-defined areas within an image (described below), (3) the number of fixations

made on the entire image, (4) the average distance between successive fixations.

To determine the area(s) of interest on the images, two trained assistants independently drew (rectangular and elliptical) areas of interest on each of the images using iView Analysis software (v. 1.09.29, SensoMotoric Instruments). An area of interest was defined as only those object(s) displayed in an image that provided decisively affective meaning to a scene depicted in the image. The areas of interest generated by each individual were then compared. An area of interest was accepted only when identified by each individual, and when the size was within approximately 20% of the other. When these criteria were not met, a third person helped determine the area(s) of interest's size and placement. In-house software was then used to determine the total time spent on the entire image, and in any given area of interest expressed as a percentage of total time spent fixating the entire image.

Algorithms implemented in LabVIEW 7.1 (National Instruments, Austin, TX) enabled the scoring of the number of fixations, and the distance between each consecutive fixation, within the 800×600 area of the image during the 4-s regulation period while the image was presented. To reduce colinearity between the number of fixations and the total time spent fixating the image, we divided the number of fixations by the number of seconds the person fixated the image, hence we obtained a number of fixations per second spent fixating the image metric. The average distance between each consecutive fixation on the image was calculated by taking the square root of the sum of the squared difference in displacements, measured in pixels, in the horizontal (X) and vertical (Y) direction (i.e. $\sqrt{((X_{t+1}-X_t)^2+(Y_{t+1}-Y_t)^2)}$, where $t=$ temporal order of fixation observation). When only one fixation was registered, a 0 was scored.

The procedures for pupil diameter analysis were identical to those described in full detail in Urry et al. (2006). In summary, the pupil dilation data were cleaned and processed using algorithms developed by Siegle, Granholm, and Steinhauer (2002, unpublished Matlab code) and adapted in our laboratory. Blinks were identified and eliminated and missing data points were then estimated using linear interpolation. A 5-sample rolling average was calculated to smooth the signal, and slow, irrelevant drifts were removed via linear detrending per run. Trials whose value fell greater than ±4 SD from the within-subjects mean were eliminated. Pupil diameter was aggregated into half-second bins. These values were range-corrected within subjects. Mean diameter for the half-second picture period immediately prior to regulation instruction was then subtracted from the mean pupil diameter during each of 8 half-second picture periods following instruction. Proportional change in diameter was then computed for each of the 8 time points following the instruction (i.e., [post–pre]/pre). For statistical analysis, to reduce the number of time levels, we aggregated across an early (first 2 s) and late (last 2 s) time window.

For each measure, the observations were averaged across trials for subject and for each of the regulation conditions, excluding trials for which 50% or more of the pupil dilation data were interpolated during the entire 8 s of picture presentation (5.0% of trials), and trials for which the total time spent fixating the picture after the onset of the regulation instruction was less than 500 ms (an additional 0.3% of trials).

Magnetic resonance imaging

Images were acquired on a General Electric (GE Medical Systems, Waukesha, WI) SIGNA 3.0 T MRI scanner with a quadrature head coil. Functional images consisted of 30 interleaved 4 mm sagittal T2*-weighted echo-planar imaging (EPI) slices covering the entire brain (1 mm interslice gap; 64×64 in-plane resolution; 240 mm field of view (FOV); 2000 ms repetition time; 30 ms echo time (TE); 60° flip angle; 244 image volumes per run). Four EPI images with identical acquisition parameters but with TEs of 30, 31, 33, and 36 ms respectively, were also acquired, and were used in calculating magnetic field maps for image distortion correction. Functional images were collected in four runs of approx. 8 min each. Immediately following acquisition of functional images, a high-resolution three-dimensional T1-weighted inversion recovery fast gradient echo image was acquired (256×256 in-plane resolution; 240 mm FOV; 124×1.2 mm axial slices).

Analysis of functional MRI data was performed with Analysis of Functional NeuroImages software (AFNI v. 2.40e, Cox, 1996). After discarding the first 5 images collected for each of the four runs during reconstruction, the images were time corrected for slice acquisition order, and motion corrected registering all the timepoints to the last timepoint of the last run. Each run was then high-pass filtered at 0.02 Hz to remove slow drift. In-house software was used to correct for image distortion at each timepoint based on the calculated field maps (J.H. Lee, 2003, unpublished Matlab code).

We then computed single-subject GLMs to estimate the hemodynamic response for each of the conditions, using a deconvolution procedure that specified a predictor for each second, for a total of 20 s starting at picture onset. Six predictors (3 translation, 3 rotation) based upon estimated motion were also included to model possible variance due to motion (Johnstone et al., 2006). Trials for which the pupil dilation data were missing for more than 50% of the total trial length, indicating that the participant was not fully attending to the picture, were eliminated, as were time-points where estimated motion peaks exceeded 1.5 mm. These criteria resulted in 5.4% of trials being deleted. Percent signal change was calculated for each time point (100* beta coefficient/baseline), and then an area-under-the-curve (AUC) metric was calculated by summing the % signal change values across an 8-s window (7th–14th timepoint inclusive after picture onset). This 8-s window maximizes chances of capturing the peak of the hemodynamic response even if the peak varies temporally as a function of brain region and/or condition. These estimates of AUC for percent signal change were transformed into Talairach space and spatially blurred with a 5-mm FWHM Gaussian filter.

Limiting analysis to the negative picture trials, statistical regions of interest for the whole brain volume were identified via voxelwise one-way mixed-effect ANOVAs treating instruction (increase vs. attend vs. decrease) as a repeated measures effect and subject as a random effect. Statistically-defined clusters of activation were identified using whole-brain Monte Carlo simulations (AFNI's AlphaSim program) to achieve a corrected cluster threshold of $p<0.05$. Mean AUC % signal change estimates, averaged across voxels in each cluster, were extracted for each subject for further analysis in SPSS 12 (SPSS Inc, Chicago, IL).

Mean AUC % signal change estimates across all voxels in two (left and right) amygdala regions of interest (ROIs), defined using the Talairach Atlas provided with AFNI, were extracted for each subject. Using SPSS 12, we then computed an across-subjects GLM to test the repeated measures effects of regulation instruction and hemisphere.

Picture ratings

Participants rated the valence and arousal of half of the picture stimuli outside the scanner. For the valence ratings, participants were asked how pleasant or unpleasant they found each picture, using 9-point Likert scales, with 1 representing "very unpleasant" and 9 "very pleasant". For the arousal ratings, participants were asked to report how calm or excited/keyed up they felt in response to the picture on the 9-point scale where 1 represented "very calm" and 9 "very excited/keyed up". These valence and arousal ratings were averaged across the 12 observations per condition.

