Review article

The neurobiology of human fear generalization: meta-analysis and working neural model

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ABSTRACT

Fear generalization to stimuli resembling a conditioned danger-cue (CS+) is a fundamental dynamic of classical fear-conditioning. Despite the ubiquity of fear generalization in human experience and its known pathogenic contribution to clinical anxiety, neural investigations of human generalization have only recently begun. The present work provides the first meta-analysis of this growing literature to delineate brain substrates of conditioned fear-generalization and formulate a working neural model. Included studies ($K = 6$, $N = 176$) reported whole-brain fMRI results and applied generalization-gradient methodology to identify brain activations that gradually strengthen (positive generalization) or weaken (negative generalization) as presented stimuli increase in CS+ resemblance. Positive generalization was instantiated in cingulo-opercular, frontoparietal, striatal-thalamic, and midbrain regions (locus coeruleus, periaqueductal grey, ventral tegmental area), while negative generalization was implemented in default-mode network nodes (ventromedial prefrontal cortex, hippocampus, middle temporal gyrus, angular gyrus) and amygdala. Findings are integrated within an updated neural account of generalization centering on the hippocampus, its modulation by locus coeruleus and basolateral amygdala, and the excitation of threat- or safety-related loci by the hippocampus.

1. Introduction

Flexible threat detection and responding is a prerequisite for survival. The dynamic environments in which we live preclude the sufficiency of innate fears for assuring safety from threat. Instead, most organisms are endowed with an associative learning system that encodes novel threat-related associations that underlie the acquisition and expression of fear-conditioning (Pavlov, 1927; Rescorla, 1988). More specifically, conditioned fear ensues when an aversive unconditioned stimulus (US) co-occurs with a benign conditioned stimulus (CS+), resulting in fear reactivity to the CS+ in the absence of the US. This process expands fear-evoking stimuli beyond a narrow range of species-specific, pre-programmed threat cues to any encountered stimulus associated with danger.

Fear conditioning is adaptive when the CS+ signals a harmful consequence but becomes maladaptive when it manifests to cues that

are not predictive of genuine threat. Two key mechanisms by which conditioned fear is expressed in the absence of threat are: (1) failure to extinguish fear, and (2) generalization of conditioned fear. Extinction failure describes the persistence of conditioned fear to a CS+ that is no longer predictive of an aversive US, and has received extensive empirical attention as a source of excessive fear in clinical anxiety (Duits et al., 2015; Lissek et al., 2005; Marin et al., 2017; Milad and Quirk, 2012; Suarez-Jimenez et al., 2020). In contrast, considerably less work has targeted conditioned fear generalization, the process by which conditioned fear transfers from the CS + to perceptually similar or conceptually related safe stimuli. Fear generalization is largely an adaptive associative learning process that obviates the need to learn all threat relations through direct experience. However, maladaptive fear generalization occurs when fear spreads to an overly inclusive set of benign stimuli that bear inconsequential resemblance to the CS+. Such over-generalization is widely accepted as a key feature of clinical anxiety by clinicians and theorists alike (e.g., Craske et al., 2009; Ehlers and Clark, 2000; Foa et al., 1989).

1.1. Lab-based studies of human fear-generalization

While experimental findings demonstrating the pathogenic potential of conditioned fear generalization in humans date back to Watson and Rayner's seminal "Little Albert" study (Watson and Rayner, 1920), systematic investigations of human fear generalization did not begin in earnest until almost a century later (Dunsmoor et al., 2009; Hajcak et al., 2009; Lissek et al., 2008). These initial studies and several conducted since (e.g., Holt et al., 2014; Kaczkurkin et al., 2017; Lissek et al., 2014b, 2010; Onat and Büchel, 2015) assess conditioned fear to both CS+ and generalization stimuli (GS) parametrically varying in perceptual similarity to CS+, and document *generalization gradients*, or slopes, with peak responding to CS+ and gradually declining levels of fear to GSs of decreasing perceptual similarity to CS+. Through this method, the strength of generalization is indexed by the steepness of gradients, with less steep downward gradients indicating greater generalization.

To date, applications of the generalization gradient method in clinical anxiety samples have documented over-generalization of conditioned fear in panic disorder (PD: Lissek et al., 2010), generalized anxiety disorder (GAD: Lissek et al., 2014b; but see Tinoco-González et al., 2015), and post-traumatic stress disorder (PTSD: Kaczkurkin et al., 2017; Lissek and van Meurs, 2015; Morey et al., 2015). These findings, together with the centrality of over-generalization to etiological accounts of clinical anxiety, have fueled interest in the neural substrates of generalized conditioned fear as candidate, brain-based markers of anxiety pathology.

1.2. Neuroimaging studies and brain-based models of human fear-generalization

A growing number of functional magnetic resonance imaging (fMRI) studies have used generalization gradient methodology to elucidate the neurobiology of generalized fear in healthy humans (Dunsmoor et al., 2011; Greenberg et al., 2013; Kaczkurkin et al., 2017; Lange et al., 2017; Lissek et al., 2014a; Morey et al., 2015; Onat and Büchel, 2015). Such studies apply Pavlovian fear conditioning preparations consisting of two phases: 1) acquisition training and 2) generalization test. During acquisition a CS+ paired with an aversive US, and a conditioned safety-cue (CS−) unpaired with the US, are repeatedly presented in quasi-random order. Next, during the generalization test, a partially reinforced CS+ and unreinforced CS− are quasi-randomly intermixed with one or more unreinforced generalization stimuli (GSs) that together form a continuum of perceptual similarity from CS + to GSs to CS−. fMRI responses to CS+, GSs, and CS− are collected and primarily assessed for continuous generalization gradients consisting of mounting activations as presented stimuli increase in similarity to CS+ (positive generalization) or declining activations with increasing CS+

resemblance (negative generalization). Brain areas coding for positive and negative generalization putatively subserve threat and safety-related processes, respectively.

Key findings from initial studies (i.e., Dunsmoor et al., 2011; Greenberg et al., 2013; Lissek et al., 2014b) included positive generalization in anterior insula, dorsomedial prefrontal cortex (dmPFC) and dorsal anterior cingulate cortex (dACC), as well as negative generalization in ventral aspects of medial prefrontal cortex (vmPFC) and anterior hippocampus. Based on a synthesis of these early results and findings from the animal literature, a provisional neural model of conditioned fear generalization was proposed (Lissek et al., 2014a). In this model, the hippocampus schematically matches visual representations of each presented GS against CS+ representations stored in memory. GSs with higher degrees of representational overlap with CS+ prompt hippocampally-mediated pattern completion that instates the CS+ representation and generates activation in such downstream regions associated with fear excitation as the amygdala, anterior insula, and dmPFC/dACC. In contrast, GSs with lower degrees of CS+ representational overlap prompt pattern separation by the hippocampus which then activates regions associated with fear inhibition such as the vmPFC.

Although many ensuing fMRI results yielded generalization-related activations in anterior insula, dmPFC/ACC, vmPFC, and anterior hippocampus in directions that are consistent with this model (Kaczkurkin et al., 2017; Lange et al., 2017; Tuominen et al., 2019), studies in this growing literature have identified a large array of brain regions instantiating generalization that are absent from the initial model. Such findings extend into all lobes of the cerebral cortex, as well as subcortical, midbrain, pons, and cerebellar structures. Furthermore, generalization-related activation patterns deviating from monotonically decreasing or increasing responses across stimuli varying in CS+ similarity have been identified (Onat and Büchel, 2015). Specifically, inferotemporal cortex (ITC), a ventral visual region implicated in object recognition, was found to form a U-shaped gradient with highest responding to CS+ and CS− and reduced responding to GSs. That ITC distinguished between stimuli with ambiguous versus more certain signal-value (GSs and CS+/CS− respectively) suggests that generalization-related activity in ITC may code for ambiguity-based uncertainty elicited by GSs.

1.3. Goals of the present study

While results from this growing fear generalization fMRI literature bring us closer to a comprehensive neural account of generalization, each study yields a unique array of wide-reaching substrates forming positive, negative, or U-shaped gradients, making it difficult to form a coherent synthesis of findings. To aggregate neural findings across existing studies, the current effort provides the first meta-analysis of fMRI investigations of generalized conditioned fear in humans. In addition to characterizing the summative strength of findings in previously reported neural substrates of generalization, this meta-analysis may reveal novel substrates that were statistically underpowered at the individual-study level. Furthermore, meta-analytic findings will be leveraged to formulate an updated neural account of conditioned fear generalization.

To these ends, we use the Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) neuroimaging meta-analytic method (Albajes-Eizagirre et al., 2019a, b) to produce voxel-wise 'brain maps' of activations forming positive and negative generalization gradients across studies, assess between-study heterogeneity and potential publication bias, and identify and control for the moderating influence of study attributes (i.e., sample characteristics, experimental-design parameters) via voxel-wise random-effects meta-analysis. To maximize statistical power and sensitivity to detect robust fear generalization loci, we relied solely on original, whole-brain statistical parametric maps (SPMs) gathered from each included dataset. Because behavioral and neural

gradients of generalized fear are typically curve-linear and include both linear and quadratic components (e.g., Kaczkurkin et al., 2017; Lissek et al., 2010), we obtained and separately meta-analyzed SPMs reflecting linear and quadratic patterns of generalization. An additional motivation for capturing both linear and quadratic effects is that included studies used different intervals of CS+ similarity across GSs, precluding a priori hypotheses regarding gradient shape. Finally, the inclusion of quadratic analyses afforded tests of gradients reflecting ambiguity-based uncertainty in which brain responses to stimuli with ambiguous signal value (i.e., GSs) diverge from responses to stimuli with more certain signal value (i.e., CS+ and CS−) (Onat and Büchel, 2015).

