

Correction

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Correction for “Exposure therapy triggers lasting reorganization of neural fear processing,” by Katherina K. Hauner, Susan Mineka, Joel L. Voss, and Ken A. Paller, which appeared in issue 23, June 5, 2012, of *Proc Natl Acad Sci USA* (109:9203-9208; first published May 23, 2012; 10.1073/pnas.1205242109).

The authors note that the x/y/z coordinates listed for brain regions in Table 1 appeared incorrectly. The corrected table appears below. This error does not affect the conclusions of the article.

Table 1. Summary of fMRI activity clusters

Region (BA)	L/R/B	Volume (mm ³)	x	y	z	Baseline, phobogenic vs. neutral		Baseline vs. posttherapy		Posttherapy vs. follow-up	
						t	P	t	P	t	P
Fig 1. regions shown in blue											
Posterior cingulate (BA 31)	B	8,343	4	-40	49	1.77	0.10	-2.82	0.02	2.03	0.07
Anterior cingulate/ vmPFC (BA 24, 32)	B	7,965	-3	20	27	3.19	0.01	-3.11	0.01	NS	
Anterior insula (BA 13)	L	2,187	-53	8	-1	2.09	0.06	-2.70	0.02	NS	
Anterior insula (BA 13)	R	1,782	37	6	6	3.91	0.00	-2.46	0.03	NS	
Posterior insula (BA 13, 19)	R	8,478	47	-45	13	2.33	0.04	-2.81	0.02	NS	
Middle temporal gyrus (BA 39)	L	1,134	-41	-51	7	3.77	0.00	-2.71	0.02	NS	
Medial frontal gyrus (BA 6)	R	1,809	6	-15	67	2.68	0.02	-2.48	0.03	NS	
Amygdala (anatomically defined)	R	891	n/a	n/a	n/a	3.65	0.00	-4.59	0.00	NS	
Fig 1. region shown in red											
dIPFC (BA 6, 8)	R	918	36	15	61	-2.38	0.04	8.27	0.00	-2.63	0.02
Superior parietal lobule (BA 7)	R	1,458	25	-72	57	NS		3.12	0.01	NS	
Fig. 2 regions shown in gray											
Fusiform/lingual gyrus (BA 18, 19)	L	8,046	-34	-81	-9	4.91	0.00	NS		-5.10	0.00
Fusiform/lingual gyrus (BA 18, 19)	R	11,367	36	-78	-11	5.14	0.00	NS		-5.36	0.00

For each activity cluster, listed are Brodmann areas (BA), hemisphere [left (L), right (R), or bilateral (B)], the volume (mm³), and stereotactic coordinates for the centrally activated voxel (x, y, z mm). Statistics are reported for all P values ≤ 0.10, and otherwise listed as nonsignificant (NS).

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Exposure therapy triggers lasting reorganization of neural fear processing

Katherina K. Hauner^{a,b,1}, Susan Mineka^b, Joel L. Voss^{c,d}, and Ken A. Paller^{b,d}

^aDepartment of Neurology, ^cDepartment of Medical Social Sciences, and ^dInterdepartmental Neuroscience Program, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611; and ^bDepartment of Psychology, Northwestern University, Evanston, IL 60208

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A single session of exposure therapy can eliminate recalcitrant and disabling fear of phobogenic objects or situations. We studied neural mechanisms of this remarkable outcome by monitoring changes in brain activity as a result of successful 2-h treatment. Before treatment, phobogenic images excited activity in a network of regions, including amygdala, insula, and cingulate cortex, relative to neutral images. Successful therapy dampened responsiveness in this fear-sensitive network while concomitantly heightening prefrontal involvement. Six months later, dampened fear-network activity persisted but without prefrontal engagement. Additionally, individual differences in the magnitude of visual cortex activations recorded shortly after therapy predicted therapeutic outcomes 6 mo later, which involved persistently diminished visual responsiveness to phobogenic images. Successful therapy thus entailed stable reorganization of neural responses to initially feared stimuli. These effects were linked to fear-extinction mechanisms identified in animal models, thus opening new opportunities for the treatment and prevention of debilitating anxiety disorders.