Results

Overview of analysis

We first present the results of the ANOVAs testing the repeated measures effects of instruction (increase vs. attend vs. decrease) for the amygdala (a-priori region of interest) and whole brain data. To assess whether exerted effort varied as a function of regulation condition, we also tested the effect of instruction and time (early vs. late) for the pupil data. Repeated measures ANOVA effects of instruction for the gaze fixation variables are then presented. Finally, we used hierarchical regression analyses to test the extent to which the gaze fixation variables predict variance in the clusters of regulation-associated activation identified with the voxelwise ANOVA. Here we determine whether there would be unique variance left in brain activation associated with the regulation main effects, after controlling for variance associated with the four gaze fixation variables.

fMRI main effects of regulation

Amygdala

In line with prior research, the regulation (increase, attend, decrease) × hemisphere (left, right) MANOVA performed on the AUC % signal change revealed a main effect for regulation condition, $F(2,27)=4.03$, $p=0.029$, and a significant linear contrast for the regulation condition, $F_{\text{linear}}(1,28)=7.526$, $p=0.01$. This linear effect confirmed that activation in both amygdalae was significantly lower when instructed to decrease negative affect, $M=0.7$, SE=0.2, relative to attend, $M=1.03$, SE=0.24, $p=0.05$ (1-tailed), and relative to the increase condition, $M=1.14$, SE=0.25, $p=0.005$ (1-tailed). Amygdalar activation was not significantly different between the increase and attend condition, $p>0.3$. We did not find a main effect of hemisphere nor an interaction effect between hemisphere and regulation condition, both $F<1$. See Fig. 1 for a depiction of the averaged estimated hemodynamic responses to the regulation instructions for left and right amygdala separately.

Whole-brain, voxelwise ANOVA results

The voxelwise ANOVA testing for main effects of regulation instruction on the BOLD response revealed a number of clusters (all $p<0.05$ corrected) in PFC, as well as in temporal and parietal cortex. Table 1 lists details of these clusters. In PFC, significant activation differences were located in (pre) supplementary motor area (SMA) including the supplementary eyefields, left middle frontal gyrus (BA6) overlapping with the left frontal eye field (FEF, Paus, 1996), dorsolateral PFC (BA9), left and right ventrolateral PFC (inferior frontal gyrus, BA44), left BA45 overlapping with Broca's area, the subgenual part of the ACC (BA25), as well as in the left and right precentral gyrus (BA4). Furthermore, clusters were also located in the retrosplenial cortex/ventral posterior cingulate cortex (PCC, BA23/30/29, Vogt et al., 2006), left and right TPJ (middle/superior temporal gyrus, BA39/19), left and right posterior hippocampus and brainstem, covering the red nucleus and substantia nigra and extending into thalamus. Replicating prior work where both an increase and decrease regulation condition were included (Urry et al., 2006), the increase condition was associated with the largest BOLD response in all of these clusters. In most clusters, the decrease condition then followed, with the attend condition showing the lowest BOLD response. In some clusters, however, decreasing negative affect was not significantly different from the attend condition (while the increase condition was still related to the highest BOLD response). These clusters were located in thalamus, right TPJ (middle temporal gyrus, BA39), pre- and postcentral gyrus (BA6, 3), subgenual ACC (BA25), and precuneus (BA7). Furthermore, a cluster in right putamen demonstrated the lowest BOLD response for the decrease condition relative to the attend condition. In contrast to the Urry et al. study, where decreasing negative affect was not significantly different from the attend condition in areas in PFC, the results of this study indicate an increase>decrease>attend linear trend in all PFC clusters, except for the cluster in subgenual ACC as mentioned above.

Changes in pupil diameter as an index of cognitive effort

To assess the extent to which the active regulation conditions (increase and decrease) were associated with expended cognitive

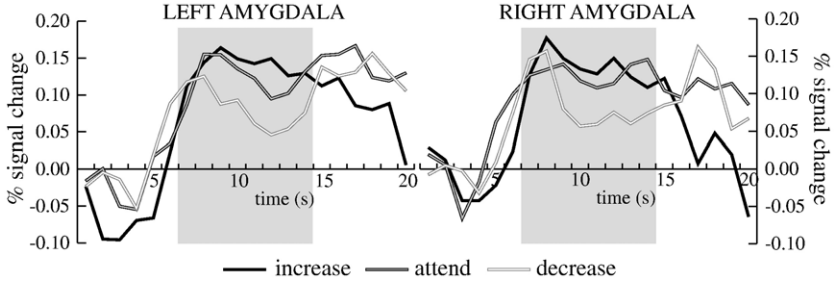

Fig. 1. Averaged estimated hemodynamic responses to the increase (black), attend (gray) and decrease (white) conditions extracted for the left and right amygdala *a priori* region of interest, defined using the Talairach Atlas provided with AFNI. This *a priori* region has a total volume of 1288 mm^3, and extends from $x=17$ to 29 (or −17 to −29 for the left amygdala ROI), $y=-11$ to 1, and $z=-22$ to −8. The responses depicted indicate lowest activity in left and right amygdala for the decrease relative to the increase and attend conditions. The calculated area-under-the-curve (AUC) metric (which is a sum of the % signal change measured at each timepoint) used in subsequent analyses is depicted in grey.

Table 1
Statistically significant clusters from the voxelwise repeated measures ANOVA testing the main effect of regulation condition on BOLD response

Region of activation	BA	Hemi	Volume (mm^3)	Location *F* max.			*F* max.
				x	*y*	*z*	
increase=attend>decrease							
Amygdala		L		a-priori ROI			
Amygdala		R		a-priori ROI			
increase>attend>decrease							
Lentiform nucleus/ putamen		R	472	29	−23	10	16.18
increase>decrease> attend							
Middle temporal gyrus	20	L	464	−55	−39	−8	14.86
Middle temporal gyrus	21	L	128	−57	−23	−8	14.57
Red nucleus/substantia nigra/thalamus		L	1272	−5	−15	−6	22.12
Middle temporal gyrus	22	L	584	−51	−41	4	23.98
Inferior frontal gyrus	45	L	160	−43	19	6	13.93
Inferior frontal gyrus	45/44	R	1080	49	25	8	10.83
Middle/Superior temporal gyrus	19/39/ 22	L	2824	−45	−65	18	33.49
Cuneus	23	R	256	7	−71	14	14.51
Posterior cingulate/ retrosplenial cortex	30/29/ 23/31	L	2944	−7	−51	16	19.33
Superior temporal gyrus	22	L	728	−51	−43	16	18.73
Caudate/putamen/ lentiform nucleus		L	320	−17	3	16	15.43
Inferior frontal gyrus	44/45	L	352	−49	11	18	17.19
Middle Frontal Gyrus	9	L	328	−43	13	30	16.71
Precentral gyrus	6	R	696	41	−9	34	16.04
Middle frontal/ precentral gyrus	6	L	1664	−35	1	48	20.86
Precentral gyrus	6/4	R	648	23	−17	52	13.32
Medial/superior frontal gyrus	6	L	2248	−3	−1	56	20.01
increase>decrease=attend							
Hippocampus		L	160	−31	−31	−10	16.61
Hippocampus		R	1032	35	−29	−8	13.68
Subgenual anterior cingulate cortex	25	L	232	−3	3	−2	14.9
Thalamus/mamillary body/lentiform nucleus/medial globus pallidus		R	744	13	−17	0	17.64
Middle temporal gyrus	39	R	496	39	−53	12	15.12
Thalamus		R	688	9	−21	14	13.44
Precentral gyrus	6	L	208	−39	−15	30	17.7
Precuneus	7	R	224	21	−49	50	12.32
Postcentral gyrus	3	L	392	−17	−27	52	11.12

