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Review

Perspectives on Fear Generalization and Its Implications for Emotional Disorders

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Although generalization to conditioned stimuli is not a new phenomenon, renewed interest in understanding its biological underpinning has stemmed from its association with a number of anxiety disorders. Generalization as it relates to fear processing is a temporally dynamic process in which animals, including humans, display fear in response to similar yet distinct cues or contexts as the time between training and testing increases. This Review surveys the literature on contextual fear generalization and its relation to several views of memory, including systems consolidation, forgetting, and transformation hypothesis, which differentially implicate roles of the hippocampus and neocortex in memory consolidation and retrieval. We discuss recent evidence on the neurobiological mechanisms contributing to the increase in fear generalization over time and how generalized responding may be modulated by acquisition, consolidation, and retrieval mechanisms. Whereas clinical perspectives of generalization emphasize a lack of fear inhibition to CS^- cues or fear toward intermediate CS cues, the time-dependent nature of generalization and its relation to traditional views on memory consolidation and retrieval are often overlooked. Understanding the time-dependent increase in fear generalization has important implications not only for understanding how generalization contributes to anxiety disorders but also for understanding basic long-term memory function.

Key words: anxiety disorder; fear conditioning; fear generalization; hippocampus; stimulus generalization; transformation theory

Classical fear conditioning is a widely used and powerful model for studying the neural basis of associative learning and memory (Maren and Fanselow, 1996; Davis, 1992; LeDoux, 2000). However, long before Pavlov, associative learning evolved because it allowed animals to predict life-threatening circumstances in their environment and ensure survival. How then do animals, including humans, react appropriately to a dynamic environment in which stimuli are almost never encountered in exactly the same form twice? The answer is *stimulus generalization*. In response to life threatening cues or contexts, generalization also serves an adaptive purpose. As was astutely noted by Roger Shepard (Shepard, 1987), "Because any object or situation experienced by an individual is unlikely to occur in exactly the same form or context, psychology's first general law should. . .be a law of generalization." The evolutionary significance of generalization is clear. However, what happens when this process goes awry? For example, if one were attacked and bitten by a dog while on a daily run, this may eventually lead to wariness of all dogs of similar size. Perhaps fear, anxiety, or worry occurs later at the sound of any dog barking, and the sight of the neighborhood in which the attack occurred also elicits a fear response. Eventually, the person may become fearful of their neighbor's harmless Chihuahua. This series of events, perhaps in the extreme, illustrates not only the spread of cues that comes to elicit fear responses but also the temporally dynamic nature of stimulus generalization and its potential contribution to the development of anxiety disorders. Although clinical perspectives of generalization emphasize a lack of fear inhibition to safety (CS^-) cues or fear toward intermediate CS cues during fear discrimination tasks (Lissek

SIGNIFICANCE

Anxiety disorders are among the most common mental disorders experienced by individuals and have an 18% 12-month prevalence rate among U.S. adults. Recent experimental evidence suggests that generalization of threat responses to neutral or ambiguous environmental stimuli plays an important role in the development and maintenance of nearly all anxiety disorders. Traditional research on generalization in rodent species with Pavlovian or instrumental fear conditioning paradigms has revealed that generalized fear increases as a function of time. In this Review, we discuss the current understanding of the neural mechanisms contributing to generalized fear, the relation of generalized fear to memory systems, and implications for anxiety disorders.

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et al., 2005, 2008, 2010, 2014; Dunsmoor et al., 2009, 2011a; Lissek, 2012; Vervliet et al., 2010; Onat and Buchel, 2015), the time-dependent nature of generalization and its relation to memory consolidation and retrieval are often overlooked in these studies. We think that an integration of current clinical views on generalization and traditional theories on the dynamic nature of memory might provide a more comprehensive understanding of the etiology of anxiety disorders, particularly related to the spreading of cues or situations that initiate anxiety symptoms

GENERALIZATION IS A TEMPORALLY DYNAMIC PROCESS

Stimulus generalization was noted by both Pavlov (1927) and Watson and Rayner (1920), but its temporally dynamic nature was not discovered until 1958 when it was demonstrated that generalization changed as a function of the retention interval (Perkins and Weyant, 1958). In that experiment, performance deficits were discovered when the color of the apparatus in a runway task was changed 1 day after training but not 1 week after training. It was noted that subjects did not forget the motor response after the long interval but instead responded equally well in both contexts. We should note that "context" is used as a very general term that often consists of a number of different stimuli including spatial, olfactory, auditory and visual cues that can be encoded in a memory trace.

In the case of context fear conditioning, placing animals in a novel context (i.e., distinct from the training context) shortly after training results in little expression of learned fear (e.g., lower levels of freezing behavior; Feinberg and Riccio, 1990; Riccio et al., 1992; Zhou and Riccio, 1996; Wiltgen and Silva, 2007; Wiltgen et al., 2010; Ruediger et al., 2011; Jasnow et al., 2012). However, as the retention interval between training and testing increases, there is a loss of memory precision (i.e., fear responses to the training context generalize over time) such that animals exhibit equivalent levels of fear expression in both the training context and the novel context (Perkins and Weyant, 1958; McAllister and McAllister, 1963; Richardson et al., 1984; Gisquet-Verrier and Alexinsky, 1986; Zhou and Riccio, 1996; Metzger and Riccio, 2009; Lynch et al., 2013; Cullen et al., 2015). These studies revealed that generalization also applies to contextual fear and indicated that the novel contextual test cues had come to function as retrieval cues. Generalization for contextual attributes has also been demonstrated with passive avoidance, a task in which the avoidance response is particularly well retained over time. Zhou and Riccio (1996) examined different components that make up the training context and found that changes in either the passive-avoidance apparatus or the room (or both) produced a profound reduction in step-through latencies with a 1-day retention test interval (i.e., animals did not display fear responses). However, after 2 weeks, the groups with only one component changed displayed similar step-through latencies as the group tested in the training context (i.e., both displayed high levels of fear memory). The reduced fear persisted in the condition in which both components were changed, presumably because the extremely different stimuli either did not serve as retrieval cues or generalization would take longer than the 2-week delay used in that experiment. Importantly, the increase in fear responses to distinct yet similar contexts as a function of time is not the result of fear incubation (Wiltgen and Silva, 2007). Although much of the extant literature on contextual generalization has used classical fear conditioning as a means to study long-term memory function, the same phenomenon is found for positively reinforced learning (Bouton et al., 1999; Winocur et al., 2007).

CONTEXTUAL FEAR GENERALIZATION: A CASE OF MEMORY (IM)PRECISION

We are beginning to understand some of the mechanisms contributing to generalized fear and how it can be supported by neural systems associated with memory function. Generalization that occurs with the passage of time can also be considered a loss of memory precision for contextual cues. Thus, it is important to consider how changes in memory precision might fit within the current views of the neural systems supporting the consolidation and storage of memories over time.

One view of what happens to memories over time is called *systems consolidation* (Zola-Morgan and Squire, 1990; Squire and Alvarez, 1995). According to systems consolidation theory, the hippocampus is involved in the consolidation and retrieval of new memories until they are ultimately represented by the neocortex. At later time points, retrieval of those original memories no longer requires the hippocampus. Thus, the hippocampus plays a time-limited role in the retrieval of memory traces that are permanently stored in the neocortex. Many studies support systems consolidation in which temporally graded retrograde amnesia is reported with hippocampal damage (e.g., Scoville and Milner, 1957). This has been extended in the rodent literature implicating the hippocampus in the retrieval of recent context-dependent memories (Kim and Fanselow, 1992; Maren et al., 1997) and the neocortex in remote memory retrieval (Suzuki et al., 2004; Frankland et al., 2006; Corcoran et al., 2011, 2015; Vetere et al., 2011). In systems consolidation, memory traces stored in the neocortex are considered identical to those originally dependent on the hippocampus and, therefore, it does not explicitly address changes in memory specificity (Fig. 1).

A traditional theoretical view of increased generalization (or loss of memory precision) as a function of time has been that memory for cues present in the training context are forgotten more rapidly than the conditioned fear response itself, a phenomenon referred to as the *forgetting of stimulus attributes* (Thomas and Riccio, 1979; Riccio et al., 1984, 1992, 1994; Zhou and Riccio, 1994; Anderson and Riccio, 2005; Riccio and Joynes, 2007;

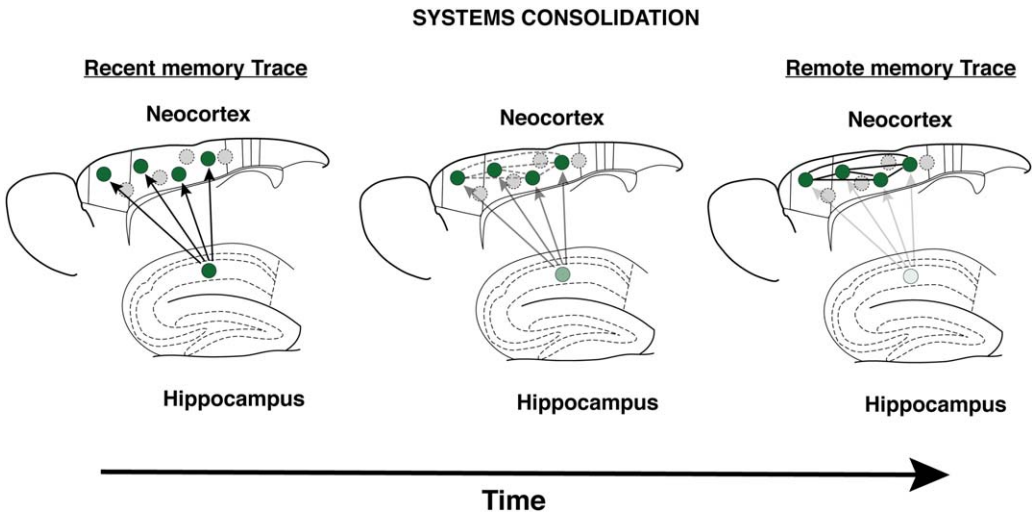

Fig. 1. Systems (standard) consolidation. According to systems consolidation theory, the hippocampus plays a time-limited role in the retrieval of memory traces that are permanently stored in the neocortex. In this case, the hippocampus is involved in the consolidation and retrieval of new memories (green circles) until they are ultimately represented in their original form by the neocortex. At later time points, retrieval of those original memories no longer requires the hippocampus. Interconnections among components of the neocortical trace presumably strengthen over time. Systems consolidation helps explain temporally graded retrograde amnesia that is reported with hippocampal damage (e.g., Scoville and Milner, 1957). This has been extended in the rodent literature, implicating the hippocampus in the retrieval of recent context-dependent memories (Kim and Fanselow, 1992; Maren et al., 1997) and the neocortex in remote memory retrieval (Suzuki et al., 2004; Frankland et al., 2006; Corcoran et al., 2011, 2015; Vetere et al., 2011). In systems consolidation, memory traces stored in the neocortex are considered identical to those originally dependent on the hippocampus and therefore does not explain how memories generalize or become less specific with the passage of time.

