

Getting Over It: Long-Lasting Effects of Emotion Regulation on Amygdala Response

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Abstract

Little is known about whether emotion regulation can have lasting effects on the ability of a stimulus to continue eliciting affective responses in the future. We addressed this issue in this study. Participants cognitively reappraised negative images once or four times, and then 1 week later, they passively viewed old and new images, so that we could identify lasting effects of prior reappraisal. As in prior work, active reappraisal increased prefrontal responses but decreased amygdala responses and self-reported emotion. At 1 week, amygdala responses remained attenuated for images that had been repeatedly reappraised compared with images that had been reappraised once, new control images, and control images that had been seen as many times as reappraised images but had never been reappraised. Prefrontal activation was not selectively elevated for repeatedly reappraised images and was not related to long-term attenuation of amygdala responses. These results suggest that reappraisal can exert long-lasting “dose-dependent” effects on amygdala response that may cause lasting changes in the neural representation of an unpleasant event’s emotional value.

Keywords

emotion regulation, reappraisal, amygdala, fMRI, long-term effects

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In the everyday sea of emotional waves and swells, the ability to exert top-down regulatory control over emotion helps people maintain an even keel. So important is this ability that problems with it are hallmarks of numerous clinical disorders (Berking et al., 2008; Kring & Sloan, 2009). Accordingly, experimental research on the behavioral and neural mechanisms of emotion regulation has grown enormously in the past decade. The scope of this work is limited, however, by its almost exclusive focus on the regulation of emotions as they happen.

For many events, however, it matters a great deal whether the effects of regulation endure over time. For example, consider how prior attempts to get over a bad breakup are tested in a chance encounter with one’s ex. It matters whether the flame still burns, takes continued effort to extinguish, or has truly gone out, such that one could be said to have truly “gotten over it.” Parallel examples abound, including in clinical contexts, where the efficacy of cognitive behavior therapies turns not just on

a patient’s ability to control his or her fears and anxieties in a given moment, but on whether those feelings return when emotional triggers are encountered in the future (Berking et al., 2008; Butler, Chapman, Forman, & Beck, 2006; Dobson, 2010; Hollon & Beck, 1994).

At present, very little is known about the neural mechanisms determining when and how the effects of emotion regulation will be long-lasting. We addressed this issue by testing for lasting effects of a well-studied cognitive regulatory strategy known as reappraisal. Reappraisal involves changing one’s emotional response by changing one’s interpretation of the meaning of a stimulus or situation (Gross, 1998b, 2013). When used to downregulate negative emotion, reappraisal can effectively attenuate

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self-report, physiological, and neural markers of affective response—particularly in the amygdala—by recruiting prefrontal systems implicated in domain-general cognitive-control functions (Davidson, 2002; Denny, Silvers, & Ochsner, 2009; Gross, 1998a; Gross & John, 2003; Ochsner & Gross, 2008; Ochsner, Silvers, & Buhle, 2012; Silvers, Buhle, & Ochsner, 2014; Walter et al., 2009). Although two recent studies found that amygdala responses to previously reappraised stimuli remained attenuated at the end of a single experimental session—10 to 15 min after regulation took place (Erk et al., 2010; Walter et al., 2009)—it is unknown whether and under what circumstances this attenuation can endure over longer periods of time, and what neural mechanisms may be involved.

Using a novel variant of an established method, we asked three novel questions about the long-lasting effects of reappraisal as a means of successfully attenuating negative emotion. First, we asked whether the downregulatory effects of reappraisal on amygdala responses can last for 1 week. To address this question, we asked participants to complete a reappraisal task with aversive images, expecting that successful reappraisal would be accompanied by increased activity in lateral prefrontal cortex and decreased activity in the amygdala. One week later, participants passively viewed brief re-presentations of previously seen images. This allowed us to determine whether attenuation of amygdala responses endured over time.

Second, we asked whether the durability of this attenuation of amygdala responses depends on how many attempts one makes at regulating a response. We compared the long-term effects of reappraising stimuli one time as compared with four times, building on clinical findings that long-lasting regulatory effects may follow from repeated attempts to reappraise a given stimulus (Dobson, 2010; Feske & Chambless, 1995). If repetition (i.e., higher “doses”) of reappraisal matters, then the attenuation of amygdala responses should be longer lasting for stimuli reappraised four times than for those reappraised once.

Third, to probe the mechanisms that underlie the maintenance of regulatory effects, we asked whether long-term attenuation of amygdala responses could occur without the continued need for top-down prefrontal regulatory control, reflecting an enduring change in initial affective response tendencies (McRae, Misra, Prasad, Pereira, & Gross, 2012; Ochsner & Gross, 2007; Ochsner et al., 2009). If reappraisal can change response tendencies—and active top-down regulation is no longer required for amygdala responses to be diminished—then sustained amygdala attenuation should be observed in the absence of a relationship with prefrontal activity. In colloquial terms, such findings would support the idea that reappraisal can help one “get over” an emotional upset such that one no longer needs to exert top-down control to regulate responses to it.

