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Contributions of the rodent cingulate-retrosplenial cortical axis to associative learning and memory: A proposed circuit for persistent memory maintenance

Sydney Trask [a], Nicole C. Ferrara [b], Aaron M. Jasnow [c], Janine L. Kwapis [d,*]

[a] Department of Psychological Sciences, Purdue University, West Lafayette, IN, 47907, United States
[b] Department of Pharmacology, Rosalind Franklin University of Medicine and Science, North Chicago, IL, 60064, United States
[c] Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine, Columbia, SC, 29209, United States
[d] Department of Biology, Pennsylvania State University, University Park, PA, 16802, United States

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ABSTRACT

While the anterior cingulate (ACC) and retrosplenial (RSC) cortices have been extensively studied for their role in spatial navigation, less is known about how they contribute to associative learning and later memory recall. The limited work that has been conducted on this topic suggests that each of these cortical regions makes distinct, but similar contributions to associative learning and memory. Here, we review evidence from the rodent literature demonstrating that while ACC activity seems to be necessary at remote time points associated with imprecise or generalized memories, the role of the RSC seems to be uniform over time. Together, the lines of evidence reviewed here suggest that the ACC and RSC likely function together to support memory formation and maintenance following associative learning.

The abilities to encode, maintain, and recall memories are crucial cognitive processes that allow organisms to function in a changing world. Disruptions in memory processes have been linked to several neuropsychiatric disorders ranging from substance abuse disorders, anxiety, and trauma-related disorders, as well as normal cognitive decline associated with aging. Understanding the neurobiological mechanisms that contribute to both normal and dysfunctional memory processing is critical to both maintaining high cognitive function and developing treatments for multiple diseases that involve memory dysfunction (e.g., anxiety disorders, trauma-related disorders, dementia, Alzheimer's disease).

Memory processes can be studied in the laboratory using simple associative learning, in which an animal learns the relationship between two or more stimuli. Pavlovian, or classical, conditioning is one associative learning paradigm that has been particularly fruitful in uncovering the cellular and molecular mechanisms that underlie memory. In this type of conditioning, a neutral conditional stimulus (CS) is paired with a biologically relevant unconditional stimulus (UCS). Following pairings of the CS with the UCS, animals learn to respond to the CS alone (Pavlov, 1927; Rescorla, 1988). Pavlovian conditioning principles are similar across valence, with rodents showing the ability to learn that discrete or diffuse stimuli predict appetitive outcomes (e.g., food or drugs; Bouton and Peck, 1989; Cunningham, 1993; Keefer et al., 2020; Khoo et al., 2020) or aversive outcomes (e.g., shock; Bouton and Bolles, 1979; 1980). Importantly, Pavlovian conditioning is passively-acquired learning in which the experimenter has control over the timing of relevant events (e.g., CS and UCS presentations) making it an ideal model to study neural mechanisms that contribute to associative learning. The neural mechanisms underlying simple delay fear conditioning (DFC; in which the CS coterminates with the UCS) have been extensively studied in subcortical structures, such as the basolateral amygdala (BLA) (see Anglada-Figueroa and Quirk, 2005) and are accordingly extremely well-characterized. However, more complex forms of Pavlovian conditioning involve recruitment of additional structures. Notably, input from the cortex becomes necessary as the associative demands increase, yet far less is understood about how these cortical regions function to support this type of learning. The current review will focus on the contributions of two key cortical structures to complex associative learning in rodents: the anterior cingulate cortex (ACC) and the retrosplenial cortex (RSC), which lies directly posterior to the ACC. Together, these two regions represent a majority of the dorsal-most cortical space of the rodent and lie directly adjacent to both

* Corresponding author.
E-mail address: jlk855@psu.edu (J.L. Kwapis).

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cortical and subcortical regions that support learning and memory, including the hippocampal formation (HF) and the prelimbic cortex (Paxinos and Watson, 2007). As such, the cingulate-retrosplenial cortical axis is well-positioned to have a crucial integrative role in memory formation and maintenance, particularly as memory begins to rely less on subcortical structures for support.

Both the ACC and RSC have been implicated in expression of spatial memory. Damage to RSC impairs both acquisition and later recall of spatial information (Vann and Aggleton, 2002; 2004; 2005; Vann et al., 2003), likely due in part to the fact that the RSC shares dense reciprocal connections with the hippocampus, a region crucially important for acquisition and recall of spatial and environmental information (Wyss and van Groen, 1992). While at least one report suggests that the effects of ACC and RSC lesions might be due to inadvertent damage to other brain regions (Neave et al., 1994a, b), lidocaine-induced reversible inactivation of the ACC produces deficits on the Morris water maze of remotely acquired (1 month), but not recently-acquired (1 day), memory (Teixeira et al., 2006). Interestingly, while the ACC seems to have a time-dependent role in spatial memory in that it is critically important for remote, but not recent, memory (Maviel et al., 2004), altering RSC activity appears to have an immediate impact on memory (Corcoran et al., 2011).

