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 the known pathogenic contribution of over-generalization to clinical anxiety, neural investigations of human generalization have only recently begun. The present work provides the first meta-analysis of this growing human 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 instantiated in nodes of the default mode (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 excitation of threat- or safety-related loci by the hippocampus.

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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 & Quirk, 2012; Suarez-Jimenez et al., 2020). In contrast, considerably less work has targeted conditioned fear generalization, the process by which conditioned fear transfers 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+. Over-generalization is widely accepted as a key feature of clinical anxiety by clinicians and theorists alike (e.g., Craske et al., 2009; Ehlers & Clark, 2000; Foa, 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 & Rayner, 1920), systematic investigations of human fear generalization did not begin in earnest until almost a century later (Dunsmoor, Mitroff, & LaBar, 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, Kaczkurkin, et al., 2014; Lissek et al., 2010; Onat & Büchel, 2015) assess conditioned fear to both CS+ and generalization stimuli (GS) parametrically varying in 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, Kaczkurkin, et al., 2014; but see Tinoco-González et al., 2015), and post-traumatic stress disorder (PTSD: Kaczkurkin et al., 2017; Lissek & 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 interrogate the neurobiology of generalized fear in healthy humans (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013a; Kaczkurkin et al., 2017; Lange et al., 2017; Lissek, Bradford, et al., 2014; Morey et al., 2015; Onat & 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, 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., 2013a; Lissek, Bradford, et al., 2014) 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 ventral 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, Bradford, et al., 2014). 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.

Though many ensuing fMRI results yielded generalization-related activations in anterior insula, dmPFC/ACC, vmPFC, and ventral 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. While these results bring us closer to a comprehensive neural account of generalization, each study yields a unique array of wide-reaching substrates making it difficult to form a coherent synthesis of findings.

1.3 Goals of the present study

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, Solanes, Fullana, et al., 2019; Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019) 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. The inclusion of quadratic generalization also 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 & 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) (Moher, Liberati, Tetzlaff, Altman, & Group, 2009); see Fig. S1 guidelines 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, two studies that masked the dorsal half of the brain (Greenberg et al., 2013a; Onat & Büchel, 2015) were 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 & 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, Davey Smith, Schneider, & Minder, 1997). Heterogeneity was assessed using the I^2 index (Ioannidis, Patsopoulos, & Evangelou, 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). For all Tables and Figures, see Webler et al., 2021, *Neuroscience and Biobehavioral Reviews.*

3.2 Neural substrates of positive generalization gradients

Tables S1 and S2 lists full statistical results and Fig. 1a-1b 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. 2-5 display select meta-analytically derived fROI that emerged from positive linear and quadratic analyses along with corresponding gradients reflecting inter (Figs. 2a-5a) and intra-study averages (Figs 2-5b) to CSs and GSs across the continuum of CS+ similarity. Only linear gradients are plotted for loci instantiating both linear and quadratic gradients. In Figs 2-5, fROI are grouped anatomically (e.g. striatal-thalamic areas, brainstem nuclei) or based on shared participation in established functional networks (cingulo-opercular, frontoparietal: (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Menon, 2011; Raichle, 2015).

3.2.1 Positive-linear gradients

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

anterior cingulate cortex (dACC). Additionally, as shown in Fig. 3, 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. 5); visual cortical areas (BA18, BA19, fusiform gyrus) (See Fig. S1) and cerebellum (culmen, declive, tuber, uvula).

3.2.2 Positive-quadratic gradients

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. Structures uniquely characterized by quadratic activation patterns included a set of brainstem structures comprised of the locus coeruleus, periaqueductal gray, and ventral tegmental area (see Fig. 5), as well as bilateral findings in the amygdala (see Fig. S2).

3.2.3 Linear versus quadratic gradients in overlapping structures

Brain activations generated from linear and quadratic analyses that centered on the same brain structure often differed in spatial extent or sub-region: 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. 6 along with corresponding generalization slopes at the group (Fig. 6a) and individual-study level (Fig. 6b).

3.3.1 Negative-linear gradients

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 ventral hippocampus/parahippocampal gyrus, anterior and posterior aspects of vmPFC, left anterior middle temporal gyrus (MTG), and left angular gyrus, and (see Fig. 6). One notable exception was negative-linear gradients found in the left amygdala (see Fig. S2), 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.

3.3.2 Negative-quadratic gradients

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 activations (negative generalization), 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 putatively indicative of uncertainty related activations, as identified in Onat & Büchel, 2015.