Jasnow et al., 2012). Thus, it is thought that generalization at remote time points is the result of the novel contextual test cues functioning as retrieval cues. This view of forgetting is supported by a study that used context fear conditioning and different pre-exposure durations to the conditioning context. In that study, reduced fear responses were observed in a context different from the training context at recent retrieval tests but not at remote tests. Exposing rats to the context prior to contextual fear training eliminated generalization to the novel context at a 15-day retention interval (Biedenkapp and Rudy, 2007). Moreover, because representations of context are highly dependent on hippocampal function (e.g., Matus-Amat et al., 2004), Beidenkapp and Rudy (2007) concluded that, as context memories age, the conjunctive representation of context supported by the hippocampus degrades and leads to generalization. Thus, older memories are harder to retrieve than newer ones. Moreover, the activity observed in the neocortex during remote memory retrieval (Frankland et al., 2004) that has traditionally been interpreted as support for systems consolidation instead reflects the demand on the hippocampus in retrieving an old degraded memory (Biedenkapp and Rudy, 2007). The forgetting view is also supported by data showing that brief reminder exposures to a training context eliminate generalization (Zhou and Riccio, 1994). These findings support the idea that stronger representations of context increase the persistence of memory precision. Exactly how hippocampal memories may degrade and how the neural signature might differ from that supporting systems consolidation, however, have not yet been addressed. One proposal is an active decay process that leads to forgetting over time (Hardt et al., 2013). This proposal of forgetting along with other similar proposals (Besnard and Sahay, 2016) draws on hippocampal indexing theory and its role in pattern separation (Teyler and DiScenna, 1986; Teyler and Rudy, 2007). Pattern separation normally allows similar yet overlapping cortical memory traces to be distinctly activated through connections with a specific hippocampal index, allowing precise memory recall. Theoretically, a time-dependent degradation of a hippocampal index would increase interference among partially overlapping cortical memory traces, thereby increasing generalization (Hardt et al., 2013; Besnard and Sahay, 2016; Fig. 2B). Although these are intriguing explanations for time-dependent generalization, cellular and molecular signatures of active forgetting have not yet been established; it is also not clear that interference with pattern separation is causally linked to remote fear generalization. In addition, most experimental manipulations with rodents to examine generalization would not theoretically involve similar yet overlapping contextual memory traces. Rodents are not typically exposed to several similar contexts in the intervening time between training and testing that would establish multiple similar overlapping traces; they are trained in one context and later tested in either the same context or a different context. Although interference of pattern separation is a

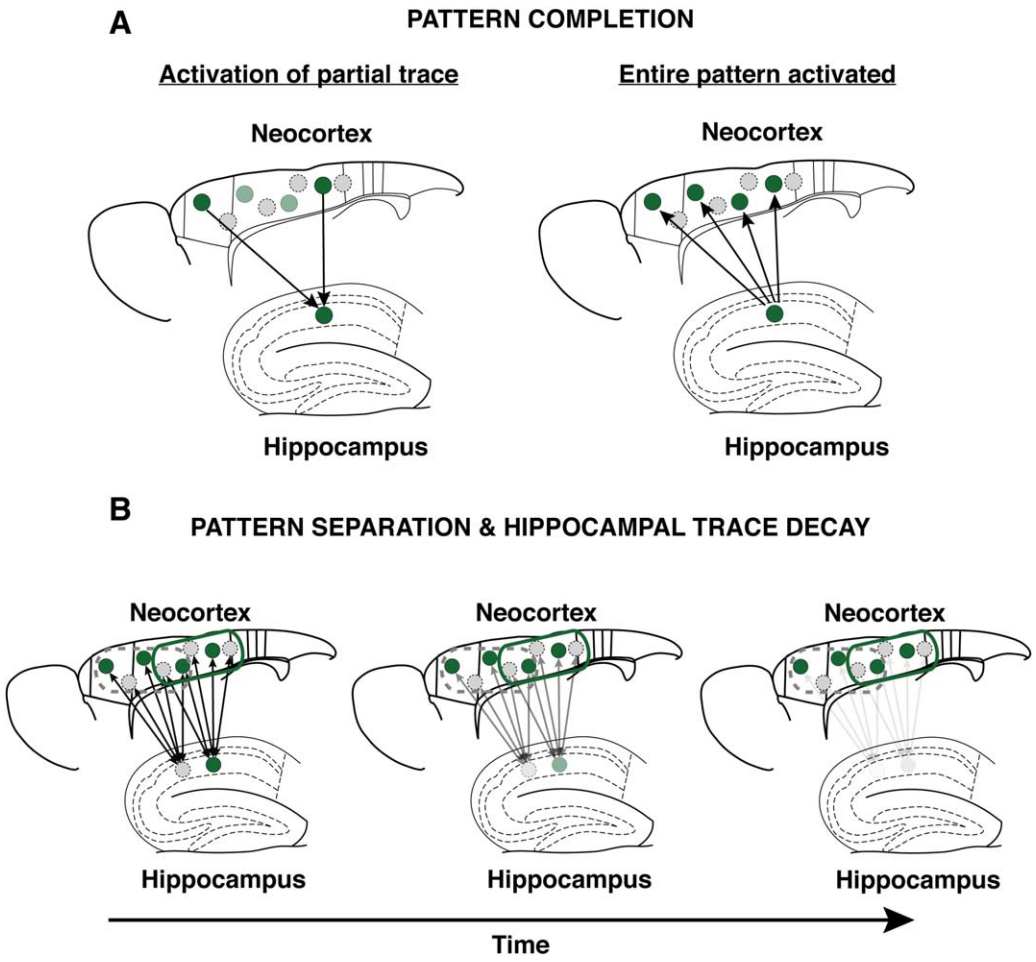

Fig. 2. Pattern completion, pattern separation, and forgetting. Pattern completion and pattern separation are ideas represented in hippocampal indexing theory. The hippocampus does not store memory traces but rather contains indexes of the specific pattern of activity in the neocortex that represent memory traces (Teyler and DiScenna, 1986; Teyler and Rudy, 2007). **A**: Pattern completion can serve as an explanation for fear generalization in which a partial memory trace can activate the hippocampal index, which in turn projects to the neocortex to activate the entire pattern. For instance, overlapping features of a similar yet distinct fear-testing context can activate the original memory trace of the training context, resulting in fear expression in the altered context. **B**: Hippocampal indexing theory also supports the idea of pattern separation. Hippocampal indices help maintain distinct representations of similar but overlapping episodes (green and grey circles in the neocortex). Hippocampal decay severs the connection between hippocampal traces and their associated neocortical representations. In the absence of the hippocampal trace, neocortical representations are poor at distinguishing among similar yet distinct episodes, which leads to generalization at the behavioral level.

plausible explanation for human forgetting, it is an unlikely neurobiological explanation for generalization in typical experimental manipulations with rodents.

An alternative to forgetting for explaining the loss of memory precision over time is the transformation hypothesis (Winocur et al., 2007, 2013). Recent studies have reported nongraded retrograde amnesia following hippocampal lesions (Nadel and Moscovitch, 1997; Cipolotti et al., 2001; Lehmann et al., 2007; Goshen et al., 2011; Broadbent and Clark, 2013; Cullen et al., 2015), and this effect is inconsistent with systems consolidation. Winocur and colleagues (2007) proposed that detailed context-specific episodic memories are initially dependent on the hippocampus but are transformed into schematic (semantic) memories as they are stored in the neocortex (Winocur et al., 2007, 2013; Fig. 3). Importantly, both context-specific episodic memories and schematic memories are accessible in the normal functioning brain without regard to their age. According to the transformation view, context-specific episodic memories will always be dependent on the hippocampus, whereas schematic memories can be accessed without the hippocampus. Thus, two memory traces exist at remote time points, one that is context specific and dependent on the hippocampus and one that is schematic and supported by extrahippocampal structures (Winocur et al., 2009). Transformation theory differs from the interpretation by Biedenkapp and Rudy (2007) in the theoretical changes to the memory trace

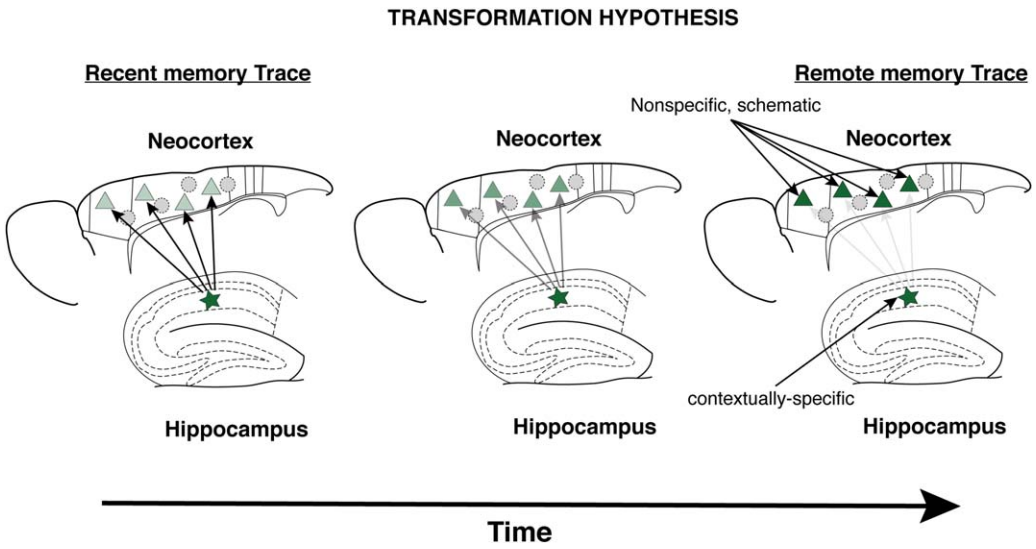

Fig. 3. Transformation hypothesis. Transformation is based on the multiple trace theory (Nadel and Moscovitch, 1997) and suggests that detailed context-specific episodic memories are initially dependent on the hippocampus but are transformed into schematic (semantic) memories as they are stored in the neocortex. In the figure, stars in the hippocampus represent contextually rich information that is transformed as it is stored in the neocortex as something with points (triangles). Both context-specific episodic memories and schematic memories are accessible without regard to their age. According to the transformation view, context-specific episodic memories will always be dependent on the hippocampus, whereas schematic memories can be accessed without the hippocampus. The task demands (contextually rich or schematic) determine which trace is required to perform the appropriate behavior. After the memory becomes independent of the hippocampus, the precision or specificity of that memory is lost, resulting in increased rates of fear generalization.

over time. In the forgetting view, the hippocampal trace degrades over time, leading to a broad generalization gradient. In transformation theory, the trace does not degrade, but different components are consolidated and retrieved by different regions over time. Transformation theory also differs from systems consolidation on the dynamic nature of memory as well as the duration and nature of hippocampal involvement in memory retrieval.