In sum, the present meta-analysis of fear-generalization findings from human fMRI studies was undertaken to quantitatively summarize neural substrates of positive and negative generalization instantiated via linear or quadratic gradients of activation, assess publication bias and heterogeneity of effect sizes, estimate moderation of findings by methodological factors, and provide an updated neural model of fear-generalization informed by meta-analytic results.

2. Methods

2.1. Search and inclusion of studies

Our protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) (see Fig. S1) and was pre-registered with PROSPERO. Two reviewers (RW, KF) searched MEDLINE, Web of Knowledge, and Scopus for studies assessing gradients of generalized conditioned fear with functional magnetic resonance imaging (fMRI) in healthy humans. The following search terms were used: ('fear generalization' OR 'Pavlovian generalization' OR 'Pavlovian fear generalization' OR 'generalized fear') AND ('neuroimaging' OR 'fMRI' OR 'magnetic resonance imaging' OR 'functional magnetic resonance imaging'). Citations of relevant studies were reviewed and researchers with records of fear generalization work in humans were queried regarding unpublished datasets.

All included studies were conducted in healthy human adults and used an aversive stimulus (e.g., shock) as an unconditioned stimulus, and an independent physiological/behavioral measure (e.g., skin conductance/expectancy ratings) confirming successful conditioning and generalization. Because the current analysis used pre-specified contrast weights that were not employed in any of the original reports, the unavailability of original group level, voxel-wise activation maps led to the exclusion of one study (Dunsmoor et al., 2011). Additionally, because SDM relies on whole-brain results, one study restricting image acquisition to the ventral half of the brain (Onat and Büchel, 2015) was also excluded. In the case of overlapping data sets, data from the first published study were used. Healthy-participant data from fMRI studies comparing fear generalization across those with and without clinical anxiety were retained. In two cases this included psychiatrically healthy trauma control participants from studies examining generalization abnormalities in PTSD (Kaczkurkin et al., 2017; Morey et al., 2015).

2.2. Meta-analytic approach

Corresponding authors of included studies were asked to provide group level, whole brain, voxel-wise activation maps reflecting results (*t*-values) of models capturing generalization gradients through linear and quadratic trends in patterns of fMRI responding across CS+, GSs, and CS− classes of stimuli. The models used pre-specified linear and quadratic contrast weights designed to identify voxels with positive and negative linear and quadratic trends. The number of contrast weights selected for a given study corresponded to the number of employed stimulus classes.

Statistical results (*t*-test) from linear and quadratic analyses were meta-analyzed using SDM-PSI. The software created a brain map of the

effect sizes for the linear and quadratic gradients for each study, and a voxel-wise random-effects meta-analysis aggregated these effect sizes after weighting each study for sample size, variance, and between-study heterogeneity. Statistical significance was set at "threshold-free cluster enhancement" (TFCE; Smith and Nichols, 2009) $p \leq 0.05$, two-tailed and corrected for multiple comparisons, with a minimum cluster extent of 50 voxels. Publication bias was measured via the Egger's test, with a significant Egger's test result indicated publication/reporting bias (Egger et al., 1997). Heterogeneity was assessed using the I^2 index (Ioannidis et al., 2007), with >50 % representing substantial heterogeneity (Fullana et al., 2020). Results were reported in Montreal Neurological Institute space.

We used meta-regression to explore the potential effects of study characteristics on the strength of linear/quadratic trends, including: control group composition (trauma versus non-trauma control), number of generalization stimuli, reinforcement rate, sex, and age. We used a more conservative threshold for these analyses to correct for multiple tests ($p \leq 0.0005$, minimum cluster extent 50 voxels).

Finally, to more closely investigate activation patterns formed by key fear generalization related brain areas, we used AFNI to delineate the structural boundaries of several functional regions of interest (fROI) that emerged from the voxel-wise positive/negative linear and positive quadratic analyses. To plot patterns of neural generalization, percent signal change in significant fROIs to each stimulus type relative to baseline were computed at the individual-study level and graphed across CSs and GSs, ordered according to the degree of CS+ similarity.

3. Results

3.1. Included studies and sample characteristics

Relevant demographic data and methodological characteristics of each study were extracted and are displayed in Table 1. We included 6 independent data-sets with a total of 176 participants (41.5 % females, mean age of 29.3 years [*SD* = 6.47]; see Table 1). Importantly, all included studies showed evidence of generalization via an independent behavioral/physiological measure (e.g., SCR, shock expectancy).

3.2. Neural substrates of positive generalization gradients

Tables S1 and S2 list full statistical results and Fig. 1A-B display meta-analytic mean maps for evoked brain responses falling along positive-linear and positive-quadratic gradients of generalization. Result for Egger's tests and the I^2 index showed no evidence of publication bias or heterogeneity across studies for most reported findings.

Figs. 2, 3 display select meta-analytically derived fROI that emerged from positive linear and quadratic analyses along with corresponding gradients reflecting inter- and intra-study averages to CSs and GSs across the continuum of CS+ similarity. Although these fROI were meta-analytically determined using all included studies, results from Tuominen et al. (2017) are not visually depicted in Figs. 2, 3 because the continuum-of-similarity across CSs and GSs in this study were derived using an individually determined 'just noticeable difference' measure. Therefore, charting neural activations across uniform intervals of CS+ similarity was not possible for Tuominen et al. (2017) and findings from this study are depicted separately in Fig. S5.

In Figs. 2, 3, fROI are grouped anatomically (e.g., striatal-thalamic areas, brainstem nuclei) or based on shared participation in established functional networks (cingulo-opercular, frontoparietal: Dosenbach et al., 2008; Menon, 2011; Raichle, 2015).

3.2.1. Linear and quadratic effects

Brain loci displaying linear increases in activation as presented stimuli increased in similarity to CS+ included cingulo-opercular regions (see Fig. 2A) comprised of bilateral anterior insula, dorsomedial prefrontal cortex (dmPFC: BA6, BA8, BA9), and dorsal anterior cingulate

Table 1
Characteristics of the 6 conditioned fear generalization fMRI studies included in the linear/quadratic fear generalization meta-analyses.

Study	N	Females (%)	Mean age	Pre-conditioning?	CS+, CS−	Type of US/ location	Reinforcement rate during acquisition (%)	Number of CS+/CS− presentations during acquisition	Number of GSs	Reinforcement rate during generalization (%)	Number of CS+, GS, and CS− presentations during generalization	Average CS-US onset delay (ms)	Degree of stimulus gradation	Independent measure of generalization
Lissek et al. (2014a), 2014b	19	55	24	yes	CS+ small or large ring; CS− smallest or largest ring and v shape	Shock/ right ankle	80	15	3	33.3	20	4200	11.9%	Subjective ratings
Morey et al. (2015)	35	28.6	41.9	yes	CS+ moderately fearful face; CS− unreinforced mildly fearful face	Shock/ right wrist	33.3	18 CS+, 12 CS−	1	33.3	12 CS+, 8 CS−, and 16 for each GS	3994	22.22%	Subjective ratings
Lange et al. (2017)	46	78.2	20.7	yes	CS+ small or large circle/ rectangle; CS− smallest or largest circle/ rectangle and triangle	Shock/ left ankle	66	12	5	50	12	4200	9.2%	Subjective ratings
Kaczkurkin et al. (2017)[1]	22	0	33.5	yes	CS+ small or large ring; CS− smallest or largest ring and v shape	Shock/ right ankle	75	15	3	33.3	30 CS+, 20 of all others	3900	11.9%	Subjective ratings
Kaczkurkin et al. (2017)[2]	17	0	28.8	yes	CS+ small or large ring; CS− smallest or largest ring and v shape	Shock/ right ankle	75	15	3	33.3	30 CS+, 20 of all others	3900	11.9%	Subjective ratings
Tuominen et al. (2019)	37	44.7	28.5	no	CS+ neutral face; CS− other neutral face	Shock/ right hand	62.5	8	5	100	5	5500	Based on individual discrimination thresholds	Subjective ratings, SCR
Total/ Mean	**176**	**41.5**	**29.3**				**63.4**	**CS+ 13.6, CS− 12.4**	**3.4**	**50.0**	**CS+ 15.8, GS 14.6, CS− 13**	**4282.3**	**13.4 (without Tuominen data)**	

Abbreviations: CS, conditioned stimulus; CS+, CS followed by unconditioned stimulus; CS−, CS not followed by unconditioned stimulus; US, unconditioned stimulus; SCR, skin conductance recording. All included studies were whole brain analyses and were not US confounded.

[1] refers to Kaczkurkin et al., 2017 trauma control sample.

