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Review article

The neurocircuitry of remote cued fear memory

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ABSTRACT

Memories of threatening, fear-evoking events can persist even over a lifetime. While fear memory is widely considered to be a highly persistent and durable form of memory, its circuits are not. This article reviews the dynamic temporal representation of remote fear memory in the brain, at the level of local circuits and distributed networks. Data from the study of Pavlovian cued fear conditioning suggests memory retrieval remains amygdala-dependent, even over protracted time scales, all the while interconnected cortical and subcortical circuits are newly recruited and progressively reorganized. A deeper understanding into how the neurocircuitry of cued fear memory reorganizes with the passage of time will advance our ongoing search for the elusive physical changes representing fear memories in the brain. Considering that persistent, pathological fear memories are a hallmark feature of post-traumatic stress disorder (PTSD), the behavioral and circuit-level study of remote cued fear memory retrieval adds a key element towards a systems understanding of PTSD.

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1. Introduction

Some of our most distant and indelible memories are perhaps our most precious. They guide adaptive decision-making, trigger complex emotion and shape our conscious experience (Kandel et al., 2014; Tulving, 1985). Despite the clear importance of very long-term (remote) memory in human cognition and behavior, the biological nature of remote memory remains unresolved. One type of memory well-known for its persistence is memory about traumatic events (i.e., "fear" memory). Fear memory is a unique form of memory; it can be formed nearly instantaneously (Fanselow, 1990) and remain intact for the lifetime of the organism (Gale et al., 2004). Remembering which environmental stimuli predict danger, and which do not, is a highly adaptive function of the central nervous system (Bolles, 1970; Mobbs et al., 2015). However, attenuated, excessive or inaccurate fear memories can be maladaptive and represent a core symptomatic dimension of fear regulatory disorders such as Post-Traumatic Stress Disorder (PTSD).

Pavlovian fear conditioning is a paradigmatic model for studying associative fear learning and memory in the brain (Bergstrom et al., 2011; Fanselow and LeDoux, 1999; Maren, 2001, 2008; Pare et al., 2004; Quirk et al., 1995). In Pavlovian cued fear conditioning, an initially non-threatening sensory stimulus, such as a tone or light, is rapidly transformed into a conditioned stimulus (CS) after being paired with an aversive stimulus (unconditioned stimulus; US) that naturally evokes a defensive response (unconditioned response). As a result of (often repeated) CS and US pairings, a stable associative fear memory about the CS is stored. Fear memory retrieval is tested by presenting the CS again, without the US, in a new environment. In an organism that has properly stored a CS/US associative memory, presentation of the CS can trigger a conditioned response (CR). One commonly measured defensive CR that has been interpreted as conscious "fear" in rodent models is freezing. Currently, there is a dialogue in the field concerning the most accurate term describing actions generated by defensive states (LeDoux, 2014). As a consensus has yet to be reached (Perusini and Fanselow, 2015), this article maintains usage of the term "fear."

Pavlovian fear conditioning is one of the leading translational behavioral platforms for studying PTSD (Briscione et al., 2014; Johnson, 2016; Johnson et al., 2012; Mahan and Ressler, 2012). PTSD is a mental disorder that can develop following exposure to a traumatic event and is characterized by feelings of fear or stress in conditions of safety. A key feature of PTSD is an intense and enduring memory for the trauma. Epidemiological data indicate that following a traumatic event, most people will experience a cluster of symptomology including avoidance, re-experiencing, mood and cognitive disruptions, and hyper-arousal (Kessler et al., 1995; Yehuda, 2004). For a majority of cases, these symptoms withdraw significantly over time. However, in a subset of individuals (estimated 7.8% lifetime prevalence in adult Americans) these problems persist (Kessler et al., 2005). A persistent cluster of PTSD symptomatology constitutes a criterion feature of the disorder that differentiates it from the acute form (acute stress disorder) (National Institute of Mental Health, 2016). This diagnostic criterion makes the preclinical study of fear memory over weeks, rather than hours, following learning an important endeavor in our understanding of PTSD.

The bulk of memory neuroscience research, and the study of Pavlovian fear conditioning processes in particular, has focused on the mechanistic aspects of acquisition, consolidation, retrieval and extinction soon after learning (24 h) (Kandel et al., 2014). Less emphasis has been placed on the study of fear memory retrieval at remote time scales following learning. This review summarizes data on the temporal dynamics of neuronal circuits that mediate discrete cued forms of Pavlovian fear conditioning over remote time frames. From a theoretical perspective, a more comprehensive account of fear memory circuit change over time will advance our continued search for the physical loci of fear memories in the brain (Do Monte et al., 2016; Josselyn, 2010). From a translational perspective, conditioned stimuli are known to elicit clinical symptomology of PTSD long after the traumatic event (National Institute of Mental Health, 2016), making the neurobiological study of remote cued fear memory retrieval clinically relevant. The pursuit of a neurobiological basis of remote fear memory retrieval may represent a critical step in advancing the eventual discovery of novel treatments for fear learning and memory pathology such as PTSD and other anxiety-related disorders.

