Skin Conductance Responses and Neural Activations During Fear Conditioning and Extinction Recall Across Anxiety Disorders

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IMPORTANCE The fear conditioning and extinction neurocircuitry has been extensively studied in healthy and clinical populations, with a particular focus on posttraumatic stress disorder. Despite significant overlap of symptoms between posttraumatic stress disorder and anxiety disorders, the latter has received less attention. Given that dysregulated fear levels characterize anxiety disorders, examining the neural correlates of fear and extinction learning may shed light on the pathogenesis of underlying anxiety disorders.

OBJECTIVES To investigate the psychophysiological and neural correlates of fear conditioning and extinction recall in anxiety disorders and to document how these features differ as a function of multiple diagnoses or anxiety severity.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a cross-sectional, case-control, functional magnetic resonance imaging study at an academic medical center. Participants were healthy controls and individuals with at least 1 of the following anxiety disorders: generalized anxiety disorder, social anxiety disorder, specific phobia, and panic disorder. The study dates were between March 2013 and May 2015.

EXPOSURES Two-day fear conditioning and extinction paradigm.

MAIN OUTCOMES AND MEASURES Skin conductance responses, blood oxygenation level-dependent responses, trait anxiety scores from the State Trait Anxiety Inventory–Trait Form, and functional connectivity.

RESULTS This study included 21 healthy controls (10 women) and 61 individuals with anxiety disorders (36 women). P values reported for the neuroimaging results are all familywise error corrected. Skin conductance responses during extinction recall did not differ between individuals with anxiety disorders and healthy controls (ηp² = 0.001, P = .79), where ηp² is partial eta squared. The anxiety group had lower activation of the ventromedial prefrontal cortex (vmPFC) during extinction recall (ηp² = 0.178, P = .02). A similar hypoactive pattern was found during early conditioning (ηp² = 0.106, P = .009). The vmPFC hypoactivation was associated with anxiety symptom severity (r = −0.420, P = .01 for conditioning and r = −0.464, P = .004 for extinction recall) and the number of co-occurring anxiety disorders diagnosed (ηp² = 0.137, P = .009 for conditioning and ηp² = 0.227, P = .004 for extinction recall). Psychophysiological interaction analyses revealed that the fear network connectivity differed between healthy controls and the anxiety group during fear learning (ηp² range between 0.088 and 0.176 and P range between 0.02 and 0.003) and extinction recall (ηp² range between 0.111 and 0.235 and P range between 0.02 and 0.002).

CONCLUSIONS AND RELEVANCE Despite no skin conductance response group differences during extinction recall, brain activation patterns between anxious and healthy individuals differed. These findings encourage future studies to examine the conditions longitudinally and in the context of treatment trials to improve and guide therapeutics via advanced neurobiological understanding of each disorder.

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Fear conditioning and extinction paradigms are relevant for studying anxiety disorders. It has been proposed that pathological anxiety could emerge from dysregulated patterns of fear learning and that maintenance of anxiety-related symptoms could be explained by extinction deficits.\(^1\) Until now, this paradigm has been mostly tested in populations with post-traumatic stress disorder (PTSD).\(^1,4\) At the psychophysiological level, they exhibit generally normal conditioning and extinction learning but impaired extinction recall.\(^9,13\) During extinction recall, individuals suffering from PTSD exhibit lower activations in brain regions promoting safety signal processing, such as the ventromedial prefrontal cortex (vmPFC) and hippocampus, and they exhibit greater activations in regions promoting fear signal detection, such as the amygdala and dorsal anterior cingulate cortex (dACC).\(^10,12,14\)

Until the DSM-5 release, PTSD was considered an anxiety disorder; it is now classified as a trauma and stress–related disorder. However, it remains unclear whether the physiological deficiencies in PTSD are also observed in conditions currently categorized as anxiety disorders. Although PTSD and anxiety disorders present overlapping features—nearly, dysregulated fear levels—DSM-5 anxiety disorders have been less studied in the context of conditioning and extinction paradigms. Results of a meta-analysis\(^15\) suggested that anxious individuals exhibit higher fear in response to safety cues during conditioning and higher fear in response to danger cues during extinction. The meta-analysis included study samples with PTSD and dealt with complex clinical portraits (ie, comorbidity from the same or different diagnostic categories). Finally, it remains to be studied whether the magnitude of the pathophysiological deficit differs based on the number of anxiety disorders, without the confounds of other comorbidities.