Method

Participants

Twenty-two healthy adult participants (mean age = 24.0 years; 15 female) were recruited and gave informed consent to participate in accordance with the human-subjects regulations of New York University. Participants were paid approximately \$120 for the entire experiment (\$50 for each of two scanning sessions plus \$10/hr for a pre-exposure session, described in the Procedure section). Exclusions were made for the following reasons: Incorrect images were shown to 1 participant at the final scanning session; 1 participant was a behavioral outlier (reported negative affect during the preexposure session $> 3 SD$ from the mean), and there was evidence that this participant had not been engaged in performing the task; because of a technical problem, the numbers of regulation and no-regulation training blocks (see Procedure) were unbalanced for 1 participant; 1 participant repeatedly fell asleep, including for entire runs; and functional image distortions for 1 participant were unacceptably large, in part because of repeated repositioning in the scanner. Thus, the reported results are based on data from 17 participants (mean age = 24.1 years; 12 female). A priori targets for sample size and when to stop data collection were based on sample and effect sizes reported in the extant literature on reappraisal (i.e., commonly around 16–18 participants; for a meta-analysis, see Buhle et al., 2014).

Materials

One hundred eighty negative images and 36 neutral images were selected from the International Affective Picture System (Lang, Greenwald, Bradley, & Hamm, 1993) on the basis of their normative ratings (negative images: mean valence = 2.42, mean arousal = 5.75; neutral images: mean valence = 5.51, mean arousal = 3.29). An additional set of 12 similarly valenced and arousing negative images was used during training prior to the preexposure and active-regulation sessions (see Procedure). The negative images were separately and randomly assigned to trial type before the task scripts were generated for each participant, with the stipulation that the randomized trial-type assignments could not result in any pairwise significant or marginal ($p < .10$, two-tailed) differences in normative valence or arousal across all trial types in the experiment.

Procedure

Participants completed three sessions over the course of 9 days: a behavior-only training session (preexposure) and two functional MRI (fMRI) scanning sessions (Fig. 1).

	Day 1: Preexposure	Day 2: Active Regulation	Day 9: Long-Term Reexposure
Session Parameters			
Location	Behavioral Lab	Scanner	Scanner
Task	Reappraisal	Reappraisal	Passive Viewing
Presentation	8 s/Trial	8 s/Trial	2 s/Trial
Trial Type			
Repeated Reappraise Negative	Reappraise ×3	Reappraise ×1	View ×1
Repeated Look Negative	Look ×3	Look ×1	View ×1
Single Reappraise Negative	—	Reappraise ×1	View ×1
Single Look Negative	—	Look ×1	View ×1
Single Look Neutral	—	Look ×1	View ×1
Novel Negative	—	—	View ×1

Fig. 1. Task paradigm. During the preexposure session on Day 1, participants completed a standard reappraisal task in the behavioral laboratory. On reappraise trials, they downregulated the negative emotions elicited by negative images, and on look trials they responded naturally to a matched set of images. This task was completed three times in succession, with a given image being reappraised each time or looked at each time. During the active-regulation session on Day 2, participants completed the reappraisal task in the scanner. On repeated-presentation trials, they once again reappraised or looked at the images from the preexposure session. On single-presentation trials, they reappraised or looked at negative and neutral images they were seeing for the first time. During the long-term reexposure session on Day 9, participants passively viewed images from the active-regulation session along with never-before-seen (novel) negative images. Inclusion of these novel images allowed us to determine whether amygdala responses to stimuli reappraised repeatedly and stimuli reappraised just once remained attenuated (as during active regulation) or returned to the level of responses to novel aversive events.

Day 1: preexposure. In the preexposure session, participants first received training in reappraisal using psychological distancing (Ochsner & Gross, 2008; Trope & Liberman, 2010). They were told that they would see a number of trials, each beginning with an instruction cue word presented in the center of a computer screen: either “LOOK” or “DECREASE.” The experimenter explained that when the cue was “LOOK,” they should look at and respond naturally to the image that followed, whereas when the cue was “DECREASE,” they should reappraise the image as a detached, objective impartial observer, imagine that the pictured event occurred far away or a long time ago, or both. Participants were then given walk-through training in reappraisal; they were asked to

self-generate appropriate reappraisals in response to two sample reappraise trials, and the experimenter did not proceed until they could adequately self-generate a reappraisal. Participants then completed a fixed-time practice set of three “LOOK” and three “DECREASE” trials.

Next, participants completed a computerized image-based reappraisal task similar to one described previously (Denny & Ochsner, 2014; McRae et al., 2010; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). On each trial, the instruction cue was presented for 2 s, followed by presentation of an image for 8 s, a jittered fixation interval of between 3 and 7 s ($M = 4$ s), a negative-affect rating period of 3 s, and a final jittered

interstimulus fixation interval of between 3 and 7 s ($M = 4$ s). Participants were instructed that during image presentation, they should keep their eyes on the image for the entire time that it was on the screen. They were also told that when they rated their negative affect (on a scale from 1, *weak*, to 5, *strong*), it was important for them to be as honest as they could be about how they felt at that moment regardless of whether their attempts to decrease their negative emotion were successful.

Participants completed six runs of trials that were blocked by trial type. Specifically, they completed three runs of reappraise (“DECREASE”) trials and three runs of look trials. Each run contained 36 trials, all with negative images, and the blocks were repeated such that each reappraise and look trial was presented three separate times. Reappraise and look blocks were presented in alternating order, and which type of block was presented first was counterbalanced across participants. Within each run, trials were presented in randomized order. Following the completion of the sixth task block, participants were reminded of the session that would take place the following day.