The article begins by outlining the temporal boundaries of remote memory retrieval and includes a brief summary of the most influential models of hippocampal-based memory circuit reorganization over time, including the standard model of systems consolidation and the multiple trace theory. The second part of this article addresses the role of the amygdala in the retrieval of cued fear memory over time. The third section of the article summarizes data on the new recruitment and the progressive rearrangement of various neocortical and other fear circuit hubs, outside of the amygdala, in remote cued fear memory retrieval. The fourth section of this article discusses the relative integrity and performance of fear memory in the face of time-dependent circuit reorganization. The final section of this article closes with a call for more research into the mechanisms of cued fear memory retrieval at remote time points following learning.

1.1. Temporal parameters of memory retrieval

Acquiring or modifying an internal representation as a result of experience can be called *learning*. The term *memory* has been used to refer to the retention of an internal representation over time (Dudai, 2004a). Accessing a stored memory can be defined as *retrieval*. Memory that endures and can be retrieved after weeks to many years or even a lifetime following learning has been termed *remote memory* (Squire and Bayley, 2007). A time-dependent process in memory storage has long been recognized (McGaugh, 1966). The temporal dynamics of memory storage is most often studied in echoic (millisecond), working (minute) and long-term memory (indefinite) timescales (McGaugh, 1966). The biological time scales for classifying a "recent" memory is generally defined as within 24 h post-encoding. The reason for this time duration is presumably because 24 h represents one circadian rhythm (Gerstner and Yin, 2010). The longest associative fear memory retention interval in a rodent model, to the author's knowledge, is 16 months (Gale et al., 2004), which approaches the lifetime of the organism. In humans, fear memory has been experimentally expressed over 1 year following the original encoding event (Mueller and Pizzagalli, 2016). Memory circuit reorganization over time is likely a gradual and protracted process guided by a multitude of factors including sleep/wake rhythms (Dudai, 2012; Hardt et al., 2013; Walker and Stickgold, 2004) and memory reactivations (Alberini, 2005; Dudai and Eisenberg, 2004; Inda et al., 2011).

1.2. Models describing the time-dependent circuit reorganization of hippocampal-dependent memory

The dominant model in memory neuroscience suggests consolidation processes occur in two phases. The critical first phase of memory consolidation is fast and requires a series of molecular and cellular modifications at the level of the synapse (Kandel et al., 2014). This process is termed "synaptic consolidation" and is thought to occur over relatively short periods of time following training (from s to h) (Schafe et al., 2000). The second phase of memory consolidation is slower and is thought to involve a protracted process of large-scale circuit reorganization (Anagnostaras

et al., 1999; Bontempi et al., 1999; Dudai, 2004b; Frankland and Bontempi, 2005; Kim and Fanselow, 1992; Marr et al., 1991; Nadel and Moscovitch, 1997; Squire and Alvarez, 1995; Squire and Bayley, 2007; Wheeler et al., 2013; Wiltgen et al., 2004; Winocur et al., 2007). This "secondary" consolidation process might occur in time frames lasting several days, to several months and even years following the original encoding event (Squire and Bayley, 2007). There are two influential models describing how hippocampal-dependent memory circuits reorganize with time. Note the neuroscience models that account for how neural circuits supporting memory retrieval change with the passage of time are exclusively derived from the study of hippocampal-dependent memory. There are no models that account for the time-dependent reorganization of circuits mediating amygdala-dependent cued fear memory retrieval.

1.2.1. The standard model of systems consolidation

The most influential model describing hippocampal-dependent memory circuit reorganization over time is called the systems consolidation (or standard) model (SCM) (Frankland and Bontempi, 2005). As time passes for a memory destined for permanent storage, there is continued interplay between the hippocampus and relevant neocortical regions. Over time, a process of memory reorganization occurs, with the hippocampus gradually becoming less involved and neocortex more involved in the recovery of the original memory trace. At some undefined point in time, recovery of the original memory becomes hippocampal-independent and cortex-dependent. In the SCM, the original memory is thought to degrade in the hippocampus, suggesting a wholesale shift in neuronal representation, from hippocampal to cortical, over time. There are several lines of evidence derived from patient case studies, experimentation in primates, and rodent models supporting the SCM (Anagnostaras et al., 2001; Kim and Fanselow, 1992; Scoville and Milner, 1957; Varela et al., 2016; Zola-Morgan and Squire, 1990). The SCM can account for several important behavioral phenomenon including influential case studies of retrograde amnesia (e.g., Henry Molaison) following hippocampal ablation (Penfield and Milner, 1958; Scoville and Milner, 1957). Despite experimental support for the SCM, there are now multiple lines of evidence calling into question its basic tenet, namely that memory representations shift from hippocampal to cortical over time (Clark and Sutherland, 2013; Sutherland and Lehmann, 2011).

