ANTECEDENT DESCRIPTIONS CHANGE BRAIN REACTIVITY TO EMOTIONAL STIMULI: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF AN EXTRINSIC AND INCIDENTAL REAPPRAISAL STRATEGY

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Abstract—In the present study we investigated whether individuals would take advantage of an extrinsic and incidental reappraisal strategy by giving them precedent descriptions to attenuate the emotional impact of unpleasant pictures. In fact, precedent descriptions have successfully promoted down-regulation of electrocortical activity and physiological responses to unpleasant pictures. However, the neuronal substrate underlying this effect remains unclear. Particularly, we investigated whether amygdala and insula responses, brain regions consistently implicated in emotional processing, would be modulated by this strategy. To achieve this, highly unpleasant pictures were shown in two contexts in which a prior description presented them as taken from movie scenes (fictitious) or real scenes. Results showed that the fictitious condition was characterized by down-regulation of amygdala and insula responses. Thus, the present study provides new evidence on reappraisal strategies to downregulate emotional reactions and suggest that amygdala and insula responses to emotional stimuli are adaptive and highly flexible. © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: amygdala, insula, ventrolateral prefrontal cortex (VLPFC), extrinsic reappraisal, incidental reappraisal, mutilation pictures.

Emotion regulatory processes may be automatic or controlled, conscious or unconscious and may have their effects at one or more points in the emotion generative

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Abbreviations: fMRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; LPP, late positive potential; ROI, regions of interest; VLPFC, ventrolateral prefrontal cortex.

process (Gross and Thompson, 2007). This regulatory process can influence which emotions individuals have, leading to changes to one or more aspects of emotion (e.g. Bargh and Williams, 2007; Gross and Thompson, 2007). In fact, emotion regulation can be achieved through a number of processes, but in general, strategies can be classified as either response or antecedent-focused (Gross, 1998; Ochsner and Gross, 2005). Response-focused strategies occur relatively late in the emotion-generation process and would include suppressing the behavioral expression of emotion. This strategy, however, seems to be ineffective in decreasing the experience of negative emotions (Gross and Levenson, 1993). On the other hand, antecedentfocused regulation strategies occur relatively early within the emotion-generation process and appear to be effective in decreasing the experience of negative emotions (Ochsner et al., 2002; Moser et al., 2006). One approach to achieve the antecedent-focused regulation is reinterpreting an unpleasant stimulus to be less negative, which is called "reappraisal." Thus, to be considered as "antecedent" this strategy should be employed before the emotion had been triggered (Gross, 1998).

One unresolved issue in this area is whether emotion regulation refers to intrinsic processes, to extrinsic processes, or to both (Gross and Thompson, 2007). The first process assumes that emotion regulation derives from a person's self-regulatory effort and the second process assumes that it results from the regulatory influences of other people (Thompson, 2011). In general, researches involving adult subjects typically focus on intrinsic processes (Thompson, 2011). However, even for adults, extrinsic emotion regulation occurs in many ways. This is generally how people intervene to manage the feelings of a spouse, friend, or acquaintance, by dissuading them from going to events that may be stressful or by giving them other interpretation about a negative ongoing situation (for review see Gross and Thompson, 2007). As pointed out by Thompson (2011) "... regulatory influences arise not just through the strategic efforts of the person to function competently but also through a variety of extrinsic, nonconscious, implicit processes by which emotion is managed in response to complex contextual demands." This type of regulatory influence can also be referred to as incidental emotion regulation, which occurs when contextual factors alter an affective response without one's intentional effort (Berkman and Lieberman, 2009).

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Regarding intrinsic process, most previous studies have investigated reappraisal strategies during which individuals are encouraged to voluntarily change how they think about a situation, in order to decrease its emotional impact (Ochsner et al., 2004; Phan et al., 2005; Moser et al., 2006). Several studies have shown that this strategy can change emotional experience and its associated physiological and functional magnetic resonance imaging (fMRI) responses (Gross and Muñoz, 1995; Gross, 1998, 2002; Ochsner et al., 2002; Ray et al., 2005; Goldin et al., 2008). Specially, amygdala activity modulation has been described as crucial to the emotion regulation process. A number of studies have demonstrated that the use of reappraisal, that is, cognitively changing the meaning of emotional stimuli, affects evoked responses in the amygdala and other brain areas (Ochsner et al., 2002, 2004). For instance, fMRI studies have shown that amygdala is sensitive to emotion regulation in that its activity is decreased during the reevaluation of negative affect while is increased during enhancement of negative emotion (Phan et al., 2005; Eippert et al., 2007). It is important to note, however, that the majority of research to date has focused on deliberate emotion regulation, which is voluntary, volitional and driven by explicit goals (Berkman and Lieberman, 2009). In these studies, participants have typically been asked to generate their own alternative interpretations after viewing an emotional stimulus. Furthermore, this strategy may introduce inter- and intra-participant variability regarding the specific way that reappraisals are performed by the participants.