[2] refers to Kaczkurkin et al., 2017 healthy control sample.
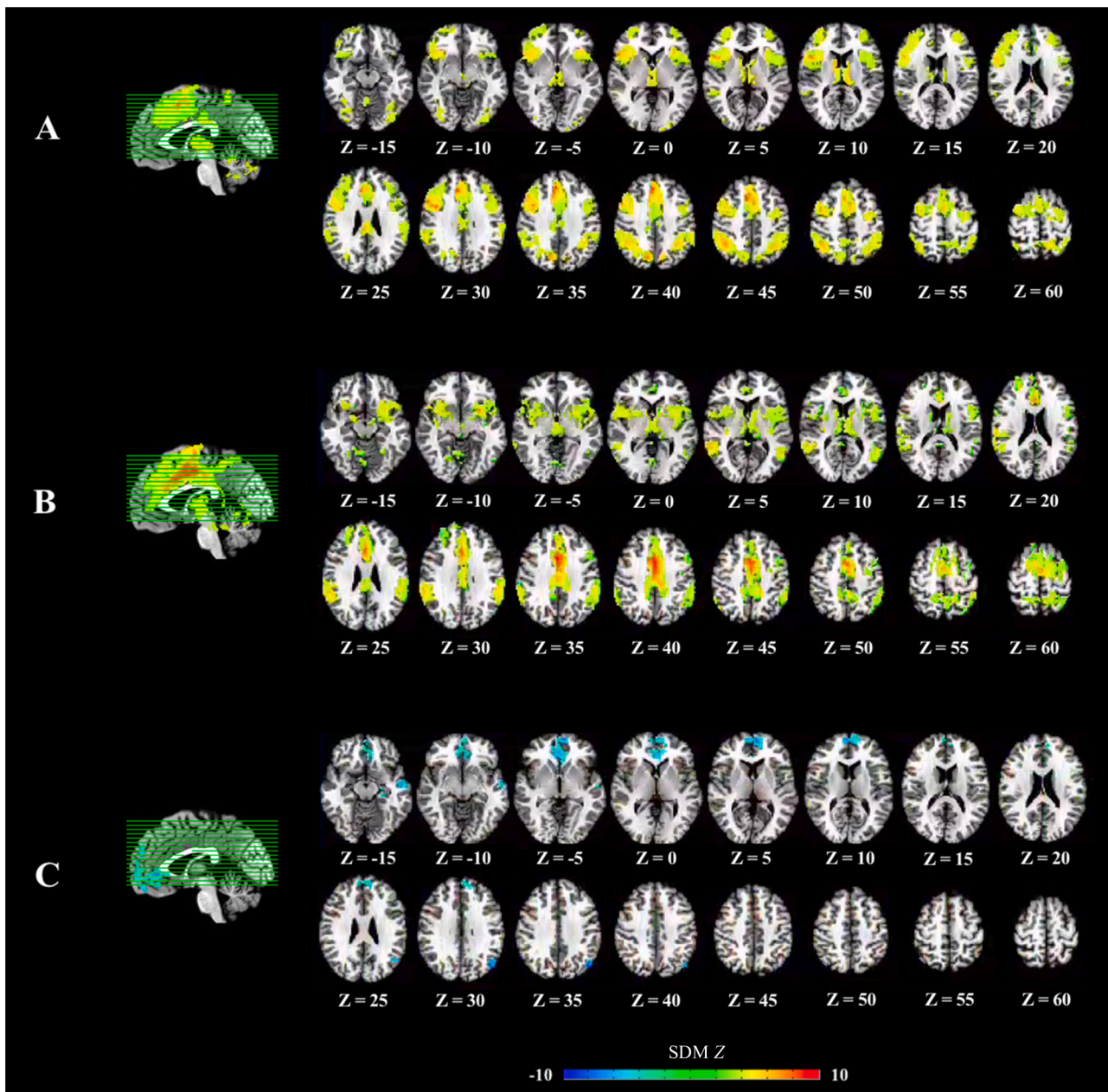
Fig. 1. Meta-analytically derived neural loci forming: (a) positive linear, (b) positive quadratic, and (c) negative linear slopes from the conditioned safety-cue to generalization stimuli to conditioned danger-cue. Results are displayed at $p < .025$ (cluster size ≥ 50) on the MNI 27 T1 template.

cortex (dACC). Additionally, as shown in Fig. 2B, frontoparietal activations fell along positive-linear gradients of generalization and included a large area of bilateral dorsolateral prefrontal cortex (dlPFC: BA6, BA8, BA9, BA10) and bilateral ventrolateral prefrontal cortex (vlPFC: BA10; BA44, BA45, BA47), with right dlPFC/vlPFC activations being more expansive than left; and bilateral inferior parietal lobule (IPL) extending from BA7 to BA40. Further positive-linear patterns of activation were found bilaterally in the caudate head/body and thalamus (primarily pulvinar and medial dorsal nucleus: MDN) (see Fig. 3A); fusiform gyrus (see Fig. S2) and cerebellum (culmen, declive, tuber, uvula).

Positive-quadratic activation patterns emerged in many of the above described regions displaying positive-linear effects including dmPFC (BA6, BA8, BA9), dorsal/ventral ACC, bilateral anterior insula, left dlPFC (BA9, BA6), bilateral vlPFC (BA44, BA47), bilateral IPL, bilateral caudate head/body, bilateral thalamus, bilateral mammillary body, and

bilateral cerebellum. That is, significant fROIs generated by linear and quadratic analyses of positive generalization overlapped extensively in such regions, indicating both linear and quadratic decreases in activation as presented stimuli differentiated from CS+. When such overlap occurred, only linear fROIs were plotted in order to restrict the paper to a reasonable length. It should thus be noted that positive generalization gradients for all linear-fROIs plotted in Fig. 2 and Fig. 3A have both linear and quadratic components.

Structures uniquely characterized by quadratic activation patterns included a set of brainstem structures comprised of the locus coeruleus, periaqueductal gray (Fig. 3B), and ventral tegmental area (Fig. 3B), as well as bilateral findings in the amygdala (see Fig. S3).

Given the centrality of locus coeruleus findings to the neural model of generalization later proposed herein (Fig. 5), along with the small size of this structure relative to the available resolution of typical fMRI protocols, we compared the location of the LC fROI generated by
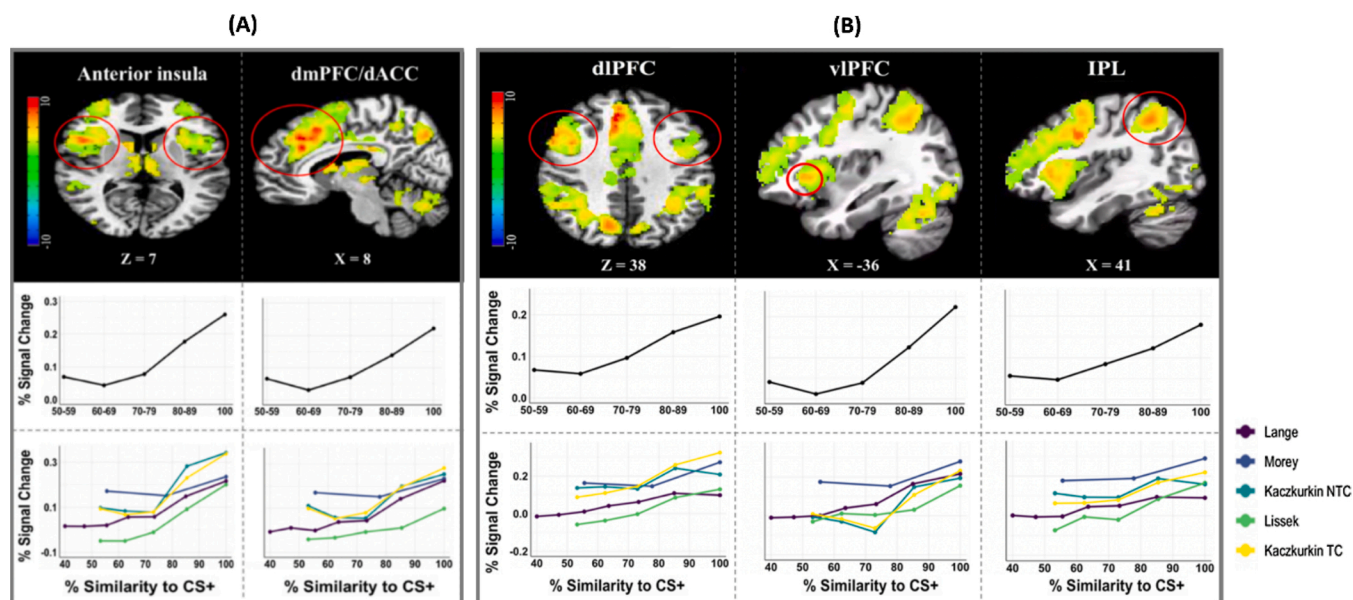
Fig. 2. Activation plots for (A) cingulo-opercular and (B) frontoparietal regions showing positive linear activation patterns across conditioned and generalization stimuli with varying degrees of resemblance to the conditioned danger-cue (CS+). The top and bottom row of line graphs plot averaged data at the study-wide and individual study level, respectively. The color bar at the top left reflects Z-values for the positive linear contrast. Abbreviations: dmPFC dorsomedial prefrontal cortex; dACC dorsal anterior cingulate cortex; dlPFC dorsolateral prefrontal cortex; vlPFC ventrolateral prefrontal cortex; IPL inferior parietal cortex; NTC non-trauma controls; TC trauma controls.
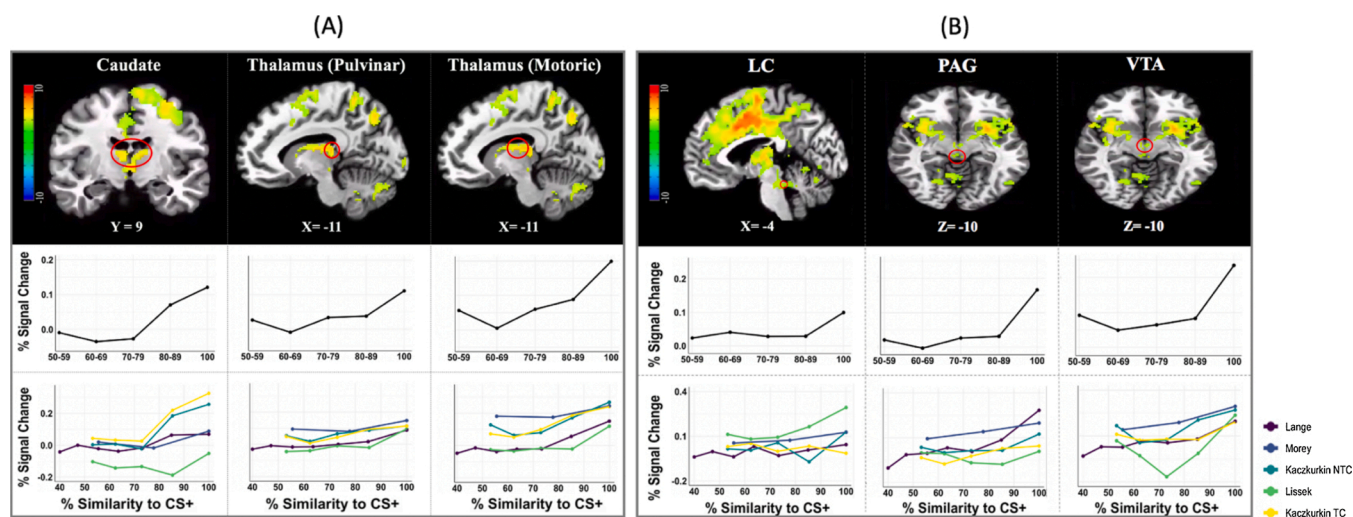
Fig. 3. Activation plots for (A) striatal-thalamic and (B) midbrain regions showing positive linear and quadratic activation patterns, respectively, across conditioned and generalization stimuli with varying degrees of resemblance to the conditioned danger-cue (CS+). The top and bottom row of line graphs plot averaged data at the study-wide and individual study level. The color bar at the top left reflects Z-values for the positive linear contrast. Thalamic motoric areas putatively include ventral lateral and ventral anterior nuclei. Abbreviations: LC locus coeruleus; PAG periaqueductal gray; VTA ventral tegmental area; NTC non-trauma controls; TC trauma controls.