In more recent experimentation using contextual fear conditioning, no evidence for retrograde amnesia following hippocampal manipulation was demonstrated even when a variety of experimental parameters were manipulated, including memory strength (Broadbent and Clark, 2013; Lehmann et al., 2013; Sparks et al., 2013), lesion or inactivation size and location (Broadbent and Clark, 2013; Cullen et al., 2015; Goshen et al., 2011; Lehmann et al., 2007; Sutherland et al., 2008) and retention interval (Broadbent and Clark, 2013; Lehmann et al., 2013; Sparks et al., 2013). The application of optogenetic and chemogenetic technology has significantly advanced our understanding of memory processes (Goshen, 2014), including the role of the hippocampus in remote contextual fear memory retrieval. Optogenetic silencing of the dorsal CA1 subfield of the hippocampus during remote contextual fear memory retrieval (28-days) disrupted fear expression, suggesting even remote fear memories remains dorsal CA1-dependent over time (Goshen et al., 2011). This finding directly contradicts the SCM. A point of emphasis is the contribution of the hippocampus in remote contextual fear memory retrieval depended not only on the anatomical extent of the inactivation but also the time frame of inactivation. When inactivation of the CA1 was extended to more closely match the time course of inactivation that approximates pharmacological studies (30 min), remote fear memory retrieval was spared. This surprising finding suggests that with prolonged inactivation of the CA1, alternative structures are capable of supporting remote contextual fear memory retrieval. Inconsistencies in the empirical evidence for systems consolidation of hippocampal-cortical memory traces calls into question exactly how contextual fear memory circuits change as they age.

1.2.2. Multiple trace theory

Multiple trace theory (MTT) is an alternative to the SCM (Nadel and Moscovitch, 1997). At the core of the MTT, and what most strikingly differentiates the MTT from the SCM, is that the hippocampus is *always* needed for episodic memory recall. In the MTT, each time a memory is reactivated a new hippocampal trace is deployed that binds neocortical representations of the memory into a unified whole. This model represents a sharp departure from the SCM. In the MTT, the hippocampus is required for retrieving even remote forms of memory. Further, this model makes no references to a slow consolidation process whereby information is transferred from the hippocampus to the cortex over time. Instead, hippocampal-cortical circuitry continually interacts from the onset of memory formation, with different aspects of the memory stored in different parts of the circuit over time. As memory ages, it is likely to be associated with a greater number of new hippocampal traces (more memory storing ensembles) rendering it less susceptible to modification. Because a newer memory is associated with fewer ensembles, it is more susceptible to modification. According to the MTT, "systems consolidation" over time has less to do with time per se and more to do with memory reactivations and updating (presumably leading to more complex memory traces), that happen as a consequence of time passing. A common thread unifying the SCM and the MTT is that over time, circuit reorganization underlying the memory is obligatory.

2. The amygdala is a long-term storage site for auditory cued fear memory

Several decades of research have decisively linked amygdala function with the acquisition, storage and retrieval of auditory cued fear conditioning (Bergstrom et al., 2011, 2013b; Maren and Fanselow, 1996; Phillips and LeDoux, 1992). Despite this, a paucity of research has attempted to define the role of the amygdala and its intra- and inter-connected circuits in the permanence of cued fear memory retrieval. This is surprising considering: 1) auditory fear memory expression has been shown to be particularly persistent, even over protracted time scales (Gale et al., 2004), 2) trauma-associated stimuli are likely to comprise not only background, contextual elements but also foreground, sensory elements (Norrholm et al., 2014), and 3) the importance of amygdala circuitry and Pavlovian fear conditioning in the preclinical study of PTSD and other anxiety-related disorders (Johnson et al., 2012; Mahan and Ressler, 2012; Yehuda and LeDoux, 2007).