Day 2: active regulation. Participants returned for an fMRI scan 1 day later. They were first given additional walk-through training in following the reappraisal instructions using unique images not shown in the actual task. Which of two sets of images was used for training on Day 1 and which was used for training on Day 2 was counterbalanced across participants. Next, participants entered the scanner and completed an 8-min resting-state scan, during which they were instructed to have whatever thoughts and feelings they naturally had and to keep their eyes closed, but to remain awake. (Data from the resting-state scans on Days 2 and 9 were not examined for the present report.) Then, participants completed the active-regulation task, which had the same trial structure and same two instruction cues (“LOOK” or “DECREASE”) as the reappraisal task in the preexposure session. This time, each of 180 images was shown once. The 36 negative images reappraised previously (*repeated-reappraise negative trials*) and the 36 images looked at previously (*repeated-look negative trials*) were presented along with 36 new negative images with reappraisal instructions (*single-reappraise negative trials*), 36 new negative images with look instructions (*single-look negative trials*), and 36 new neutral images with look instructions (*single-look neutral trials*). These 180 trials were evenly distributed into six functional runs, with 6 trials of each trial type included in each run. Within each run, trials were presented in randomized order.

Immediately following active regulation, participants completed another 8-min resting scan, followed by a passive-viewing scan in which half of the images presented

during active regulation and 18 novel negative images were presented. This initial passive-viewing scan is not the focus of the current study.

Day 9: long-term reexposure. One week after the active-regulation session, participants returned for an fMRI scan. They first underwent an 8-min resting-state scan. This was followed by a passive-viewing scan during presentation of 108 images: the images from active regulation that had not been shown during the initial passive-viewing scan (i.e., 18 single-look neutral trials, 18 single-look negative trials, 18 single-reappraise negative trials, 18 repeated-look negative trials, and 18 repeated-reappraise negative trials), plus 18 novel negative images (*novel negative trials*). Participants were instructed to simply view the images, keeping their eyes on them the entire time; no instruction cues were presented. Each image was presented for 2 s, followed by a jittered interstimulus fixation interval of between 3 and 7 s ($M = 4$ s). All 108 images were presented in a single run, in a novel randomized order for each participant. Following this last passive-viewing scan, a final 8-min resting-state scan was performed.

Data acquisition and analysis

Behavioral data. Stimulus presentation and behavioral-data acquisition were controlled using E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA). Behavioral data were analyzed using linear mixed models incorporating fixed effects for valence (negative vs. neutral), instruction type (reappraise vs. look), and number of presentations (repeated vs. single), and a random effect consisting of an intercept for each participant.

fMRI data. Whole-brain fMRI data were acquired on a 3.0-T Siemens Allegra MRI system. Anatomical and functional images were acquired with a T2*-sensitive echo planar imaging (EPI) blood-oxygen-level-dependent (BOLD) sequence (repetition time = 2,000 ms, echo time = 15 ms, flip angle = 82°, 34 slices, 3-mm isometric voxels, no interslice gap). Functional images were preprocessed using SPM8 software (Wellcome Trust Centre for Neuroimaging, University College London, London, England), with slice-timing correction, realignment, and coregistration between each participant’s functional and anatomical data. Images were normalized to a standard template (Montreal Neurological Institute, or MNI) with 3-mm isometric voxels and were spatially smoothed using a Gaussian kernel (6 mm full-width at half-maximum).

A random-effects general linear model (GLM) was then run using NeuroElf Version 0.9c software (neuroelf.net). For active regulation, the model specified separate regressors for fMRI responses to the cue (differentiated

by two cues: “LOOK” and “DECREASE”), stimulus presentation (differentiated by five trial types: single-look neutral, single-look negative, single-reappraise negative, repeated-look negative, and repeated-reappraise negative), and rating period (undifferentiated by trial type). For the passive-viewing scan at long-term reexposure, regressors were specified for each stimulus presentation period (differentiated by six trial types: single-look neutral, single-look negative, single-reappraise negative, repeated-look negative, repeated-reappraise negative, and novel negative). All task regressors were convolved with a canonical hemodynamic response function. Participants’ six motion parameter estimates were also entered into the GLM as covariates of no interest. Participants’ time courses underwent percentage-signal-change transformation. The GLM was computed using ordinary least squares regression and random-effects modeling. Contrasts between various trial types at active regulation and at long-term reexposure were then performed. We did not perform intersession contrasts (i.e., active regulation vs. long-term reexposure) among trial types, however, given that the differences in duration of stimulus presentation (i.e., 8 s vs. 2 s) and in the task performed (i.e., reappraisal vs. passive viewing) would limit the interpretability of the results.

Data were visualized and statistically thresholded using NeuroElf. Beta estimates were extracted for a priori regions of interest (ROIs; i.e., amygdala and ventrolateral prefrontal cortex, or vlPFC) and analyzed using linear mixed models, as described earlier for the behavioral analysis. All functional ROIs in the amygdala were masked with a Brodmann-atlas-based anatomical boundary using NeuroElf. Whole-brain family-wise error (FWE) multiple-comparison correction thresholds were determined using AlphaSim (Ward, 2000). In small-volume a priori ROIs (i.e., amygdala), FWE extent thresholds were small-volume-corrected using a bilateral Brodmann-atlas-based anatomical amygdala mask. Anatomical labels were determined by converting MNI coordinates to Talairach space (Talairach & Tournoux, 1988) and using the Talairach Daemon brain atlas (Lancaster et al., 2000). Reported coordinates are in MNI space.