Although the studies by Winocur and colleagues (2007, 2009, 2013) suggest transformation, alternative interpretations of their findings are possible. The most convincing support for the transformation view, however, is provided by a recent study by Wiltgen et al. (2010) who showed that successful discrimination between training and novel contexts at a remote testing time in a contextual fear paradigm was dependent on activity of the hippocampus. Importantly, they showed that when rodents generalize fear, the memory is no longer dependent on the hippocampus, suggesting that the cortex supports generalized contextual fear memories. After the memory becomes independent of the hippocampus, the precision or specificity of that memory is lost, resulting in increased rates of fear generalization. Two more-recent studies also have supported the transformation view of memory generalization. The first showed that inactivation of the anterior cingulate cortex (ACC) only at a remote time point after re-exposure to the training context selectively disrupted fear to a novel context (Einarsson et al., 2015). This suggested that the ACC plays a selective role in generalized fear memories. In another study, inactivation of the ACC at recent and remote time points selectively disrupted generalized fear memory only at remote testing, without the requirement for reactivation in the training context (Cullen et al., 2015). These findings are inconsistent with the systems consolidation view of long-term memory and, instead, support the transformation view of memory consolidation.

Most existing literature on consolidation and generalization has focused solely on cortical sites or dorsal hippocampus, overlooking the potentially important role of the ventral hippocampus. The study cited above by Cullen et al. (2015) also used activity-dependent neural activation and reversible inactivation to assess brain regions involved in generalized context fear memory. First, they found that expression of a contextually precise memory was associated with increased activity of the ACC, infralimbic cortex (IL), and prelimbic cortex (PL). The ventral hippocampus was also consistently active during recent and remote contextually precise memory recall, but the activity declined as a function of time. Activity of the ACC and ventral hippocampus remained more stable over time when animals were tested in a novel context, suggesting that activity of these regions supported expression of generalized fear. As noted above, pharmacological inactivation of the ACC selectively reduced fear to a novel context at remote time points only. In other words, the memory was returned to a more precise state by inactivation of the ACC, supporting a selective role of this region

in generalized memory (Cullen et al., 2015; also see Einarsson et al., 2015). This is in contrast to other reports demonstrating that the ACC and other cortical regions play a critical role in memory retrieval of the training context at both recent and remote time points (Frankland et al., 2004; Teixeira et al., 2006; Ding et al., 2008; Corcoran et al., 2011). These studies, however, never tested animals in an alternate context for precision of memory retrieval. Given the persistent activity of the ventral hippocampus, a subsequent experiment pharmacologically inactivated the ventral CA1 hippocampus prior to recent or remote context memory retrieval tests in either the training context or a novel context. Similar to the results observed for the ACC, inactivation of the ventral CA1 at a remote testing point returned the context memory to a more precise state (i.e., rodents did not freeze in the novel context). Inactivation of ACC or ventral CA1 regions had no effect on fear memory in the training context at either time point. The interpretation of these results is that the dorsal hippocampus supports remote contextually precise memories and that the ACC supports remote generalized contextual fear memories. These results are in line with the transformation hypothesis. Indeed, Cullen et al. (2015) showed that the dorsal CA1 was involved in context specific fear memory recall at remote testing, yet the finding that concurrent activity of the ventral CA1 was associated with generalized contextual fear memory was not predicted by the transformation hypothesis. This seems to suggest that, in addition to recruitment of cortical sites as memories age and are transformed, the ventral CA1 is also recruited, further contributing to generalized memory. These data also support a continued role of the hippocampus in remote memory regardless of specificity.

Are the activities of the ACC and the ventral CA1 during remote recall directly linked? The ACC and ventral CA1 do not share robust direct projections (Fanselow and Dong, 2010), and, therefore, their activity is likely connected through another structure. One possibility is that "transformed" contextual information from the ACC and the ventral CA1 during remote testing converges concurrently on the amygdala, resulting in generalized fear in the novel context. Alternatively, at remote testing points, the ACC may activate the ventral hippocampus through the nucleus reuniens, resulting in generalized fear (Dolleman-Van der Weel et al., 1997; Davoodi et al., 2011; Loureiro et al., 2012; Xu and Südhof, 2013). These predictions must be systematically tested to determine the direction of information flow among brain regions during generalized fear responding. Given that transformation cannot completely account for the results described above, it is possible that additional processes underlie the dynamic nature of fear generalization. There is evidence that, at some level, rodents can perceive differences between the training context and a novel context at remote time points even though they show similar fear responses in both (Winocur et al., 2009). This would suggest that generalization is not only based on perceptual similarities among the contexts but may also be an active response to an uncertain environment. Given the role of the ACC in interpreting contextual cues (Xu et al., 2012; Xu and Südhof, 2013), this region and its concurrent activity with the ventral hippocampus may support active fear at remote time points.

Although we are making great strides in understanding the cellular and circuit level mechanisms contributing to generalized fear, it is difficult to integrate all the extant data into a single current interpretation of long-term memory. As a result, the debate remains open with regard to whether time-dependent generalization is a function of disrupted consolidation, storage, or retrieval. As we discuss in the next sections, multiple mechanisms exist that influence generalization during both memory consolidation and retrieval and may provide some alternative interpretations on time-dependent generalization.

HOW ARE PRECISE CONTEXTUAL MEMORIES FORMED?

Most of the studies discussed above examined generalization during the retrieval stage and inferred changes in long-term memory storage through posttraining manipulations. But, how do animals encode and consolidate precise fear memories? This is particularly relevant for many anxiety disorders in which a pre-existing difference in brain function can significantly contribute to the development of psychiatric disease. A recent study by Ruediger et al. (2011) demonstrated that context fear learning induces a specific increase in filopodial contacts onto parvalbumin-expressing fast spiking interneurons in the CA3 region of the hippocampus. These filopodial contacts emanated from large mossy fiber terminals of dentate gyrus neurons and functioned to enhance feedforward inhibition. The number of filopodial contacts diminished as a function of time, and this correlated with the mice exhibiting fear (freezing) to a novel context (i.e., behavioral fear generalization). Deletion of key synaptic plasticity genes *Rab3a* and *Add2* in two separate mouse lines eliminated both long-lasting long-term potentiation (LTP) and feedforward inhibitory growth from large mossy fibers. Both lines of mice were able to learn context fear normally but generalized fear to a novel context after 1 day. These data suggest that synaptic plasticity is required for the growth of feedforward inhibitory filopodia and that feedforward inhibition likely contributes to the consolidation of a precise contextual fear memory. Additionally, presynaptic inhibition within the hippocampus may play an essential role in the consolidation of precise contextual memories, thereby limiting fear generalization. Two γ-aminobutyric acid $(GABA)_{B1}$ subunit isoforms are expressed in the brain, $GABA_{B1(a)}$, which is selectively associated with presynaptic terminals, and $GABA_{B1(b)}$ which is associated with postsynaptic membranes (Vigot et al., 2006). $GABA_{B1(a)}$ receptors contribute to GABA-mediated presynaptic inhibition in the hippocampus (Gassmann and Bettler, 2012), and genetic deletion of these receptors in mice results in contextual fear generalization 1 day after training (Cullen et al., 2014). These knockout mice were able to acquire

contextual fear normally and express contextual discrimination up to 2 hr after training (Cullen et al., 2014). This effect was also not limited to contextual fear; knockout mice showed similar discrimination deficits on hippocampally dependent novel object recognition and location tasks. Overall, these data suggest that feedforward inhibitory growth in the CA3 region of the hippocampus is essential for consolidating and potentially maintaining precise contextual fear memories over time but not essential for establishing the memory itself. These data seem to fit with the forgetting view of memory generalization (Rudy, 2005; Biedenkapp and Rudy, 2007; Riccio and Joynes, 2007), suggesting that, during consolidation, a type of trace degradation occurs in the hippocampus. This results in imprecise memory retrieval at test and is exhibited as fear generalization in the novel context. These data also fit with the idea that the hippocampus is always involved in memory, especially when that memory is context specific (Wiltgen et al., 2010; Ruediger et al., 2011).

An interesting recent finding is that pretraining inactivation of the medial prefrontal cortex (mPFC) that included the ACC induced generalization of fear responses to novel contexts at recent time points but impaired contextual fear in both the training and novel contexts at remote time points (Xu et al., 2012). Furthermore, pretraining inactivation of neurons within the nucleus reuniens receiving synaptic input from the mPFC induced fear generalization at a recent time point (Xu and Südhof, 2013), but posttraining infusions had no effect on fear memory. These data suggest that the mPFC is involved in encoding the specificity of contexts and relays that information to the hippocampus through the nucleus reuniens. The neural activity data of Cullen et al. (2015) also seem to support this idea; the ACC was highly active when mice were in a novel context, whether it was at a recent or remote time after training. This is further supported by electrophysiological (Dolleman-Van der Weel et al., 1997) and functional inactivation experiments in behaving rats (Loureiro et al., 2012). One study did, however, find that immediate pretesting inactivation of the nucleus reuniens impaired memory recall in a passive avoidance task (Davoodi et al., 2011), suggesting that the nucleus reuniens may be essential for both the acquisition of memory and its recall. If the mPFC is involved in encoding specificity of the context then it is not currently clear why activity of the ACC (part of the mPFC) becomes associated with generalized fear at remote time points. In addition, activity of the ACC does not appear to be associated with recall of recent precise contextual memory; inactivation at a recent time point had no effect on fear in the training or novel context (Cullen et al., 2015). One possibility for the shift over time in the role of the ACC from one of memory specificity to one of generalization may be due to a shift in its outputs. Remote contextual generalization may be due to converging outputs of the ACC and ventral hippocampus through the amygdala rather than through the nucleus reuniens to the dorsal CA1 during acquisition or recent retrieval.

MODULATION OF MEMORY RETRIEVAL: ESTRADIOL-INDUCED FEAR GENERALIZATION?