Note. BA=Brodmann Area; Hemi=Hemisphere; L=Left; R=Right. Ordering of region of activation is based upon the results of the pairwise comparisons between the three conditions ($p<0.05$). Coordinates of the location of the cluster's maximum *F* are in Talairach space.

effort, we calculated the proportional change in pupil diameter over time after the onset of the regulation instruction. The findings indicated changes in pupil diameter as a function of the regulation condition, and that these changes in pupil diameter varied across time, Regulation × Time, $F(2, 19)=8.1$, $p=0.003$ (see Fig. 2). As predicted, but observed in the late period only, both increasing, $M=0.040$, SD=0.016, and decreasing negative affect, $M=0.044$, SD=0.022, were related to increased pupil dilation relative to the attend condition, $M=-.009$, SD=0.013, $p=0.015$ and $p=0.040$ respectively, while the two active regulation conditions did not differ from each other, $p>0.8$. In the early period, decreasing negative affect, $M=0.062$, SD=0.013, was related to significantly increased pupil dilation relative to increasing negative affect, $M=0.027$, SD=0.011, $p=0.013$, while attending, $M=0.042$, SD=0.009, was not significantly different from either active regulation conditions, increase vs. attend $p=0.126$; decrease vs. attend $p=0.109$. These data suggest sustained cognitive effort, which took a few seconds to be fully deployed particularly upon hearing the "increase" instruction, when instructed to regulate relative to the attend condition.

Regulation main effects on gaze fixations

The total time spent fixating the picture during the regulation period differed as a function of the type of instruction provided, $F(2,40)=5.92$, $p=0.006$. When instructed to decrease, participants spent less time fixating the picture, $M=3088$ ms, SD=128.8, than when instructed to increase negative affect, $M=3323$ ms, SD=83.88, $p=0.04$, or to attend to the picture, $M=3373$ ms, SD=84.80, $p=0.013$. Similarly, the time spent fixating relevant objects in the image relative to the total time spent fixating the picture differed significantly as a function of the instruction provided, $F(2,40)=3.99$, $p=0.026$. As with the total time spent fixating the picture, the proportion of time spent fixating the relevant object(s) was lowest for the decrease condition, $M=0.70$, SD=0.03, relative to the attend condition, $M=0.78$, SD=0.02, $p=0.021$, while the difference between the decrease and increase condition, $M=0.75$, SD=0.03, represented a trend, $p=0.084$. Thus, when instructed to decrease negative affect, participants fixated the image less relative to when the participants were instructed to increase negative affect or to

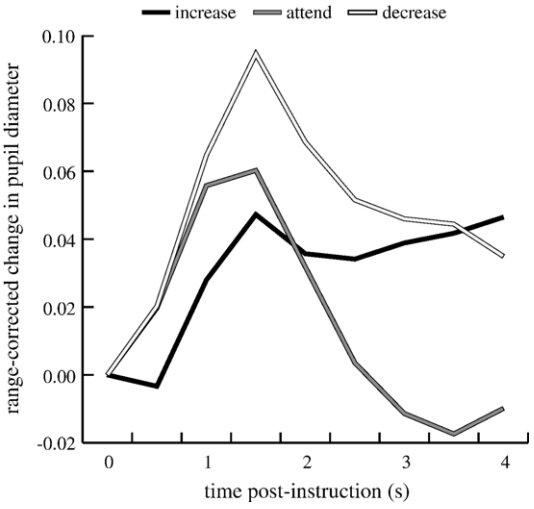

Fig. 2. Change in pupil diameter, plotted per half second, in response to the increase (black line), attend (gray) and decrease (white) instructions provided during the presentation of negative pictures. For statistical purposes, the pupil data were aggregated across time for the early (first 2 s) and late (last 2 s) window.

attend to the picture. Furthermore, the proportion of time spent on the objects suggests that, relative to the attend condition, participants looked at other, non-emotion-relevant, details more in the decrease condition (i.e. fixated on the relevant objects less) and the increase condition.

The number of fixations per second and the average distance between successive fixations, further help in identifying whether participants move their gaze around more or whether they fixated an emotionally irrelevant part of the picture. For each second the participant spent fixating the image, the regulation instruction impacted how many fixations the participant made, $F(2,40)=6.59$, $p=0.003$. When instructed to regulate, participants on average made more fixations relative to the attend condition (increase, $M=4.06$, SD=0.25, vs. attend, $M=3.68$, SD=0.26, $p=0.004$; decrease, $M=4.18$, SD=0.28, vs. attend, $p=0.005$), with no significant difference between the two regulation conditions. The instruction also had an effect on the mean distance between consecutive fixations, $F(2,40)=7.4$, $p=0.002$, with the longest average distance for the decrease condition, $M=81$ pixels, SD=3.94, relative to the attend condition, $M=70$ pixels, SD=3.13, $p=0.005$, and to the increase condition, $M=75$ pixels, SD=2.73, $p=0.054$. See Fig. 3a for an example of eyetracking data of one participant in each of the 3 conditions, and Figs. 3b–e for a depiction of the mean gaze fixation data. These data suggest that the participants shifted their gaze more when instructed to regulate their emotional response, and when instructed to decrease this response, participants tended to shift their gaze a greater distance.

Regressions with gaze fixation variables

For each regulation contrast (decrease-attend and increase-attend), clusters which showed a significant or near-significant ($p<0.1$) effect of regulation in a separate regression analysis for the