emotion | functional MRI | specific phobia

The anxiety disorder known as “specific phobia” is characterized by intense, persistent, and excessive fear of an object or situation (1). This fear can be so disabling that sufferers restructure aspects of their lives to avoid it. However, some anxiety disorders, phobias in particular, can be eliminated in mere hours via one session of exposure therapy (2–4). Exposure therapy is an effective clinical intervention based on progressive confrontation with the pathologically feared stimuli (5). Approximately 95% of patients treated for phobia in one several-hour session maintain significant improvement in symptoms after 1 y (2, 3). Despite abundant evidence supporting the efficacy of exposure therapy, the neurophysiological mechanisms by which it reduces fear have yet to be discovered (6).

Exposure therapy is derived from principles of classical conditioning (5, 7). Fear can be conditioned by pairing a neutral stimulus with an aversive stimulus until the neutral stimulus alone elicits a fear response. Conditioned fear can then be extinguished by repeatedly presenting the neutral stimulus alone until the fear response is diminished. Both fear learning and fear extinction involve the amygdala (8), but only fear extinction is thought to also involve recruitment of the prefrontal cortex (PFC) for inhibition of fear-related amygdala processing (7, 9–11). Although conditioned fear in nonhuman animals arguably provides a suitable model for anxiety disorder (8), evidence is lacking to directly link such neurophysiological mechanisms with the presentation and treatment of phobic symptoms in human patients (6).

An important feature of fear extinction in both human and nonhuman animals is its time course, as fear extinction is not instantaneous. Rather, a process of consolidation is essential for stabilizing the fear-extinction memory (12, 13). Opposing views of how consolidation serves to sustain fear extinction have been suggested. Consolidation may entail the strengthening of “top-down” influences whereby cognitive control is exerted over fear responses via PFC-mediated inhibition of the amygdala (11, 14, 15). Alternatively, consolidation may depend on “bottom-up”

influences, such as changes in sensory processing of feared stimuli. Whereas the amygdala can facilitate threat detection by enhancing sensitivity for sensory processing of feared stimuli (16, 17), a gradual reduction in fear may involve restructured connectivity between sensory-processing networks and the amygdala. Understanding these putative mechanisms in the context of exposure therapy requires analyzing both immediate and long-term neural consequences of this treatment.

Single-session exposure therapy presents a valuable opportunity whereby immediate changes in neural processing of feared stimuli can be identified and compared with long-term changes. To accomplish this comparison, we used functional MRI (fMRI) to observe neural processing of phobogenic images in adult volunteers who were successfully treated for spider phobia with single-session exposure therapy. Neural responses to phobogenic (versus neutral) images were assessed immediately before and after single-session exposure therapy, and again during a 6-mo follow-up visit. These procedures allowed us to provide a unique comparison of initial alterations caused by therapy with neural reorganization maintained over time.

Results

During all fMRI scanning sessions, neural activity elicited by phobogenic images (spiders) was computed relative to that elicited by neutral images (moths). This strategy allowed us to eliminate nonspecific effects common to both stimulus categories (e.g., visual stimulation, perceptual processing), so as to isolate activity related specifically to processing phobogenic images. Subjects performed a challenging visual detection task to ensure careful foveal processing of all images. The initial scanning session provided a baseline against which to assess neural changes due to treatment. At baseline, self-reported fear ratings collected during scanning (Fig. 1*A*) were significantly higher for phobogenic versus neutral stimuli [$t(11) = 15.55, P < 0.0001$]. As expected, brain activity for phobogenic versus neutral images was greater in limbic, paralimbic, and related regions, including right amygdala, bilateral insula, and cingulate cortex (Fig. 1*B* and *C*, shown in blue, Table 1, and Fig. S1).

Despite lifetime histories of spider phobia, all subjects were successfully treated within 3 h or less. Therapy involved a progressive series of tasks to approach the live tarantula, with each step first demonstrated by the therapist (18). Reduced fear after treatment was evident in decreased ratings on two standard questionnaires (19, 20), subjects’ ability to approach and touch the tarantula, and decreased fear ratings during scanning (all $P < 0.001$) (Fig. 1*A*).