In the present study we extend research on emotion regulation data by employing a subtle and *less deliberate* strategy. Specifically, we investigated whether individuals would take advantage of an *extrinsic* and *incidental* emotion regulation strategy by giving them precedent descriptions to attenuate the emotional impact of unpleasant images. In this case, regulation starts *before* the emotion is completely triggered. First of all, participants were told that they would see very unpleasant images such as mutilated bodies. After that, they received descriptions, which gave them the opportunity to adjust their responses according to each emotional context. In one context, unpleasant images were described as taken from real situations (real) and in the other, from movie scenes (fictitious).

In fact, this kind of subtle reappraisal strategy has successfully promoted down-regulation of electrocortical activity and physiological responses during the viewing of emotional pictures (Foti and Hajcak, 2008; Oliveira et al., 2009; Mocaiber et al., 2009, 2010). However, the neuronal substrate underlying this effect remains an open question. In the present study, we employed fMRI to investigate whether amygdala and insula responses, brain regions consistently implicated in emotional processing (e.g. Morrison et al., 2007; Pereira et al., 2010; Pessoa and Adolphs, 2010), would be modulated by this strategy.

Thus, we hypothesized that the differential brain responses between unpleasant and neutral pictures would be attenuated (or even eliminated) in the fictitious condition compared to the real condition. Particularly, we predicted

that the activity of amygdala and insula to highly arousing unpleasant images would be flexible and adaptive in the context of an extrinsic and incidental reappraisal strategy.

EXPERIMENTAL PROCEDURES

Participants

Twenty-two healthy volunteers (12 male, mean age of 26.61 years, SD=4.72) participated in this study. Volunteers were selected among students, and had normal or corrected-to-normal vision. They reported no psychiatric or neurologic problems and were not under medication with nervous system action. Participants were naive as to the purpose of the experiment. Before data collection, all procedures were approved by the local ethics committee and participants gave informed consent.

Stimuli

Two classes of images (72 neutral and 72 unpleasant) were employed. Neutral pictures consisted of photographs of people "in normal life" and unpleasant images consisted of photographs of mutilated bodies. Pictures were taken from the International Affective Picture System (IAPS)—(Center for the Study of Emotion and Attention and (CSEA-NIMH), 1999), from the World Wide Web, or photographed by the authors. Additional pictures were selected apart from the IAPS, since the IAPS database was not large enough for the conduction of this study. We attempted to match unpleasant and neutral stimuli in terms of both color content and complexity (e.g. number of faces, number of body parts, etc.). Following the protocol developed by the CSEA (Bradley and Lang, 1994), all images were assessed on a 1-9 scale in terms of valence (from negative to positive) and arousal (from low to high) by a separate group of participants (n=20) with ages similar to the participants of the current study (22.3, SD=1.8). Thus, all images employed in the present experiment (pictures from the IAPS catalogue and from the web) had their valence and arousal assessed according to the IAPS rating procedure. Unpleasant and neutral images differed significantly from each other in IAPS normative valence (M=2.08 and 5.21, respectively, t=-58.02, P<0.001) and arousal (M=6.6 and 3.4, respectively, t=34.43, P<0.001) ratings. Each picture was repeated just once within the fictitious and the real contexts. Thus, the repetition of one specific picture always occurred within the same context.

Procedure

Participants performed an emotional judgment task, in which they had to decide whether the presented picture was neutral or unpleasant, pressing one of two buttons with the right hand. The judgment task was performed in two contexts: fictitious and real. Initially, participants were told that they would see very unpleasant images such as mutilated bodies. After that, they received descriptions, which gave them the opportunity to adjust their responses according to each emotional context. In one context, they were instructed that the unpleasant pictures had been taken from movie productions (fictitious condition) whereas in the other context, they were instructed that the pictures corresponded to real scenes (real condition). In the fictitious condition, the precedent descriptions represented a safety signal, which encouraged participants to down-regulate their responses to an upcoming highly provocative set of pictures. Neutral pictures were also presented so that we could assess the differential responses to mutilation stimuli in both contexts.

Therefore, the experiment consisted of a 2 (context: fictitious and real) \times 2 (valence: neutral and unpleasant) factorial design. Experimental session comprised four runs (two real contexts and two fictitious contexts runs) counterbalanced across participants.

Each run comprised four interleaved blocks of task and rest periods. Rest periods consisted of a fixation cross presented for 15 s. Task blocks were composed of nine trials (four unpleasant and five neutral pictures in two blocks, and five unpleasant and four neutral in the two others). Every run contained the same number of neutral and emotional trials that were randomly presented within each task block. Task blocks were preceded by a 3-s black screen to warn subjects of its beginning. Every single trial was initiated by a 500-ms fixation cross, followed by a central picture presented for 200 ms and masked by a gray-scale checkerboard until the volunteer emitted a response. The trial duration was fixed to 3 s, corresponding exactly to one repetition time (TR). Participants were instructed to respond as quickly and as accurately as possible, indicating whether the pictures were neutral or unpleasant. Pictures were presented with Presentation software (Neurobehavioral Systems, http://nbs.neuro-bs.com) running in a Windows notebook and projected inside the scanner through a projection screen and mirror system fixated on the head coil. Responses were collected with an MRI-compatible button system. Participants performed a practice session before the experiment to ensure that they completely understood the instructions.