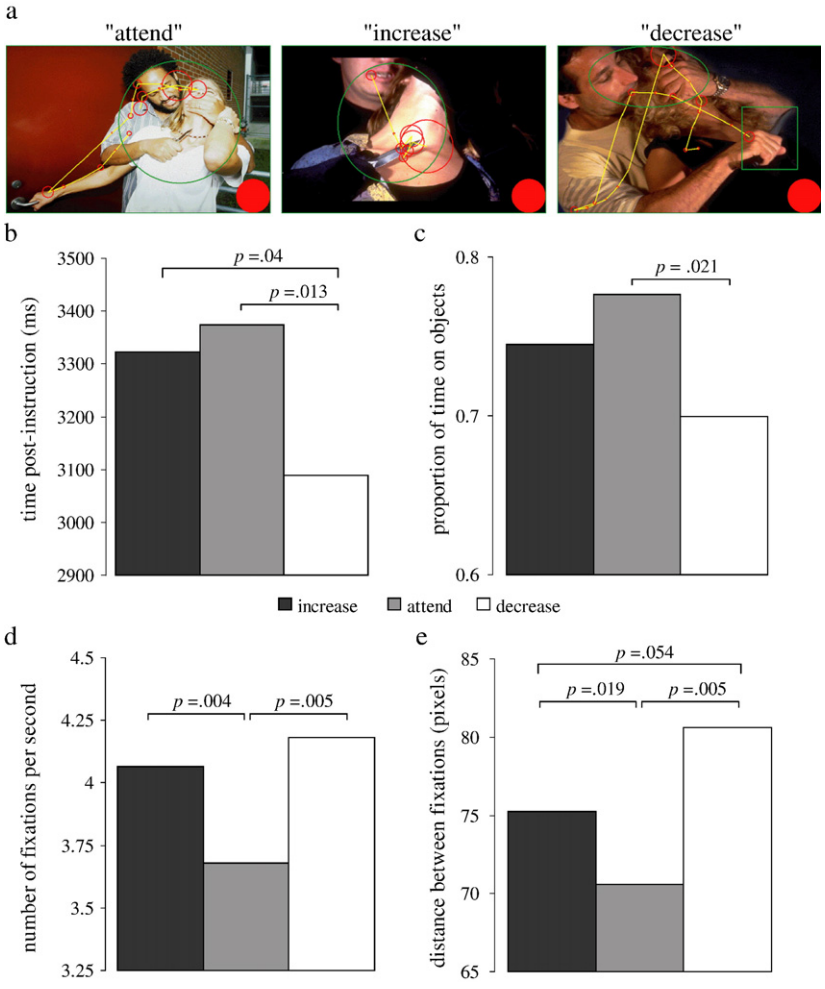

Fig. 3. (a) Example of the gaze fixations made by one participant on images with similar content and normative valence and arousal ratings when attending to the image (left), increasing (middle) or decreasing (right) negative affect. This example illustrates that only in the decrease condition did the participant look away from the scene depicted. The green lines demarcate the "object(s)" of the image that renders the image negative. The size of the red reference circle in the lower right corner represents a 1-s fixation. (b) Average time (in ms) spent fixating the entire image after the presentation of the regulation instruction. (c) Average time spent fixating the object(s) that rendered the image negative in valence, as a proportion of time spent on the entire image. (d) Average number of fixations made per second fixating the entire image. (e) Average distance between each consecutive fixation (in pixels). Averages are for the increase (black bars), attend (gray bars) and decrease (white bars) conditions, and are based on the observations of 21 participants. The *p*-values of each of the simple comparisons are provided in the graphs.

sample with valid eye tracking data ($N=21$), as well as the data from the amygdala ROIs, were submitted to a hierarchical regression analysis to assess the impact of removing variance explained by gaze fixations on the regulation effect. A relatively liberal alpha was chosen to include potential areas for which the regulation contrast might explain a significant amount of unique variance after accounting for variance due to gaze fixations (i.e. areas for which inclusion of gaze fixation increases significance of the regulation effect by accounting for otherwise unexplained variance). Twenty-seven clusters were included for the increase-attend contrast and 14 clusters for the decrease-attend contrast. The hierarchical regression analysis proceeded as follows for each cluster and regulation contrast: In a first step, we entered all four gaze fixation variables (total time spent fixating the image, proportion time spent fixating the relevant objects, number of fixations made per second, and average distance between consecutive fixations), predicting AUC % signal change. As a second step, we estimated the amount of residual variance from the first step that was uniquely explained by the regulation conditions. It should be noted that such an analysis cannot assess the causal effects of gaze fixation on AUC % signal change *per se*, but rather indicate the extent to which brain activation previously ascribed to cognitive reappraisal processes might alternatively, or additionally, reflect shifts in gaze fixation.

Amygdala

The increase-attend difference was not significant in this dataset and therefore not further examined. For the $N=21$ group for whom we obtained valid eye tracking data, the decrease-attend difference showed a trend in the left amygdala, $R^2=0.08$, $F(1,20)=1.65$, $p=0.107$ (1-tailed), while the difference in right amygdala was not significant, $R^2=0.05$, $F<1$ and hence not further considered. For the left amygdala, gaze fixation accounted for 35% of the variance in decrease-attend brain activation, $F(4,17)=2.33$, $p=0.049$ (1-tailed), while the unique variance left explained by regulation after variance due to gaze fixation was accounted for increased by 2% and approached significance, $\Delta R^2=0.1$, $F(1,16)=2.87$, $p=0.055$ (1-tailed).

Regulation main effects clusters

Table 2 summarizes the results of the regressions performed on the clusters from our voxelwise ANOVA for the decrease-attend contrast, and Table 3 for the increase-attend contrast. Fig. 4 displays the location of these clusters for the decrease-attend contrast and Fig. 5 for increase-attend. The color in both figures represents the variance explained by the regulation contrast after controlling for variance explained by gaze fixation, as a proportion of the amount of variance originally explained by the regulation contrast with no gaze fixation covariate (i.e. (R^2 of original variance $-R^2$ after controlling for gaze fixation)/R^2 of original variance). Higher values reflect more brain activation variance being accounted for by the gaze fixation variables.

To summarize the findings, we observed that the gaze fixation variables account for a sizeable proportion of variance (35–78%) in roughly half of the clusters revealed by the main effects whole-brain ANOVA, in particular for the increase-attend contrast. For the right cuneus (cluster #5 in Fig. 4; cluster #14 in Fig. 5), gaze fixations are associated with 72–78% or more of the variance, in PCC (Fig. 4 cluster #6; Fig. 5 cluster #16) this percentage is 55–62%, with a mere 1–8% of the variance left uniquely explained by the regulation contrast. For the increase-attend contrast, unique variance left explained by regulation is significant in clusters in frontal and temporal regions. For the decrease-attend contrast, the only cluster for which regulation explains a significant amount of unique variance after removal of variance associated with the gaze fixations is in SMA (BA6, Fig. 4 cluster #14; Fig. 5 cluster #27).

These results also show that the regulation conditions differ with respect to the amount of variance associated with gaze fixations in areas in PFC: For decrease-attend, gaze fixations accounted for a significant amount of variance for all clusters in PFC, except for left ventrolateral PFC (left inferior FG, BA45). For increase-attend, the only clusters in PFC for which gaze fixation was associated with a significant amount of variance were in left FEF (BA6, see #23 in Fig. 5) and in SMA (#27 in Fig. 5), although the variance explained is borderline significant at $p=0.054$ for this latter cluster. Note that the increase-attend

Table 2
Regression results for the decrease-attend contrast

FIG #	Brain region	BA	Hemi	Regulation contrast			Step 1: Gaze variables			Step 2: Regulation contrast		
				R^2	F	p	R^2	F	p	ΔR^2	F	p
1	Middle temporal gyrus	21	L	0.15	3.50	0.076	0.44	3.31	0.035	0.00	0.01	0.922
2	Red nucleus/substantia nigra/thalamus		L	0.23	6.08	0.023	0.36	2.43	0.088	0.06	1.52	0.236
3	Inferior frontal gyrus	45	L	0.23	5.80	0.026	0.18	0.95	0.457	0.12	2.71	0.119
4	Inferior frontal gyrus	45/44	R	0.30	8.60	0.008	0.42	3.08	0.045	0.08	2.47	0.136
5	Cuneus	23	R	0.39	12.73	0.002	0.72	11.08	0.000	0.05	3.27	0.089
6	Posterior cingulate cortex incl. retrosplenial cortex	30/29/ 23/31	L	0.16	3.78	0.066	0.62	6.86	0.002	0.01	0.24	0.634
7	Superior temporal gyrus	22	L	0.26	7.17	0.014	0.35	2.33	0.098	0.05	1.33	0.265
8	Caudate/putamen/lentiform nucleus		L	0.23	5.99	0.024	0.28	1.68	0.202	0.12	3.27	0.089
9	Inferior frontal gyrus	44/45	L	0.38	12.24	0.002	0.56	5.34	0.006	0.06	2.37	0.143
10	Middle frontal gyrus	9	L	0.31	8.99	0.007	0.47	3.69	0.024	0.06	1.98	0.178
11	Precentral gyrus	6	R	0.19	4.68	0.043	0.35	2.33	0.098	0.06	1.69	0.212
12	Middle frontal/precentral gyrus	6	L	0.28	7.87	0.011	0.46	3.62	0.026	0.02	0.67	0.426
13	Precentral gyrus	6/4	R	0.17	4.03	0.058	0.24	1.32	0.301	0.03	0.72	0.410
14	Medial/superior frontal gyrus	6	L	0.42	14.17	0.001	0.45	3.44	0.031	0.15	5.82	0.028