Positive generalization effects were evident in an array of brain areas, including nodes of the cingulo-opercular (anterior insula, dmPFC/dACC) and frontoparietal (lPFC, IPL) networks, striatal-thalamic regions (caudate, thalamus), and brain-stem nuclei (LC, PAG, VTA). Additionally, negative generalization effects spanned a more limited set of

brain areas including aspects of the default mode network (ventral 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 & Pine, 2016; Paulus, 2006; Zaki, Davis, & Ochsner, 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, Padilla-Coreano, & Quirk, 2011; Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006) and its human homolog, dACC (Fullana et al., 2016; Linnman, Rougemont-Bücking, Beucke, Zeffiro, & Milad, 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, Cohen, & Carter, 2004; Kalisch & Gerlicher, 2014; Mechias, Etkin, & Kalisch, 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 & Dosenbach, 2018; Rees G, 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, Chang, Caparelli, & Ernst, 2007). According to attentional control theory (Eysenck, Derakshan, Santos, & Calvo, 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, Gross, & Ochsner, 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 valenced 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 re-orienting (Corbetta, 1998), working memory (Wang et al., 2019), and retrieval of semantic and episodic memory (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Wagner, Shannon, Kahn, & Buckner, 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, Ciaramelli, & Moscovitch, 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, Edlow, & Immordino-Yang, 2017), three brainstem nuclei – the LC, PAG, and VTA – activated more strongly as presented stimuli increased in CS+ resemblance.

4.1.3.1 Locus coeruleus

In response to threat, the LC modulates autonomic arousal, attentional orienting, and learning and memory processes via noradrenergic (NE) transmission to widespread brainstem, subcortical, and cortical projections (Díaz-Mataix et al., 2017; Samuels & Szabadi, 2008). One such projection with particular relevance to generalization extends to the hippocampus where LC inputs exert influence on plasticity with the effect of enhancing the acquisition and retrieval of threat-related memories (Kempadoo, Mosharov, Choi, Sulzer, & Kandel, 2016; Lemon N, 2009; Wagatsuma et al., 2018). As such, threat-related LC-hippocampal signaling 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.

4.1.3.2 Periaqueductal gray

The PAG has been linked to the production of threat-elicited defensive behaviors including freezing (Motta, Carobrez, & Canteras, 2017; Vianna, Graeff, Brandão, & Landeira-Fernandez, 2001) and escape (e.g., Deng, Xiao, & Wang, 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, Wiggert, Wicker, & Lissek, 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 & D'Esposito, 1999) and VLN and/or VAN (Neafsey, Hull, & Buchwald, 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, Pietrelli, Braghittoni, & Làdavas, 2018; Grieve, Acuña, & Cudeiro, 2000; Robinson & 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, Ohman, & Dolan, 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, Smallwood, & Spreng, 2014), retrospective/prospective memory (Buckner, Andrews-Hanna, & Schacter, 2008) and, more recently, safety responding in threatening contexts (Marstaller, Burianová, & Reutens, 2017). Default mode nodes showing negative generalization effects included bilateral vmPFC, as well as left lateralized MTG, AG, and ventral 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 & Koenigs, 2018). To account for this parcellation, we generated separate neural activation gradients for anterior and posterior vmPFC clusters. As depicted in Figure 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 & Sonuga-Barke, 2016; Seghier, 2013; Xu, Yuan, & Lei, 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 Ventral hippocampus

Lesions of either ventral/dorsal hippocampus (Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Solomon & Moore, 1975; Wild & Blampied, 1972) or cortical inputs to the hippocampus (i.e. postrhinal and perirhinal cortex: Bucci, Saddoris, & Burwell, 2002) have been found to increase generalization of fear from CS+ to CS− in animals. 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 & Rudy, 2001), through which brain representations of resembling, yet distinct, sensory experiences are discriminated. Thus, presently found negative hippocampal gradients of generalization are 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+.

The hippocampus is also thought to play a central role in *pattern completion*, whereby partial activation of the neural representation of a stored memory results in retrieval of the full memorial representation (Nakazawa, McHugh, Wilson, & Tonegawa, 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+ via hippocampally-mediated 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, Gilman, Winiecki, Riccio, & Jasnow, 2015) and lesions (Freeman & Kramarcy, 1974; Quinn, Wied, Liu, & Fanselow, 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+ that increased as presented stimuli differentiated from CS+. This negative generalization effect in the amygdala may reflect the activation of a distinct sub-population of basolateral amygdala neurons that have been implicated in reward and safety-related inhibitory learning (Barad, Gean, & Lutz, 2006; Zhang, Kim, & Tonegawa, 2020). Alternatively, this

amygdala effect may be driven by GABAergic intercalated cells, which inhibit threat-related amygdala outputs form the central nucleus of the amygdala and have been shown to regulate fear generalization in animal studies (Ciocchi et al., 2010). Therefore, increased amygdala activation commensurate with the dissimilarity of presented stimuli to CS+ may reflect safety-related reward or the inhibition of fear.