Participants were first told that they would see a variety of pictures including a very unpleasant category, mutilated bodies. After that, and before the beginning of each run, participants had to read a text informing the source of the forthcoming pictures. In *fictitious context* runs, the pictures were announced to be fictitious scenes, whereas, in *real context* runs, pictures were described as real-life scenes. This experimental manipulation was done in a very subtle way, so that participants could not suspect of the key manipulation.

For the fictitious context, participants read the following text: "... The pictures that will be shown to you in the next trials were obtained from movies with the aim of convincing the audience... Therefore, the pictures were produced by means of diverse techniques such as make-up, and do not correspond to real situations". For the real context, participants read the following text: "... The IAPS is a set of standardized colored photographs of a wide range of situations ... All the pictures are real and were obtained from the web, media, or taken by the group that developed the IAPS." The aim of this manipulation was to attenuate the emotional impact of the pictures during the fictitious context compared to the real context. This experimental procedure was previously validated by recent studies (Oliveira et al., 2009; Mocaiber et al., 2010).

In summary, each subject participated in one experimental session that comprised four counterbalanced runs (two fictitious and two real runs). Each run contained four blocks comprising nine unpleasant and neutral trials each. Unpleasant and neutral pictures were equal in number and randomly presented within each run. The pictures that were presented to some participants in the real context were presented in the fictitious context to others, guaranteeing that any attenuation effect would not be associated to a specific pool of pictures.

In order to confirm the credibility of our key manipulation, we ran a behavioral experiment with an additional sample outside the scanner (n=27; mean age of 19 years, SD=2.09) and asked the participants to rate a set of pictures presented in the *fictitious* and real contexts. This behavioral experiment was very similar to the fMRI experiment described before. First, participants performed an emotional judgment task, where they had to decide whether the picture presented was neutral or unpleasant, pressing one of two buttons with the right hand. At the end of each block, participants additionally rated the set of pictures just shown by means of the Self Assessment Manikin (SAM) valence and arousal scales (Bradley and Lang, 1994). This rating test was not applied in the scanner sample to prevent participants from suspecting the key experimental manipulation.

fMRI recording. MRI data were collected using a 1.5 T MRI scanner (Magnetom Vision Plus, Siemens, Erlangen, Germany). Functional images were acquired using a gradient-echo planar imaging sequence (TR=3 s; TE=60 ms; FOV=240; flip angle=90°; 64×64 matrix). Whole brain coverage was obtained with 25 axial slices (thickness=4 mm; in-plane resolution=3.75×3.75 mm). Echo-planar images were co-registered to a high-resolution structural T1-weighted image obtained during the same session (TR/TE=9.7/4.0 ms; flip angle=12°; 160 slices; thickness=1 mm; 256×256 matrix; FOV=256 mm). Head movements were restrained with foam padding. Stimulus presentation was synchronized with functional images acquisition.

fMRI data analysis

The statistical parametric mapping software package (SPM5, Wellcome Department of Cognitive Neurology, London) was used for preprocessing and statistical analyses. The first three functional volumes of each run were removed to eliminate non-equilibrium magnetization effects. The remaining images were corrected for head movement by realigning all the images to the first image via rigid body transformations. The images were then corrected for differences in slice acquisition time. For each participant, functional and structural images were co-registered. Structural data were normalized by matching them to the standardized MNI template, and the transformation parameters estimated in this step were applied to all functional images. Functional images were spatially smoothed with an 8-mm full width at half maximum Gaussian kernel prior to statistical analysis.

Data analysis was performed according to the general linear model framework, as implemented in SPM5 (Friston et al., 1995). Data obtained from the 22 participants were analyzed. Functional data quality was checked by means of Artifact Repair (version 4) toolbox (Mazaica et al., 2005), a package of tools developed for SPM to check and correct motion and other artifacts. This allowed signal quality checking before reaching General Linear Model (GLM).

The main goal of the present study was to determine the effects of a *less deliberate* reappraisal of emotional stimuli on amygdala and insula activation. However, we also performed a whole-brain voxel-wise analysis to investigate general task-related activations, as well as to further investigate emotional brain responses. A standard two-stage mixed-effects analysis was performed

The first (fixed) level involved determining the regression coefficients of the variables of interest, which modeled the effects of each experimental condition: judging neutral pictures (real context), judging unpleasant pictures (real context), judging neutral pictures (fictitious context) and judging unpleasant pictures (fictitious context). Before estimation via multiple regressions, regressors of interest were convolved with a canonical hemodynamic response function.

Second-level group analyses were conducted by means of Student t-tests. Since random effects analyses may be fairly conservative in the context of fMRI data (Worsley et al., 2002), we employed a threshold of P=0.001 (uncorrected), as is commonly employed in the literature. A clusters size threshold was established at 10 contiguous voxels.