The first regression results summarize the percent variance explained by the decrease-attend contrast. The second set of results summarizes the hierarchical regressions, where the gaze fixation variables were entered at a first step, and the regression contrast at a second step. The numbers in the first column correspond to the cluster indications in Fig. 4.

Table 3
Regression results for the increase-attend contrast

FIG #	Brain region	BA	Hemi	Regulation contrast			Step 1: Gaze variables			Step 2: Regulation contrast		
				R^2	F	p	R^2	F	p	ΔR^2	F	p
1	Hippocampus		L	0.36	11.44	0.003	0.44	3.40	0.032	0.09	2.94	0.106
2	Hippocampus		R	0.38	12.10	0.002	0.55	5.20	0.006	0.07	2.74	0.117
3	Middle Temporal Gyrus	20	L	0.49	19.02	0.000	0.43	3.18	0.040	0.17	6.78	0.019
4	Middle temporal gyrus	21	L	0.39	12.69	0.002	0.42	3.07	0.045	0.07	2.14	0.163
5	Red nucleus/substantia nigra/thalamus		L	0.43	14.91	0.001	0.47	3.74	0.023	0.10	3.54	0.078
6	Subgenual anterior cingulate cortex	25	L	0.38	12.07	0.002	0.42	3.05	0.046	0.07	0.17	0.690
7	Thalamus/mamillary body/lentiform nucleus/medial globus pallidus		R	0.40	13.25	0.002	0.47	3.82	0.022	0.09	3.10	0.098
8	Middle temporal gyrus	22	L	0.58	27.48	0.000	0.41	2.93	0.052	0.30	16.52	0.001
9	Inferior frontal gyrus	45	L	0.62	32.41	0.000	0.27	1.54	0.237	0.39	17.99	0.001
10	Inferior frontal gyrus	45/44	R	0.43	15.30	0.001	0.27	1.59	0.222	0.26	9.00	0.008
11	Lentiform Nucleus/Putamen		R	0.33	9.82	0.005	0.29	1.76	0.184	0.10	2.65	0.123
12	Middle temporal gyrus	39	R	0.50	19.88	0.000	0.38	2.63	0.071	0.17	5.91	0.027
13	Middle/superior temporal gyrus	19/39/22	L	0.72	50.13	0.000	0.60	6.41	0.002	0.26	30.88	0.000
14	Cuneus	23	R	0.53	22.26	0.000	0.78	14.97	0.000	0.04	3.83	0.068
15	Thalamus		R	0.28	7.93	0.011	0.33	2.09	0.126	0.05	1.39	0.256
16	Posterior cingulate/retrosplenial cortex	30/29/23/31	L	0.48	18.07	0.000	0.55	5.25	0.006	0.08	3.52	0.079
17	Superior temporal gyrus	22	L	0.59	28.22	0.000	0.57	5.56	0.005	0.15	8.85	0.009
18	Caudate/putamen/lentiform nucleus		L	0.45	16.05	0.001	0.36	2.38	0.093	0.14	4.35	0.053
19	Inferior frontal gyrus	44/45	L	0.59	28.42	0.000	0.33	2.06	0.131	0.28	11.58	0.004
20	Middle frontal gyrus	9	L	0.48	18.15	0.000	0.35	2.26	0.106	0.17	5.62	0.031
21	Precentral gyrus	6	L	0.50	20.32	0.000	0.59	6.05	0.003	0.09	4.27	0.055
22	Precentral gyrus	6	R	0.56	25.25	0.000	0.48	3.90	0.020	0.16	6.98	0.018
23	Middle frontal/precentral gyrus	6	L	0.64	36.03	0.000	0.49	4.03	0.018	0.24	13.80	0.002
24	Precuneus	7	R	0.46	17.14	0.001	0.38	2.57	0.076	0.14	4.77	0.044
25	Precentral gyrus	6/4	R	0.39	13.73	0.001	0.33	2.11	0.124	0.14	4.25	0.056
26	Postcentral gyrus	3	L	0.31	8.90	0.007	0.55	5.19	0.006	0.01	0.49	0.495
27	Medial/superior frontal gyrus	6	L	0.54	23.02	0.000	0.41	2.90	0.054	0.18	6.72	0.020

The first regression results summarize the percent variance explained by the increase-attend contrast. The second set of results summarizes the hierarchical regressions, where the gaze fixation variables were entered at a first step, and the regression contrast at a second step. The numbers in the first column correspond to the cluster indications in Fig. 5.

and decrease-attend differences were significant in all of these prefrontal clusters.

Finally, while the gaze fixation variables are associated with a significant amount of variance in a number of brain regions thought to underlie attentional control, it is noteworthy that regulation still significantly explains unique variance after removing variance due to gaze fixations. This is particularly the case for (pre)cuneus, FEF, SEF, middle and superior temporal gyrus (BA22). For other regions, notably PCC but partly also the hippocampus, which are more often related to memory-related than to attentional processes, gaze fixation explains most of the variance in the cluster, with less than 10% left explained by regulation.

Picture ratings

The ratings of valence and arousal of the negative images provided by our participants after the scanning session for a subset of the pictures presented in the scanner were similar to the normative ratings of the same subset of pictures: $M=2.66$, SD=1.17 for the valence ratings compared to $M=2.51$ for the normative valence ratings; $M=5.39$, SD=1.83 for the arousal ratings vs. $M=5.92$ for the normative ratings. There was no significant effect of regulation strategy employed in the scanner on the ratings of these pictures in the post-scan rating session, for valence $F=1.2$, n.s., for arousal $F<1$.

Discussion

We replicated previous findings that voluntary emotion regulation is associated with a widespread network of neural activations, including the amygdala and prefrontal areas as described in-depth previously (see Ochsner et al., 2002; Phan et al., 2005; Urry et al., 2006), but also within temporal and parietal cortex, hippocampus, thalamus, basal ganglia, and brain stem, similar to those areas reported by Ochsner et al. (2004) and Urry et al. (2006). We also measured gaze fixations while participants were regulating their feelings in response to negative pictures, to test whether the regulation instruction had an impact on differential scanning of the images. The results demonstrate that as a function of regulation instruction, participants spent less time fixating the image and emotion-relevant parts therein when instructed to decrease relative to the attend (and increase) condition, while more and bigger gaze movements were made in both increase and decrease conditions relative to the attend condition. Importantly, we demonstrate that the gaze fixations are predictive of BOLD signal change in brain areas responsive to the regulation task. Furthermore, when instructed to decrease negative affect, gaze fixations account for a significant portion of the variance in areas of PFC, but not when increasing negative affect. These results suggest that overt attention was controlled in a different fashion depending on whether the regulatory goal was to decrease or increase negative affect.