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¹To whom correspondence should be addressed. E-mail: hauner@u.northwestern.edu.

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presumably occurred for bilateral ventral visual cortex, resulting in significant reductions in fear-related perceptual processing only at follow-up.

Discussion

Our results provide evidence that the beneficial effects of exposure therapy derive from neurophysiological processes typical of fear extinction. These neurophysiological processes include immediate increases in prefrontal activity in conjunction with decreases in activity of the amygdala, as well as a consolidation process that eventually allows decreased amygdala and limbic responsivity to occur independently from PFC involvement. Although neural inhibition is difficult to demonstrate in human studies, our findings show altered neural processing patterns in regions homologous to PFC-amygdala inhibitory circuitry in rodents that have undergone extinction (26). While the dlPFC subregion identified in this study does not project directly to amygdala (27), it may inhibit amygdala via projections to additional regions, particularly vmPFC—a region implicated in fear-extinction recall and considered a homolog of extinction-sensitive infralimbic structures in rodents (14, 15, 27, 28). In the present study, activity in the vmPFC was significantly decreased after therapy (Fig. S1B), consistent with prior studies reporting decreased vmPFC activity during classically conditioned fear extinction in humans (15). Critically, a model of dlPFC inhibition of amygdala activity, mediated via the vmPFC, has been specifically implicated in studies of cognitive reappraisal (22), a form of emotion regulation that is considered a potential mechanism for exposure therapy (29). Thus, our identification of significant posttherapy changes in the same regions brings clinical models appreciably closer into alignment with animal models of fear extinction, such that the detailed neurophysiological processes studied in animals can be linked more firmly to clinical practice.

By making use of therapy that was successfully completed in a single brief session, we were able to observe changes that occurred immediately after therapy and also compare them to results obtained 6 mo later. Neurophysiological observations shortly after therapy are vital, as activity changes in amygdala-PFC interactivity are generally identified in close proximity to fear-extinction learning (9, 10, 15). Indeed, prior neuroimaging experiments have not identified concomitant PFC-amygdala changes related to exposure therapy, perhaps because 1- to 4-wk delays were interposed between therapy completion and subsequent measurements of brain activity (30–33). In the present study, comparison between immediate and long-term effects of therapy on neural activity revealed a time-limited role of dlPFC. Because dlPFC activity is thought to reflect therapeutic techniques promoting deliberate, cognitive control of fear (22)—in particular, the dlPFC-associated technique of cognitive reappraisal mentioned above (23)—our results suggest that the utility of these cognitive techniques may be similarly time-limited. This possibility would have major implications for clinicians' approaches to understanding and refining such cognitive techniques during the course of treatment, as the degree of emphasis on such techniques in anxiety treatment has long been debated (34).

Comparison of immediate versus long-term changes also allowed us to identify a shift from “top-down” prefrontal influences to the “bottom-up” changes in visual cortex responsivity that occurred via consolidation. Presumably, this shift orchestrated the long-term reorganization of sensory processing of initially feared stimuli. Exaggerated visual cortex responses to spiders persisted even after subjects had successfully completed therapy, indicating that perceptual threat detection may be more automatic and enduring than the conscious experience of fear. Only after a longer delay did heightened perceptual activity diminish, to the point of disappearing at 6 mo. Activity in a restricted portion of the same visual cortical region immediately after therapy predicted long-term outcome, suggesting that the

initial stages of this consolidation process in perceptual processing were triggered following therapy.

In characterizing the time course of neural changes that accompany therapeutic success, we identified a major brain-behavior link with respect to the elimination of anxiety symptoms and the proposed neural mechanisms previously studied in animal models. Novel aspects of recovery from phobia were highlighted by the evolution of brain responses to phobogenic stimuli, which transitioned from the baseline stage of exaggerated fear, to the initial elimination of fear a few hours later, to the final stage of a possibly permanent alleviation of symptoms. This neurophysiological evidence provides unique insights into fear-extinction mechanisms with respect to time-sensitive changes in cognitive control and threat detection, thus reinforcing the value of a neurobiologically informed perspective on anxiety disorders.