Critical analyses were performed within the amygdala and insula, which have been pointed out by the literature as a crucial part of the emotional network. Functional regions of interest (ROI) of these structures were selected based on the contrast unpleasant pictures vs. neutral pictures during the real context (a threshold of P=0.001, uncorrected, was employed). These same ROIs were used for a paired t-tests comparison between the critical conditions (unpleasant pictures vs. neutral pictures) during the t-fictitious context. Functional ROIs construction and signal extraction were performed using the MarsBar toolbox (version 0.41)

Table 1. Brain regions activated for the unpleasant>neutral contrast

Brain region	Hemisphere	Coordinates MNI (x y z)	Cluster size	t (score z)
Real context (unpleasant>neutral)				
Cerebellum	R	32 - 76 - 34	30	4.89 (3.95)
Cerebellum	L	-34 - 52 - 34	29	4.26 (3.57)
Mid cingulate	L	-14 -40 50	46	5.09 (4.06)
Insula	L	-34 -22 18	19	4.06 (3.45)
Amygdala	R	34 -2 -24	18	4.54 (3.74)
Mid frontal gyrus	L	-22 14 42	26	4.35 (3.63)
Suplementar motor area	R	6 22 58	31	3.84 (3.31)
Superior frontal gyrus	R	4 38 46	18	4.13 (3.49)
Fictitious context (unpleasant>neutral)				
Lingual gyrus	L	-8 -46 2	13	4.41 (3.67)
Caudate nucleus	L	-20 12 16	55	6.44 (4.73)
Caudate nucleus	R	22 26 4	27	5.49 (4.28)
Inferior frontal gyrus (ventrolateral prefrontal cortex)	R	40 32 0	81	4.70 (3.84)
Mid frontal gyrus (ventrolateral prefrontal cortex)	L	-30 40 4	15	3.88 (3.33)
Superior frontal gyrus (ventromedial prefrontal cortex)	L	-24 50 6	13	4.26 (3.58)

All regions at P threshold of .001, uncorrected. L=left, R=right; x y z=MNI coordinates of the maximally active voxel; t=maximum t value.

(Brett et al., 2002) for SPM5. Mean β values for each condition were extracted.

RESULTS

Ratings

Data on mean ratings showed that images presented in the real context were more arousing than the images presented in the fictitious context (M=5.55, SD=2.01 and 4.68, SD=2.48, respectively, P<0.01). Also, pictures in the real context were marginally more unpleasant than in the fictitious context (M=3.60, SD=1.47 and 3.93, SD=1.24, P=0.07).

Behavioral results

Median reaction times and accuracy (number of correct responses emitted by the participant in each experimental condition) were determined for 19 of the 22 participants; because of equipment malfunction, behavioral data from three participants were not analyzed. Paired t-tests revealed that the mean reaction time did not differ between the unpleasant and neutral pictures for both the real (M=934.5 ms, SE=28.59 vs. 935.4 ms, SE=25.35) and the fictitious context (M=928.6 ms, SE=25.45 vs. 924.6 ms, SE=26.25). However, the overall performance to judge unpleasant pictures (M=73.3%, SD=1.59) was significantly higher in comparison to neutral ones (M=68.71%, SD=1.68) in the real context (P < 0.04). This difference was not observed for the fictitious context (M=71.78%, SD=2.16 and M=71.2%, SD=1.59, for unpleasant and neutral pictures, respectively) (P>0.8).

Brain imaging results

Functional MRI data were first analyzed on a voxel-byvoxel basis across the whole brain for each experimental context. We will first present the whole brain data for the following contrasts: unpleasant>neutral pictures (real context) and unpleasant>neutral pictures (fictitious context) (Table 1). Brain regions showing greater activation during the judgment of unpleasant pictures in comparison to neutral pictures in the *real context* are shown in Table 1. They include bilateral cerebellum, mid-cingulate cortex, right amygdala, left insula, left mid-frontal gyrus, right supplementary motor area (SMA) and right superior frontal gyrus. As expected, the real context contrast revealed an "emotional network" previously described by other studies.

Brain regions showing greater activation during the judgment of unpleasant pictures in comparison to neutral pictures in the *fictitious context* included a group of prefrontal regions (inferior frontal gyrus, mid-frontal gyrus and superior frontal gyrus), lingual gyrus and caudate nucleus (Fig. 1). It is important to note that the "emotional network" revealed in the real context contrast was not found in the fictitious context contrast, suggesting that the activation of the emotional network was attenuated.

Our main focus of interest was to investigate the effects of emotion regulation on critical brain regions previously described in the literature as part of an emotional network (amygdala and insula). Therefore, we conducted a ROI analysis of these structures, defined via the contrast unpleasant pictures>neutral pictures during the real context. The mean β parameters for unpleasant and neutral pictures in the fictitious context were extracted and compared by paired t-test. This analysis showed no statistical difference of the amygdala (x y z=34 -2 -24) and insula (x y z=-34 -22 18) activity as a function of stimulus valence (P=0.5), suggesting an attenuation of emotional effects during the fictitious context (Fig. 2).