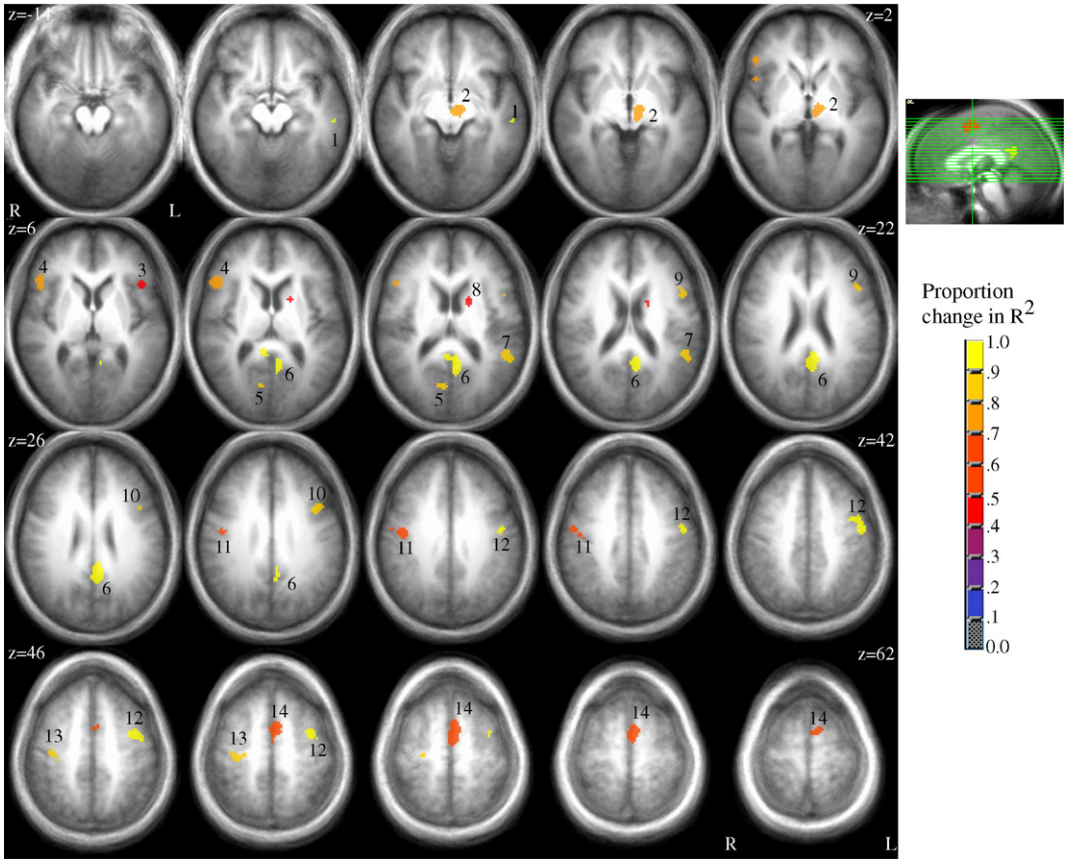

Fig. 4. Clusters for which the amount of variance explained by the eye movement variables is displayed for the *decrease*-attend contrast. Axial slices from inferior to superior. The numbers in the figure correspond to the numbers in Table 2, 1st column. The color represents the change in the amount of unique variance explained by the decrease-attend contrast after controlling for variance explained by gaze fixation, as a proportion of the amount of variance originally explained by decrease-attend (i.e. (R^2 of original variance − R^2 after controlling for gaze fixation)/R^2 of original variance). Higher values reflect more brain activation variance being accounted for by the gaze fixation variables.

Main effects of regulation in amygdala and cortical regions, and on pupil dilation

As predicted, bilateral amygdalar activation linearly decreases across the increase, attend and decrease conditions. In contrast with our previous study (Urry et al., 2006) where the increase condition significantly increased amygdalar activation with little effect of the decrease condition, the current data yield the strongest effects for the decrease condition in both amygdalae. Thus, on average, participants were successful in diminishing their negative affect when instructed to decrease, relative to the increase and attend conditions.

A number of studies on voluntary emotion regulation report activation differences, mostly between a decrease versus a passive control condition, in dorsomedial/lateral (BA9/10) and ventrolateral (BA44/45) regions of PFC, (pre)SMA (BA6), dorsal ACC (BA32), as well as more posterior regions including precuneus/superior parietal lobule (BA7), TPJ (BA21/22/39) and PCC (BA23/30/31). Our study largely replicates these findings, with the exception of dorsal ACC (BA32) and BA10. For most of the clusters the increase condition accounted for the largest percent signal change, followed by the decrease condition, with the attend condition being related to the smallest percent signal change. This is consistent with our previous study (Urry et al., 2006), although in that work there were few clusters demonstrating a significant difference between decreasing and attending. In this study, activation in clusters in thalamus, right TPJ (middle temporal gyrus, BA39), left and right hippocampus, left pre- and postcentral gyrus (BA6,3), subgenual ACC, and right precuneus (BA7) was higher the increase condition relative to the decrease and attend conditions, the latter which were not significantly different. Given the role of a number of these areas in processes underlying, among other, spatial attention (e.g. Corbetta and Shulman, 2002; Rosen et al., 1999), encoding and retrieval of information (e.g. Schacter and Wagner, 1999), and processes related to the self (Arzy et al., 2006; Saxe and Powell, 2006), these data suggest that considering the personal relevance of the negative scenes while scanning the images may be a common strategy used to increase negative affect.

Furthermore, contrary to our earlier study but in line with findings of others (e.g. Ochsner et al., 2004; Phan et al., 2005), we demonstrate that for most of the clusters observed in PFC, with the exception of the cluster in subgenual ACC, the BOLD signal for the decrease condition is significantly stronger than for the attend condition. These findings are especially noteworthy given that the age of our sample is higher (61–65 years) than the usual college-aged participants more commonly recruited. Thus, while we postulated that the age of our participants may have contributed to a relative lack of main effect differences between the decrease and attend condition in our prior study (see Urry et al., 2006, supplemental material, for a discussion), the current findings