In the preceding section, we discussed the emerging understanding of the neural control of fear generalization as it relates to its temporally dynamic nature. Over the past several years, our laboratory has investigated gonadal hormone modulation of fear generalization in female rodents. This is particularly relevant because fear generalization is a key symptom of nearly all anxiety disorders, in which females represent a disproportionately large percentage (McLean et al., 2011). Unlike the time-dependent generalization discussed above, we find that fear generalization can be induced relatively rapidly in females (within 24 hr), placing this type of generalization outside the realm of systems consolidation or transformation theory.

In our initial studies, we found that female rats displayed a faster rate of fear generalization to a neutral context after passive avoidance training than male rats (Lynch et al., 2013). Subsequent experiments revealed that this effect was due, in part, to the presence of estradiol. Importantly, chronic estradiol treatment in ovariectomized female rats caused contextual fear generalization without increasing overall fear and anxiety levels (Lynch et al., 2013). The use of chronic estradiol treatment in these experiments did not allow us to determine if estrogens increased fear generalization through an effect on fear acquisition, consolidation, or retrieval. The consensus is that the processes involved during acquisition/consolidation and retrieval of fear memory involves distinct molecular and cellular mechanisms, with some manipulations affecting either acquisition/consolidation or retrieval but not necessarily both (Miserendino et al., 1990; Abel and Lattal, 2001; Matus-Amat et al., 2004; Walker and Davis, 2008; Antoniadis et al., 2009). An extensive set of experiments found that acute estradiol increased fear generalization through an effect on memory retrieval but not acquisition or consolidation of contextual memory (Lynch et al., 2014). This study also found that estradiol induced fear generalization primarily through its activity at estrogen receptor-β (ERβ). From these results, particularly the timing of the effect, the interpretation was that estradiol had a genomic effect on retrieval, but this would require further confirmatory experiments. In addition, estradiol-induced generalization was temporally limited, lasting approximately 48 hr, suggesting that whatever genomic or structural changes had taken place as the result of acute estradiol treatment subsided as the effect of estradiol subsided.

A subsequent series of experiments characterized the specific brain regions and downstream mechanisms through which estrogens modulated the precision of contextual memory retrieval and generalization. Considerable data indicate that estrogens have classical genomic effects occurring within a time frame of hours to days that are

driven by cytosolic estrogen receptors (O'Malley and Means, 1974; Etgen, 1984; Couse and Korach, 1999; Falkenstein et al., 2000; McKenna and O'Malley, 2002). In addition to classical activation, estrogens can also have rapid signaling through membrane-bound receptors, with effects occurring within a time frame of seconds to minutes (Vasudevan and Pfaff, 2007). Several recent studies have suggested that estradiol enhances object recognition through activation of membrane-bound ERs within the hippocampus and through subsequent metabotropic glutamate receptor signaling (Gresack and Frick, 2006; Fernandez et al., 2008; Lewis et al., 2008; Fan et al., 2010; Zhao et al., 2010). As discussed above, however, the timing of estradiol-induced fear generalization suggested genomic actions of classical estrogen receptors rather than an effect driven by membrane-bound receptor activation. This hypothesis was verified through a series of experiments demonstrating the importance of cytosolic ERs in estradiol-induced fear generalization. In an initial experiment, intracerebroventricular infusions of the cytosolic estrogen receptor antagonist ICI 182,780 blocked fear generalization when estradiol was administered either peripherally or locally in the dorsal CA1 hippocampus. This effect again required ERβ but not ERα (Lynch et al., 2016) and also established the hippocampus as an important locus for the effects of estradiol on fear generalization. These results, however, did not rule out the contribution of membrane-bound receptors to fear generalization. Subsequent experiments with estradiol conjugated to bovine serum albumin activating only membrane-bound receptors failed to induce fear generalization, and intrahippocampal coinfusions of an MEK inhibitor (blocking membrane-bound ER intracellular signaling) with estradiol failed to block fear generalization. Overall, the results of these experiments suggest that estradiol induces fear generalization through activation of hippocampal cytosolic ERβ and that membrane-bound ERs do not contribute significantly to estradiol-induced fear generalization in females.

Through what mechanisms does estradiol induce fear generalization? ERβ activation promotes increased glutamate release through presynaptic mechanisms (Smejkalova and Woolley, 2010), but this rapid effect does not match the timing of behavioral fear generalization we have observed. Alternatively, ERβ activation enhances postsynaptic glutamate signaling mechanisms such as PSD95 and AMPA and NMDA receptor subunits (Weiland, 1992; Gazzaley et al., 1996; Waters et al., 2009). These postsynaptic effects may be the genomic mechanisms through which estradiol functions to induce fear generalization. Recent experiments functionally tested whether increased glutamate signaling in the dorsal CA1 contribute to estradiol-induced fear generalization and appear to confirm this mechanism. Immediate pretesting infusions of low doses of NBQX (AMPAR antagonist) or APV (NMDA antagonist) significantly attenuate estradiol-induced fear generalization without impairing memory recall to the training context (Lynch et al., 2015). Additionally, administration of either antagonist had no effect on generalization when administered alone. Thus, rapid estradiol-induced fear generalization may be due, in part, to enhanced postsynaptic glutamatergic signaling within the dorsal CA1.

The findings above describing estradiol-induced fear generalization add to the growing literature on the effects of estrogens on the inhibition of fear to neutral or safety cues (Toufexis et al., 2007; Nofrey et al., 2008). Overall, these findings suggest that high levels of estrogens disrupt the ability of animals to inhibit a fear response to a neutral environment or a discrete neutral stimulus. Unlike the well-established effect of estrogens enhancing extinction retention, in which new learning occurs with regard to the relationship between the conditioned stimulus and absence of the unconditioned stimulus (Milad et al., 2009; Graham and Daher, 2015; McDermott et al., 2015), the present findings are not a result of estrogens enhancing memory formation, as has been demonstrated repeatedly (Packard et al., 1996; Packard and Teather, 1997; Packard, 1998; Daniel and Dohanich, 2001; Frye and Rhodes, 2002; Gibbs, 2002; Rhodes and Frye, 2004; Sandstrom and Williams, 2004; Daniel et al., 2005; Walf et al., 2006, 2008; Frye et al., 2007; Fernandez et al., 2008; Fan et al., 2010; Zhao et al., 2010; Fortress et al., 2013), but rather changing the cues that elicit the fear memory response. Given that the timing of estradiol-induced fear generalization does not fit within transformation or systems consolidation, it is possible that estradiol interferes with the rats' ability to inhibit a previously learned response despite the shift in context. Although clearly speculative, this might suggest that, in addition to the hippocampus, estradiol acts on the dorsomedial striatum, a region critical to action–outcome learning (Yin et al., 2004, 2005). There is evidence that the dorsomedial striatum is also important for active and passive avoidance learning (Mazzucchelli et al., 2002). Alternatively, estradiol may enhance pattern completion or impair pattern separation, two processes that depend on the hippocampus (Matus-Amat et al., 2004; Rudy et al., 2004; Nakashiba et al., 2008, 2012; Rudy, 2009; Besnard and Sahay, 2016). In pattern completion, a subset or portion of the contextual cues present during the initial learning can activate the original memory trace as a whole. This could explain estradiol-induced fear generalization, in which a similar yet distinct context activates the fear memory. On the other hand, pattern separation normally allows similar yet overlapping cortical memory traces to be distinctly activated, allowing precise memory recall. If estradiol administration interferes with the process of pattern separation, a similar yet distinct context may activate the original fear memory trace, promoting fear generalization (but see above). These possibilities have yet to be systematically tested, which will be required to determine the exact mechanisms through which estradiol promotes generalized fear in females.

CUED FEAR GENERALIZATION

It has generally been recognized that cue-dependent and context fear memory are regulated by overlapping yet

different neurobiological mechanisms (Phillips and LeDoux, 1992; Frankland et al., 1998; Maren and Holt, 2004; Fanselow, 2010). Specifically, the amygdala is essential in the acquisition, consolidation, and extinction of cue-dependent and context fear, whereas the hippocampus is generally thought to be essential in the regulation of contextual fear (Kim and Fanselow, 1992; Fanselow and Kim, 1994; Helmstetter and Bellgowan, 1994; Maren et al., 1996; Davis, 1992; Schafe et al., 2001; Ressler et al., 2002; Phelps et al., 2004; Myers and Davis, 2006). Most studies examining generalization of cued fear conditioned responses use discrimination training. This is both experimentally and conceptually different from contextual generalization studies, in which animals normally are not exposed to the novel context until testing. In cued discrimination experiments, animals are assessed for fear to the CS^-, which represents a learned safety cue. These studies have shown that mice lacking the 65-kD form of glutamic-acid decarboxylase ($GAD65^{-/-}$ mice), the biosynthetic enzyme for GABA, display reduced freezing compared with their wild-type littermates, suggesting reduced fear memory. These knockout mice, however, were unable to distinguish the CS^- from the CS^+ during testing 24 hr or 14 days later, suggesting that GABA synthesis is critical not only for forming fear memory but also for stimulus-specific fear memory (Bergado-Acosta et al., 2008). As described above for contextual fear generalization, presynaptic $GABA_B$ receptors also play an important role in cued fear generalization. In the lateral amygdala, $GABA_{B1(a)}$ receptors seem to be responsible specifically for presynaptic LTP at corticoamygdala afferents, whereas $GABA_{B1(b)}$ receptors are responsible for LTP at thalamic afferents, suggesting pathway-specific regulation of LTP in the lateral amygdala (Shaban et al., 2006). Moreover, $GABA_{B1(a)}$ knockout mice display stimulus intensity-dependent generalization of fear to CS^- cues when tested after discrimination training. These data suggest that presynaptic inhibition in the corticoamygdala pathway is important to preserve stimulus discrimination during discrimination training. Additionally, it was concluded that the lack of presynaptic inhibition in $GABA_{B1(a)}$ knockout mice resulted in a shift in the threshold for generalization of fear responses to lower US intensities. However, if this were the case, it would be expected that $GABA_{B1(a)}$ knockout animals trained with high shock intensities would fail to discriminate contextual cues at any posttraining interval. In the experiments describing a rapid generalization of contextual memory, $GABA_{B1(a)}$ knockout mice were able to discriminate among contexts up to 2 hr posttraining but not at 1 day (Cullen et al., 2014). Furthermore, a similar rapid decline in memory precision was observed with nonfear tasks, providing additional support against a threshold shift phenomenon and suggesting a more integral role in regulating the precision of contextual, spatial, and potentially auditory cued memories.