In one model of Pavlovian cued fear conditioning (LeDoux, 1998), information about the CS and US converges in the amygdala via thalamic and cortical inputs. It is thought that the convergence of CS/US input onto lateral amygdala (LA) neurons triggers Hebbian learning processes necessary for memory consolidation (Quirk et al., 1995). Output pathways from the LA, or indirectly from the basal amygdala (B), can modulate activity in the central nucleus of the amygdala (CeA). Additional GABAergic modulation of CeA circuits is derived from intercalated cell masses located in "islands" surrounding the LA and B. The CeA (medial division in particular) is generally considered the major output center for projections that control brainstem and hypothalamic systems necessary for the expression of conditioned defensive neurobehavioral responses, including freezing. Although this standard model overly simplifies the local micro- and long-range circuitry responsible for fear condi-

tioning (Bergstrom et al., 2013a; Duvarci and Pare, 2014; Herry and Johansen, 2014; Johnson et al., 2008), it places the amygdala at its root. Note there are alternative perspectives on the relative role and contribution of the amygdala and alternative areas in emotional memory consolidation (McGaugh, 2002; Weinberger, 2011).

An experimental approach for studying the dependence of the amygdala, or any other brain region, on memory retrieval over time is to lesion or inactivate it at either a recent (1-day) or remote (typically ~30-days) time point following the initial encoding (learning) event. The previously stored memory is then detected behaviorally by presenting the CS again in a novel context. In one of the only studies to date using lesioning methodology to directly test the reliance of fear memory expression on the integrity of the amygdala over time, the basolateral amygdala (BLA) was lesioned 7-days prior, 1-day, 7-days and 28-days following auditory cued Pavlovian fear conditioning (Maren et al., 1996). At each time point, the expression of cued and contextual fear memory was abolished. These data convincingly demonstrate the dependence of cued and contextual fear memory retrieval on amygdala function, even over a long retention interval (28-days). While remote memory is typically tested 30-days following learning in rodent models there have been studies that have examined the neuronal substrates of remote fear memory retrieval at even more remote time frames following acquisition. In one study, rats underwent fear conditioning with two distinct tone CSs in one of two distinct contextual environments 16 months apart (Gale et al., 2004). Then, the BLA was lesioned and rats were presented with the identical CS in an entirely novel context. Similar to prior results (Maren et al., 1996), BLA lesions significantly reduced both the cued and contextual fear response relative to a sham lesion control at 1-day and 16-months following conditioning. Again, these data demonstrate the importance of the amygdala in the behavioral expression of both auditory cued and contextual forms of fear memory at vast retention intervals spanning at least 16-months. A time-independent role for the amygdala in auditory fear conditioning represents a sharp departure from some hippocampal lesion data suggesting a time-limited or dispensable role for the hippocampus in remote contextual fear memory retrieval (Frankland and Bontempi, 2005).

Visualization of cellular plasticity underlying memory storage can be accomplished by imaging various plasticity-related proteins (e.g., ERK1/2, Arc/arg 1.3, PKMzeta) and immediate early genes (IEGs) (e.g., c-fos, zif268). In an imaging study of cellular plasticity using the protein coded by zif268, an increased density of zif268-postive neurons in the LA was found at both recent (1-day) and remote (28-days) time points following auditory cued fear memory retrieval (Kwon et al., 2012). These results are supported by another data set showing an elevation in the number of zif268-positive cells in the LA and CeA, but not B, following retrieval at a remote time point (30-days) following conditioning (Sacco and Sacchetti, 2010). Together, these data support previously discussed lesion data indicating a persistent role for the amygdala in the remote retrieval of a previously conditioned auditory fear memory. There is some evidence, however, that conflicts with the notion that the amygdala is always required for the retrieval of a conditioned fear memory over time. In an IEG mapping study using c-fos, BLA activity was reduced over 7-days (Do-Monte et al., 2015). This data suggests activity in the BLA is not required for the recovery of a 7-day old auditory cued fear memory. This disparate finding might be accounted for by anatomical differences in the expression of plasticity-related markers among the various subregions of the BLA complex (Bergstrom et al., 2013b) or may indicate an IEG expression profile with temporal dynamics on a finer time scale than previously appreciated (Antoine et al., 2014). Together, IEG mapping and lesion data mostly support a long-term, potentially permanent role for the BLA in auditory cued fear memory expression.

3. The status of the neocortex in cued fear memory performance over time

While the amygdala has clearly been established as a key circuit element in the generation of cued fear conditioning, a complete neurobiological understanding of fear memory represents a systems-level neuroscience problem. A more thorough understanding of which cortical circuits are recruited for long-term fear memory storage is a paramount endeavor considering most studies support an increasingly dependent role for neocortical circuitry on contextual fear memory retrieval over time (Frankland et al., 2004). One consistent finding unifying nearly all accounts of fear memory reorganization over time is that the cortex represents a key site for permanent storage. The conventional view in neuroscience is that the neocortex is gradually incorporated into the fear memory trace over time (Frankland et al., 2004). According to SCM, if memory is progressively transferred out of the hippocampus and into the cortex over time, lesions of the cortex at remote time points following learning should block fear memory expression while lesions at recent time points should spare fear memory retrieval.