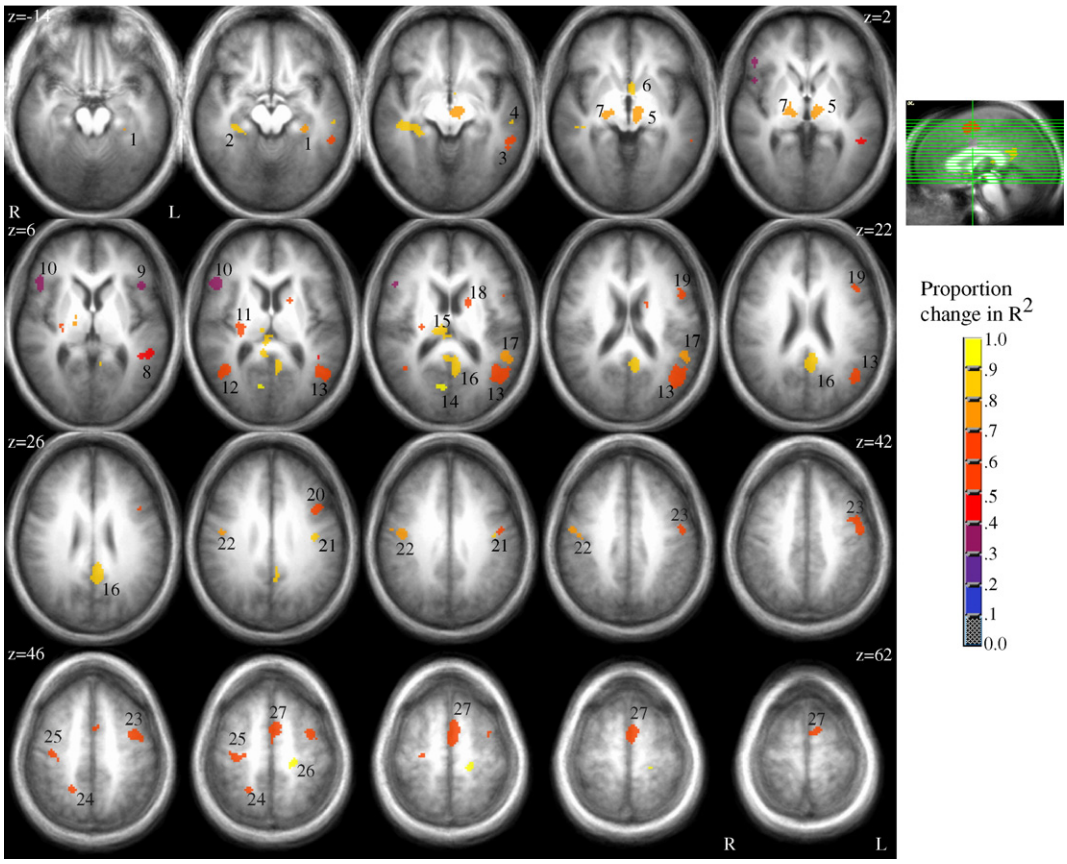

Fig. 5. Clusters for which the amount of variance explained by the eye movement variables is displayed for the *increase*-attend contrast. Axial slices from inferior to superior. The numbers in the figure correspond to the numbers in Table 3, 1st column. The color represents the change in the amount of unique variance explained by the increase-attend contrast after controlling for variance explained by gaze fixation, as a proportion of the amount of variance originally explained by increase-attend (i.e. (R^2 of original variance $-R^2$ after controlling for gaze fixation)/R^2 of original variance). Higher values reflect more brain activation variance being accounted for by the gaze fixation variables.

suggest that age may not necessarily be associated with reduced recruitment of PFC when downregulating emotion. Future studies should include participants sampled from a large range of ages to better examine exactly how emotion regulation changes across the lifespan, if at all.

The results for pupil dilation, employed as an index of arousal expended due to cognitive effort, suggest that both regulation conditions were associated with extended cognitive processing relative to the control condition, particularly during the second period of regulation, replicating our previous findings (Urry et al., 2006). Unlike our prior findings where the increase condition showed the strongest dilation in the early period of regulation, in this study the decrease condition was related to strong dilation shortly after the instruction onset. The reason for this difference is unclear and requires further study. Regardless, the finding of sustained pupil dilation in response to both regulation conditions rules out the possibility that participants in our study were not expending effort to regulate their affect.

Change in patterns of gaze fixations as a function of regulatory goal

Eye movements are often made to regulate an affective response, such as when one looks away from an unpleasant scene. We demonstrate that when instructed to decrease negative emotion, participants tended to look less at the entire image relative to when they were instructed to increase negative affect or to attend to the image, despite explicit instruction not to look away from the image. Our data also indicate that when asked to decrease negative affect, participants looked at the image's relevant object(s) less as a proportion of time spent fixating the image, relative to when instructed to increase negative affect or to maintain attention to the image. Furthermore, the number of fixations made per second fixating the entire image, and the average distance between each consecutive fixation, were larger for both active regulation conditions relative to the attend condition.

These findings suggest that people scanned the image more, looking at all aspects of the scenes and not just at the relevant objects, possibly to construct a reappraisal narrative. While the number of fixations per second was not different between the active regulation conditions, the decrease condition was associated with longer distances between each consecutive fixation relative to the increase condition. This suggests that participants tended to direct their attention to the extremities of the image, often depicting the least relevant parts of the scene, relatively more when decreasing than when increasing negative affect. Note that the average differences between the conditions for all variables are statistically significant, but small in magnitude.

Gaze fixations are associated with variance in brain regions underlying emotion regulation

While the average differences between the conditions on the gaze fixation variables are reliable but small, these variables accounted for a relatively large portion of the variance observed in brain activation associated with regulation. Approximately 35–78% of the variance observed in roughly half of the brain areas showing a main effect of regulation can be attributed to the gaze fixation variables. Areas for which gaze fixations accounted for the most variance included cuneus, just posterior to the PCC, and PCC proper for both regulation conditions relative to the attend condition, with little variance left uniquely explained by regulation. The cluster in PCC was the largest in size, similar to our previous work (Urry et al., 2006). Activity in the PCC has been related to a number of different functions, including spatial navigation and memory (e.g. Burgess et al., 2001; Maguire, 2001), anticipatory biasing of visuospatial attention (Small et al., 2003), eye movements (Pierrot-Deseilligny et al., 2004), and a baseline state ("default mode") of brain function (Raichle et al., 2001). The large amount of variance explained in PCC and cuneus activation by gaze fixation in our study is in line with this prior work and underscores the likely role of this region in motivated biasing of overt visual attention shifts.

Furthermore, the center of mass of the PCC cluster in our study is located in the ventral part of the PCC (vPCC) and retrosplenial cortex (BA29/30; see Vogt et al., 2006), an area that has been shown to be strongly interconnected with the subgenual ACC. Vogt et al. (2006) propose that the vPCC, rather than being part of an emotion system per se, is involved in a more intermediate stage of information processing, such as that between visual recognition or other visual cortex-related processes and evaluative/emotion-related processes associated with subgenual ACC. Indeed, activation in vPCC has also been reported in studies on evaluating words or short sentences (e.g. Maddock et al., 2003; Zysset et al., 2002) and self-reflection (Johnson et al., 2002). Given that the study involves images depicting complex emotion-laden scenes, which require visual scanning to capture the essence of the scene depicted, our data support Vogt and colleagues' contention of the role of this area in processing of potentially emotion-relevant material.