Additionally, the absence of positive generalization effects in the amygdala may reflect effects of fMRI repetition suppression, the attenuation of fMRI responses to repeated presentations of a given stimulus (Henson & 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 (Büchel, Dolan, Armony, & Friston, 1999; Büchel, Morris, Dolan, & Friston, 1998; Ishai, Pessoa, Bikle, & Ungerleider, 2004; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Morris, Buchel, & Dolan, 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. 1), 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 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 hippocampus via adrenergic projections (Bari & Aston-Jones, 2013; Berridge & Waterhouse, 2003; Mason & Fibiger, 1979), releasing norepinephrine (NE) into multiple hippocampal subfields and cell types including CA_3 pyramidal cells (Walling, Brown, Miyasaka, Yoshihara, & Harley, 2012) – the athorny subtype of which has been implicated centrally in hippocampally-mediated pattern completion (Hunt, Linaro, Si, Romani, & Spruston, 2018). The model thus contends that threat-related activation of LC during GS presentations biases the hippocampus toward pattern

completion, a possibility supported by studies finding that memory retrieval reliant on pattern completion is impaired following inactivation of the LC (Khakpour-Taleghani, Lashgari, Motamedi, & Naghdi, 2009) and enhanced by stimulating LC (Devauges & Sara, 1991; Sara & Devauges, 1988) or pharmacologically upregulating adrenergic transmission in LC (Sara & Devauges, 1989) or the hippocampus (Piña et al., 2020).

Next, fine-grained visual representations of the GS generated by the 'high road' reach the hippocampus where the overlap between the neural representation of the currently presented GS and the previously encoded CS+ is assessed through a *schematic matching*, or same-different assessment (Otto & Eichenbaum, 1992; Sander, Grandjean, & Scherer, 2005). With sufficient and insufficient overlap, CA3 and dentate gyrus neurons are thought to initiate pattern completion and pattern separation, respectively (e.g. McHugh et al., 2007; Treves & Rolls, 1994).

Importantly, the previously described LC-CA3 pathway triggered by rapid low-road processing of the GS, is proposed to increase the neural gain in CA3-based pattern completion circuits with the effect of predisposing the hippocampus toward pattern completion. That is, less representational overlap between the GS and CS+ may be needed to elicit pattern completion following CA3 innervation by arousal-related LC signals. With the right mix of GS-CS+ representational overlap and GS-evoked LC signaling to CA3, the hippocampus initiates pattern completion resulting in excitation of the total pattern of brain activity subserving the CS+ including 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 mix of GS-CS+ representational overlap and LC-CA3 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, Bradford, et al., 2014).

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-hippocampal signaling, which may bias the hippocampus towards pattern completion during high arousal. 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.

4.8 Clinical implications

Our neural account posits that fear generalization emerges as a result of dynamic interactions within and between distributed threat and safety regions. 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). At the brainstem level, LC hyperactivity to threat, which has been implicated in clinical anxiety (Morris, McCall, Charney, & Murrough, 2020), could be evoked by GSs and unduly bias the hippocampus toward pattern completion, and deficits in VTA-based PPE signaling could impair GS-related safety learning (Kalisch, Gerlicher, & Duvarci, 2019). At the level of the hippocampus, abnormalities in the dentate gyrus, potentially due to deficient adult neurogenesis, could impair pattern separation of GS and CS+ neural representations leading to excessive generalization among those with clinical anxiety (Kheirbek, Klemenhagen, Sahay, & Hen, 2012). Finally, at the cortical level, aberrant vmPFC activity could weaken fear inhibition to GSs (Cha, Greenberg, et al., 2014); and dysfunction in frontoparietal regions could hamper emotion regulation or adaptive disengagement from potential threat during GS exposures (Balderston, Hsiung, Ernst, & Grillon, 2017; Balderston, Vytal, et al., 2017).

Although these possibilities and manifold 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, Carlson, et al., 2014; Cha, Greenberg, et al., 2014; 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.

4.9 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, Gavaghan, & Egger, 2000). Factors mitigating such concerns include our exclusive use of original brain maps which serve to increase statistical power, and the replicable and highly consistent nature of current findings across studies using different conditioning procedures and stimulus sets which supports the strength of our findings.

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, Kaczkurkin, et al., 2014; Lissek et al., 2010; Lissek & 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 communications across cortical, subcortical, and brainstem regions giving rise to generalized conditioned fear.

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