Materials and Methods

Subject Characteristics. Subjects (nine female, three male; mean age = 22.3 y, SD = 4.5 y) met diagnostic criteria for specific phobia of spiders (1), as assessed by an experienced clinician who administered the Structured Clinical Interview for DSM-IV (35). Diagnosis of specific phobia included the following symptoms: (i) excessive fear of spiders, (ii) invariable response of anxiety in the presence of spiders, (iii) recognition of this fear as excessive, (iv) consistent avoidance of spiders, (v) interference in daily routines due to spider fear, and (vi) minimum 6-mo duration of these five symptoms. For all subjects, phobia onset occurred in childhood. No subject had ever received exposure therapy or psychotropic medication. None reported fear of moths. All participants provided written, informed consent prior to their enrollment in the study. Data from one additional subject were excluded due to excessive head movement in the scanner.

Procedure. Subjects were taught the Subjective Units of Distress Scale (SUDS) (36) to communicate fear level throughout the study (score range 0–100). A range of anchors, including physiological symptoms of anxiety, was pre-defined on this scale to facilitate meaningful between-subjects comparisons. Subjects completed the SPQ (score range 0–31) (20) and the SBQ (score range 0–7,800) (19) to assess phobic symptom severity and catastrophic beliefs about spiders, respectively. All subjects scored in the upper 95th percentile on these questionnaires (19, 20). Subjects were then asked to approach a live Chilean Rose tarantula; the tarantula was ~5 inches in diameter and contained in a closed terrarium at a 6.3-m distance (approach task). Ability to approach was measured as the closest distance achieved (average distance = 3.1 m from cage, SD = 1.5 m).

Subjects were then positioned for structural and functional scans. Responses to phobogenic stimuli (color photographs of spiders) versus neutral stimuli (color photographs of moths) were estimated. Stimuli were presented within a blocked design, in which 10 blocks of phobogenic stimuli alternated with 10 blocks of neutral stimuli. Each single block included five images displayed for 4 s each, followed by a 20-s rest period during which subjects used MRI-compatible buttons to enter the average fear level (SUDS) experienced while viewing the previous five images (either five spiders or five moths). To confirm that subjects perceived all stimuli, accuracy in detecting a small red square that could appear on any part of the spider or moth (for 20% of trials) was assessed. Red squares were sized and located to preclude perifoveal detection, such that fixation on the center of each spider/moth image was required to successfully perform the detection task. Subjects made a button response to each square, and responses were at least 95% accurate per scan for all subjects. Response speed did not vary as a function of stimulus type, block, or scanning session, either as a main effect (all $P > 0.33$) or as an interaction [$F(2,22) = 2.18, P = 0.14$]. All fMRI scans throughout the study followed the same protocol. Images were randomized across all scans without replacement, such that no image was repeated during the entire course of the experiment. Novel images decreased the possibility of habituation to phobogenic stimuli within runs, which helped to focus analyses on therapy-related changes rather than potential habituation-related changes. Post hoc RM-ANOVA analyses confirmed that habituation to images did not take place within runs [$F(1,11) = 2.46, P = 0.15$] and that there were no changes in habituation as a function of the run [$F(2,22) = 2.09, P = 0.15$].

Following the baseline fMRI scan, subjects followed one of two protocols (randomly assigned before the study day to an equal number of subjects): immediate therapy or wait control. For the immediate therapy group, remaining phases included: (i) exposure therapy (M = 2 h, SD = 0.5); (ii) posttherapy behavioral measures (SPQ, SBQ, approach task) and fMRI scan;

and (iii) 6-mo follow-up behavioral measures and fMRI scan. For the wait control group, remaining phases included: (i) waiting period (2 h), during which subjects were permitted to do anything not involving spiders or moths; (ii) postwait behavioral measures and fMRI scan; (iii) exposure therapy ($M = 2$ h, $SD = 0.4$); (iv) posttherapy behavioral measures and fMRI scan; and (v) 6-mo follow-up behavioral measures and fMRI scan.