Using this strategy, there are now a series of studies examining the role of the sensory cortices in both recent and remote cued fear memory retrieval. Sensory cortices are reciprocally connected with the amygdala (McDonald, 1998) and carry divergent information about the CS to the amygdala for associative fear memory consolidation (Bergstrom and Johnson, 2014; LeDoux, 2003; Weible et al., 2014; Weinberger, 2004). Therefore, the sensory cortices are in prime anatomical position to store sensory cued fear memory. Using an extensive series of highly localized excitotoxic lesions to various sensory cortices, Sacco and Sacchetti (2010) demonstrated temporally graded, sensory modality-dependent deficits in the retrieval of remote fear memory. Lesions of the auditory cortex (TE1 and TE2) disrupted remote, but spared recent, auditory cued fear memory retrieval. Likewise, lesions of the olfactory (Piriform) cortex and visual cortex (Oc2L) disrupted remote but not recent olfactory and visual cued fear memory, respectively. Expression of zif268 was found to be elevated in TE2 at remote, but not recent, time points. This finding has been supported by other data showing an increase in zif268 in TE2 after memory reactivation of a remote, but not recent, auditory cued fear conditioned memory (Kwon et al., 2012). These data were supported by microinjections of the protein kinase M zeta inhibitor (ZIP) into TE2, Piriform and Oc2L cortex at recent and remote time points following fear conditioning to auditory, olfactory and visual stimuli, respectively. ZIP injections produced sensory-modality-dependent amnesia at remote but not recent time points (Sacco and Sacchetti, 2010). Intact fear memory consolidation after sensory cortex lesioning soon after learning supports classic lesion studies of the sensory cortices (LeDoux et al., 1989). Together, these experiments demonstrate that fear memory expression over time progressively relies on the sensory cortices, a finding predicted by the SCM. However, a systems-level framework in which the amygdala is always necessary for retrieval and the cortex is gradually incorporated with time might also be predicted by the MTT.

The emergence of synchronized oscillatory neuronal activity in the theta range between brain regions during fear memory retrieval is a physiological correlate of learning-induced functional integration (Fitzgerald et al., 2015; Seidenbecher et al., 2003). In a recent study (Cambiaghi et al., 2016), simultaneous local field potential (LFP) recordings were conducted in TE2 and BLA at recent (1-day) and remote (30-day) time points following auditory fear conditioning. Retrieval of the fear memory formed 30-, but not 1-day prior, evoked oscillatory activity in the theta range in both regions. Oscillatory activity was not present at the recent time point, suggesting interplay between TE2 and BLA only at the remote time point. These data were interpreted to suggest that emergent func-

tional connectivity between TE2 and BLA differentiates 1- from 30-day old auditory cued fear memory. When TE2 was inactivated using muscimol during presentation of the auditory CS at a remote time point, recall was impaired, suggesting the TE2 is required for remote retrieval. These data support the hypothesis that cortical networks are recruited and become necessary for cued fear memory retrieval at remote time points following learning.

Although the sensory cortices were found to be unnecessary for early cued fear memory retrieval, one particularly intriguing question is how early involvement of the cortex might contribute to the expression of fear memory at remote time frame. To test this question, area TE2 (auditory association cortex) was pharmacologically inactivated (tetrotoxin or muscimol) 1-day following auditory Pavlovian fear conditioning (Grosso et al., 2015). When cued fear memory retrieval was tested 7- and 30-days later, results showed that cued memory retrieval was reduced at 30-, but not 7-days, following learning, indicating early involvement of TE2 in auditory fear memory persistence over time. What makes this experiment particularly interesting is the suggestion that ongoing activity in the TE2 shortly after cued fear memory acquisition is required for remote memory retrieval. These data suggest an early involvement of the auditory cortex in remote, but not recent, fear memory storage (Grosso et al., 2015).

Data summarized thus far has indicated a dispensable role for the auditory cortex in the retrieval of a recently formed auditory cued fear memory. However, there are other lesion data challenging this view. Post-training lesions of the auditory cortex (TE1, TE2/TE3, and the perirhinal cortex) completely abolished auditory cued fear retrieval 24 h following conditioning (Boatman and Kim, 2006), suggesting the sensory cortical pathway is necessary for the retrieval of a recently formed auditory cued fear memory. These findings call into question the application of the SCM principles to auditory cued fear conditioning, and perhaps better fit within the principles of the MTT. A decisive role for the auditory cortex in both recent and remote auditory fear memory retrieval remains unresolved (Grosso et al., 2015; Weinberger, 2004).