positive-quadratic analyses to coordinates from Keren et al. (2009), an authoritative human in-vivo LC mapping study that has been used by other studies purporting to measure LC activation (i.e., Murphy et al., 2014; Lee et al., 2018). Our original LC fROI was closely adjacent but slightly anterior to Keren and colleagues' coordinates. Therefore, we created a new fROI using AFNI's draw function to form a mask using a 3 mm, 3D sphere placed adjacent to the fourth ventricle and overlapping with −3.7, −34, −27, an LC coordinate cited by Keren et al. (2009). Next, we multiplied this mask by our functional data to identify voxels within the mask that showed positive quadratic activations. Significant results were present in the left but not right LC (see Fig. S4 for high-resolution images of these LC findings). LC gradients of

generalization derived from the updated fROI aligned to LC coordinates specified by Keren et al. (2009) are displayed in Fig. 3B.

3.2.2. Differences in linear versus quadratic findings in overlapping structures

Brain activations generated from linear and quadratic analyses that centered on the same brain structure often differed in spatial extent: 1) Quadratic dmPFC responses both encompassed linear dmPFC activations (BA6, BA8, BA9) and extended anteriorly into BA32 and posteriorly into the paracentral lobule (BA4) and anterior precuneus (BA7); 2) Quadratic activations in dlPFC (BA 9, BA6) and vlPFC (BA44, BA47) were less expansive than linear responses in these regions (dlPFC: BA6,

BA8, BA9; vlPFC: BA44, BA45, BA47); 3) Right IPL findings generated by linear but not quadratic analyses extended medially to the precuneus; 4) Quadratic versus linear activations in the thalamus covered more ventral areas of MDN, and encompassed a larger portion of the red nucleus; and 5) Quadratic activations in the cerebellum included larger areas of bilateral culmen, while linear cerebellar activations entailed more bilateral declive and right uvula.

3.3. Neural substrates of negative generalization gradients

Full statistical results and meta-analytic mean maps for brain areas instantiating negative generalization can be found in Table S3 and Fig. 1C, respectively. As can be seen in Table S3, no evidence of heterogeneity or publication bias was found for any negative generalization findings. Additionally, meta-analytically derived fROIs that significantly fell along negative generalization gradients are pictured in Fig. 4 along with corresponding generalization slopes at the group and individual-study level, with the exception of results from Tuominen et al. (2017) which can be found in the supplement (Fig. S6).

3.3.1. Linear and quadratic effects

Linear decreases in activation to stimuli bearing increasing resemblance to CS+ were largely found within regions associated with the default-mode network (DMN: Raichle, 2015) including left anterior hippocampus/parahippocampal gyrus, anterior and posterior aspects of vmPFC, left anterior middle temporal gyrus (MTG), and left angular gyrus (see Fig. 4). One notable exception was negative-linear gradients found in the left amygdala (see Fig. S3), a region falling outside the DMN that is generally ascribed to the salience network. All negative-linear activations, including those found in the amygdala, plausibly reflect safety-related processes as negative gradients indicate rising activations to stimuli with increasing safety value. No regions displaying negative-quadratic activation patterns were found.

3.4. Effects of sample characteristics and conditioning parameters on generalization gradients

Meta-regression analyses revealed no significant relationships between neural gradient effects (linear or quadratic) and study characteristics.

4. Discussion

The present study is the first meta-analytic investigation of the neural substrates of conditioned fear generalization in healthy humans. Findings elucidate a consistent and replicable set of brain areas coding for positive or negative generalization as indicated by increasing (positive generalization) or decreasing (negative generalization) activations, as presented stimuli more closely resemble CS+. Neural activations falling along positive and negative gradients putatively reflect fear- and safety-related processes, respectively. Of note, no activation patterns across stimuli showed an inverted U-shape form (i.e., elevated responses to GSs versus both CS+ and CS−) that would be consistent with the ambiguity-related uncertainty perspective on generalization (Onat and Büchel, 2015). Nevertheless, the literature would benefit from future attempts to characterize neural and behavioral processes sensitive to threat ambiguity during generalization given the strong face validity of the ambiguity-based account and empirical support deriving from fear generalization studies finding either neural loci (inferotemporal cortex) differentiating GSs from both CS+ and CS− (Onat and Büchel, 2015) or associations between high trait intolerance of uncertainty and increased fear generalization (Morriss et al., 2016; but see Nelson et al., 2015).

In order to increase the sensitivity of our approach for identifying all neural substrates of generalization, which typically have both linear and quadratic components (e.g., Kaczkurkin et al., 2017; Lange et al., 2017), we conducted voxelwise tests of both linear and quadratic patterns of positive and negative generalization. Positive-linear and positive-quadratic generalization effects emerged in an array of brain areas, including nodes of the cingulo-opercular (anterior insula, dmPFC/dACC) and frontoparietal (dlPFC, vlPFC, IPL) networks, as well as striatal-thalamic regions (caudate, thalamus), indicating that positive
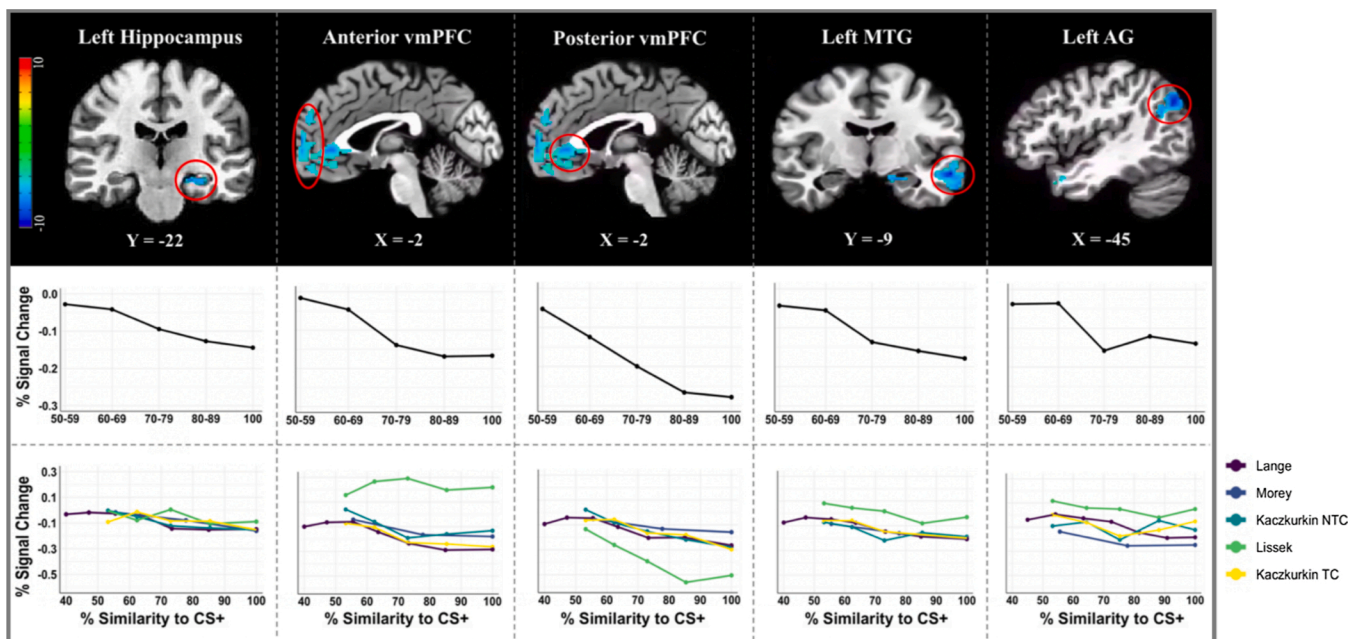