This study aimed to elucidate some of these issues in individuals having anxiety disorders without other comorbidities. Using psychophysiological and neuroimaging tools, this study investigated how anxiety disorders influence the circuitry of fear conditioning and extinction recall. We then examined whether the presence of multiple anxiety disorders influences the circuitry relative to a single disorder. We hypothesized that, relative to healthy controls, individuals with anxiety disorders (1) would have lower differential fear conditioning and deficient extinction recall in terms of skin conductance response (SCR) and (2) would exhibit dysregulated activation patterns in the fear circuitry nodes during fear learning and extinction recall. We also hypothesized that there would be more pronounced dysregulations in those with multiple anxiety disorders. We conclude with a mechanistic focus investigating how activations during fear memory encoding relate to activations during recall.

### Methods

#### Participants

We recruited 61 individuals meeting criteria for at least 1 of the following anxiety disorders: generalized anxiety disorder, social anxiety disorder, specific phobia, and panic disorder (45 had 1 disorder and 16 had ≥2 disorders), with no other current comorbidities. We included previous data from 21 healthy controls\(^16\) who underwent identical experimental procedures with use of the same scanner. For exclusion criteria and a description of the study sample, see the eAppendix in the Supplement.

#### Procedure

Participants provided written informed consent in accord with the requirements of the Partners Healthcare Institutional Review Board, who approved the study. Participants underwent a Structured Clinical Interview for DSM-IV with one of us (N.B.L.) to determine the diagnoses and eligibility. They filled out the State Trait Anxiety Inventory–Trait Form (STAI-T\(^17\), examining self-reported anxiety levels. Participants underwent a 2-day fear conditioning and extinction paradigm\(^9,10,13,14,16,18,19\) in a functional magnetic resonance imaging scanner that included conditioned stimuli (CS) (eAppendix in the Supplement). On day 1, fear conditioning occurred, during which 2 cues (CS+) were reinforced and 1 cue (CS−) was not. This conditioning was followed by extinction learning, where 1 CS+ and the CS− were presented. The next day, extinction recall was tested, where the extinguished CS+ (CS + E), the nonextinguished CS+ (CS + NE), and the CS− were presented (details are provided in the eAppendix in the Supplement).

#### Data Processing

Skin conductance response and imaging data were computed using the previously used methods.\(^9,10,13,16,18,19\) Details are provided in the eAppendix in the Supplement.

#### Analytic Approach

For conditioning, equal numbers of trials are used for CS+ and CS−. However, 2 CS+s and only one CS− are used, suggesting that there might be more habituation to CS− (16 trials of 1 cue) relative to CS+ (16 trials based on 2 cues). We performed analyses to assess habituation effects between groups (eAppendix in the Supplement). For conditioning, a stimulus (CS+ vs CS−) × time (early vs late) × group (healthy vs anxiety) analysis of covariance (ANCOVA) was performed on SCR. For the imaging analysis,
between-group differences were investigated for early, late, and all conditioning. Additional analyses examined whether both groups had similar fear extinction levels (eAppendix in the Supplement). For extinction recall, a stimulus (CS + E vs CS + NE) x group (healthy vs anxiety) ANCOVA was performed on SCR. Similar analyses were performed for the imaging data.

To investigate differences between single vs multiple anxiety disorders, analyses were repeated for the anxiety cohort alone. For these analyses, group (single vs multiple) was the between-group factor.

To assess associations between anxiety severity and the fear network within the anxiety group, a voxelwise analysis was performed with STAI-T scores as a regressor for early conditioning (CS+ vs CS−), late conditioning (CS+ vs CS−), and extinction recall (CS + E vs CS + NE). Beta weights were extracted from the peak voxel to generate a correlation coefficient.

Psychophysiological interaction (PPI) analyses were performed during early conditioning and extinction recall. For these analyses, vmPFC was used as the seed.