Functional connectivity. Finally, as part of an assessment of whether results at long-term reexposure were driven by top-down or bottom-up mechanisms, we performed functional-connectivity analyses (psychophysiological interaction, or PPI, analyses; Friston et al., 1997) using as a seed region the 40-voxel right amygdala cluster that showed long-term attenuation of activity on repeated-reappraise negative trials (see Table S2 in the Supplemental Material available online). A GLM was then computed incorporating regressors for the within-participant coupling of activity between this right amygdala

seed region and other brain areas, as well as a PPI term representing the within-participant coupling of the seed region and other brain areas as modulated by the psychological context of interest, which in this case was the difference between repeated-reappraise negative trials and all other negative trial types at long-term reexposure (i.e., repeated-reappraise negative $- 0.25 * [\text{repeated-look negative} + \text{single-reappraise negative} + \text{single-look negative} + \text{novel negative}]$). Participants’ six motion parameter estimates were also entered into the GLM as covariates of no interest. Participants’ time courses underwent percentage-signal-change transformation. Following GLM estimation, random-effects analyses were performed, as described earlier for the whole-brain analyses, with contrasts for regions showing a significant PPI effect. Results were statistically thresholded as described earlier for the whole-brain analyses.

Results

Preexposure and active-regulation sessions

As the focus of this report is the long-term reexposure session, we summarize the results of the preexposure and active-regulation sessions only briefly here (for more details, see the Supplemental Material). For present purposes, three findings are important to document. First, during the preexposure session, reappraisal was effective in decreasing negative affect (see Fig. S1A in the Supplemental Material). Second, during the active-regulation session, reappraisal was effective in decreasing negative affect for both repeated-presentation stimuli (i.e., those that had been presented in the preexposure session) and single-presentation stimuli (i.e., those that were presented for the first time; see Fig. S1B in the Supplemental Material). Third, the fMRI data mirrored these effects, revealing attenuation of right amygdala activity and engagement of left vlPFC regions typical of reappraisal for both repeated- and single-presentation stimuli (see Fig. S2 and Table S1 in the Supplemental Material).

Apart from largely replicating prior work on the neural correlates of reappraisal during individual sessions (Buhle et al., 2014), these data are important because they set the stage for determining whether and how effective reappraisals (which had occurred four times for repeated-presentation stimuli and just once for single-presentation stimuli by the conclusion of the active-regulation session) led to long-lasting effects on amygdala responsivity 1 week later. In addition, because only self-report data were collected during the preexposure session, it was important to perform a manipulation check for the validity of these self-report data. To do this, we

correlated regulatory success for repeated-presentation stimuli during preexposure and active regulation (i.e., the within-participant difference in average negative-affect ratings between repeated-look negative and repeated-reappraise negative trials) with the magnitude of amygdala attenuation for repeated-reappraise negative trials 1 week later at long-term reexposure. This correlation was significant (see the Supplemental Material, including Fig. S3), which suggests that regulatory success during the preexposure session contributed to long-term durability of reappraisal-related amygdala modulation.

Long-term reexposure session

In the long-term reexposure session, participants passively viewed images in six trial types (see Fig. 1). Four trial types were of primary interest because they allowed us to directly examine whether and under what circumstances reappraisal has long-lasting effects on amygdala response. On repeated-reappraise negative and repeated-look negative trials, participants viewed images that had been previously presented in both the preexposure session and the active-regulation session, for a total of four prior presentations per image. And on single-reappraise negative and single-look negative trials, participants viewed images that had been previously presented only in the active-regulation session, for only one prior presentation per image.

Two additional trial types were included. On single-look neutral trials, participants viewed neutral images that had been seen once in the active-regulation session. Inclusion of these trials allowed us to determine whether amygdala responses to previously seen negative images were similar to the responses to previously seen nonaversive stimuli (i.e., whether amygdala responses were attenuated on trial types containing previously seen negative images). By contrast, on novel negative trials, participants viewed never-before-seen images. These trials allowed us to determine whether responses to previously seen negative images had returned to the level of responses to negative images that had never been seen before.

Can amygdala attenuation be long-lasting, and if so, under what conditions?

Our first two questions about the long-term effects of reappraisal were whether attenuation of amygdala responsivity may be observed 1 week after reappraisal and whether such effects can occur after a single attempt at reappraisal or require repeated reappraisal opportunities. To answer these questions, we examined the data from the long-term reexposure session to see whether there were main effects of instruction type (i.e., reappraise negative vs. look negative trials, collapsing across number of presentations) or number of presentations (collapsing across instruction type) on the amygdala response (within an

anatomically defined ROI). Neither effect exceeded small-volume-corrected FWE thresholds.

We then tested whether there was a lasting effect of instruction type for either repeated- or single-presentation stimuli considered separately that was not evident in the nonsignificant overall main effect of instruction type. We found that right amygdala activity remained attenuated on repeated-reappraise negative trials relative to repeated-look negative trials (73 voxels; peak coordinates: [27, -9, -27]; FWE small-volume-corrected $p < .05$, two-tailed). However, the contrast of single-reappraise negative versus single-look negative trials did not yield results that exceeded small-volume-corrected FWE thresholds in the amygdala or any other brain region. Further, a direct comparison of repeated-reappraise negative and single-reappraise negative trials revealed reduced activity in right amygdala for repeated-reappraise negative trials (21 voxels; peak coordinates: [24, -6, -24]; FWE small-volume-corrected $p < .05$, two-tailed).

Taken together, these results suggested that amygdala responses showed long-term attenuation for negative stimuli only if those stimuli had been repeatedly reappraised. To confirm this, we tested the 2 (instruction type) \times 2 (number of presentations) interaction (i.e., including only repeated-reappraise negative, repeated-look negative, single-reappraise negative, and single-look negative trials) within the ROI defined by the contrast of repeated-reappraise negative versus single-reappraise negative trials. Note that this ROI definition was independent of look negative trials and their contribution to the 2 \times 2 interaction. We found that the interaction was significant within this ROI, $F(1, 48) = 5.22$, $p < .03$; activity was significantly lower for repeated-reappraise negative trials relative to all other negative trial types and was not significantly different between repeated-look negative and single-look negative trials (see Fig. S4 in the Supplemental Material).