DISCUSSION

In the present study we examined the effects of an extrinsic, incidental and less deliberate reappraisal strategy on unpleasant image processing. Specifically, we observed that precedent descriptions, aimed to attenuate the impact of emotional pictures, produced changes on behavioral

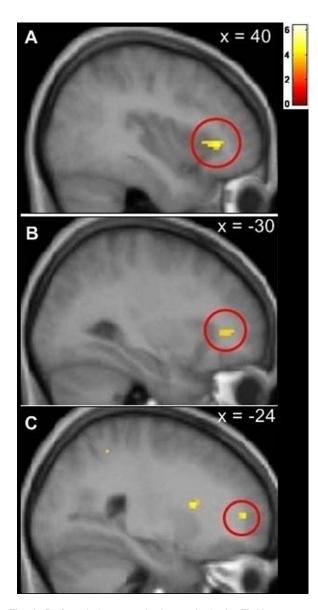


Fig. 1. Prefrontal clusters activation peaks in the Fictitious context contrast (unpleasant > neutral). (A) Top panel shows right ventrolateral prefrontal cortex (VLPFC) activation (xyz=40 32 0); (B) Middle panel shows left VLPFC activation (xyz=-30 40 4) and (C) Bottom panel shows ventromedial prefrontal cortex (VMPFC) activation (xyz=-24 50 6). Activations are overlaid on subject's average anatomical image at a level of P<.001, uncorrected. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

and brain responses, reducing amygdala and insula reactivity during the viewing of highly unpleasant stimuli.

As expected, during the *real* condition the reactivity of an emotional network including amygdala, SMA, cingulate cortex and insula was modulated by stimulus valence (Lane et al., 1999; Phan et al., 2002; Pereira et al., 2010). Increased responses in the amygdala are consistent with a considerable body of data that has documented how this structure is involved in affective processing (Phan et al., 2005; Pessoa, 2008). A large body of studies has shown that amygdala is implicated in responses to visual emo-

tional stimuli involving fear and negative emotions (Ochsner et al., 2002; Phan et al., 2002; Hariri et al., 2003; Phelps and LeDoux, 2005; Eippert et al., 2007; Del-Ben et al., in press). Moreover, the visualization of the mutilation pictures evoked increased responses in insula and cingulate cortex, which are regions associated with the monitoring of the ongoing internal emotional state of the organism (Craig, 2009) and the implementation of defensive responses (Azevedo et al., 2005; Morrison et al., 2007; Milad et al., 2007; Pereira et al., 2010), respectively.

Interestingly, during the *fictitious* context, we did not find greater activation for brain regions associated with emotional processing, such as amygdala, cingulate cortex, insula and SMA. This finding is remarkable since we used a very subtle strategy to down-regulate highly aversive and provocative pictures. Actually, we chose mutilation pictures because we intended to test this strategy using stimuli that evoke strong aversive reaction (Pereira et al., 2004, 2006, 2010; Azevedo et al., 2005; Erthal et al., 2005; Facchinetti et al., 2006; Oliveira et al., 2009). Thus, subtle changes in the situational context (precedent descriptions) resulted in activation of structures involved in affect (amygdala and insula) in one condition (real) coupled with increases in PFC activity in the other condition (fictitious).

Previous studies have shown that instructions to purposefully modulate emotional responding to unpleasant stimuli affect physiology and brain activity (Ochsner et al., 2004; Phan et al., 2005; Goldin et al., 2008). However, these studies used voluntary strategies, which are intrinsic, volitional and driven by overt goals. In the majority of these studies, participants have typically been asked to generate their own alternative interpretations after viewing an emotional stimulus. Here, participants were persuaded to down-regulate the impact of aversive pictures via antecedent written instructions that indicated that the stimuli were fictitious. This key experimental manipulation changed the nature of the pictures presented, in the sense that their relevance appeared to be attenuated, resulting in diminished brain activation in structures critical to emotional processing. A potential strength of the present study is that all participants were provided texts that equally influenced the meaning of the upcoming pictures, rather than being left to generate their own interpretation. In addition, we believe that with this procedure, task difficulty was more similar between participants. This procedure can also be referred to as an incidental emotion regulation in which changes in contextual factors alter an affective response (Berkman and Lieberman, 2009).

Another possible interpretation of the present results is that the precedent descriptions changed the expectations about upcoming stimuli, altering the initial processing of emotional stimuli. In fact, adjustment of expectations about upcoming stimuli may represent a powerful antecedent-focused strategy for the cognitive control of emotion (Foti and Hajcak, 2008). In the present study, participants were first told that they would see very unpleasant images such as mutilated bodies. Thus, in the beginning of the experiment, participants were aware that they would judge mutilation pictures. After that, they read precedent descriptions, which gave them the opportunity to adjust their ex-