More recently, the medial prefrontal cortex (mPFC) has emerged to play a key role in the expression of cued fear conditioning (Arruda-Carvalho and Clem, 2015; Courtin et al., 2013; Peters et al., 2009; Sotres-Bayon and Quirk, 2010). There are now several lines of evidence linking activity in the mPFC, in particular the prelimbic (PL) cortex, with the retrieval of auditory cued fear conditioning (Arruda-Carvalho and Clem, 2014; Burgos-Robles et al., 2009; Choi et al., 2010; Corcoran and Quirk, 2007; Do-Monte et al., 2015; Senn et al., 2014). Considering the involvement of the PL cortex in early fear memory expression, it seems likely that the PL cortex would remain involved in retrieval over time. Currently there are only sparse and conflicting findings establishing a firm role for the PL cortex in the retrieval of cued fear memory at remote time points. One study found an increase in c-fos in the PL cortex compared to controls following auditory cued retrieval of a 6-h, 24-h, and 7-day old fear memory (Do-Monte et al., 2015). However, in a study using a different marker of neuronal activity (zif268), there were no difference in the density of zif268-postive cells located in the PL between a recent (1-day) and remotely (15-day) cued auditory fear memory (Fitzgerald et al., 2015). This discrepancy in results may be related to a lack of a non-reactivated memory control group, differences in the type of activity marker used, or the temporal dynamics of remote cued fear memory circuit reorganization. Could the PL cortex have disengaged from the fear memory trace and its expression between 7 and 15 days following learning? No study has systematically tested either the temporal profile of activity or necessity of PL circuitry in cued fear memory retrieval over time frames longer than 15-days.

What other prefrontal cortical regions might be associated with the retrieval of a conditioned fear memory? Fitzgerald et al. (2015) established post-synaptic density 95 protein (PSD-95) to be critical for fear memory stabilization over time using a PSD-95 knockdown (KD) mouse. In the same study, IEG mapping (zif268) revealed a higher density of zif268-postive cells in the infralimbic (IL) cortex after the cued retrieval of a remote (15-days) compared to recently (1-day) formed fear memory. Subsequent PSD-95 knockdown (KD) localized to the IL led to a reduction in cued fear memory retrieval at the remote (15-days) time point only. The effect was specific to the IL, as PSD-95 KD in the ACC was insufficient to alter cued fear responsivity at either recent or remote time points. This finding is of interest because IL cortex has classically been associated with the extinction, rather than acquisition, of fear memory (Milad and Quirk, 2002). Another intriguing aspect of this study is that knockdown of PSD-95 in the IL occurred prior to the acquisition of the memory, suggesting the retrieval of a remote fear memory requires ongoing stabilization (via PSD-95) in the IL. The fact that the recent form of the memory was intact following retrieval suggests the molecular manipulation did not interrupt the first consolidation phase. These results establish PSD-95 as a critical molecular substrate and the IL causally implicated in the stabilization of cued fear memory at later time points (post–24 h) following learning. In addition, these findings also raise an important question as to the role of the anterior cingulate cortex (ACC) in remote cued fear memory retrieval. The ACC has consistently been associated with the retrieval of both spatial memory and contextual fear memory at remote time points (Cullen et al., 2015; Frankland et al., 2004; Restivo et al., 2009; Vetere et al., 2011). These data indicate a specific role for the ACC in remote, but not recent, hippocampal-dependent contextual fear memory. While PSD-95 KD in the ACC was insufficient to disrupt the retrieval of a recent or remotely cued auditory fear memory, the status of the ACC in amygdala-dependent cued retrieval memory retrieval over time remains an open question.

The retrospenial cortex (RSC) has also been implicated in the retrieval of remote contextual fear memory (Corcoran et al., 2016, 2011, 2013). To test the question of whether the RSC is also involved in remote auditory cued fear memory retrieval, both physical lesions (electrolytic and neurotoxic) and chemogenetic (DREADDs) inactivation of the RSC during retrieval were conducted 28-days following conditioning (Todd et al., 2016). All manipulations resulted in a reduction in freezing to the CS, indicating a new role for the RSC in remote auditory cued fear memory retrieval. In line with previous studies of the RSC and BLA, remote contextual fear memory expression was also diminished. A central question is when does the RSC become necessary for cued fear memory retrieval? The involvement of the RSC in consolidation of recently formed auditory cued fear memory retrieval has yet to be examined.