In order to provide a complementary, single-step, and direct test of the existence of this critical 2 \times 2 “dose-dependence” interaction effect in the amygdala, we computed the 2 \times 2 interaction contrast: (repeated-reappraise negative – repeated-look negative) – (single-reappraise negative – single-look negative). This contrast yielded a significant result in right amygdala, again showing lowest activity for repeated-reappraise negative trials (30 voxels; peak coordinates: [27, -9, -21]; FWE small-volume-corrected $p < .05$, two-tailed).

Finally, in order to further assess the extent to which this effect of relative attenuation on repeated-reappraise negative trials extended to all negative trial types at long-term reexposure, we computed the corresponding contrast including novel negative trials: repeated-reappraise negative – 0.25 * [repeated-look negative + single-reappraise negative + single-look negative + novel negative] (see Fig. S5 and Table S2 in the Supplemental

Material). This contrast showed that responses in right amygdala were significantly lower on repeated-reappraise negative trials than on all other negative trial types (40 voxels; peak coordinates: [30, -3, -21], FWE small-volume-corrected $p < .05$, two-tailed; see the brain image in Fig. 2a).

Because we scanned participants during both the active-regulation and the long-term reexposure sessions, we then used a conjunction analysis to determine whether the amygdala region showing these long-term effects of repeated reappraisal overlapped with the region showing the concurrent effects of reappraisal during active regulation. Although the two regions had different peak foci, they showed significant overlap in the right dorsal amygdala (9 voxels; peak coordinate: [24, -9, -15], FWE small-volume-corrected for right amygdala $p < .05$, two-tailed; see the brain image in Fig. 2a). Crucially, these overlap voxels showed main effects of reappraisal and repeated presentation during active regulation (Fig. 2a, left graph) and showed long-lasting attenuation for repeated-reappraise negative trials during long-term reexposure (Fig. 2a, right graph). Figure 2a also shows activity within these overlap voxels in the right amygdala for all other trial types at active regulation (left graph) and long-term reexposure (right graph).

Does long-lasting amygdala attenuation require continued prefrontal engagement?

Our third question concerned the potential mechanisms underlying amygdala attenuation at long-term reexposure—in particular, whether attenuation reflected a lasting change in the amygdala's bottom-up, stimulus-driven response profile (McRae et al., 2012; Ochsner et al., 2009) as opposed to ongoing prefrontally mediated top-down regulation. Although the long-term reexposure session did not involve active demands to reappraise the presented negative images, it is possible that these images, particularly those that had already been reappraised four times, triggered spontaneous reappraisal or recollection and reinstatement of prior reappraisals. By contrast, it is possible that repeated reappraisal can result in long-term attenuation in the image-evoked amygdala response even without invoking active reappraisal. We performed four analyses to address this question.

First, we sought to determine whether a critical cognitive-control-related region that had been recruited during initial reappraisal showed a response profile suggestive of ongoing regulation at long-term reexposure. For this analysis, we focused on a region of left vlPFC that meta-analyses have shown is the region most typically associated with reappraisal (Buhle et al., 2014; Ochsner & Gross, 2008) and that was active during reappraisal in the active-regulation session. If regulation occurred at long-term reexposure, we would expect the pattern of left vlPFC activity to be the mirror image of what was

observed for the amygdala; that is, we would expect vlPFC activity to be greatest when there was long-term amygdala attenuation (repeated-reappraise negative trials) and lowest when amygdala attenuation was not observed (trials with all other types of negative images). Using the left vlPFC ROI defined at active regulation (see the brain image in Fig. 2b and also the left graph, which shows activity for all trial types at active regulation), we extracted beta estimates for the long-term reexposure session. As shown in the right graph in Figure 2b, in contrast to amygdala activity, vlPFC activity did not show a significant difference between repeated-reappraise negative and repeated-look negative trials at long-term reexposure, but rather showed a main effect of number of presentations, $F(1, 80) = 8.55$, $p < .01$, with activity being greatest for repeated-presentation trials overall relative to single-presentation trials (including single-reappraise negative, single-look negative, and single-look neutral trials) and novel negative trials. This pattern is consistent with left vlPFC's role in retrieval of semantic information about stimuli (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Badre & Wagner, 2007; Thompson-Schill, Bedny, & Goldberg, 2005), as such retrieval may have been more likely for repeatedly presented stimuli.

Second, we followed up this targeted search with a whole-brain analysis using the contrast that showed that long-term attenuation of amygdala response was observed only for repeatedly reappraised stimuli (i.e., repeated-reappraise negative trials vs. all other negative-image trial types) to determine whether there were any regions at long-term reexposure whose activity might be indicative of prefrontally mediated regulation (i.e., any regions showing greatest activity for repeated-reappraise negative trials). Figure S5 and Table S2 in the Supplemental Material show that at long-term reexposure, no regions exhibited activity that was greatest for repeated-reappraise negative trials.