Imaging analyses were performed with an initial threshold of $P < .005$ and 10 contiguous voxels. Activations detected with that threshold within the fear circuitry (amygdala, hippocampus, insular cortex, ACC, and vmPFC) were then tested for small-volume correction.

## Results

### Demographics

This study included 21 healthy controls, with a mean (SD) age of 25.8 (4.8) years, 47.6% (10 of 21) of whom were female, and 61 individuals with anxiety disorders, with a mean (SD) age of 30.4 (11.5) years, 59.0% (36 of 61) of whom were female. Healthy controls were younger ($t_{77} = 2.559, P = .01$) and more educated ($t_{780} = 1.922, P = .06$) than the anxiety group. Both groups had similar shock levels ($t_{73} = 0.346, P = .18$) and sex distributions ($q_{1} = 0.824, P = .36$). Analyses comparing these groups were run with (main text) and without (eAppendix in the Supplement) age and educational level as covariates. Analyses comparing the single disorder group with the multiple disorders group did not include covariates because the groups did not statistically differ on any demographics.

### Healthy Group vs Anxiety Group

During conditioning (Figure 1A), the SCR ANCOVA yielded a marginal effect of stimulus ($F_{1,77} = 3.009, P = .09, \eta^2 = 0.038$), an effect of group ($F_{1,77} = 11.126, P = .001, \eta^2 = 0.126$), and a time x group interaction ($F_{1,77} = 5.110, P = .03, \eta^2 = 0.062$), where $\eta^2$ is partial eta squared. Compared with the anxiety group, healthy controls exhibited greater vmPFC activation during early conditioning (Montreal Neurological Institute x, y, z coordinates [hereafter MNI] −8, 50, −28; cluster size of 12; $t_{77} = 2.999, P = .009$ familywise error; $\eta^2 = 0.106$) and greater hippocampal activation during late conditioning (MNI 32, −30, −6; cluster size of 10; $t_{72} = 2.999, P = .007$ familywise error; $\eta^2 = 0.113$). Both groups underwent successful extinction learning (eAppendix in the Supplement).

For extinction recall, the SCR ANCOVA did not yield any significant results, ($F_{1,67} = 1.109$ for all, $P > .30$ for all, $\eta^2 = 0.016$ for all). Relative to healthy controls, the anxiety group exhibited less activation in the rostral ACC (rACC) (MNI −12, 44, 8; cluster size of 26; $t_{63} = 3.211, P = .007$ familywise error; $\eta^2 = 0.117$), the vmPFC (MNI −14, 46, −18; cluster size of 169; $t_{63} = 3.411, P = .01$ familywise error; $\eta^2 = 0.178$), and the insular cortex (MNI −36, 10, −12; cluster size of 18; $t_{63} = 3.444, P = .003$ familywise error; $\eta^2 = 0.136$).

### Number of Anxiety Disorders

During conditioning (Figure 2A), the SCR ANOVA yielded a main effect of stimulus ($F_{1,56} = 46.005, P < .001, \eta^2 = 0.442$), a main effect of time ($F_{1,56} = 36.010, P < .001, \eta^2 = 0.383$), a main effect of group ($F_{1,56} = 5.671, P = .042, \eta^2 = 0.089$), a marginal time x group interaction ($F_{1,56} = 3.580, P = .06, \eta^2 = 0.204$), and a time x stimulus interaction ($F_{1,56} = 14.876, P < .001, \eta^2 = 0.058$). During early conditioning, the multiple disorders group had greater insular cortex activation (MNI −36, 2, 4; cluster size of 67; $t_{56} = 4.21, P = .001$ familywise error; $\eta^2 = 0.179$) but less vmPFC activation (MNI 8, 48, −26; cluster size of 33; $t_{56} = 3.19, P = .009$ familywise error; $\eta^2 = 0.137$) relative to the single disorder group. For late conditioning, the multiple disorders group also had greater activation in the insular cortex (MNI −34, 10, 4; cluster size of 42; $t_{56} = 3.28, P = .008$ familywise error; $\eta^2 = 0.162$) more than the single disorder group. When examining conditioning across all trials, the multiple disorders group had greater activation in the amygdala (MNI 14, −2, −18; cluster size of 86; $t_{56} = 3.999, P = .002$ familywise error; $\eta^2 = 0.231$), the insular cortex (MNI −36, 0, 4; cluster size of 219; $t_{56} = 3.91, P = .006$ familywise error; $\eta^2 = 0.228$), and the dACC (MNI 0, 28, 16; cluster size of 59; $t_{56} = 3.39, P = .008$ familywise error; $\eta^2 = 0.151$).