Fig. 4. Activation plots for default mode network regions showing negative linear activation patterns across conditioned and generalization stimuli with varying degrees of resemblance to the conditioned danger-cue (CS+). The top and bottom row of line graphs plot averaged data at the study-wide and individual study level. The color bar at the top left reflects Z-values for the positive linear contrast. Abbreviations: vmPFC ventromedial prefrontal cortex; MTG middle temporal gyrus; AG angular gyrus; NTC non-trauma controls; TC trauma controls.
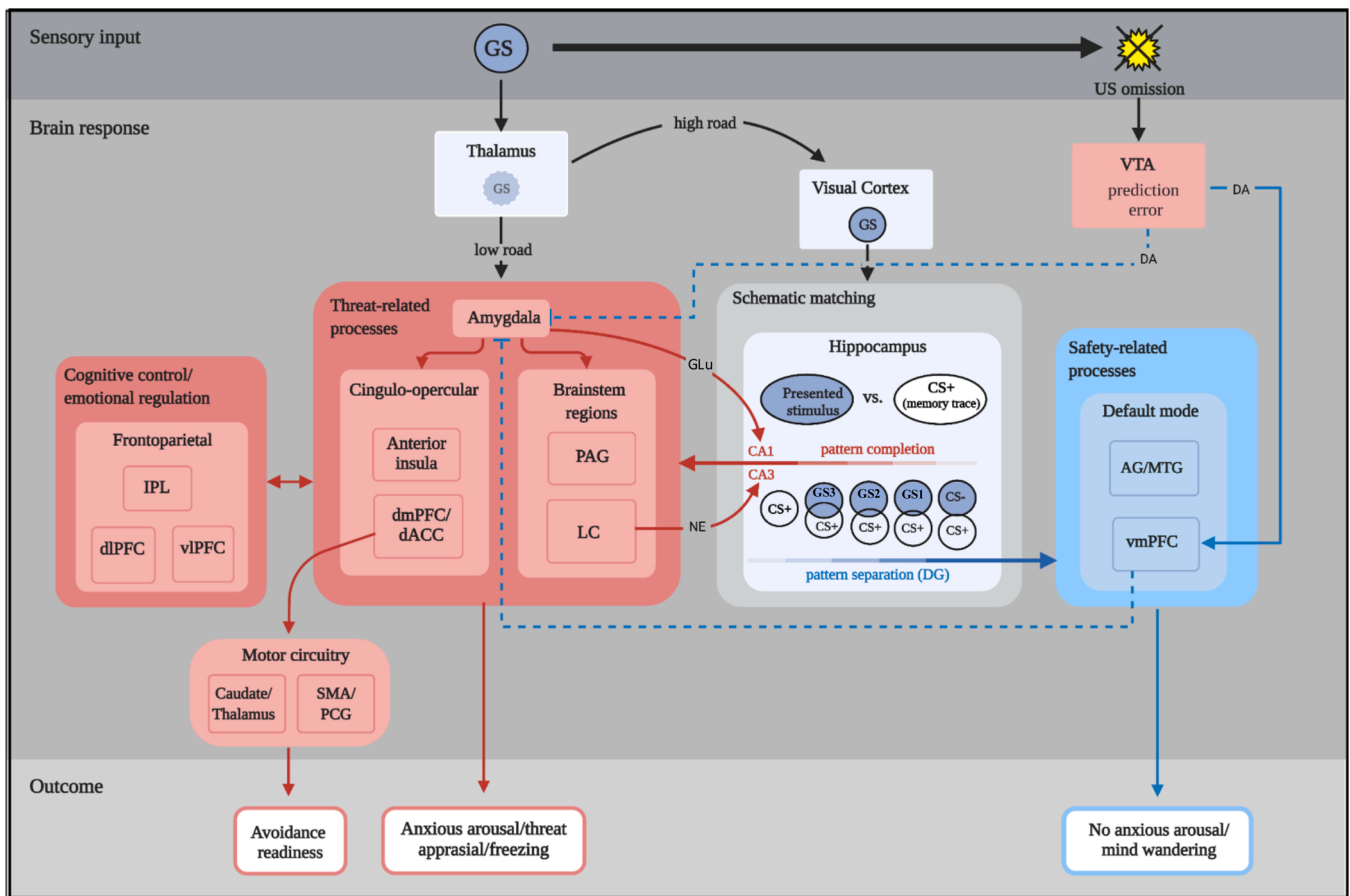
Fig. 5. Updated neural working model of conditioned fear generalization incorporating neural structures with activations shown or proposed to fall along positive (red structures) and negative gradients of generalization (blue structures). Following acquisition of fear to a visual conditioned danger-cue (CS+), exposure to a resembling but safe generalization stimulus (GS) activates sensory thalamic nuclei which send visual information about the GS to amygdala-based fear circuits via a quick and dirty 'low road' and to visual cortices via a 'high road'. Through the low road, thalamic signals activate the amygdala, triggering rapid activation of subcortical (e.g., LC, PAG) and cortical (AI, dmPFC/dACC) aspects of the amygdala-based threat network. Projections from the basolateral amygdala (BLA) and LC, evoked by low road cascades, target CA1 and CA3 hippocampal subfields, respectively, predisposing the hippocampus toward pattern completion. Next, fine-grained visual representations of the GS generated by the 'high road' reach the hippocampus where the overlap between the cortical representation of the GS and the previously encoded CS+ is assessed. With sufficient synergy between GS/CS+ representational overlap and GS-evoked activity in BLA-CA1 and LC-CA3 pathways, the hippocampus is thought to initiate pattern completion resulting in activation of brain structures associated with threat processing (amygdala, AI, dmPFC, PAG, LC), and triggering the autonomic, neuroendocrine and behavioral constituents of the generalized threat response. These threat-related activations next engage executive control areas of the brain (IPL, dlPFC, vlPFC), through which attentional and emotion-regulation processes are deployed in the service of response optimization. In the event of an insufficient mix of GS/CS+ representational overlap and LC signaling, dentate gyrus neurons in the hippocampus are thought to implement 'pattern separation', propagating activity in default mode structures associated with fear inhibition and the resumption of a resting state (vmPFC, MTG, AG). Such default mode activations then reduce ongoing activity in amygdala-based fear networks initiated earlier by the low road, thereby stemming generalized anxiety. Finally, when GS presentations are unexpectedly followed by the absence of an aversive US, a dopaminergic, positive prediction error signal in VTA may be triggered, supporting safety learning (i.e., strengthening of the GS/no-US association) through its innervation of safety coding neurons in the amygdala and vmPFC. This prediction error process is a promising mechanism for attenuation of generalized fear with repeated exposure to unreinforced GSs. Abbreviations: PAG periaqueductal gray; LC locus coeruleus; NE norepinephrine; GLu glutamate AI anterior insula; dmPFC dorsomedial prefrontal cortex; dACC dorsal anterior cingulate cortex; PCG precentral gyrus; SMA supplementary motor area; dlPFC dorsolateral prefrontal cortex; vlPFC ventrolateral prefrontal cortex; IPL inferior parietal lobule; VTA ventral tegmental area; DA dopamine; MTG middle temporal gyrus; AG angular gyrus; vmPFC ventromedial prefrontal cortex; CA1 cornu Ammonis 1; CA3 cornu Ammonis 3; DG dentate gyrus; CS+ conditioned danger-cue; CS− conditioned safety-cue; GS generalization stimulus with either high (GS3) moderate (GS2), or low (GS1) resemblance to the CS+; US unconditioned stimulus.

generalization gradients in such areas included both linear and quadratic components. Additionally, positive-quadratic but not positive-linear gradients were identified in such brain-stem nuclei as LC, PAG, and VTA. In contrast to positive generalization findings, negative generalization effects fell along linear but not quadratic gradients and spanned a more limited set of brain loci including aspects of the default mode network (anterior hippocampus, vmPFC, MTG, AG) and amygdala. Below, we detail the putative psychological contributions of key positive and negative generalization loci and then delineate an updated working neurobiology of generalized conditioned fear.

4.1. Neural substrates of positive generalization

4.1.1. Cingulo-opercular loci

The cingulo-opercular network has been implicated in the detection of salient environmental events and the recruitment of relevant cognitive processes to optimize responses to such events (e.g., Seeley et al., 2007). Current results identify two central nodes of this network, AI and dmPFC/dACC (both bilateral), as substrates of positive generalization suggesting robust, threat-related salience detection of CS+ that gradually declines as stimuli differentiate from CS+.

In addition to contributing to the superordinate function of the

cingulo-opercular network, AI and dmPFC/dACC may each subserve unique generalization-related processes. Given that anterior insula has been linked to interoceptive awareness of the somatic correlates of fear (LeDoux and Pine, 2016; Paulus and Stein, 2006; Zaki et al., 2012), positive generalization effects in AI may reflect graded increases in conscious awareness that one's body is in an anxious state as presented stimuli become more similar to CS+. In terms of dmPFC/dACC, a broad, cross-species literature has linked the expression of fear-related responses to the rodent prelimbic (PL) cortex (Sierra-Mercado et al., 2011; Vidal-Gonzalez et al., 2006) and its human homolog, dACC (Fullana et al., 2016; Linnman et al., 2011; Milad et al., 2007; Sierra-Mercado et al., 2011; Vidal-Gonzalez et al., 2006). Findings from functional neuroimaging studies of instructed threat have further specified a role for the rostral dACC and adjacent dmPFC in the risk-appraisal component of the fear response (Botvinick et al., 2004; Kalisch and Gerlicher, 2014; Mechias et al., 2010). As such, positive generalization effects in dmPFC/dACC may reflect rising levels of perceived risk as presented stimuli increase in CS+ similarity.

4.1.2. Frontoparietal regions

The frontoparietal network is involved in a range of higher-order cognitive functions including attention, cognitive control, and emotional regulation (Marek and Dosenbach, 2018; Rees et al., 2002). Two bilateral frontoparietal areas showed positive generalization effects in the present study: the lPFC (including dlPFC and vlPFC) and IPL.