Although these first two analyses showed that no control-related regions exhibited greater average levels of activity when long-lasting amygdala attenuation was observed, we performed our third and fourth analyses to determine whether lasting attenuation was associated with differential patterns of functional connectivity between the amygdala and control regions. In the third analysis, we examined between-participants connectivity. For this analysis, we extracted activation from the right amygdala region showing long-term attenuation for repeatedly reappraised stimuli (see the brain image in Fig. 2a, yellow and green regions, indicating the 40-voxel region where activity was attenuated during long-term reexposure). A whole-brain correlational analysis was then used to determine whether participants showing greater attenuation in this seed region also showed greater activity in any other brain regions at long-term reexposure. No FWE-corrected effects were observed in PFC.

a

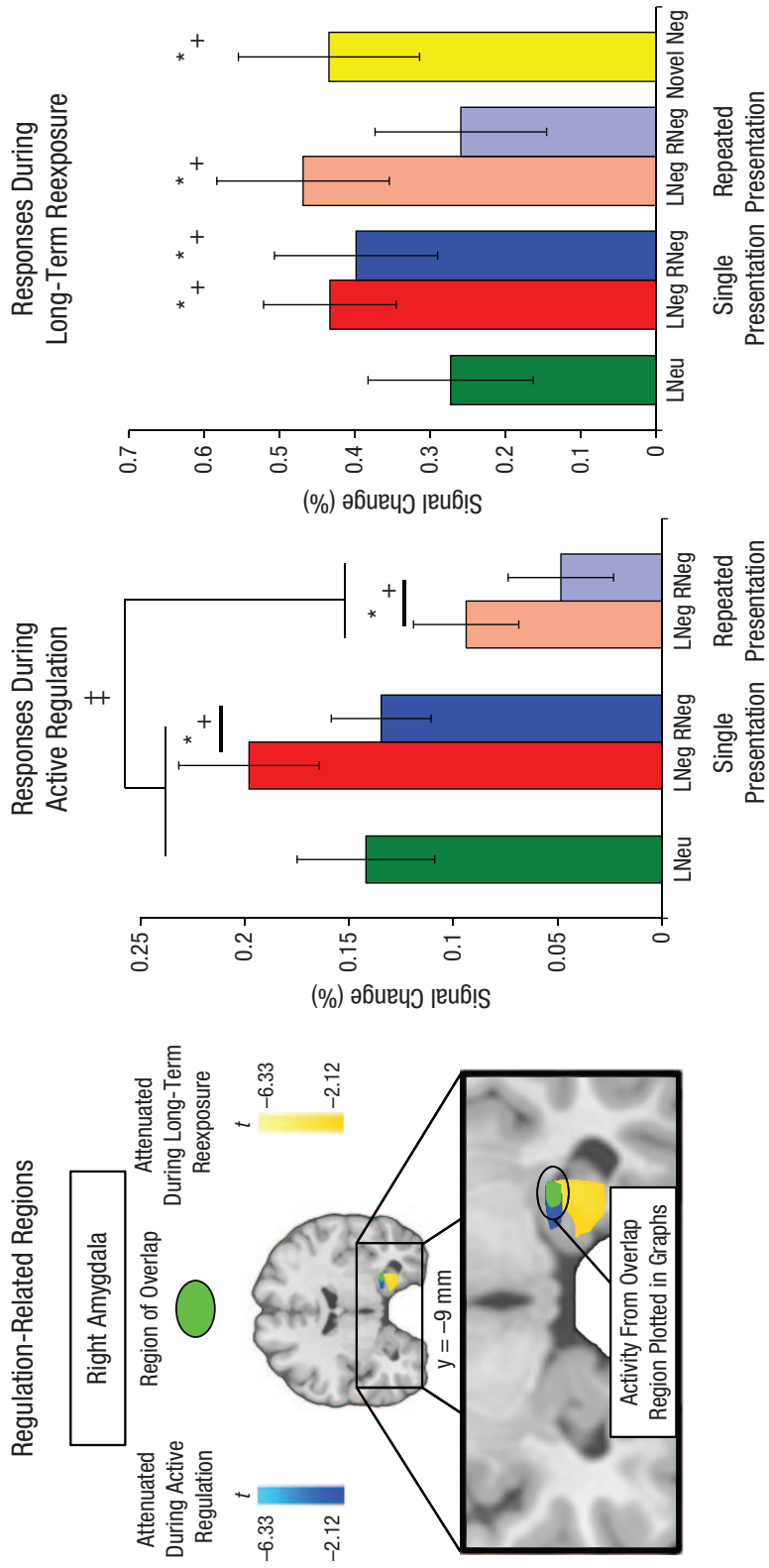


Fig. 2. (continued on next page)