Other regions which play a pivotal role in oculomotor/attentional control include the FEF, SEF/(pre)SMA, and precuneus/TPJ. In our work, while we observed regulation differences in these regions, gaze fixations did not explain all variance in these brain regions, with a significant portion of variance in most of these clusters left explained uniquely by regulatory processes other than shifting the gaze. The precise reason for this is unclear, and will need further clarification in future research. It may be that the manner in which we quantified eye movements in this study does not capture variance due to underlying FEF/SEF-relevant saccadic/oculomotor processes. Alternatively, while activation in these areas has been related to attentional/oculomotor behavior (e.g. Corbetta et al., 1998; Gitelman et al., 2002), activation in these areas has also been observed in studies of (working) memory. Indeed, Makino et al. (2004) argue that when performing either a visual or a memory search on the identical visual stimuli, the left FEF is activated, thus suggesting that this region plays a role in cognitive planning in general, of which oculomotor planning is a sub-process. A multitude of cognitive processes involved in the voluntary regulation of emotion could thus be responsible for observed regulation activation in these areas. Following Ochsner et al. (2004) who trained different groups of participants on specific regulatory strategies (involving/distancing the self vs. imagining different outcomes), future studies should more specifically explicitly manipulate the different sub-processes thought to underlie emotion regulation, to better understand the patterns of brain activations underlying the task.

The pattern of brain activation associated with gaze fixations differed with the type of regulation performed: For the decrease-attend contrast, gaze fixations accounted for a significant amount of variance (41–56%) in all but one of the frontal clusters, but the fixations did not account for as much variance for the increase-attend contrast (27–35%). The difference in variance accounted for by gaze fixation between the regulation conditions was particularly striking for the clusters in ventrolateral (inferior FG, BA44/45) and dorsolateral PFC (middle FG, BA9). These ventrolateral regions of PFC are well connected with dorsolateral and ventromedial PFC (Miller and Cohen, 2001), and have been involved, among other, in orienting to non-attended information (Corbetta and Shulman, 2002) and with processes underlying working memory, including maintenance and interference resolution, and the manipulation of information in working memory (D'Esposito et al., 2000).

This different pattern of PFC activation covarying with gaze fixations across the regulation conditions points to a qualitatively different implementation of gaze control when decreasing relative to increasing negative affect. Given the gaze fixation findings for the decrease condition, where participants looked away more and at irrelevant parts of the image relative to the increase and attend condition, we propose that the association between prefrontal activation and gaze fixation for the decrease condition may reflect processes of biasing attention away from negative information. The gaze fixation findings for the increase condition suggest greater attention to visual information, hence possibly relatively less covariation between activation in PFC areas and gaze fixation, and relatively more between activation in posterior/visual areas and gaze fixation. These notions require explicit testing in future work.

Gaze fixations accounted for a significant amount of variance in the left amygdala for the decrease-attend condition. These results are in line with those of Dalton et al. (2005) where amygdalar activation was associated with gaze fixations away from the eyes in autistic individuals. However, unique variance left explained by the regulation contrast, after removing the variance associated with gaze fixations, did not decrease, suggesting that effects of regulatory processes were independent of the effects of gaze fixations. These effects for left amygdala were not strong, however, and need to be replicated.

It is important to note that the associations we demonstrate between gaze fixation and patterns of brain activation are correlational in nature. Furthermore, statistical variance due to gaze control or reappraisal processes may overlap and hence, in a statistical sense, be confounded. As such, we cannot infer primary causality of either cognitive reappraisal or gaze control underlying the patterns of brain activation associated with emotion regulation. Our contention is that without any control over what the participants are doing when instructed to regulate their response, we cannot ascertain whether patterns of brain activation underlie reappraisal processes or any other process that may be called upon when regulation affect in the laboratory setting, pointing again to the importance of experimentally dissociating different mechanisms underlying emotion regulation. Our findings illustrate the impor-

tance of experimentally dissociating different mechanisms underlying emotion regulation.

Thus far, we have established that regulatory goal has an impact on how the participant scans visual information. Furthermore, our results for the amygdala suggest successful downregulation of negative affect, and that the effects of gaze fixation on left amygdala activation seem to be partially independent from other regulatory processes such as reappraisal. Prior research from our laboratory on voluntary emotion regulation through reappraisal demonstrated effects of regulatory goal on outcome measures previously identified as reliable indicators of felt positive and negative affect, such as the modulation of eyeblink startle and electromyographic (EMG) activity measured over the corrugator muscle surface area e.g., (Jackson et al., 2000). Since both eyeblink startle and corrugator activity reflect the output of the regulatory processes, it is possible that a substantial portion of variance in these measures would be associated with gaze fixation if we had measures of gaze during these studies. Whether or not these associations would be independent from other regulatory processes, as with our amygdala findings, remains to be determined in future studies.

Recently, event-related potentials (ERP) have been measured in two studies (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006). The advantage of the use of event-related potentials is their high time resolution (milliseconds) relative to fMRI. They can therefore provide important information regarding the temporal process of emotion regulation. Results of both studies indicate modulation of early attentional components – as early as 200–250 ms after stimulus onset – where the amplitude of the components was reduced for the decrease condition relative to the increase and attend condition. These findings suggest reduced visual intake and attention allocation for the decrease condition. In light of our findings with respect to patterns of gaze fixation, these results can be accommodated by our hypothesis of reduced viewing of the emotion-eliciting stimulus when instructed to decrease the emotional response. Given that the instruction was provided prior to the stimulus onset, participants had time to anticipate and prepare for the upcoming negative stimulus to direct their gaze and/or covertly shift their attention away from the stimulus, affecting ERP components as early as 200–250 ms after stimulus onset. Future research is needed to evaluate this possibility.

Emotion regulation in daily life is a complex task requiring integration and inhibition of information from various sources, and its mechanisms are not yet well understood. The study of emotion regulation in the laboratory therefore is an important endeavor, but one that is not without its challenges. Importantly, in studies of voluntary emotion regulation we rely on the participants performing the regulation strategies that we ask them to perform, without knowing whether and how well they perform this task. While self-report assessments of strategies adopted, thoughts related to the task, or feelings experienced while performing the task may provide the researcher with some potentially useful information, many of the processes of interest are implicit and thus opaque to conscious reports. It has been shown that experts in any knowledge domain consistently report having used a logical strategy which bears only limited resemblance to the one they actually used (see e.g. Berry, 1987, for a review). Measuring behavior objectively and unobtrusively, such as participants' gaze fixations, provides an important manipulation check to assess whether at least the instruction to look at the image without averting the gaze has been followed. Additionally, the measurement of gaze fixations can provide valuable insights into one of the core processes underlying emotion regulation, namely control of attention. Furthermore, the use of stimuli other than the complex pictures of the type used in our study and in that of many others, or of non-visual stimuli such as thermally induced pain (Kalisch et al., 2005), can provide important information on exactly what brain systems are involved in reappraising emotion-relevant information, without confounding these with those involved in scanning visual stimuli or processing other modality-specific information.

While our main research focus is emotion regulation, the message of this study stretches beyond this specific field of affective neuroscience and applies to any study where (complex) visual stimuli are presented while the gaze is not held constant: Gaze fixations can statistically account for a substantial portion of activation in different brain areas, which may or may not be related to the mechanism or process under study. The simultaneous measurement of eye tracking while participants perform a visual task in the scanner will help disentangle some of the myriad contributions to the brain activations observed.

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