During extinction recall, the SCR ANOVA yielded no significant results ($F_{1,46} = 0.281$ for all, $P > .59$ for all; $\eta^2 \leq 0.006$ for all). The functional magnetic resonance imaging analysis revealed less vmPFC (MNI 0, 38, −30; cluster size of 32; $t_{47} = 3.48, P = .004$ familywise error; $\eta^2 = 0.227$) and less subgenual ACC (sgACC) (MNI 2, 18, −14; cluster size of 23; $t_{47} = 3.11, P = .009$ familywise error; $\eta^2 = 0.206$) activations in the multiple disorders group compared with the single disorder group.

Given the different weights of the specific phobias in the single disorder group (n = 17) compared with the multiple disorders group (only present as comorbidity and not as the main disorder), we conducted analyses to rule out the possibility that the effects obtained were driven only by the specific phobias. Details are provided in the eAppendix in the Supplement.

### Correlates of STAI-T Scores During Conditioning and Extinction Recall

For early conditioning (Figure 3A), STAI-T scores were positively correlated with sgACC activation (MNI −10, 16, −14; cluster size of 25; $t_{47} = 3.21, P = .008$ familywise error; $r = 0.424$) and negatively correlated with insular cortex (MNI −34, −28, 18; cluster size of 31; $t_{47} = 3.16, P = .001$ familywise error; $r = −0.414$) and vmPFC (MNI 14, 54, −18; cluster size of 38; $t_{47} = 3.11, P = .001$ familywise error; $r = −0.387$).

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**Figure 1**

A comparison of healthy and anxiety groups during conditioning and extinction recall, showing significant differences in the amygdala, hippocampus, insular cortex, ACC, and vmPFC. The graph depicts the percentage change in activation relative to baseline for each condition (CS+ vs CS−) and group (healthy vs anxiety). The results are corrected for multiple comparisons using small-volume correction.

**Figure 2**

A comparison of healthy and anxiety groups during conditioning and extinction recall, showing significant differences in the amygdala, hippocampus, insular cortex, ACC, and vmPFC. The graph depicts the percentage change in activation relative to baseline for each condition (CS+ vs CS−) and group (healthy vs anxiety). The results are corrected for multiple comparisons using small-volume correction.

**Figure 3**

A comparison of healthy and anxiety groups during conditioning and extinction recall, showing significant differences in the amygdala, hippocampus, insular cortex, ACC, and vmPFC. The graph depicts the percentage change in activation relative to baseline for each condition (CS+ vs CS−) and group (healthy vs anxiety). The results are corrected for multiple comparisons using small-volume correction.
Responses and Activations in Fear Conditioning and Extinction Recall

Original Investigation Research

and vmPFC (MNI −10, 60, −20; cluster size of 14; familywise error; r ter size of 231; familywise error; ηp2 = 0.095) but greater connectivity in the anxiety group with the amygdala (MNI −26, −24, −12; cluster size of 17; t_{41} = 2.81; P = .02 familywise error; ηp2 = 0.101), the amygdala (MNI 26, −4, −26; cluster size of 384; t_{37} = 3.71; P = .02 familywise error; ηp2 = 0.176), and the insular cortex (MNI −38, 6, −12; cluster size of 13; t_{51} = 2.80; P = .01 familywise error; ηp2 = 0.088). These results are shown in Figure 4A.