Exposure Therapy. Exposure therapy consisted of a standard, 14-step series of progressive approach tasks (37) using the same live tarantula presented during the approach task. Each step was first demonstrated by the therapist, and the subject was then asked to repeat it when he or she felt able. Treatment was considered successful when subjects completed the final step, in which the subject touched or held the tarantula with a bare hand, with SUDS < 25 . All subjects were rated as treatment successes.

fMRI Acquisition and Analysis. fMRI data were collected using a Siemens TRIO 3T MRI scanner. Functional data included whole-brain gradient-recalled echoplanar images obtained every 2 s (35 3-mm axial slices, 0-mm gap, repetition time = 2,000 ms; echo time = 25 ms; flip angle = 80° ; field-of-view = 22 cm; 64×64 acquisition matrix; voxel size = $3.44 \times 3.44 \times 3$ mm). High-resolution whole-brain structural images were collected to provide anatomical localization (3D MP-RAGE T1-weighted scans, voxel size = $0.859 \times 0.859 \times 1$ mm; 160 axial slices).

fMRI analyses made use of the AFNI software package (38). For standard whole-brain analyses, preprocessing included the following: coregistration through time for motion correction, slice timing correction, removal of voxels with low signal (i.e., $< 30\%$ of mean whole-brain signal), spatial smoothing (7-mm FWHM Gaussian kernel), coregistration with the structural image, transformation to standard Talairach-Tournoux stereotactic space (Montreal Neurological Institute-305), and conversion of raw signal intensity values to percent-change values using the mean level of activity for each run. Functional and structural images were aligned across scanning sessions using a cost-function fitting approach on local correlations between signal intensities (39).

Neural activity was estimated using a standard statistical parametric mapping approach. A canonical hemodynamic response function was convolved with a 20-s boxcar function that corresponded to stimulus periods and baseline (no-stimulus) periods, with phobogenic and neutral stimulus periods modeled separately. This ideal hemodynamic timeseries was fit to the actual time series using a deconvolution analysis with a general linear model (GLM).

The GLM provided estimates of neural activity that differed for phobogenic and neutral stimuli. T_1 and T_0 components of the MRI signal and subjects' head motion in six translations and rotations were included in all GLMs as nuisance factors. Regions exhibiting group-level activation

differences were identified via a two-pass random-effects analysis. Activity sensitive to phobogenic (vs. neutral) stimuli that changed between scanning sessions was tested via planned within-subjects (paired) t tests. RM-ANOVA results provided in Fig. S1 replicate the between-session findings of planned comparisons.

For each experimental contrast, Monte Carlo simulations were used to estimate the likelihood of detecting false positives over multiple voxel-wise comparisons (i.e., whole-brain correction). For an individual-voxel probability threshold of $P = 0.01$, the cluster-size threshold necessary to achieve an overall corrected threshold of $P = 0.01$ was identified via simulation (39). For each contrast, 30,000 simulation iterations were performed, in which two suprathreshold voxels were considered contiguous if at least one vertex was touching. The most stringent resulting cluster-size threshold of 30 voxels was applied to each contrast, to provide a conservative threshold for guarding against false positives.

An across-subjects correlation was performed between behavioral measures at follow-up and the whole-brain activity difference (for phobogenic versus neutral images) at posttherapy. One whole-brain correlation was performed for each of the four behavioral fear measures (SPQ, SBQ, approach task, fear rating), and significant regions of correlation were determined as the conjunction of the individual maps, each thresholded at a voxel-wise $r = 0.40$. Simulations performed using the same processing steps on randomly generated fMRI data matching the noise distribution of the actual data (1,000 iterations) confirmed that the resulting cluster size of 13 voxels (Fig. 2A) was unlikely to have been identified by chance ($P < 0.001$).

Anatomically constrained analysis was used to scrutinize amygdala activity (40, 41). For this analysis, spatial smoothing and normalization to standardized stereotactic space were not performed. The amygdala was defined in each hemisphere using the high-resolution (1-mm³) T1 structural image for each subject in native MRI space. A 6-mm-radius sphere was centered in the middle of the amygdala, such that all amygdala nuclei were captured. The amygdala was drawn with a resolution equivalent to that of the functional images (3-mm³ voxels). Regions of interest were aligned across scans using the transformation matrix derived from the whole-brain cost-function alignment, and anatomical alignment was confirmed visually.

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