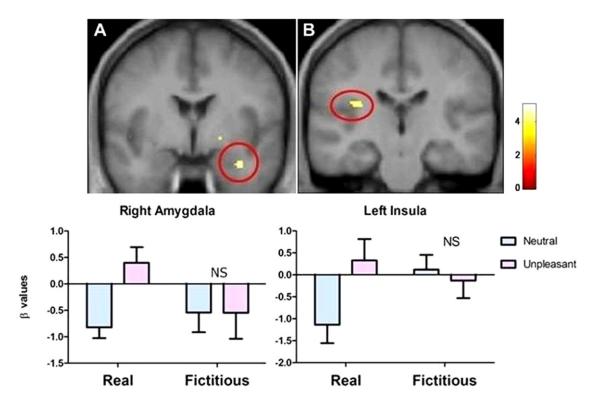


Fig. 2. Top panel: Voxelwise group maps illustrate increased activation of (A) amygdala, (B) and insula regions for the (unpleasant > neutral) contrast during the real context. Activations are overlaid on subject's mean anatomical image at a level of P < .001 uncorrected; the gradient scale denotes t-values. The clusters illustrated above were further interrogated as shown in the bar plots in the bottom panel. Bottom panel: The two first bars of each plot show differential responses to unpleasant vs. neutral pictures during the real context, which were used as a selection criterion and are shown for comparison only. The remaining bars represent the responses during the fictitious context. Importantly, there was no difference between the responses for unpleasant stimuli relative to neutral during the fictitious context. Error bars represent the standard errors of the means. NS, not significant; P < 0.005. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

pectations according to each emotional context. In the fictitious context, the precedent descriptions might have represented a safety signal, which led participants to down-regulate their responses to a highly provocative set of pictures. Therefore, it is possible that the reappraisal was performed by changing the expectations about the upcoming stimuli. In fact, pioneer works by Lazarus and colleagues employing threatening films showed that manipulation of beliefs about the scenes could reduce the expected autonomic responses (Lazarus and Alfert, 1964). Their strategy was to give safety hints that subtly implied a reduced aversiveness of the films' stressful events.

The experimental procedure employed here has been previously validated by previous studies of our group using distinct physiological measures (Oliveira et al., 2009; Mocaiber et al., 2009, 2010). Participants that scored high in positive affect exhibited attenuated autonomic reactions (heart rate and galvanic skin response) to mutilation pictures when they believed that the images had been obtained from movie production (Oliveira et al., 2009). Also, Mocaiber et al. (2010) investigated the modulation of the Late Positive Potential (LPP) by an extrinsic reappraisal strategy in two distinct contexts in which a prior description presented pictures as taken from either movie scenes or real situations. Results showed that the interference produced by mutilation pictures under the real context (indexed by reaction time and LPP amplitude) was attenuated under the fictitious

context, providing evidence that extrinsic reappraisal modulates eletrocortical processing. Previous studies using evoked potential recordings also corroborate with the idea that precedent descriptions are effective in down-regulating responses to motivationally relevant stimuli (Foti and Hajcak, 2008; Macnamara et al., 2009). For instance, Foti and Hajcak (2008) examined whether a more or less negative description preceding the presentation of unpleasant images would modulate electrophysiological activity. Participants heard a brief description of the upcoming picture: prior to unpleasant images, this description was either more neutral or more negative. Following the more neutral description, the magnitude of the LPP, unpleasant ratings, and arousal ratings were all reliably reduced, indicating that changes in narrative were sufficient to modulate the electrocortical response (Foti and Hajcak, 2008). These findings give support to the effectiveness of the emotion regulation strategy employed in the present study.

Interestingly, in the present study, we found that amygdala reactivity to a highly provocative stimulus was modulated by the extrinsic and incidental strategy employed. This flexibility of the amygdala response described here is remarkable, as amygdala has been traditionally considered as a key brain structure to "automatic" responses to dangerous stimuli (Globisch et al., 1999; Morris et al., 1999; Vuilleumier et al., 2001). Thus, contrary to this view, our findings reveal that amygdala activity is not im-

mune from regulatory processes and that emotional processing is under top-down control. The novelty of the present study is to show that the impact of emotion over behavior and brain activity can be modulated by a less effortful and deliberate emotion regulation strategy.

In the fictitious context we observed a pattern of activation characterized by more prefrontal clusters, when compared to the real context, which is in accordance with the role of prefrontal cortex in emotional regulation. The literature on voluntary emotion regulation has extensively shown the activation of the prefrontal cortex during effortful reappraisal of emotional material (Ochsner and Gross, 2005; Eippert et al., 2007). Here, we found two main clusters implicated in the less deliberate reappraisal strategy (extrinsic), including right and left ventrolateral prefrontal cortex (VLPFC). These clusters overlap PFC systems implicated in reappraisal mechanisms or placebo manipulations (Beauregard et al., 2001; Ochsner et al., 2004; Lieberman et al., 2004; Wager et al., 2004). Interestingly, we did not find any DLPFC activation in the present study. This is quite interesting as we employed a subtle regulation strategy that changed the interpretation of emotional material in a less effortful way.

Although the results pointed above are quite interesting, there are some limitations. The results were obtained with contrasts performed within each experimental context. We reported the contrasts of mutilation vs. neutral images within the "real" and "fictitious" context, separately. Particularly, to investigate the prefrontal brain regions associated with the emotional regulation it would be interesting to conduct a whole brain analysis directly comparing both contexts. In fact, we also conducted a whole brain analysis sensitive to Fictitious>Real (data not shown). However, the prefrontal cluster obtained with the standard threshold (P<0.001) was small (less than 10 voxels) and we did not perform additional ROI analyses. Further studies should be performed to clarify the prefrontal brain network associated with this kind of emotional regulation.