4.1.2.1. Lateral prefrontal cortex (lPFC).
One interpretation of current lPFC findings derives from previous work linking increases in cognitive load to heightened lPFC activity (e.g. Tomasi et al., 2007). According to attentional control theory (Eysenck et al., 2007), anxiety impairs goal-directed attention via an increase in cognitive load driven by heightened stimulus-driven attention. In addition to attending to each stimulus, participants in the included studies were asked to provide subjective risk/fear ratings at particular time-points and remain still on the scanner bed while receiving aversive USs. Consistent with attentional control theory, anxiety-driven increases in cognitive load may have required increased engagement of the lPFC to perform study-related tasks. Positive generalization effects in this region may thus reflect threat-related increases in cognitive load which scale to CS+ resemblance.

A second interpretation receives support from the well documented role of dlPFC and vlPFC in emotion regulation (Braunstein et al., 2017). Neuromodulation studies suggest that the lPFC may down-regulate negative emotion by inhibiting subcortical valence structures such as the amygdala. For example, excitatory stimulation of the dlPFC via both repetitive transcranial magnetic stimulation (rTMS) (Baeken et al., 2010) and transcranial direct current stimulation (tDCS) (Ironside et al., 2019) has been shown to dampen amygdala activation to negatively valent stimuli in healthy individuals and individuals with high trait anxiety, respectively. These results suggest that presently reported positive lPFC gradients of generalization may reflect increased attempts to regulate fear through inhibition of the amygdala-based fear network, commensurate with the degree of similarity between a presented stimulus and CS+.

4.1.2.2. Inferior parietal lobule (IPL).
Although the IPL has been implicated in a variety of cognitive functions – including attentional reorienting (Corbetta, 1998), working memory (Wang et al., 2019), and retrieval of semantic and episodic memory (Cabeza et al., 2008; Wagner et al., 2005) – a recent theoretical account that integrates IPL activations across these cognitive domains asserts that the overarching function of IPL involves a stimulus-driven attentional shift toward salient external events or attention capturing episodic memories (Cabeza et al., 2012). According to this account, positive generalization in the IPL may reflect attentional shifting toward the external cue, or related internal

representations, that peaks to the maximally threatening CS+ and diminishes with increasing perceptual dissimilarity.

4.1.3. Brainstem nuclei

Consistent with the brainstem's central role in the production of autonomic and behavioral responses to emotionally salient stimuli (Venkatraman et al., 2017), three brainstem nuclei – the LC, PAG, and VTA – showed positive generalization effects.

4.1.3.1. Locus coeruleus.
In response to threat, the LC modulates autonomic arousal, attentional orienting, and learning and memory processes via noradrenergic transmission to widespread brainstem, subcortical, and cortical projections (Díaz-Mataix et al., 2017; Ross and Van Bockstaele, 2021; Samuels and Szabadi, 2008). One such projection with particular relevance to generalization extends to the hippocampus (Loughlin et al., 1986), where noradrenergic signaling exerts influence on plasticity with the effect of enhancing retrieval of threat-related memories (Murchison et al., 2011, 2004; Zhang et al., 2005). As such, activation of the LC-hippocampal pathway may strengthen retrieval of the CS+ memory when a perceptually resembling stimulus (i.e., GS) is encountered, resulting in greater generalization of conditioned fear. Positive generalization effects in the LC may thus reflect the propensity of the danger cue and its close perceptual approximates to trigger increased arousal, attention, and hippocampally-mediated retrieval of the CS+ memory trace.

As displayed in Fig. 3, the group averaged LC results indicate elevated activations to the CS+ that diminish somewhat equally across GSs and CS−. However, given stimulus set differences across studies, the group average necessarily collapsed stimuli within a range of CS+ similarity, which afforded depiction of group-level results at the cost of information loss. Results at the individual-study level, which are not subject to this limitation, indicate that LC gradients for 3 of 5 studies plotted in Fig. 3 (Lissek et al., 2014a, 2014b; Lange et al., 2017; Morey et al., 2015) fall along positive generalization slopes, with peak activations to CS+ that generally decline as presented stimuli perceptually differentiate from CS+. Gradients from the remaining two datasets plotted in Fig. 3 (Kaczkurkin et al., 2017 [NTC data, TC data]), as well as the LC gradient from Tuominen et al. (2017) displayed in Fig. S5B, provide less compelling evidence of generalization effects. Thus, overall, findings from 3 of 6 meta-analyzed studies evidence generalization effects in LC.

While this level of support for LC as a substrate of generalization is modest, a variety of findings in lower mammals suggest that LC may serve a central role in fear generalization through its contribution to pattern completion, a hippocampally-dependent process whereby partial activation of the neural representation of a stored memory results in retrieval of the full memorial representation (Nakazawa et al., 2004). In our context, due to its resemblance to CS+, the GS partially activates the CS+ memory which may lead to excitation of the total pattern of brain activity subserving the CS+ (i.e., retrieval) via hippocampally-mediated pattern completion. For one, the rodent LC releases norepinephrine (NE) into multiple hippocampal regions including the CA3 subfield (Walling et al., 2012)—the very aspect of the hippocampus most centrally implicated in pattern completion (Deuker et al., 2014; Rolls, 2016). Additionally, memory retrieval reliant on pattern completion in rodents is impaired following inactivation of the LC (Khakpour-Taleghani et al., 2009) and strengthened by stimulating LC (Devauges and Sara, 1991; Sara and Devauges, 1988) or pharmacologically upregulating the release of NE in LC (Sara and Devauges, 1989) or the hippocampus (Piña et al., 2020), suggesting that the LC and its noradrenergic influence on the hippocampus play a modulatory role in pattern completion. Furthermore, involvement of the LC-hippocampal pathway in affective pattern completion is evidenced by the above described findings that noradrenergic signaling in the hippocampus, which is sourced primarily, if not solely, by the LC (Loy et al., 1980), strengthens retrieval of

threat-related memories (Murchison et al., 2011, 2004; Zhang et al., 2005). All these rodent findings, together with the high conceptual relevance of pattern completion to fear generalization, the modest support for generalization effects in LC from present meta-analyses, and the known contribution of the LC to autonomic arousal, form a compelling case for LC as a candidate locus of arousal-based enhancement of pattern completion processes that promote generalized fear-conditioning.

4.1.3.2. Periaqueductal gray. The PAG has been linked to the production of threat-elicited defensive behaviors including freezing (Motta et al., 2017; Vianna et al., 2001) and escape (e.g., Deng et al., 2016; Evans et al., 2018). Positive generalization in the PAG may therefore reflect freezing or escape preparedness that peaks at the maximally threatening CS+ and diminishes to stimuli with increasing perceptual dissimilarity.

4.1.3.3. Ventral tegmental area. While LC and PAG are thought to respond to the onset of CSs and GSs, VTA activity may be triggered following the unexpected omission of the US on trials including unreinforced CS+ and its unreinforced perceptual approximates (i.e., GSs). Cross-species evidence implicates VTA in contingency updating via the production of dopaminergic, prediction errors: a learning signal produced by the mismatch between received and predicted hedonic outcomes (Schultz, 2016). During fear extinction, unreinforced CS+ presentations elicit VTA-mediated, positive prediction errors (PPE), signaling a 'better than expected' no-US outcome (Luo et al., 2018; Salinas-Hernández et al., 2018). Positive generalization effects in VTA may plausibly reflect graded magnitudes of this same kind of PPE signaling following unexpected omissions of the US across CS+ and GSs. Specifically, peak PPE responding may follow partially reinforced CS+ (presumably during unreinforced CS+ trials) with decreasing PPE as GSs perceptually diverge from CS+. This assertion is consistent with a number of studies from our group finding gradually decreasing US expectancies as unreinforced GSs differentiate from CS+ (e.g., Lissek et al., 2008; van Meurs et al., 2014), suggesting a corresponding decrease in expectancy violations. In the context of generalization, PPEs instantiated by VTA following non-reinforcement of GSs putatively increase safety learning (reduce fear generalization) by updating GS-US associations to reflect the experience of the GS in the absence of the US. Increased dopaminergic transmission in VTA following the presentation of unreinforced GSs thus represents a promising generalization-dampening mechanism that awaits testing.

4.1.4. Striatal-thalamic areas

The striatum and thalamus form key aspects of an 'action-selection' circuit that facilitates the selection and execution of motivated behaviors. Striatal nuclei – including the caudate – form the input of this circuit and signal whether a given action should be performed or inhibited. After further processing in additional basal ganglia nuclei, selected actions are executed via disinhibition of motoric thalamic nuclei (ventral lateral and ventral anterior nuclei; VLN, VAN). Present findings of positive generalization effects in key regions of the action-selection circuit (caudate, VLN, VAN) may therefore reflect increased defensive response readiness to cues with heightened threat value. Though speculative, this interpretation is consistent with previous studies linking motor preparation to activation of the caudate (Postle and D'Esposito, 1999) and VLN and/or VAN (Neafsey et al., 1978; Raeva, 1986; Rebert, 1972).

In addition to motoric-nuclei, the thalamus includes sensory processing areas. The pulvinar, the largest thalamic nucleus, has been implicated in the processing of salient visual information (Bertini et al., 2018; Grieve et al., 2000; Robinson and Petersen, 1992). Additionally, increased connectivity between the pulvinar and amygdala during the presentation of masked compared to unmasked conditioned cues has

been identified, providing support for the existence of a rapid pulvinar-amygdala visual pathway (Morris et al., 1999). In the present study, positive generalization effects in the pulvinar may thus reflect amplified visual processing of the biologically relevant CS+ and its close perceptual approximates and the engagement of a rapid thalamic-amygdala threat processing circuit.

4.2. Neural substrates of negative generalization

4.2.1. Regions implicated in the default mode network

The default mode network is associated with self-referential, stimulus-free mentation (Andrews-Hanna et al., 2014), retrospective/prospective memory (Buckner et al., 2008) and, more recently, safety responding in threatening contexts (Marstaller et al., 2017). Default mode nodes showing negative generalization effects included bilateral vmPFC, as well as left lateralized MTG, AG, and anterior hippocampus.