During extinction recall, the vmPFC seed showed greater functional connectivity in healthy controls with the sgACC (MNI −8, 16, −24; cluster size of 10; t_{63} = 2.95; P = .007 familywise error; ηp2 = 0.111) but greater connectivity in the anxiety group with the amygdala (MNI −24, −10, −24; cluster size of 305; t_{63} = 4.26; P = .002 familywise error; ηp2 = 0.235), the insular cortex (MNI 40, 10, −22; cluster size of 169; t_{63} = 3.39; P = .02 familywise error; ηp2 = 0.158), and the vmPFC (MNI 6, 38, −26; cluster size of 37; t_{63} = 3.37; P = .006 familywise error; ηp2 = 0.143). These results are shown in Figure 4B.

Exploratory Analyses of Associations

As an exploratory analysis, we examined whether dysregulated activation patterns observed during conditioning could account for or be related to the activation pattern observed in extinction recall. Hippocampus activation during conditioning was not associated with vmPFC activation during recall (r = 0.098, P = .44). There was a suggestion of an association between vmPFC activation during conditioning and vmPFC activation during recall (r = 0.232, P = .06). We examined the

Figure 1. Comparison of Healthy Controls and Individuals With Anxiety Disorders During Fear Conditioning and Extinction Recall

Shown are skin conductance response (SCR) and voxelwise analyses contrasting healthy controls with individuals with anxiety disorders. A. On the left, SCR is shown during early and late conditioning as a function of conditioned stimuli (CS) type and group. On the right, significant group differences are shown in terms of brain activation during the early CS+ vs CS− contrast and late CS+ vs CS− contrast from fear conditioning. B. On the left, SCR is shown during early extinction recall as a function of CS type and group. On the right, brain regions are shown for which the 2 groups differed during extinction recall for the CS + E vs CS + NE contrast. Hot colors indicate greater activation in healthy controls relative to the anxiety group. P = .005 is used for all results. Error bars are SEM.

CS+ indicates cues that were partially reinforced with a shock; CS−, cue that was never reinforced with a shock; CS + E, extinguished CS+; CS + NE, nonextinguished CS+; rACC, rostral anterior cingulate cortex; and vmPFC, ventromedial prefrontal cortex.

PPI Analyses

During early conditioning, the vmPFC seed had greater functional connectivity in healthy controls with the sgACC (MNI −14, 34, −12; cluster size of 10; t_{47} = 3.40; P = .003 familywise error; ηp2 = 0.095) but greater connectivity in the anxiety group with the hippocampus (MNI −26, −24, −12; cluster size of 17; t_{41} = 2.81; P = .02 familywise error; ηp2 = 0.101), the amygdala (MNI 26, −4, −26; cluster size of 384; t_{37} = 3.71; P = .02 familywise error; ηp2 = 0.176), and the insular cortex (MNI −38, 6, −12; cluster size of 13; t_{51} = 2.80; P = .01 familywise error; ηp2 = 0.088). These results are shown in Figure 4A.

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Exploratory Analyses of Associations

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pattern within each group and found that it was only present in healthy controls \((r = 0.643, P = 0.004)\) and not in anxious individuals \((r = -0.151, P = 0.3)\) (Figure 5A). We tested if similar patterns of associations were present for the SCR data. An exploratory analysis examined correlations between SCR during recall (SCR to the first 4 trials of CS + E minus SCR to the first 4 trials of CS + NE) and the connectivity values between the vmPFC and the following regions: sgACC, amygdala, insular cortex, and vmPFC. The connectivity value between vmPFC and sgACC was negatively associated with SCR \((r = -0.281, P = 0.03)\), whereas the connectivity value between vmPFC and amygdala was positively associated with SCR \((r = 0.271, P = 0.04)\) (Figure 5B). The vmPFC-vmPFC \((r = 0.101, P = 0.44)\) and vmPFC-insula \((r = -0.001, P = 0.99)\) connectivity values were not associated with SCR.

During conditioning, SCR was blunted in the anxiety group relative to healthy controls. However, both groups differentiated between the CS+ and the CS−. This blunted pattern seems to be driven by individuals with a single disorder. The literature has suggested larger responses to the CS− in anxious individuals, which could result in lower differential acquisition. \(^{15}\) Based on our results, the number of diagnoses is an important factor to consider that could be used as an index of clinical severity.