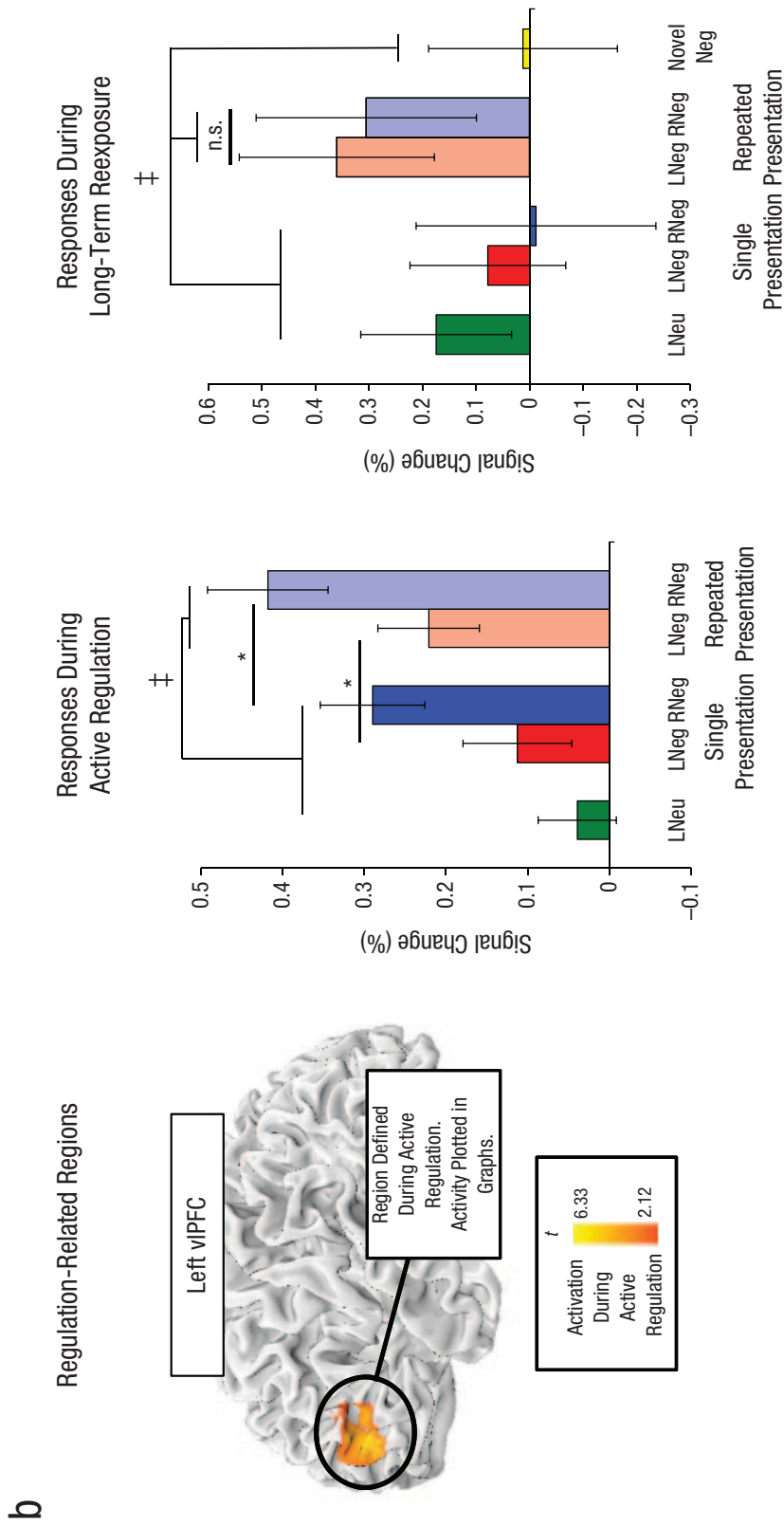


Fig. 2. Results for (a) the amygdala and (b) left ventrolateral prefrontal cortex (vIPFC) during active regulation and long-term reexposure. The brain image in (a) shows the location of the conjunction region of interest (ROI) in right amygdala that was defined by the regions showing regulation-related attenuation during active regulation and long-term reexposure (see Tables S1 and S2 in the Supplemental Material). To the right are graphs showing activity of this ROI for each trial type during active regulation and long-term reexposure. For active regulation, asterisks indicate significant differences between the indicated trial types ($p < .05$, two-tailed), and plus signs indicate comparisons that are nonindependent of the selection criteria for the ROI during this phase of the study (i.e., activation on reappraise negative trials $>$ activation on look negative trials, collapsed across number of presentations); these comparisons marked with plus signs are shown for illustration of the selection criteria only. For long-term reexposure, asterisks indicate significant differences from repeated-reappraise negative trials ($p < .05$, one-tailed), and plus signs indicate comparisons that are nonindependent of the selection criteria for the ROI during this phase of the study (i.e., activation on repeated-reappraise negative trials vs. activation on all other negative trial types); these comparisons marked with plus signs are shown for illustration of the selection criteria only. The brain image in (b) shows the location of the left vIPFC ROI that was defined by the contrast of reappraise negative trials $>$ look negative trials (collapsed across number of presentations) during active regulation. To the right are graphs showing activity of this ROI for each trial type during active regulation and long-term reexposure. For active regulation, asterisks indicate significant differences between the indicated trial types ($p < .05$, two-tailed). In all the graphs, daggers indicate a main effect of number of presentations ($p < .01$), and error bars represent ± 1 SEM. L = look trials; Neu = neutral images; Neg = negative images; R = reappraise trials.

This analysis was then repeated using activity on repeated-reappraise negative trials alone (rather than activity on these trials relative to all other negative trial types), and again, no FWE-corrected PFC effects were observed.

Finally, in the fourth analysis, we used a within-subjects measure of connectivity implemented as a PPI analysis (Friston et al., 1997). This analysis tested whether the amygdala region used in the preceding analysis showed a stronger time-series correlation with PFC on repeated-reappraise negative trials compared with other negative trial types at long-term reexposure. No PFC regions showed an FWE-corrected PPI effect. Thus, taken together, these analyses yielded no evidence that top-down prefrontally mediated control is required at long-term reexposure in order for amygdala attenuation to endure.