4.2.1.1. Ventromedial prefrontal cortex (vmPFC). Although the vmPFC has been broadly implicated in safety processing, recent meta-analytic investigations reveal an anterior-posterior functional specialization, with anterior portions of the vmPFC tracking value of anticipated outcomes and posterior portions inhibiting fear (Hiser and Koenigs, 2018). To account for this parcellation, we generated separate neural activation gradients for anterior and posterior vmPFC clusters. As depicted in Fig. 3, activation patterns in both clusters showed clear negative generalization effects, with activations peaking to the CS– and diminishing to cues with increasing similarity to the CS+. Consistent with an anterior-posterior functional parcellation account, negative generalization effects in anterior vmPFC may reflect increasing positive valuation of stimuli with decreasing CS+ resemblance, while posterior vmPFC activations may reflect fear inhibitory responses to CS– like cues that degrade as stimuli increase in CS+ resemblance.

4.2.1.2. Middle temporal gyrus (MTG) and angular gyrus (AG). Various forms of internal mentation, including episodic retrospection, dynamic self-referencing, and mental simulations (Hsu and Sonuga-Barke, 2016; Seghier, 2013; Xu et al., 2016) have been attributed to MTG and AG. Negative generalization effects in these regions may therefore reflect gradually less disruption of ongoing internal mentation to cues with decreasing CS+ resemblance. Alternatively, based on links between the default mode network and safety-related processes (Marstaller et al., 2017), such effects may indicate increasing thoughts of security and relief as presented stimuli perceptually deviate from CS+.

4.2.1.3. Anterior hippocampus. The human anterior and posterior hippocampus are homologous to the rodent ventral and dorsal hippocampus, respectively. Lesions or inactivation of either ventral/dorsal hippocampus (Cullen et al., 2015; Frankland et al., 1998; Ortiz et al., 2019; Solomon and Moore, 1975; Wild and Blampied, 1972) or cortical inputs to the hippocampus (i.e., postrhinal and perirhinal cortex: Bucci et al., 2002) have been found to increase generalization of fear from a dangerous context (CS+) to a safe context (CS–) in rodents. These findings suggest that hippocampal activations are necessary for successful discrimination of CS+ from CS–, potentially attributable to the pattern separation function of the hippocampus (e.g., O'Reilly and Rudy, 2001), through which brain representations of resembling, yet distinct, sensory experiences are discriminated. Thus, presently found negative gradients of generalization in anterior hippocampus seem consistent with the notion that GSs most distinguishable from CS+ elicited the strongest hippocampally-mediated pattern separation of GS and CS+ neural representations, with decreasing levels as the GS became more similar to CS+. Before accepting this interpretation, there are two potential problems with drawing pattern-separation inferences from our hippocampal findings that should be addressed.

First, findings from most of the aforementioned rodent studies and current meta-analytic results implicate the ventral/anterior hippocampus in fear generalization, while work on hippocampally-mediated pattern separation most often focuses on dorsal aspects of the hippocampus (Yeates et al., 2020). Second, the majority of fear-generalization and pattern-separation studies in rodents use spatial or contextual stimuli rather than the kind of discrete cues used by studies presently meta-analyzed. There are, however, a substantial number of studies in the pattern-separation literature that assess and identify substrates of pattern separation in the human or non-human-primate anterior hippocampus using stimulus sets consisting of perceptually or conceptually similar images of discrete objects, rather than contexts (e.g., Fujii et al., 2014; Sakon and Suzuki, 2019; Pidgeon and Morcom, 2016; Stevenson et al., 2020). These primate findings support a role for anterior hippocampus in pattern separation/completion processes during same-different assessments of resembling discrete stimuli of the kind used by studies in this meta-analysis.

Further evidence supporting the plausibility of the pattern-separation interpretation of negative generalization gradients in anterior hippocampus comes from a study assessing both generalized fear and behavioral indices of pattern separation (Lange et al., 2017). Here, pattern separation was tested within a separate object recognition memory task requiring participants to discriminate (i.e., pattern separate) previously encoded, neutral target stimuli from perceptually resembling lures (i.e., the mnemonic similarity task: Stark et al., 2019). Results revealed an inverse relationship between behavioral measures of fear generalization (generalized shock expectancy) and pattern separation, associating stronger fear generalization with poorer pattern separation. Although Lange and colleagues did not collect neuroimaging data during the mnemonic similarity task, this same task has been shown by others to generate pattern-separation related activity in the anterior hippocampus (Pidgeon and Morcom, 2016; Stevenson et al., 2020). Together with present anterior hippocampal findings, this result supports the possibility that fear generalization and pattern separation share underlying mechanisms that are putatively localized in the anterior hippocampus.

The hippocampus is also thought to play a central role in pattern completion. Though generalization-related hippocampal activations consistent with pattern completion (i.e., positive generalization) were not found in the present study, the compelling conceptual link between generalization and pattern completion, as well as past findings of increased and decreased generalized conditioned responding following hippocampal activations (e.g., Cullen et al., 2015) and lesions (Freeman and Kramarcy, 1974; Quinn et al., 2009), respectively, continue to implicate pattern completion by the hippocampus as a plausible mechanism of generalization.

4.2.2. Amygdala

Consistent with many past fMRI studies of fear-conditioning in humans (Fullana et al., 2016), no increased amygdala activation to the CS+ was found in current analyses. Rather, the amygdala showed relative decreases in reactivity to CS+ with increased responses as presented stimuli differentiated from CS+. This negative generalization effect in the amygdala may reflect activity within sub-populations of basolateral amygdala neurons implicated in reward and safety-related inhibitory safety learning (Barad et al., 2006; Zhang et al., 2020). Alternatively, this amygdala effect may be driven by GABAergic intercalated cells, which inhibit threat-related amygdala outputs from the central nucleus of the amygdala and have been shown to regulate fear generalization in animal studies (Ciocchi et al., 2010).

Additionally, the absence of positive generalization effects in the amygdala may be due to effects of fMRI repetition suppression, the attenuation of fMRI responses to repeated presentations of a given stimulus (Henson and Rugg, 2003). Specifically, generalization data in all studies were collected after participants had multiple exposures to CS+ during acquisition training. These pre-generalization CS+ exposures may have reduced the proportion of threat-sensitive amygdala neurons showing increased activation to CS+ and perceptually similar cues through repetition suppression, rendering fear-related amygdala responses during generalization undetectable by standard fMRI techniques. Consistent with this possibility, several previous studies have identified decreasing amygdala activations to CS+ with increasing numbers of CS+ presentations (e.g., LaBar et al., 1998; Morris et al., 2001).

4.3. Updated neural account of fear generalization

Although individual brain regions may perform specific generalization-related functions, fear generalization likely emerges from a complex series of interactions across regions. Here, we integrate the separate contributions of above described brain loci to construct an updated neurobiology of fear generalization. This updated model substantially expands on our previous account by incorporating a variety of new cortical, striatal-thalamic, and brainstem areas found to code for positive or negative generalization in the current meta-analysis. While this account is largely predicated on present results, it also incorporates other animal and human findings relevant to generalization and its underlying sub-processes.

According to the revised model (see Fig. 5), during post-acquisition exposures to a visual stimulus resembling a CS+ (i.e., a GS), the thalamus relays sensory information about the GS to amygdala-based fear circuits via a quick and dirty 'low road', resulting in a rapid initial threat response to the GS. The thalamus simultaneously sends sensory GS information via the 'high road' to visual cortices for higher level sensory processing—a slower route through which fine grained neural representations of GS are activated in visual cortex. Through the low road, thalamic signals enter the basolateral amygdala (BLA) and activate the adjoining central nucleus of the amygdala (CeA), triggering rapid propagation of activity across subcortical (e.g., locus coeruleus [LC], periaqueductal gray [PAG]) and cortical (anterior insula, dorsomedial prefrontal cortex [dmPFC]) aspects of the amygdala-based threat network. LC activation by CeA is next proposed to engage the LC-hippocampus adrenergic pathway (Bari and Aston-Jones, 2013; Berridge and Waterhouse, 2003; Mason and Fibiger, 1979), releasing NE into the CA3 hippocampal subfield associated with pattern completion (Rolls, 2016).

An additional, low-road evoked mechanism targeting hippocampal substrates of pattern completion during fear generalization may arise from monosynaptic excitatory projections from BLA to the CA1 hippocampal subfield (Felix-Ortiz et al., 2013; Yang et al., 2016). Indeed aspects of CA1 most proximal to the dentate gyrus are thought to receive pattern-completion related inputs from CA3 (Lee et al., 2020) with which unified retrieval cues are produced and optimized by CA1 (Rolls, 2016). Thus, low-road activations of the BLA during GS presentations may relay threat-related signals to CA1 that facilitate retrieval of the CS+ memory via pattern completion. This possibility is supported by multiple electrophysiology studies in rodents finding theta rhythm synchrony between the lateral amygdala and CA1 during successful retrieval of contextual or cued fear, (Lesting et al., 2011; Narayanan et al., 2007; Seidenbecher et al., 2003), and functional coupling of amygdala and CA1, during affective pattern completion in humans (McMakin et al., 2020).