Regarding the behavioral findings, we observed that the mean accuracy to judge a mutilation picture in the real context was superior in comparison to the judgment of neutral images. This can be interpreted as facilitation for recognizing mutilation images, which can be biologically relevant, as it indicates a potentially life-threatening situation. Interestingly, this effect was not found during the judgment of mutilation pictures in the fictitious context. It is possible that during the fictitious context, mutilation pictures did not elicit strong emotions, leading participants to judge them more often as neutral than negative. This result suggests that when the emotional impact of an unpleasant picture was down-regulated by a preceding safety narrative it no longer influenced the behavioral performance.

CONCLUSION

In summary, the present study provides new evidence on strategies to down-regulate emotional reactions, suggesting high flexibility on brain responses to emotional stimuli. During an extrinsic and incidental reappraisal of mutilation pictures, participants exhibited a down-regulation of amygdala and insula responses. The procedure used for

such demonstration is innovative as the strategy employed is less deliberate and seems to require less cognitive effort (Berkman and Lieberman, 2009). Understanding the beneficial effects of emotion regulation becomes particularly interesting to psychotherapeutic interventions that target anxiety disorders. In fact, therapeutic protocols for psychopathological conditions involving anxiety disorders have incorporated approaches to reestablish the abilities to regulate negative emotions (Mennin et al., 2005; Campbell-Sills et al., 2006; Berking et al., 2008). Actually, deficits in emotion regulation skills have been described not only in anxiety disorders but seem to be critical to the development and maintenance of a wide range of mental disorders (Gross and Muñoz, 1995). Thus, the extrinsic manipulation employed here can be seen as external information, which safely drives one's reactivity to emotional challenges. In this vein, anxiety patients, who frequently manifest reduced ability to voluntarily control their own emotions (Mennin et al., 2005) could take advantage of the exposure to safety signals during stressful events recall. Over time, this could have the potential role to teach patients the use of particular strategies that may be useful for the reduction of emotion arousal. Thus, the strategy employed here broadens the theoretical horizons and traditional forms of emotion regulation, suggesting new avenues of research.

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REFERENCES

- Azevedo TM, Volchan E, Imbiriba LA, Rodrigues EC, Oliveira JM, Oliveira LF, Lutterbach LG, Vargas CD (2005) A freezing-like posture to pictures of mutilation. Psychophysiology 42:255–260.
- Bargh J, Williams L (2007) The case for nonconscious emotion regulation. In: Handbook of emotion regulation (Gross JJ, ed), pp 429–445. New York: Guilford Press.
- Beauregard M, Levesque J, Bourgouin P (2001) Neural correlates of conscious self-regulation of emotion. J Neurosci 21:RC165.
- Berking M, Wupperman P, Reichardt A, Pejic T, Dippel A, Znoj H (2008) Emotion-regulation skills as a treatment target in psychotherapy. Behav Res Ther 46:1230–1237.
- Berkman ET, Lieberman MD (2009) Using neuroscience to broaden emotion regulation: theoretical and methodological considerations. Soc Personal Psychol Compass 3/4:475–493.
- Bradley MM, Lang PJ (1994) Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 25:49–59.
- Brett M, Anton J, Valabregue R, Polie J (2002) Region of interest analysis using an SPM toolbox. Presented at the 8th International Conference on Functional Mapping of the Human Brain 16[2].
- Campbell-Sills L, Barlow DH, Brown TA, Hofmann SG (2006) Effects of suppression and acceptance on emotional responses of individuals with anxiety and mood disorders. Behav Res Ther 44: 1251–1263.
- Center for the Study of Emotion and Attention and (CSEA-NIMH) (1999) The International Affective Picture System (IAPS). Gainesville, FL: University of Florida.
- Craig AD (2009) How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci 10:59-70.
- Del-Ben CM, Ferreira CA, Sanchez TA, Alves-Neto WC, Guapo VG, de Araujo DB, Graeff FG (in press) Effects of diazepam on