Discussion

This study began with the question of whether we could find neural evidence that individuals can use cognitive regulatory strategies to “get over” unpleasant events, such that their subsequent emotional responses to these events remain diminished. One week after participants successfully used cognitive reappraisal to diminish behavioral (negative affect) and neural (right amygdala) markers of emotional response, the amygdala’s response remained attenuated for images that had been reappraised four times, but not for images that had been reappraised only once. Critically, we found no evidence that these enduring changes in amygdala response required ongoing recruitment of prefrontal regions involved in top-down control (including those that were engaged during active regulation). Taken together, these findings provide evidence that cognitive regulation can create long-lasting changes in the ability of stimuli to elicit affective responses. They therefore have important implications for both basic and translational research.

This study builds on prior basic research in three ways. First, it builds on studies showing that reappraisal-related effects on the amygdala can last for periods of up to 15 min (Erk et al., 2010; Walter et al., 2009) by elucidating conditions sufficient for, and the mechanisms underlying, regulatory effects that can last over many days. Second, our results suggest that there may be different routes by which cognitive forms of regulation—as opposed to related, but distinct, forms of affective learning—exert lasting changes on affective response. For example, extinction leads to lasting reductions in amygdala responses to stimuli that previously elicited conditioned fear responses via top-down signals from ventromedial prefrontal regions thought to inhibit amygdala-mediated responding (Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk, Garcia, & Gonzalez-Lima, 2006; Sotres-Bayon, Cain, & LeDoux, 2006). By contrast, although lateral

prefrontal regions associated with cognitive control are important for initially reappraising a stimulus in an effective manner, we found that lasting effects on amygdala response occurred in the absence of continued prefrontal control. Future research could test whether and how regulatory strategies differ in requiring continued involvement of prefrontal control systems in order for lasting effects on affective responses to be observed. Third, given that the amygdala has multiple subnuclei, it is tempting to ask which of these subnuclei (and their associated functions) are reflected in the right dorsal amygdala region that showed both concurrent and lasting effects of reappraisal. Because we did not acquire functional data of sufficient resolution to draw strong inferences on this point, high-resolution imaging is needed to more precisely determine which amygdala subnuclei are influenced by reappraisal in the short and long term.

Our results also have translational implications for clinical contexts. First, they may provide insights into some of the mechanisms by which cognitive therapies can result in lasting changes in affective responses. We found that four attempts, but not one attempt, to reappraise the meaning of an aversive stimulus led to a lasting change in affective responding. To the extent that reappraisal provides a laboratory model of the cognitive regulatory processes involved in cognitive behavior therapy, the present study suggests that changes in amygdala responses could be a dose-dependent marker for successful therapeutic outcomes (Dobson, 2010; Feske & Chambless, 1995). This leads to a second point. The methods and results of this study could serve as a new framework for probing regulatory abilities in clinical, developmental, or aging populations in which these abilities are not yet mature or have broken down. For example, future work could determine the conditions under which a given population can effectively reappraise stimuli in the moment, as well as how long the effects of reappraisal last. Reports that the effects of a single reappraisal on amygdala responses lasted 15 min for healthy adults (Walter et al., 2009), but did not last for individuals with major depressive disorder (Erk et al., 2010), highlight how valuable such work could be.

Overall, there remain important questions about the boundary conditions for the observed effects. Our results demonstrate that the effects of cognitive regulation on amygdala responses can last a week if one has reappraised a stimulus four times. But it is not yet known whether these effects can last for even longer time periods, how smaller and larger numbers of reappraisal attempts may alter the durability of the effects over longer time periods, or how much the detectability of long-term effects depends on how one is reexposed to previously reappraised stimuli (e.g., the duration of the reexposure and whether reexposure occurs during

passive viewing or active regulation). Future research could address these issues.

Another issue for future work is whether it may be necessary in some cases for the prefrontal involvement seen during active regulation to be reevoked during subsequent reexposures in order for long-term effects of regulation to be observed. To address this issue, it could be useful, for example, to directly compare prefrontal activity during active regulation and reexposure, which we could not do in the present study because of the differences in stimulus presentation duration and task across the testing sessions. Further, in the present study, our inferences about long-term changes in the emotional value of negative stimuli are qualified by the fact that we measured only neural responses at long-term reexposure (albeit with a focus on neural activity with clearly established links to negative affective responses). Future research may clarify whether effects of repeated reappraisal on amygdala responses are paralleled by long-term changes in other response channels, such as self-reported emotional experience, facial expressive behavior, autonomic responses, and memory for regulated events. Finally, although participants were instructed to fixate on presented images during the entire time they were presented, it will be important for future work to assess eye-gaze patterns in order to substantiate the unique effects of reappraisal after controlling for eye gaze; it is promising that previous single-session studies of reappraisal that have controlled for eye gaze have found that reappraisal has unique effects on amygdala activity (van Reekum et al., 2007), as well as self-reported emotional experience and psychophysiology (Urry, 2010).

In summary, the capacity for emotion regulation is critical for responding adaptively to life's stressors. Although researchers' understanding of the behavioral consequences and neural bases of emotion regulation has grown tremendously in the past decade, in this study we addressed unanswered questions concerning how long such effects last, and what mechanisms underlie their durability. By showing that regulation can cause lasting changes in emotional responses, these findings deepen current understanding of when and why regulation is successful in both everyday and clinical contexts.

Author Contributions

B. T. Denny, L. Davachi, and K. N. Ochsner designed the research. B. T. Denny, M. C. Inhoff, and N. Zerubavel performed the research, and B. T. Denny analyzed the data. B. T. Denny, L. Davachi, and K. N. Ochsner wrote the manuscript. All authors approved the final version of the manuscript for submission.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at <http://pss.sagepub.com/content/by/supplemental-data>

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