4. Subcortical neuronal circuits and remote cued fear memory retrieval

The core behavioral expression of cued fear conditioning is thought to remain relatively stable, even over vast time frames (Gale et al., 2004). Somewhat paradoxically, evidence suggests a remarkable amount of plasticity in fear memory circuitry days after stimulus exposure. IEG (c-*fos*) mapping revealed activation in the paraventricular nucleus of the thalamus (PVT) at later (24 h – 7-days) but not early (6 h) time points following auditory fear conditioning. When PL projections to the PVT were optogenetically silenced (eNpHR-eYFP), retrieval was impaired at later time points only. Conversely, optogenetic inhibition of PL projections to the BLA impaired retrieval at 6 h but not 7-days after fear conditioning. These experiments suggest that fear memory retrieval requires PL – BLA at very early (6 h) time points but shifts to PL – PVT at later (24 h and 7-days) following conditioning. Silencing PVT projections to

CeA also impaired late but not early fear memory expression. These studies bring new attention to the PVT as a critical fear memory circuit node that is gradually incorporated into the cortico-amygdala fear memory circuit with time. These findings support the viewpoint that auditory cued fear memory storage involves both circuit expansion and reorganization. The progressive reorganization of the fear memory trace over time may depend on a broader, more temporally dynamic memory circuit than previously thought. However, a 7-day retrieval post-encoding is not typically considered to be a remote time frame. Whether the incorporation of the PVT into the fear memory network persists, or continues to change, over longer periods of time (i.e., >30-days) is an outstanding question.

There is also evidence for elevated plasticity in the auditory thalamus at remote time points following auditory fear memory consolidation. Zif268 was enhanced in the auditory thalamus (MGN and the PIN) at remote (28-days), but not early (1-day), time frames following cued retrieval (Kwon et al., 2012). The auditory thalamus has traditionally been thought of as a discrete relay unit for the transfer of CS information to the amygdala for the generation of auditory cued fear memory. However, some data conflicts with this notion, indicating plasticity in the auditory thalamus (Ota et al., 2010; Weinberger, 2011) at recent time point following fear learning. Together, these data suggest a persisting form of plasticity in auditory thalamus may underlie both recent and remote cued fear memory retrieval.

5. Time and fear memory performance

If consolidation processes continue over time (Dudai, 2012), how stable is the performance of fear memory retrieval in the face of continued circuit plasticity? Cued fear learning and memory is somewhat unique in nature because over time the magnitude of the behavioral response remains remarkably stable (Gale et al., 2004; Poulos et al., 2009). This means that the level of emotional arousal evoked by remembering features of the traumatic event is, more or less, equivalent to that when it was first formed. Behavioral responses that precisely reflect previous learned contingencies about environmental threat are a useful adaptive feature of the nervous system. These types of memories serve as enduring emotional heuristics that function to align nervous system responsivity with a dangerous and ever-changing external environment. Evidence indicating that the original strength of the fear CR persists over time supports the view that at least the core structure of the memory remains relatively resistant to modification. Although the core integrity of the fear memory structure is thought to endure over time, there is evidence to suggest that some of its components are lost over time through processes that resemble forgetting (Bouton et al., 1999; Jasnow et al., 2012; Riccio et al., 1992; Tulving, 1974). There are several fundamental memory phenomena associated with the passage of time that resemble a form of forgetting with regards to the accuracy of fear memory retrieval: incubation and generalization.

5.1. Generalization

Generalization has been conceptualized as a loss of stimulus attributes associated with the original memory (Jasnow et al., 2012, 2016; Riccio et al., 1992; Zhou and Riccio, 1996). Generalization of memory is logical, evolutionarily-wise. Like emotional memory in general, generalization serves as a cognitive shortcut in decision-making. There is a significant advantage in rapidly reacting to threat with the cost of imperfection in responsivity. Within this framework, generalization is adaptive especially considering that environmental contingencies rarely stay the same, especially over time (Jasnow et al., 2016). However, over-generalization can be maladaptive and has been implicated in PTSD (Dunsmoor and Paz, 2015; Morey et al., 2015; Norrholm et al., 2014). If the amygdala remains actively engaged in auditory fear memory retrieval over time, an important question is how might this impact the precision of auditory fear memory performance? This question is of high theoretical value considering that contextual fear memory is well-known to generalize over time (Biedenkapp and Rudy, 2007; Cullen et al., 2015; Poulos et al., 2016; Wiltgen and Silva, 2007). Might cued fear memory retrieval also generalize over remote time frames? Cued fear stimulus generalization over time could be conceptualized as a transformation of the memory into a more generic form, which would support the MTT.