In addition to the lateral and basolateral amygdala (BLA), the central nucleus of the amygdala (CeA) has been identified as an essential structure undergoing plasticity in support of fear learning (Jasnow and Huhman, 2001; Samson and Pare, 2005; Wilensky et al., 2006). The CeA is composed predominantly of GABAergic inhibitory neurons, of which the medial subdivision of the CeA (CeM) is under tonic inhibition by the lateral/capsular CeA (CeL; Cassell et al., 1986; Sun and Cassell, 1993; Ciocchi et al., 2010; Haubensak et al., 2010). Using a discrimination task and in vivo electrophysiological recordings, Ciocchi et al. (2010) showed that a decrease in tonic activity of CeM neurons was associated with generalization to the CS^-. The opposite was true for the CeL; an increase in tonic activity was associated with generalization. In addition, changes in tonic activity of the CeL were higher in generalizing mice. However, increased CeL activity associated with generalization might be cell-type specific. Mice with precise cell-specific ablation of NMDA receptor function exclusively in corticotropin releasing factor (CRF)-expressing neurons, which are localized to the CeL, show generalized responding to CS^- cues in fear discrimination tasks (Gilman et al., 2015). These data suggest that specificity of fear responses may be partially regulated by changes in activity within the inhibitory neural circuitry of the CeA. A similar generalization to frequency-modulated cues is observed in mice with targeted ablation of NMDA receptor function in the mPFC, which presumably dampens responses to excitatory input (Vieira et al., 2015). Evidence also suggests that dysfunctional communication between the BLA and the mPFC, a circuit that is critical for discrimination learning, results in fear generalization. In this case, the top–down communication (mPFC-to-BLA) is disrupted, resulting in greater fear responses to CS^- cues (Likhtik and Paz, 2015).

Generalization to fearful cues may also recruit activity of additional brain regions, including the bed nucleus of the stria terminalis (BNST). BNST-lesioned rats freeze less to CS^- cues and are able to discriminate between a CS^+ and CS^-, whereas sham-lesioned rats display a continuum of responses ranging from high to low fear generalization (Duvarci et al., 2009). From the limited available data, it appears that the inhibitory network within the amygdala plays an essential role in regulating stimulus-specific behavioral responses and ultimately limits generalization. This could be cell-type specific within the CeA. For instance, the role of CRF in response to stressors may actually be a homeostatic attempt to diminish reactivity and reduce hypervigilance. In addition, recruitment of the BNST, which is involved in regulating anxiety-like behavior, may contribute to fear generalization. Alternatively, generalization of auditory cued fear may be due to changes in afferent or efferent structures containing direct connections with the amygdala, such as the auditory thalamus or auditory cortex (Weinberger, 2007). In the case of the auditory thalamus, enhanced fear generalization to alternative tones that were not previously paired with shock has been observed following increased cAMP-response element binding protein overexpression in the medial geniculate nucleus (Han et al., 2008). This would

allow relatively quick generalization of fear responses to alternate cues because broadening of auditory thalamus tuning may occur during or shortly after conditioning.

The time-dependent nature of contextual fear generalization most likely involves reorganization of synaptic connections involved in the consolidation, storage, and retrieval of a contextual memory trace. Given the current evidence, systems consolidation, the forgetting view, and the transformation hypothesis each in isolation do not necessarily account for contextual fear generalization. The most recent evidence suggests that there may be an interaction between cortical structures and the ventral hippocampus during remote contextual fear generalization (Cullen et al., 2015; Einarsson et al., 2015). What then, happens to cued fear memories as they age? One interpretation is that the hippocampus initiates pattern completion from similar cues present during training and during testing, resulting in fear generalization (Lissek, 2012; Lissek et al., 2014). The problem with applying this view to the temporally dynamic nature of fear generalization is that the same cues result in pattern separation (i.e., little fear generalization) at recent time points and pattern completion (i.e., considerable fear generalization) at remote time points (Fig. 2). Similarly, Onat and Buchel (2015) suggest that stimulus generalization is an active process based on the identification of threat and ambiguity of intermediate CS cues, allowing flexible behavioral responses. However, this also cannot explain why the threat assessment of cues changes as a function of time; the same cues (or context) are interpreted as *safe* and *nonambiguous* at recent tests and *dangerous* and *ambiguous* at remote testing.

It must be noted that many of the studies examining cued fear generalization used discrimination training, which does not address the question of generalization to novel cues. It is likely, however, that generalization to novel cues involves similar neurobiological mechanisms, as described in these studies. In the case of the loss of contextual memory precision over time (i.e., increased generalization), perception is still intact but the memory for that which was perceived has changed (Riccio et al., 1994; Zhou and Riccio, 1996; Anderson and Riccio, 2005; Jasnow et al., 2012; Cullen et al., 2014, 2015). With auditory cued fear conditioning, several studies have shown that, in rodents, the lateral and/or basolateral complex of the amygdala may be the locus of fear memory storage (Schafe et al., 2005; Kwon and Choi, 2009; Poulos et al., 2009). In fact, there is evidence that specific neurons within the lateral amygdala itself switch from responding to a CS^+ (cue-specific) to responding to a CS^- (generalization) when the animals shift from fear discrimination to generalization (Ghosh and Chattarji, 2014). In this experiment, however, animals were always tested at recent time points after training, so it is unclear what might happen in the lateral amygdala at remote time points. Alternatively, the amygdala may modulate memories that are stored in the cortex (McGaugh, 2004; Chavez et al., 2009), or circuit reorganization may occur for auditory fear memories as a function of time (Do-Monte et al., 2015). For instance, the paraventricular nucleus of the thalamus and its connections to the CeA are involved in retrieval of remote but not recent auditory fear memories. Inhibition of prelimbic axons to the BLA, normally important for fear retrieval at recent testing, had no effect on fear memory retrieval at remote time points, indicating a time-dependent shift away from involvement of the BLA in fear memory retrieval (Do-Monte et al., 2015). Although this study does not directly address cued fear generalization as a function of time, it illustrates the time-dependent circuit reorganization that occurs for remote cued fear memory retrieval, which seems to mirror that which is happening for remote contextual fear memory. A final possibility is that a time-dependent loss of feedforward inhibition onto parvalbumin-expressing interneurons in the BLA occurs similarly to that which has been observed in the hippocampus (Ruediger et al., 2011). Thus, it is possible that cued fear memories undergo a transformation from cue-specific to cue-general representation within the same region and may occur at a faster rate than context memories.

FEAR GENERALIZATION AND ANXIETY DISORDERS

In the previous sections, we have discussed the neural circuitry and memory systems currently identified in regulating generalized fear responses with traditional Pavlovian fear conditioning paradigms. Fear conditioning has also been implicated in the etiology of anxiety disorders (Öhman and Mineka, 2001; Bouton, 2002; Mineka and Zinbarg, 2006). In addition, generalization has been linked to anxiety pathology and has recently been considered a biomarker for many anxiety disorders (Lissek et al., 2005, 2008, 2010, 2014; Dunsmoor et al., 2009, 2011a,b; Lissek, 2012; Morey et al., 2015). The story above with regard to the dog is an example of how generalization relates to anxiety disorders; anxiogenic properties are associated with stimuli that are similar yet distinct from the original conditioning stimulus, thereby eliciting and maintaining anxiety responses long after the original conditioning occurred. In humans, increased generalization to fear cues is one the most common findings among studies of anxiety patients (Lissek et al., 2005, 2008; Lissek, 2012). Support for this is derived from a meta-analysis of 20 laboratory-based studies that examined Pavlovian fear conditioning and simple discrimination in patients with anxiety disorders and in healthy controls (Lissek et al., 2005). Among the fear discrimination studies, the findings implicated increased fear responding to CS^- cues. A more detailed analysis has shown that studies of posttraumatic stress disorder (PTSD) patients largely account for this pattern of results (Lissek et al., 2008). To characterize the link between fear generalization and anxiety disorders further, recent studies have begun investigating fear generalization in clinical populations using gradients of stimuli that resemble the CS^+ or CS^- in either perceptual similarity or intensity (Lissek et al., 2008, 2014; Dunsmoor et al., 2009; Lissek, 2012; Morey et al., 2015). The reason for including a gradient of cues

that resembles the CS^+ and CS^- during the test phase is that anxiety triggers rarely resemble the exact cues present during a traumatic event and may differ on a variety of dimensions. For example, in a study with fearful faces along a gradient of intensity, PTSD patients more often misidentified an intensely fearful face as the CS^+ even when it was never paired with the aversive stimulus, suggesting a bias toward generalization (Morey et al., 2015). In that study, PTSD patients also exhibited greater activation compared with controls in a number of brain regions, including the fusiform gyrus, insula, visual cortex, locus coeruleus, and thalamus. In another study with a gradient of shape stimuli, this time differing in size resembling the CS^+ and CS^-, panic disorder patients generalized their fear responses much further along the gradient of test cues compared with healthy controls (Lissek et al., 2010). Altogether, these data suggest that generalization is a pathogenic biomarker of anxiety disorders and can be used in laboratory settings to examine the neural substrates of generalization and its contribution to anxiety disorders.

In a recent study examining neural substrates of generalization in healthy subjects with cued discrimination and functional MRI, the general finding was that the insula responded most strongly to the CS^+, whereas the ventral hippocampus and ventromedial prefrontal cortex (vmPFC) responded most strongly to the CS^- (Lissek et al., 2014). Activation gradients exist within each of these regions that are related to the degree of similarity of generalized cues to the CS^+ or CS^-. It should be noted that the insula has also been reported to respond when healthy individuals generalize to stimuli that vary on an intensity gradient (Dunsmoor et al., 2011a). Nevertheless, the findings from Lissek et al. (2014) can be interpreted to suggest that neural activation and behavioral generalization are linked to the perceptual similarity of cues to the CS^+. More recently, evidence in humans has emerged indicating that fear generalization is not solely dependent upon perception but is more active and complex, involving higher order cognitive processes (Dunsmoor and Murphy, 2014). Using discrimination fear conditioning to face stimuli along a circular gradient, Onat and Buchel (2015) showed the expected hippocampal and vmPFC responses to the CS^+ and CS^-; the hippocampus and vmPFC responded most robustly to the CS^-, and these related to the degree of behavioral output. That is, these regions were tuned to the CS^-, and their activity was associated with less fear, presumably because they play a role in safety learning. However, they found other areas not tightly linked to behavioral output. Most notably, activity of the anterior insula and inferotemporal cortex, which is involved in object and facial processing, did not match the degree of behavioral generalization. The insula displayed "hypersharp" tuning to the CS^+, meaning its activity was more selective than behavioral responses. The inferotemporal cortex, however, displayed the greatest activity to intermediate CS stimuli, and this was interpreted to mean that it responds to the ambiguity of the stimuli. Thus, activity of the insula and inferotemporal cortex did not match behavioral generalization. The authors interpreted this to mean that fear generalization is the result of integration of hypersharp responses to threat in the insula and uncertainty-based responses in the inferotemporal cortex rather than perceptual differences among stimuli. They suggest that pathological generalization may stem from an inability to identify the specific source of fear (insula) and a dysfunctional uncertainty evaluation system (inferotemporal cortex). These recent studies have important implications for understanding how an adaptive response, such as stimulus generalization, contributes to pathological conditions in humans.