Following these low road cascades, fine-grained visual representations of the GS generated by the 'high road' reach the hippocampus where the overlap between the cortical representation of the currently presented GS and the previously encoded CS+ is assessed through a *schematic matching*, or same-different assessment (Otto and Eichenbaum, 1992; Sander et al., 2005). With sufficient and insufficient overlap, CA3/CA1 and dentate gyrus neurons are thought to initiate pattern completion and pattern separation, respectively (e.g., McHugh et al., 2007; Treves and Rolls, 1994). Importantly, the LC-CA3 and BA-CA1 pathways earlier triggered by rapid low-road processing of the GS, are

proposed to increase the neural gain in CA3/CA1-based pattern completion circuits with the effect of predisposing the hippocampus toward pattern completion. That is, less overlap in cortical representations of GS and CS+ may be needed to elicit pattern completion following CA3 and CA1 innervation by threat-related LC and BLA signals, respectively. With the right mix of GS/CS+ representational overlap and GS-evoked LC-CA3 and BLA-CA1 signaling, the hippocampus initiates pattern completion resulting in excitation of the total pattern of brain activity subserving the CS+. This includes activation of brain structures associated with fear excitation (amygdala, AI, dmPFC, PAG, LC) and motor readiness to avoid (caudate, thalamus, SMA, precentral gyrus), culminating in generalized threat responding to the GS. Next, excitation of these threat-related brain processes engage neural substrates of executive control (IPL, dlPFC, vlPFC) (Menon, 2011), mobilizing attentional and emotion-regulation resources to optimize responses to the GS.

In the event of an inadequate synergy between GS/CS+ representational overlap and LC-CA3/BLA-CA1 signaling, dentate gyrus neurons in the hippocampus are proposed to initiate 'pattern separation', resulting in the spread of activation to default mode structures associated with fear inhibition and the resumption of a resting state (vmPFC, MTG, AG). Such activations are then proposed to attenuate ongoing activity in amygdala-based fear networks (Marstaller et al., 2017) initiated earlier by the quick and dirty low route, resulting in the discontinuation of anxious arousal. Of note, the centerpiece of this model in which hippocampus propagates activity in fear and safety related brain areas in response to stimuli with high and low CS+ similarity, respectively, is consistent with past findings of increased connectivity between VH and fear-related brain areas (amygdala, anterior insula) to GSs resembling CS+, and heightened VH-vmPFC connectivity to safety cues with little CS+ resemblance (Lissek et al., 2014a).

While all generalization processes proposed thus far in the model are elicited by the onset of GS presentations, one final component putatively occurs in response to US omissions occurring shortly after GS onset. Specifically, expectations of the aversive US in the presence of the danger-resembling GS are violated when the GS results in no aversive outcome. This better-than-expected GS outcome triggers a dopaminergic, positive prediction error (PPE) signal in VTA which has been found necessary for fear reduction following surprising omissions of an aversive US (Luo et al., 2018; Salinas-Hernández et al., 2018). Recent evidence attributes this fear-reducing property to the influence of VTA-based PPE signals on plasticity in safety coding neurons in the amygdala and infralimbic cortex, the animal homolog of vmPFC (Luo et al., 2018). As such, this final model component represents a means by which GS-related responses in VTA and its downstream targets may facilitate safety learning with the effect of reducing generalized fear over repeated exposures to unreinforced GSs.

In summary, our updated neural model of fear generalization preserves key features of the original model, including hippocampally-mediated schematic matching resulting in either: (1) pattern completion followed by activation of threat excitatory regions such as the amygdala, striatal-thalamic, and cingulo-opercular regions; or (2) pattern separation followed by activation of the fear inhibiting vmPFC. However, the model now details the modulatory role of LC-CA3 and BLA-CA1 signaling, which may bias the hippocampus towards pattern completion. Furthermore, the model features a putative fear inhibitory role of VTA-dopaminergic prediction errors, which may be a promising generalization–dampening learning mechanism. Finally, the contributions of additional defensive response areas (PAG) and higher-order cortical areas that shape attention, cognitive control, and emotional regulation (lPFC, IPL), and mind wandering/safety-related internal mentation (MTG, AG), are also included.

4.4. Clinical implications

Our neural account posits that fear generalization emerges as a result

of dynamic interactions within and between distributed threat and safety circuits. According to this account, overgeneralization may occur as a result of abnormal threat/safety tuning at multiple levels. For example, at the basic sensory level, thalamic abnormalities could lower the threshold by which the thalamus-amygdala 'low-road' is triggered, increasing the probability that a benign GS evokes an erroneous amygdala threat signal and a corresponding cascade of activations in downstream threat/fear processing regions (Young et al., 2007), including biasing the hippocampus toward pattern completion via activation of BLA terminals in CA1. At the brainstem level, LC hyperactivity to threat, which has been implicated in clinical anxiety (Morris et al., 2020), could be evoked by GSs and further predispose the hippocampus toward pattern completion, and deficits in VTA-based PPE signaling could impair GS-related safety learning (Kalisch et al., 2019). Finally, in terms of cortical contributions, aberrant vmPFC activity may weaken fear inhibition to GSs (Cha et al., 2014b); and dysfunction in frontoparietal regions could hamper emotion regulation or adaptive disengagement from potential threat during GS exposures (Balderston et al., 2017a, b).

Although these possibilities and many others remain speculative, recent studies in anxiety patients have identified shallower disorder-related response gradients indicative of overgeneralization in several regions featured in the model (Cha et al., 2014a, b; Kaczkurkin et al., 2017). These include areas found to code for positive generalization (LC, VTA, caudate, thalamus, insula, dmPFC/dACC, dlPFC) and negative generalization (hippocampus, vmPFC) in the present study. If confirmed by future studies in anxiety-related disorders, these activations may represent: (1) reliable generalization-related markers of clinical anxiety; and (2) neuromodulatory targets for clinically anxious patients suffering from overgeneralization.

4.5. Limitations and conclusions

One limitation of the present study derives from the relatively small number of included studies, which may have reduced the statistical power of applied analyses (Sterne et al., 2000). Factors mitigating such concerns include our exclusive use of original, voxel-wise brain maps which serve to increase statistical power, and the replicable and consistent nature of current findings across studies using different conditioning procedures and stimulus sets, which supports the strength of findings. Nevertheless, the somewhat small number of studies meta-analyzed warrants a look at the fit between current results and those reported by the three generalization studies omitted from present analyses in order to form a fuller picture of results. Two of these omitted studies included whole brain fMRI (Dunsmoor et al., 2011; Greenberg et al., 2013), while the third collected fMRI data only in the ventral half of the brain (Onat and Büchel, 2015). In line with meta-analytic findings, all three studies reported effects of positive and negative generalization in AI and vmPFC, respectively, and two reported positive generalization effects in the caudate head and dorsal or posterior thalamus. Additionally, one of two studies imaging the dorsal half of the brain reported positive generalization instantiated in such dorsal areas as dmPFC, dlPFC, and IPL (Greenberg et al., 2013), consistent with present findings in these regions.

Results less consistent with our meta-analytic findings were reported for hippocampal and brainstem structures, with only 1 of 3 omitted studies reporting results consistent with present findings in anterior hippocampus (Onat and Büchel, 2015), PAG (Dunsmoor et al., 2011), and VTA (Greenberg et al., 2013), and none reporting generalization effects in LC. While these inconsistencies may seem problematic, there are reasons to believe individual studies were underpowered to detect generalization related activity at many of these loci. Specifically, the majority of studies included in present meta-analyses did not find generalization effects in PAG, VTA, or LC at the individual-study level, and instantiation of generalization in these midbrain regions emerged only after quantitative aggregation across studies. This suggests that individual studies in the meta-analysis tended to be insufficiently

powered to detect generalization effects in PAG, VTA, or LC, potentially due to the small size of these structures, and the largely absent PAG, VTA, and LC findings in each of three omitted studies may likewise derive from inadequate statistical power. In terms of hippocampal findings, while only 1 of 3 excluded studies reported negative generalization effects in the hippocampus analogous to those found meta-analytically, 5 of 6 studies included in the meta-analysis report such effects in their respective papers. Thus, across studies included and excluded from the current meta-analysis, 6 of 9 implicate the hippocampus in negative generalization, which, overall, is a fairly reliable finding across existing studies. All this said, current meta-analytic results should be interpreted with some caution due to the relatively small sample size, and future meta-analyses based on a more substantial number of neuroimaging investigations of fear generalization are needed to replicate and expand upon findings reported herein.

Limitations inherent to fMRI must also be acknowledged. Although fMRI may identify neural correlates of fear generalization, neuromodulation studies that manipulate these correlates and measure corresponding changes in fear generalization are necessary to causally implicate them (Etkin, 2018). Additionally, while fMRI is spatially precise relative to other human neuroimaging modalities, it lacks the precision of invasive animal techniques capable of identifying activations and projections of particular neuronal subpopulations of key structures.

Finally, despite growing evidence that fear generalization is a key pathogenic mechanism of anxiety and trauma-related disorders (Lissek et al., 2014b, 2010; Lissek and van Meurs, 2015), the current study focused exclusively on findings in healthy controls. As data in anxiety-related disorders accumulate, future meta-analyses will be needed to aggregate findings across studies to identify neural processes that may instantiate putative excesses in generalization among anxiety patients.

In conclusion, this first quantitative aggregation of fMRI studies testing conditioned fear generalization in healthy humans sheds light on the neural substrates of a basic classical conditioning process with high relevance to clinical anxiety. Positive generalization effects, characterized by stronger fMRI activations to stimuli with increasing perceptual similarity to CS+, emerged in cingulo-opercular, frontoparietal, striatal-thalamic, and midbrain regions (locus coeruleus, periaqueductal grey, ventral tegmental area). Effects of negative generalization reflected by weaker fMRI responses to stimuli with increasing CS+ resemblance were evidenced in nodes of the default mode network (ventromedial prefrontal cortex; hippocampus, middle temporal gyrus, angular gyrus) and amygdala. Such meta-analytically derived substrates of generalization were integrated to form a working neurobiology of generalization that specifies the putative flow of neural communication across cortical, subcortical, and brainstem regions giving rise to generalized conditioned fear.

Declaration of Competing Interest

The authors report no conflict of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.06.035.

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