In terms of imaging, individuals with multiple disorders activated more fear encoding and expression regions (amygdala, insular cortex, and dACC) during conditioning. This finding is consistent with studies \(^{20-28}\) that have shown hyperactivation of fear-promoting regions during emotional tasks. During early conditioning, the vmPFC was less activated in the anxiety group compared with healthy controls. The number of diagnoses modulated that vmPFC hypoactivation such that individuals having multiple anxiety disorders showed reduced vmPFC activation compared with those having a single disorder. Moreover, vmPFC activation during early conditioning showed a negative correlation with STAI-T scores. These results suggest vmPFC hypoactivation in anxious individuals, an effect that is more pronounced in more severe cases (either greater symptoms or more disorders).

Previous studies \(^{29-33}\) performed in social anxiety disorder and generalized anxiety disorder have also reported lower

Figure 2. Comparison of One Anxiety Disorder With Multiple Anxiety Disorders During Fear Conditioning and Extinction Recall

![Figure 2](https://jamanetwork.com/)

**A** Fear conditioning

![Graph A](https://jamanetwork.com/)

**B** Extinction recall

![Graph B](https://jamanetwork.com/)
activation in the medial PFC during emotional tasks. Our PPI analyses revealed that this region was more functionally coupled with the sgACC in healthy controls but showed more functional coherence with the hippocampus, amygdala, and insular cortex in the anxiety group. This finding suggests that, for the anxious group, the vmPFC region that
showed lower activation during early conditioning was also more coupled with regions known to support fear encoding and processing, which are typically more activated in anxious individuals.

Contrary to our hypothesis, during extinction recall, no SCR deficits were found between the healthy controls and the anxiety group. This result is in contrast with various psychopathological conditions, such as PTSD, obsessive-compulsive disorder, and schizophrenia, in which deficits were noted at the SCR level.9,10,12,13,34-36 This finding is an important psychophysiological distinction between PTSD and the anxiety disorders tested in our study, and it is also contrary to our hypothesis. Despite no group differences for SCR during extinction recall, brain activation patterns differed between the groups. In fact, the healthy controls activated the vmPFC, rACC, and insular cortex more relative to the anxious individuals. This result is consistent with investigations that have shown dysregulated rACC and vmPFC activation patterns in anxious individuals using various emotion regulation tasks.37 Focusing on the anxiety group, results showed that vmPFC activation was reduced in those with multiple disorders. The regression analyses also revealed a negative correlation between the vmPFC activation and the trait anxiety levels. When looking at PPI analyses with the vmPFC as the seed, we again observed higher functional coherence with the sgACC in healthy controls. On the other hand, the same seed showed more connectivity with the amygdala and insular cortex in the anxiety group, as was the case in the PPI analyses conducted during conditioning, as well as with a vmPFC area. Similar to conditioning, the hypoactive vmPFC region in the anxiety group showed more functional coherence during extinction recall in anxious individuals with fear-promoting regions, which tend to be hyperactive in that same sample.

Similar patterns emerged during early conditioning and extinction recall with regard to vmPFC activation and its modulation by the number of diagnoses and trait anxiety levels, as well as with its functional coherence with the rest of the network. Activation of the vmPFC during early conditioning was positively associated with vmPFC activation during extinction recall but only in healthy controls. These exploratory analyses emphasize the importance of assessing 

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**Figure 4. Psychophysiological Interactions With Ventromedial Prefrontal Cortex (vmPFC) as the Seed During Fear Conditioning and Extinction Recall**