CONCLUSIONS

Stimulus generalization is not a new phenomenon, but the recent attention paid to the neural mechanisms underlying fear generalization has revealed some important findings and highlighted the complex nature of this phenomenon. Understanding the time-dependent increase in contextual fear generalization has important implications not only for understanding how generalization contributes to anxiety disorders but also for understanding basic long-term memory function. From the existing literature, the dorsal hippocampus plays an essential role in memory traces that involve specific contextual information. Specific structural changes within the hippocampus leading to increased feedforward inhibition may underlie the mechanism by which this structure maintains a precise memory trace. However, debate remains with regard to the involvement of the hippocampus in the retrieval of remote memories and whether those memories are context specific or generalized. The most recent data suggest that the relevant structures involved in generalization change as a function of time and can be modulated by sex steroids. Estradiol can induce rapid fear generalization in females by acting directly on the dorsal hippocampus and may partially underlie the large sex difference in rates of anxiety disorders between males and females. At remote time points, the emphasis shifts to the ACC and the ventral hippocampus, especially when retrieval cues are novel, leading to generalized fear. It is unclear why the ACC is important for contextual specificity during acquisition but then shifts to controlling generalization at remote time points. It is not likely to be the result of perceptual inaccuracies because rodents seem able to distinguish between the training and novel contexts even though they freeze equivalently to both. This may relate to recent findings in humans suggesting that cued fear discrimination is an active and integrative process between identification of threat and uncertainty of the context. These recent findings in humans are particularly intriguing because they suggest a more complex, top–down processing model that accounts for stimulus generalization. Given that generalized fear is strongly linked to many anxiety disorders, understanding the neurobiological mechanisms of generalized fear and its expansion with the passage of time will be critical for developing effective treatments for these disorders. Convergent data from both nonhuman animal models of fear and concurrent studies in

humans will allow a more robust understanding of the environmental, genetic, and neurobiological mechanisms underlying generalized fear and its contribution to a number of neuropsychiatric disorders of emotion.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ROLE OF AUTHORS

AMJ wrote the manuscript, JL collected data and edited the manuscript, TLG collected data and edited the manuscript, DCR edited the manuscript.

REFERENCES

Abel T, Lattal KM. 2001. Molecular mechanisms of memory acquisition, consolidation, and retrieval. Curr Opin Neurobiol 11:180–187.

Anderson MJ, Riccio DC. 2005. Ontogenetic forgetting of stimulus attributes. Learn Behav 33:444–453.

Antoniadis EA, Winslow JT, Davis M, Amaral DG. 2009. The nonhuman primate amygdala is necessary for the acquisition but not the retention of fear-potentiated startle. Biol Psychiatry 65:241–248.

Bergado-Acosta JR, Sangha S, Narayanan RT, Obata K, Pape H-C, Stork O. 2008. Critical role of the 65-kDa isoform of glutamic acid decarboxylase in consolidation and generalization of Pavlovian fear memory. Learn Mem 15:163–171.

Besnard A, Sahay A. 2016. Adult hippocampal neurogenesis, fear generalization, and stress. Neuropsychopharmacology 41:24–44.

Biedenkapp JC, Rudy JW. 2007. Context preexposure prevents forgetting of a contextual fear memory: implication for regional changes in brain activation patterns associated with recent and remote memory tests. Learn Mem 14:200–203.

Bouton ME. 2002. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol Psychiatry 52:976–986.

Bouton ME, Nelson JB, Rosas JM. 1999. Stimulus generalization, context change, and forgetting. Psychol Bull 125:171–186.

Broadbent NJ, Clark RE. 2013. Remote context fear conditioning remains hippocampus-dependent irrespective of training protocol, training-surgery interval, lesion size, and lesion method. Neurobiol Learn Mem 106:300–308.

Cassell MD, Gray TS, Kiss JZ. 1986. Neuronal architecture in the rat central nucleus of the amygdala: a cytological, hodological, and immunocytochemical study. J Comp Neurol 246:478–499.

Chavez CM, McGaugh JL, Weinberger NM. 2009. The basolateral amygdala modulates specific sensory memory representations in the cerebral cortex. Neurobiol Learn Mem 91:382–392.

Ciocchi S, Herry C, Grenier F, Wolff S, Letzkus J, Vlachos I, Ehrlich I, Sprengel R, Deisseroth K, Stadler M, Muller C, Luthi A. 2010. Encoding of conditioned fear in central amygdala inhibitory circuits. Nature 468:277–282.

Cipolotti L, Shallice T, Chan D, Fox N, Scahill R, Harrison G, Stevens J, Rudge P. 2001. Long-term retrograde amnesia. . .the crucial role of the hippocampus. Neuropsychologia 39:151–172.

Corcoran KA, Donnan MD, Tronson NC, Guzman YF, Gao C, Jovasevic V, Guedea AL, Radulovic J. 2011. NMDA receptors in retrosplenial cortex are necessary for retrieval of recent and remote context fear memory. J Neurosci 31:11655–11659.

Corcoran KA, Leaderbrand K, Jovasevic V, Guedea AL, Kassam F, Radulovic J. 2015. Regulation of fear extinction versus other affective behaviors by discrete cortical scaffolding complexes associated with NR2B and PKA signaling. Transl Psychiatry 5:e657.

Couse JF, Korach KS. 1999. Estrogen receptor null mice: what have we learned and where will they lead us? Endocr Rev 20:358–417.

Cullen PK, Dulka BN, Ortiz S, Riccio DC, Jasnow AM. 2014. GABA-mediated presynaptic inhibition is required for precision of long-term memory. Learn Mem 21:180–184.

Cullen PK, Gilman TL, Winiecki P, Riccio DC, Jasnow AM. 2015. Activity of the anterior cingulate cortex and ventral hippocampus underlie increases in contextual fear generalization. Neurobiol Learn Mem 124:19–27.

Daniel JM, Dohanich GP. 2001. Acetylcholine mediates the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and the associated improvement in working memory. J Neurosci 21:6949–6956.

Daniel JM, Hulst JL, Lee CD. 2005. Role of hippocampal M2 muscarinic receptors in the estrogen-induced enhancement of working memory. Neuroscience 132:57–64.

Davis M. 1992. The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353–375.

Davoodi FG, Motamedi F, Akbari E, Ghanbarian E, Jila B. 2011. Effect of reversible inactivation of reuniens nucleus on memory processing in passive avoidance task. Behav Brain Res 221:1–6.

Ding HK, Teixeira CM, Frankland PW. 2008. Inactivation of the anterior cingulate cortex blocks expression of remote but not recent conditioned taste aversion memory. Learn Mem 15:290–293.

Do-Monte FH, Quinones-Laracuente K, Quirk GJ. 2015. A temporal shift in the circuits mediating retrieval of fear memory. Nature 519:460–463.

Dolleman-Van der Weel MJ, Lopes da Silva FH, Witter MP. 1997. Nucleus reuniens thalami modulates activity in hippocampal field CA1 through excitatory and inhibitory mechanisms. J Neurosci 17:5640–5650.

Dunsmoor JE, Murphy GL. 2014. Stimulus typicality determines how broadly fear is generalized. Psychol Sci 25:1816–1821.

Dunsmoor JE, Mitroff SR, LaBar KS. 2009. Generalization of conditioned fear along a dimension of increasing fear intensity. Learn Mem 16:460–469.

Dunsmoor JE, Prince SE, Murty VP, Kragel PA, LaBar KS. 2011a. Neurobehavioral mechanisms of human fear generalization. Neuroimage 55: 1878–1888.

Dunsmoor JE, White AJ, LaBar KS. 2011b. Conceptual similarity promotes generalization of higher order fear learning. Learn Mem 18:156–160.

Duvarci S, Bauer E, Pare D. 2009. The bed nucleus of the stria terminalis mediates inter-individual variations in anxiety and fear. J Neurosci 29:10357–10361.

Einarsson EÖ, Pors J, Nader K. 2015. Systems reconsolidation reveals a selective role for the anterior cingulate cortex in generalized contextual fear memory expression. Neuropsychopharmacology 40:480–487.

Etgen AM. 1984. Progestin receptors and the activation of female reproductive behavior: a critical review. Horm Behav 18:411–430.

Falkenstein E, Tillmann H-C, Christ M, Feuring M, Wehling M. 2000. Multiple actions of steroid hormones—a focus on rapid, nongenomic effects. Pharmacol Rev 52:513–556.

Fan L, Zhao Z, Orr PT, Chambers CH, Lewis MC, Frick KM. 2010. Estradiol-induced object memory consolidation in middle-aged female mice requires dorsal hippocampal extracellular signal-regulated kinase and phosphatidylinositol 3-kinase activation. J Neurosci 30:4390–4400.

Fanselow MS. 2010. From contextual fear to a dynamic view of memory systems. Trends Cogn Sci 14:7–15.

Fanselow MS, Dong H-W. 2010. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65:7–19.

Fanselow MS, Kim JJ. 1994. Acquisition of contextual Pavlovian fear conditioning is blocked by application of an NMDA receptor antagonist D,L-2-amino-5-phosphonovaleric acid to the basolateral amygdala. Behav Neurosci 108:210–212.

Feinberg G, Riccio DC. 1990. Changes in memory for stimulus attributes: implications for tests of morphine tolerance. Psychol Sci 1:265–267.

Fernandez SM, Lewis MC, Pechenino AS, Harburger LL, Orr PT, Gresack JE, Schafe GE, Frick KM. 2008. Estradiol-induced enhancement of object memory consolidation involves hippocampal extracellular signal-regulated kinase activation and membrane-bound estrogen receptors. J Neurosci 28:8660–8667.

Fortress AM, Fan L, Orr PT, Zhao Z, Frick KM. 2013. Estradiol-induced object recognition memory consolidation is dependent on activation of mTOR signaling in the dorsal hippocampus. Learn Mem 20: 147–155.