- BOLD activation during the processing of aversive faces. J Psychopharmacol, in press.
- Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S (2007) Regulation of emotional responses elicited by threat-related stimuli. Hum Brain Mapp 28:409–423.
- Erthal FS, de OL, Mocaiber I, Pereira MG, Machado-Pinheiro W, Volchan E, Pessoa L (2005) Load-dependent modulation of affective picture processing. Cogn Affect Behav Neurosci 5:388–395.
- Facchinetti LD, Imbiriba LA, Azevedo TM, Vargas CD, Volchan E (2006) Postural modulation induced by pictures depicting prosocial or dangerous contexts. Neurosci Lett 410:52–56.
- Foti D, Hajcak G (2008) Deconstructing reappraisal: descriptions preceding arousing pictures modulate the subsequent neural response. J Cogn Neurosci 20:977–988.
- Friston K, Holmes A, Worsley K, Poline J, Frith C (1995) Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 2:189–210.
- Globisch J, Hamm AO, Esteves F, Ohman A (1999) Fear appears fast: temporal course of startle reflex potentiation in animal fearful participants. Psychophysiology 36:66–75.
- Goldin PR, McRae K, Ramel W, Gross JJ (2008) The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biol Psychiatry 63:577–586.
- Gross J, Muñoz R (1995) Emotion regulation and mental health. Clin Psychol Sci Practice 2:151–164.
- Gross J, Thompson RA (2007) Emotion regulation: conceptual foundations. In: Handbook of emotion regulation (Gross JJ, ed), pp 3–24. New York: Guilford Press.
- Gross JJ (1998) Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. J Pers Soc Psychol 74:224–237.
- Gross JJ (2002) Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 39:281–291.
- Gross JJ, Levenson RW (1993) Emotional suppression: physiology, self-report, and expressive behavior. J Pers Soc Psychol 64: 970–986.
- Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003) Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry 53:494–501.
- Lane RD, Chua PM, Dolan RJ (1999) Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. Neuropsychologia 37:989–997.
- Lazarus RS, Alfert E (1964) Short-circuiting of threat by experimentally altering cognitive appraisal. J Abnorm Psychol 69:195–205.
- Lieberman MD, Jarcho JM, Berman S, Naliboff BD, Suyenobu BY, Mandelkern M, Mayer EA (2004) The neural correlates of placebo effects: a disruption account. Neuroimage 22:447–455.
- Macnamara A, Foti D, Hajcak G (2009) Tell me about it: neural activity elicited by emotional pictures and preceding descriptions. Emotion 9:531–543.
- Mazaica P, Whitfield S, Cooper J (2005) Detection and repair of transient artifacts in fMRI data. Human Brain Mapping Conference.
- Mennin DS, Heimberg RG, Turk CL, Fresco DM (2005) Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. Behav Res Ther 43:1281–1310.
- Milad MR, Quirk GJ, Pitman RK, Orr SP, Fischl B, Rauch SL (2007) A role for the human dorsal anterior cingulate cortex in fear expression. Biol Psychiatry 62:1191–1194.
- Mocaiber I, Pereira MG, Erthal FS, Figueira I, Machado-Pinheiro W, Cagy M, Volchan E, Oliveira L (2009) Regulation of negative emotions in high trait anxious individuals: an ERP study. Psychol Neurosci 2:211–217.
- Mocaiber I, Pereira MG, Erthal FS, Machado-Pinheiro W, David IA, Cagy M, Volchan E, de OL (2010) Fact or fiction? An event-related potential study of implicit emotion regulation. Neurosci Lett 476:84–88.

- Morris JS, Ohman A, Dolan RJ (1999) A subcortical pathway to the right amygdala mediating "unseen" fear. Proc Natl Acad Sci U S A 96:1680–1685.
- Morrison I, Peelen MV, Downing PE (2007) The sight of others' pain modulates motor processing in human cingulate cortex. Cereb Cortex 17:2214–2222.
- Moser JS, Hajcak G, Bukay E, Simons RF (2006) Intentional modulation of emotional responding to unpleasant pictures: an ERP study. Psychophysiology 43:292–296.
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD (2002) Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci 14:1215–1229.
- Ochsner KN, Gross JJ (2005) The cognitive control of emotion. Trends Cogn Sci 9:242–249.
- Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ (2004) For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 23:483–499.
- Oliveira LA, Oliveira L, Joffily M, Pereira-Junior PP, Lang PJ, Pereira MG, Figueira I, Volchan E (2009) Autonomic reactions to mutilation pictures: positive affect facilitates safety signal processing. Psychophysiology 46:870–873.
- Pereira MG, de OL, Erthal FS, Joffily M, Mocaiber IF, Volchan E, Pessoa L (2010) Emotion affects action: midcingulate cortex as a pivotal node of interaction between negative emotion and motor signals. Cogn Affect Behav Neurosci 10:94–106.
- Pereira MG, Volchan E, de Souza GG, Oliveira L, Campagnoli RR, Pinheiro WM, Pessoa L (2006) Sustained and transient modulation of performance induced by emotional picture viewing. Emotion 6:622–634.
- Pereira MG, Volchan E, Oliveira L, Machado-Pinheiro W, Rodrigues JA, Nepomuceno FV, Pessoa L (2004) Behavioral modulation by mutilation pictures in women. Braz J Med Biol Res 37:353–362.
- Pessoa L (2008) On the relationship between emotion and cognition. Nat Rev Neurosci 9:148–158.
- Pessoa L, Adolphs R (2010) Emotion processing and the amygdala: from a "low road" to "many roads" of evaluating biological significance. Nat Rev Neurosci 11:773–783.
- Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME (2005) Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry 57:210–219.
- Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16:331–348.
- Phelps EA, LeDoux JE (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48:175–187.
- Ray RD, Ochsner KN, Cooper JC, Robertson ER, Gabrieli JD, Gross JJ (2005) Individual differences in trait rumination and the neural systems supporting cognitive reappraisal. Cogn Affect Behav Neurosci 5:156–168.
- Thompson RA (2011) Emotion and emotion regulation: two sides of the developing coin. Emot Rev 3:53–61.
- Vuilleumier P, Armony JL, Driver J, Dolan RJ (2001) Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 30:829–841.
- Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303:1162–1167.
- Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, Evans AC (2002) A general statistical analysis for fMRI data. Neuroimage 15:1–15.