**A** Fear conditioning (early CS+ vs early CS−)

- Healthy Controls > Anxiety Group
- Anxiety Group > Healthy Controls

**B** Extinction recall (early CS+E vs early CS+NE)

- Healthy Controls > Anxiety Group
- Anxiety Group > Healthy Controls

Shown are between-group psychophysiological interaction analyses contrasting healthy controls with individuals with anxiety disorders during early fear conditioning (A) and extinction recall (B). Hot colors indicate that the healthy controls exhibited greater connectivity than the anxiety group between the seed and the given region. Cold colors indicate that the anxiety group exhibited greater connectivity than the healthy controls between the seed and the given region. *P* = .005 is used for all results. CS indicates conditioned stimuli; CS+ indicates cues that were partially reinforced with a shock; CS−, the cue that was never reinforced with a shock; CS + E, extinguished CS+; and CS + NE, nonextinguished CS+.
how fear is initially encoded, which seems to influence how the safety memory will be retrieved later. In fact, deficits that have been reported in terms of activation patterns during extinction recall in different disorders might potentially be traced back to dysregulated activation patterns during the initial fear memory formation. In support of this hypothesis, Livneh and Paz\textsuperscript{38} showed that the synchronization of amygdala and dACC activity during fear encoding predicts higher resistance to extinction.

As an exploratory analysis, we next examined whether brain activation patterns were associated with fear expression during extinction recall. Although both groups had similar SCR during recall, this measure carries great variability in individuals. The analysis revealed that greater connectivity between the vmPFC and the sgACC, which was more coupled in healthy controls, was associated with better extinction recall. In contrast, the connectivity value between the vmPFC and the amygdala, which was higher in the anxiety group, was associated with worse extinction recall. This finding is in line with animal investigations showing that specific patterns of medial PFC-amygdala correlate with fear expression.\textsuperscript{39} These exploratory models highlight the need for studies to further examine such questions with cross-validation techniques in larger sample sizes.

**Limitations**

Some limitations of this study should be highlighted. First, the anxiety group was older and less educated than the healthy controls. We have covaried for these variables throughout our analyses. We have also rerun all analyses without covariates, and most of our findings remained unchanged. Furthermore, the covariates were not significantly associated with any of our main outcomes (eAppendix in the Supplement). Second, the specific phobias were more represented in the single disorder group, which could suggest that the comparisons made for the number of diagnoses reflect a difference between specific phobia and the other disorders. Our supplemental analyses ruled out this effect by showing that the single disorder group with specific phobia was comparable to the single disorder group without specific phobia and that the differences between the single disorder group and the multiple disorders group remained when excluding individuals with only specific phobia. Third, there are sex differences pertaining to the prevalence of anxiety disorders,\textsuperscript{40-42} and sex hormones modulate extinction learning.\textsuperscript{43-46} We did not assay gonadal hormones, making it impossible to measure their influence. Fourth, we draw some parallels between our findings and brain activation patterns highlight aspects of the category of anxiety disorders\textsuperscript{DSM-5} that excludes trauma-related and stress-related conditions. Although we used a categorical approach, it would be informative to test similar questions using a dimensional approach. The correlations between the anxiety symptoms and brain activation patterns highlight aspects of the research domain criteria method and the importance of examining more extensively these questions from this approach.\textsuperscript{47} From a clinical standpoint, our results provide a rationale for future work in further classifying each anxiety disorder because not all disorders may be equivalent. Understanding the similarities and differences between anxiety disorders may enable neurobiologically driven treatment development and selection tailored to a patient’s diagnosis, comorbidities, and level of anxiety severity.

**Conclusions**

Our results reveal no SCR deficits for differential acquisition and extinction recall. However, the imaging data suggest that the fear circuitry is dysregulated in individuals with anxiety disorders and that some differences are modulated by the number of disorders or the self-reported anxiety symptoms. The PPI analyses highlighted the importance of investigating the whole fear network and the association between its main nodes because an imbalance in the activation of fear-promoting regions and extinction-promoting regions at different stages throughout the paradigm may synergistically act in conveying a greater vulnerability to anxiety disorders. This study allowed identification of patterns applicable to the DSM-5 category of anxiety disorders that excludes trauma-related and stress-related conditions. Nevertheless, we used a categorical approach, it would be informative to test similar questions using a dimensional approach. The correlations between the anxiety symptoms and brain activation patterns highlight aspects of the research domain criteria method and the importance of examining more extensively these questions from this approach.\textsuperscript{47} From a clinical standpoint, our results provide a rationale for future work in further classifying each anxiety disorder because not all disorders may be equivalent. Understanding the similarities and differences between anxiety disorders may enable neurobiologically driven treatment development and selection tailored to a patient’s diagnosis, comorbidities, and level of anxiety severity.