Frankland PW, Cestari V, Filipkowski RK, McDonald RJ, Silva AJ. 1998. The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. Behav Neurosci 112:863–874.

Frankland PW, Bontempi B, Talton LE, Kaczmarek L, Silva AJ. 2004. The involvement of the anterior cingulate cortex in remote contextual fear memory. Science 304:881–883.

Frankland PW, Frankland PW, Ding H-K, Takahashi E, Suzuki A, Kida S, Silva AJ. 2006. Stability of recent and remote contextual fear memory. Learn Mem 13:451–457.

Frye CA, Rhodes ME. 2002. Enhancing effects of estrogen on inhibitory avoidance performance may be in part independent of intracellular estrogen receptors in the hippocampus. Brain Res 956:285–293.

Frye CA, Duffy CK, Walf AA. 2007. Estrogens and progestins enhance spatial learning of intact and ovariectomized rats in the object placement task. Neurobiol Learn Mem 88:208–216.

Gassmann M, Bettler B. 2012. Regulation of neuronal $GABA_B$ receptor functions by subunit composition. Nat Rev Neurosci 13:380–394.

Gazzaley AH, Weiland NG, McEwen BS, Morrison JH. 1996. Differential regulation of NMDAR1 mRNA and protein by estradiol in the rat hippocampus. J Neurosci 16:6830–6838.

Ghosh S, Chattarji S. 2014. Neuronal encoding of the switch from specific to generalized fear. Nat Neurosci 18:112–120.

Gibbs RB. 2002. Basal forebrain cholinergic neurons are necessary for estrogen to enhance acquisition of a delayed matching-to-position T-maze task. Horm Behav 42:245–257.

Gilman TL, DaMert JP, Meduri JD, Jasnow AM. 2015. Grin1 deletion in CRF neurons sex-dependently enhances fear, sociability, and social stress responsivity. Psychoneuroendocrinology 58:33–45.

Gisquet-Verrier P, Alexinsky T. 1986. Does contextual change determine long-term forgetting? Anim Learn Behav 14:349–358.

Goshen I, Brodsky M, Prakash R, Wallace J, Gradinaru V, Ramakrishnan C, Deisseroth K. 2011. Dynamics of retrieval strategies for remote memories. Cell 147:678–689.

Graham BM, Daher M. 2015. Estradiol and progesterone have opposing roles in the regulation of fear extinction in female rats. Neuropsychopharmacology 4:774–780.

Gresack JE, Frick KM. 2006. Posttraining estrogen enhances spatial and object memory consolidation in female mice. Pharmacol Biochem Behav 84:112–119.

Han JH, Yiu AP, Cole CJ, Hsiang HL, Neve RL, Josselyn SA. 2008. Increasing CREB in the auditory thalamus enhances memory and generalization of auditory conditioned fear. Learn Mem 15: 443–453.

Hardt O, Nader K, Nadel L. 2013. Decay happens: the role of active forgetting in memory. Trends Cogn Sci 17:111–120.

Haubensak W, Kunwar PS, Cai H, Ciocchi S, Wall NR, Ponnusamy R, Biag J, Dong H-W, Deisseroth K, Callaway EM, Fanselow MS, Lüthi A, Anderson DJ. 2010. Genetic dissection of an amygdala microcircuit that gates conditioned fear. Nature 468:270–276.

Helmstetter FJ, Bellgowan PS. 1994. Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats. Behav Neurosci 108:1005–1009.

Jasnow A, Huhman K. 2001. Activation of GABA receptors in the amygdala blocks the acquisition and expression of conditioned defeat in Syrian hamsters. Brain Res 920:142–150.

Jasnow AM, Cullen PK, Riccio DC. 2012. Remembering another aspect of forgetting. Front Psychol 3:1–8.

Kim JJ, Fanselow MS. 1992. Modality-specific retrograde amnesia of fear. Science 256:675–677.

Kwon J-T, Choi J-S. 2009. Cornering the fear engram: long-term synaptic changes in the lateral nucleus of the amygdala after fear conditioning. J Neurosci 29:9700–9703.

LeDoux J. 2000. Emotion circuits in the brain. Annu Rev Neurosci 23: 155–184.

Lehmann H, Lacanilao S, Sutherland RJ. 2007. Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. Eur J Neurosci 25:1278–1286.

Lewis MC, Kerr KM, Orr PT, Frick KM. 2008. Estradiol-induced enhancement of object memory consolidation involves NMDA receptors and protein kinase A in the dorsal hippocampus of female C57BL/6 mice. Behav Neurosci 122:716.

Likhtik E, Paz R. 2015. Amygdala-prefrontal interactions in (mal)adaptive learning. Trends Neurosci 38:158–166.

Lissek S. 2012. Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. Depress Anxiety 29:257–263.

Lissek S, Powers AS, McClure EB, Phelps EA, Woldehawariat G, Grillon C, Pine DS. 2005. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav Res Ther 43:1391–1424.

Lissek S, Biggs AL, Rabin SJ, Cornwell BR, Alvarez RP, Pine DS, Grillon C. 2008. Generalization of conditioned fear-potentiated startle in humans: experimental validation and clinical relevance. Behav Res Ther 46:678–687.

Lissek S, Rabin S, Heller RE, Lukenbaugh D, Geraci M, Pine DS, Grillon C. 2010. Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. Am J Psychiatry 167:47–55.

Lissek S, Bradford DE, Alvarez RP, Burton P, Espensen-Sturges T, Reynolds RC, Grillon C. 2014. Neural substrates of classically conditioned fear generalization in humans: a parametric fMRI study. Soc Cogn Affect Neurosci 9:1134–1142.

Loureiro M, Cholvin T, Lopez J, Merienne N, Latreche A, Cosquer B, Geiger K, Kelche C, Cassel J-C, Pereira de Vasconcelos A. 2012. The ventral midline thalamus (reuniens and rhomboid nuclei) contributes to the persistence of spatial memory in rats. J Neurosci 32:9947–9959.

Lynch IJ, Cullen PK, Jasnow AM, Riccio DC. 2013. Sex differences in the generalization of fear as a function of retention intervals. Learn Mem 20:628–632.

Lynch JF, Dejanovic D, Winiecki P, Mulvany J, Ortiz S, Riccio DC, Jasnow AM. 2014. Activation of ERβ modulates fear generalization through an effect on memory retrieval. Horm Behav 66:421–429.

Lynch JF 3rd, Winiecki P, Vanderhoof T, Riccio DC, Jasnow AM. 2016. Hippocampal cytosolic estrogen receptors regulate fear generalization in females. Neurobiol Learn Mem 130:83–92.

Maren S, Fanselow MS. 1996. The amygdala and fear conditioning: has the nut been cracked? Neuron 16:237–240.

Maren S, Holt W. 2004. Hippocampus and Pavlovian fear conditioning in rats: muscimol infusions into the ventral but not dorsal hippocampus impair the acquisition of conditional freezing to an auditory conditional stimulus. Behav Neurosci 118:97–110.

Maren S, Aharonov G, Stote DL, Fanselow MS. 1996. N-methyl-D-aspartate receptors in the basolateral amygdala are required for both acquisition and expression of conditional fear in rats. Behav Neurosci 110:1365–1374.

Maren S, Aharonov G, Fanselow MS. 1997. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res 88:261–274.

Matus-Amat P, Higgins EA, Barrientos RM, Rudy JW. 2004. The role of the dorsal hippocampus in the acquisition and retrieval of context memory representations. J Neurosci 24:2431–2439.

Mazzucchelli C, Vantaggiato C, Ciamei A, Fasano S, Pakhotin P, Krezel W, Welzl H, Wolfer DP, Pages G, Valverde O, Marowsky A, Porrazzo A, Orban PC, Maldonado R, Ehrengruber MU, Cestari V, Lipp HP, Chapman PF, Pouyssegur J, Brambilla R. 2002. Knockout of ERK1 MAP kinase enhances synaptic plasticity in the striatum and facilitates striatal-mediated learning and memory. Neuron 34:807–820.

McAllister WR, McAllister DE. 1963. Increase over time in the stimulus generalization of acquired fear. J Exp Psychol 65:576–582.

McDermott CM, Liu D, Ade C, Schrader LA. 2015. Estradiol replacement enhances fear memory formation, impairs extinction, and reduces COMT expression levels in the hippocampus of ovariectomized female mice. Neurobiol Learn Mem 118:167–177.

McGaugh JL. 2004. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 27:1–28.

McKenna NJ, O'Malley BW. 2002. Combinatorial control of gene expression by nuclear receptors and coregulators. Cell 108:465–474.

McLean CP, Asnaani A, Litz BT, Hofmann SG. 2011. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity, and burden of illness. J Psychiatr Res 45:1027–1035.

Metzger MM, Riccio DC. 2009. The forgetting of stimulus attributes in latent inhibition. Physiol Behav 96:194–198.

Milad MR, Igoe SA, Lebron-Milad K, Novales JE. 2009. Estrous cycle phase and gonadal hormones influence conditioned fear extinction. Neuroscience 164:887–895.

Mineka S, Zinbarg R. 2006. A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. Am Psychol 61:10–26.

Miserendino M, Sananes C, Melia K, Davis M. 1990. Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature 345:716–718.

Morey RA, Dunsmoor JE, Haswell CC, Brown VM, Vora A, Weiner J, Stjepanovic D, Wagner HR 3rd, Workgroup VAM-AM, LaBar KS. 2015. Fear learning circuitry is biased toward generalization of fear associations in posttraumatic stress disorder. Transl Psychiatry 5:e700.

Myers K, Davis M. 2006. Mechanisms of fear extinction. Mol Psychiatry 12:120–150.

Nadel L, Moscovitch M. 1997. Memory consolidation, retrograde amnesia, and the hippocampal complex. Curr Opin Neurobiol 7:217–227.

Nakashiba T, Young JZ, McHugh TJ, Buhl DL, Tonegawa S. 2008. Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. Science 319:1260–1264.

Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, McHugh TJ, Rodriguez Barrera V, Chittajallu R, Iwamoto KS, McBain CJ, Fanselow MS, Tonegawa S. 2012. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell 149:188–201.

Nofrey BS, Ben-Shahar OM, Brake WG. 2008. Estrogen abolishes latent inhibition in ovariectomized female rats. Brain Cogn 66:156–160.

Öhman A, Mineka S. 2001. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol Rev 108:483–522.

O'Malley BW, Means AR. 1974. Female steroid hormones and target cell nuclei: the effects of steroid hormones on target cell nuclei are of major importance in the induction of new cell functions. Science 183:610–620.