There is some neurobiological work examining the generalization of auditory CSs at recent time points following conditioning. A broad fear memory network has been linked with the expression of auditory cued fear memory generalization at recent time points following learning, including the prefrontal cortex (Vieira et al., 2015), bed nucleus of the stria terminalus (BNST) (Duvarci et al., 2009), medial geniculate nucleus (MGN) and posterior intralaminar nucleus (PIN) (Han et al., 2008), dorsal hippocampus (Quinn et al., 2009), central amygdala (Ciocchi et al., 2010) and lateral amygdala (Ghosh and Chattarji, 2015). One interesting finding is that lesions of the auditory cortex fail to affect auditory cued fear memory generalization (Armony et al., 1997), suggesting the amygdala and related circuits are capable of making fine-grain auditory stimulus discriminations without sensory cortical involvement. Overall, it appears that an overlapping fear memory circuit controls stimulus discrimination and generalization for auditory cues. There is very little data examining these same circuit elements at remote time points.

In one of the only studies to date examining the neurobiology of auditory cued fear memory generalization over time, targeted genetic disruption of GABAergic system in the dorsal hippocampus and BLA enhanced generalization at long-term (24 h) and remote (14-days), but not recent (30 min) time points following learning (Bergado-Acosta et al., 2008). These data support the viewpoint that a lack of GABAergic control over fear memory circuitry may result in generalized CS responses. A recent study using targeted, cell-type specific silencing of GABA-containing parvalbumin neurons in the BLA (DREADDs) increased the size of the cued fear memory trace as indexed by the proportion of Arc/Arg3.1-positive neurons following conditioning (Morrison et al., 2016). How the relative size of fear memory traces might relate to fear memory generalization and the passage of time is an interesting question for future research.

5.2. Incubation

Incubation describes how, under certain conditions, fear memory CRs increase with time. Time-dependent growth in CRs occur without reinforcement, are not related to non-associative mechanisms (sensitization), and have been demonstrated up to two months following learning (Houston et al., 1999; Pickens et al., 2009). Incubation of fear has also been linked with PTSD symptoms, especially delay-onset PTSD (Pickens et al., 2009). Incubation of cued fear conditioning has most often been demonstrated using stronger conditioning protocols (Pickens et al., 2013). When rats were presented with 100 CS/US pairing over 10-days and tested for memory expression at various intervals following conditioning (Pickens et al., 2009), CRs were elevated at 31- and 61-, but not 2- and 15-days, following conditioning, indicating an incubation of the CR at remote but not recent time points following learning. Although fear incubation has been consistently demonstrated using stronger cued fear conditioning protocols, it has also been demonstrated using cued fear conditioned paradigms of weaker stimulus strength (Houston et al., 1999), and contextual fear conditioning protocols (Poulos et al., 2016).

There has been only limited investigation into the neuronal mechanisms of fear incubation. Several neuronal circuits have been identified to contribute to the incubation of conditioned fear, including the medial nucleus of the thalamus (Tsuda et al., 2015) and BNST (Elharrar et al., 2013). Clearly more work is required to delineate the neuronal circuits of fear incubation. Tracking the time-dependent reorganization of neuronal circuits underlying the incubation of CRs is of substantial theoretical and clinical interest, especially considering the linkage with PTSD (Pickens et al., 2009).

6. Conclusions

A majority of the experimental work testing how fear memory retrieval is reorganized in the brain over time has derived from contextual, hippocampal-dependent forms of fear memory. Fewer studies have characterized the time-dependent circuit reorganization of cued, amygdala-dependent forms of fear memory. A review of the literature generally supports the viewpoint that the integrity of the amygdala is indispensable for the recovery of new and old fear memories. At the level of the cortex, interconnected circuitry that includes the prelimbic, infralimbic, retrospenial and sensory cortices are involved, or reorganized, or both with time. At the subcortical level, a relatively small region of the thalamus (PVT) is newly incorporated and becomes indispensable for the retrieval of the fear memory. It is widely acknowledged that a fear memory is one of the most durable forms of memory. Despite this, it is not known how circuit reorganization might impact the integrity of fear memory performance upon retrieval. The study of fundamental behavioral phenomenon such as generalization and incubation may reveal key insight into how time acts as an interacting variable in the precision of fear memory retrieval. A review of the literature has raised a pressing need for more data on the neurocircuitry of cued fear memory retrieval and the passage of time. Considering the viewpoint that PTSD is a highly persisting psychiatric disorder characterized by pathological fear memories, the study of remote cued fear memory retrieval may inform therapeutic strategies for combating PTSD and other anxiety-related disorders.

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