Onat S, Buchel C. 2015. The neuronal basis of fear generalization in humans. Nat Neurosci 18:1811–1818.

Packard MG. 1998. Posttraining estrogen and memory modulation. Horm Behav 34:126–139.

Packard MG, Teather LA. 1997. Posttraining estradiol injections enhance memory in ovariectomized rats: cholinergic blockade and synergism. Neurobiol Learn Mem 68:172–188.

Packard MG, Kohlmaier JR, Alexander GM. 1996. Posttraining intrahippocampal estradiol injections enhance spatial memory in male rats: interaction with cholinergic systems. Behav Neurosci 110:626–632.

Pavlov I. 1927. Conditioned reflexes: an investigation of the physiological processes of the cerebral cortex. London: Oxford University Press.

Perkins CC Jr, Weyant RG. 1958. The interval between training and test trials as a determiner of the slope of generalization gradients. J Comp Physiol Psychol 51:596–600.

Phelps EA, Delgado MR, Nearing KI, LeDoux JE. 2004. Extinction learning in humans. Neuron 43:897–905.

Phillips RG, LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106:274–285.

Poulos AM, Li V, Sterlace SS, Tokushige F, Ponnusamy R, Fanselow MS. 2009. Persistence of fear memory across time requires the basolateral amygdala complex. Proc Natl Acad Sci U S A 106:11737–11741.

Ressler K, Paschall G, Zhou X, Davis M. 2002. Regulation of synaptic plasticity genes during consolidation of fear conditioning. J Neurosci 22:7892–7902.

Rhodes ME, Frye CA. 2004. Estrogen has mnemonic-enhancing effects in the inhibitory avoidance task. Pharmacol Biochem Behav 78:551–558.

Riccio DC, Joynes RL. 2007. Forgetting of stimulus attributes: some implications for hippocampal models of memory. Learn Mem 14:430–432.

Riccio DC, Richardson R, Ebner DL. 1984. Memory retrieval deficits based on altered contextual cues: a paradox. Psychol Bull 96:152–165.

Riccio DC, Ackil J, Burch-Vernon A. 1992. Forgetting of stimulus attributes: methodological implications for assessing associative phenomena. Psychol Bull 112:433–445.

Riccio DC, Rabinowitz VC, Axelrod S. 1994. Memory: when less is more. Am Psychol 49:917–926.

Richardson R, Williams C, Riccio DC. 1984. Stimulus generalization of conditioned taste aversion in rats. Behav Neural Biol 41:41–53.

Rudy JW. 2005. Prefrontal cortex and the organization of recent and remote memories: an alternative view. Learn Mem 12:445–446.

Rudy JW. 2009. Context representations, context functions, and the parahippocampal-hippocampal system. Learn Mem 16:573–585.

Rudy JW, Huff NC, Matus-Amat P. 2004. Understanding contextual fear conditioning: insights from a two-process model. Neurosci Biobehav Rev 28:675–685.

Ruediger S, Vittori C, Bednarek E, Genoud C, Strata P, Sacchetti B, Caroni P. 2011. Learning-related feedforward inhibitory connectivity growth required for memory precision. Nature 473:514–518.

Samson R, Pare D. 2005. Activity-dependent synaptic plasticity in the central nucleus of the amygdala. J Neurosci 25:1847–1855.

Sandstrom NJ, Williams CL. 2004. Spatial memory retention is enhanced by acute and continuous estradiol replacement. Horm Behav 45:128–135.

Schafe G, Nader K, Blair H, LeDoux J. 2001. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. Trends Neurosci 24:540–546.

Schafe GE, Doyere V, LeDoux JE. 2005. Tracking the fear engram: the lateral amygdala is an essential locus of fear memory storage. J Neurosci 25:10010–10014.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21.

Shaban H, Humeau Y, Herry C, Cassasus G, Shigemoto R, Ciocchi S, Barbieri S, van der Putten H, Kaupmann K, Bettler B, Luthi A. 2006. Generalization of amygdala LTP and conditioned fear in the absence of presynaptic inhibition. Nat Neurosci 9:1028–1035.

Shepard RN. 1987. Toward a universial law of generalization for psychological science. Science 237:1317–1223.

Smejkalova T, Woolley CS. 2010. Estradiol acutely potentiates hippocampal excitatory synaptic transmission through a presynaptic mechanism. J Neurosci 30:16137–16148.

Squire LR, Alvarez P. 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 5:169–177.

Sun N, Cassell M. 1993. Intrinsic GABAergic neurons in the rat central extended amygdala. J Comp Neurol 330:381–404.

Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. 2004. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 24:4787–4795.

Teixeira CM, Pomedli SR, Maei HR, Kee N, Frankland PW. 2006. Involvement of the anterior cingulate cortex in the expression of remote spatial memory. J Neurosci 26:7555–7564.

Teyler TJ, DiScenna P. 1986. The hippocampal memory indexing theory. Behav Neurosci 100:147–154.

Teyler TJ, Rudy JW. 2007. The hippocampal indexing theory and episodic memory: updating the index. Hippocampus 17:1158–1169.

Thomas DA, Riccio DC. 1979. Forgetting of a CS attribute in a conditioned suppression paradigm. Anim Learn Behav 7:191–195.

Toufexis DJ, Myers KM, Bowser ME, Davis M. 2007. Estrogen disrupts the inhibition of fear in female rats, possibly through the antagonistic effects of estrogen receptor α (ERα) and ERβ. J Neurosci 27:9729–9735.

Vasudevan N, Pfaff DW. 2007. Membrane-initiated actions of estrogens in neuroendocrinology: emerging principles. Endocr Rev 28:1–19.

Vervliet B, Kindt M, Vansteenwegen D, Hermans D. 2010. Fear generalization in humans: impact of prior nonfearful experiences. Behav Res Ther 48:1078–1084.

Vetere G, Vetere G, Restivo L, Restivo L, Cole CJ, Cole CJ, Ross PJ, Ross PJ, Ammassari-Teule M, Ammassari-Teule M, Josselyn SA, Josselyn SA, Frankland PW, Frankland PW. 2011. Spine growth in the anterior cingulate cortex is necessary for the consolidation of contextual fear memory. Proc Natl Acad Sci U S A 108:8456–8460.

Vieira PA, Corches A, Lovelace JW, Westbrook KB, Mendoza M, Korzus E. 2015. Prefrontal NMDA receptors expressed in excitatory neurons control fear discrimination and fear extinction. Neurobiol Learn Mem 119:52–62.

Vigot R, Barbieri S, Bräuner-Osborne H, Turecek R, Shigemoto R, Zhang Y-P, Lujan R, Jacobson LH, Biermann B, Fritschy J-M. 2006. Differential compartmentalization and distinct functions of $GABA_B$ receptor variants. Neuron 50:589–601.

Walf AA, Rhodes ME, Frye CA. 2006. Ovarian steroids enhance object recognition in naturally cycling and ovariectomized, hormone-primed rats. Neurobiol Learn Mem 86:35–46.

Walf AA, Koonce CJ, Frye CA. 2008. Estradiol or diarylpropionitrile administration to wild-type but not estrogen receptor beta knockout mice enhances performance in the object recognition and object placement tasks. Neurobiol Learn Mem 89:513–521.

Walker D, Davis M. 2008. Amygdala infusions of an NR2B-selective or an NR2A-preferring NMDA receptor antagonist differentially influence fear conditioning and expression in the fear-potentiated startle test. Learn Mem 15:67–74.

Waters EM, Mitterling K, Spencer JL, Mazid S, McEwen BS, Milner TA. 2009. Estrogen receptor alpha and beta specific agonists regulate expression of synaptic proteins in rat hippocampus. Brain Res 1290:1–11.

Watson JB, Rayner R. 1920. Conditioned emotional reactions. J Exp Psychol 3:1–14.

Weiland NG. 1992. Estradiol selectively regulates agonist binding sites on the N-methyl-D-aspartate receptor complex in the CA1 region of the hippocampus. Endocrinology 131:662–668.

Weinberger NM. 2007. Associative representational plasticity in the auditory cortex: a synthesis of two disciplines. Learn Mem 14: 1–16.

Wilensky AE, Schafe GE, Kristensen MP, LeDoux JE. 2006. Rethinking the fear circuit: the central nucleus of the amygdala is required for the acquisition, consolidation, and expression of Pavlovian fear conditioning. J Neurosci 26:12387–12396.

Wiltgen BJ, Silva AJ. 2007. Memory for context becomes less specific with time. Learn Mem 14:313–317.

Wiltgen BJ, Zhou M, Cai Y, Balaji J, Karlsson MG, Parivash SN, Li W, Silva AJ. 2010. The hippocampus plays a selective role in the retrieval of detailed contextual memories. 20:1336–1344.

Winocur G, Moscovitch M, Sekeres M. 2007. Memory consolidation or transformation: context manipulation and hippocampal representations of memory. Nat Neurosci 10:555–557.

Winocur G, Frankland PW, Sekeres M, Fogel S, Moscovitch M. 2009. Changes in context-specificity during memory reconsolidation: selective effects of hippocampal lesions. Learn Mem 16:722–729.

Winocur G, Sekeres MJ, Binns MA, Moscovitch M. 2013. Hippocampal lesions produce both nongraded and temporally graded retrograde amnesia in the same rat. Hippocampus 23:330–341.

Xu W, Südhof TC. 2013. A neural circuit for memory specificity and generalization. Science 339:1290–1295.

Xu W, Morishita W, Buckmaster PS, Pang ZP, Malenka RC, Südhof TC. 2012. Distinct neuronal coding schemes in memory revealed by selective erasure of fast synchronous synaptic transmission. Neuron 73: 990–1001.

Yin HH, Knowlton BJ, Balleine BW. 2004. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur J Neurosci 19:181–189.

Yin HH, Knowlton BJ, Balleine BW. 2005. Blockade of NMDA receptors in the dorsomedial striatum prevents action-outcome learning in instrumental conditioning. Eur J Neurosci 22:505–512.

Zhao Z, Fan L, Frick KM. 2010. Epigenetic alterations regulate estradiol-induced enhancement of memory consolidation. Proc Natl Acad Sci U S A 107:5605–5610.

Zhou Y, Riccio D. 1994. Pretest cuing can alleviate the forgetting of contextual stimulus attributes. Learn Motiv 3:233–244.

Zhou Y, Riccio D. 1996. Manipulation of components of context: the context shift effect and forgetting of stimulus attributes. Learn Motiv 27:400–407.

Zola-Morgan SM, Squire LR. 1990. The primate hippocampal formation: evidence for a time-limited role in memory storage. Science 250: 288–290.