The goal of the present review is to summarize work from the rodent literature demonstrating that the anterior cingulate and retrosplenial cortices are especially important for distinct aspects of associative learning. Along with their roles in spatial memory, both the ACC and RSC are well-positioned to contribute to associative learning and memory, with extensive connections to temporal lobe structures (such as the entorhinal cortex) and subcortical limbic structures (such as the hippocampus and amygdala). These cortical regions are therefore situated at a crucial intersection where information about the environment and the events within that environment can be integrated. Below, we review converging lines of evidence demonstrating that while both the ACC and RSC are important to learning and memory, the ACC seems to have a more limited role in precise memory, controlling either generalized or remote memories, while the contributions of the RSC seem to be invariable across time.

1. The role of the anterior cingulate cortex in learning and memory

The ACC has been linked to attention and uncertainty during learning and memory recall (Kim et al., 2016; see Weible, 2013, for a review), particularly for remote memory or as a result of complex or weak conditioning (Styolyarova et al., 2019). This has been studied using trace and delay fear conditioning (TFC and DFC, respectively) paradigms, where the CS typically coterminates with the UCS in DFC and the CS and UCS are briefly separated in time in TFC. During DFC, the ACC might be especially important in situations in which the meaning of the CS is unclear. One example of this is the ACC's role in weak, but not strong, DFC (Bissière et al., 2008). In this case, inactivation of the ACC induced by muscimol infusion impairs acquisition and subsequent fear expression to a CS the following day unless several CS-UCS trials were added. Similarly, damage to the ACC prior to training impairs the ability to acquire fear to a CS in a TFC procedure (Han et al., 2003). The same lesion has no effect on DFC where CS-UCS contingencies are clear. The authors attributed this dissociation to the increased attentional demands required for trace fear learning. For example, when a distractor stimulus was included during TFC, the authors observed impaired performance at a retention test the following day. However, the same distractor stimulus left delay and contextual fear memories intact. Because ACC activity was selectively heightened during trace fear (indicated by increased c-Fos expression) when compared to delay fear, this suggests a selective role for the ACC when attention is required to learn CS-UCS contingencies (Han et al., 2003). Together, this work highlights a role for ACC activity in the formation of memories that have an additional layer of complexity or when the contingencies are ambiguous. The ACC appears to be recruited in response to uncertainty, in response to weak conditioning, or when tasks require increased attentional demands, as is the case when the CS and UCS are temporally separated by a trace interval.

Often with behavioral procedures like DFC, TFC, and contextual fear conditioning (CFC), animals show selective fear responding to the context in which shocks were delivered compared to other contexts at recent time points. These context fear memories are unique, as a heightened fear response occurs over time; rodents typically show increased freezing to both trained and novel contexts at remote time points. Elevated fear responding outside of the conditioning context is indicative of generalization, and suggests that the conditioning memory is no longer precise (Onat and Büchel, 2015; see Jasnow et al., 2012, for a review). Remote fear expression and memory retention has been linked to a process in which memories are transferred to cortical regions from the hippocampus, resulting in a less precise or "gist-like" memory. The ACC has been largely tied to remote memory storage, in line with its role in uncertainty. The role of the ACC in remote memory was initially demonstrated when it was shown that inactivation (induced by lidocaine infusion) of the ACC had no impact on a recently acquired (i.e., one day or three days) memory, but blocked the recall of a remotely acquired (i.e., 18 or 36 days) memory (Frankland et al., 2004). A direct role for the ACC in remote fear generalization was established when it was demonstrated that reversible inactivation of the ACC improved context discrimination at remote timepoints (14 days), reducing fear to a novel context while leaving fear to the trained context intact (Cullen et al., 2015). While these results appear slightly contradictory in that Frankland et al. (2004) found an effect on memory recall via lidocaine infusion to the ACC and Cullen et al. (2015) did not, it is likely that differences in experimental procedure (including training, testing, and intracranial infusion parameters) contributed to this discrepancy. Additional and more precise experiments using chemogenetic inhibition of glutamatergic neurons within the ACC or their projections to the BLA also found a specific role for the ACC in fear to a novel context at a remote time point while leaving fear to the conditioning context unaltered (Ortiz et al., 2019). Importantly, all sets of experiments described here show a time-dependent role for the ACC.

The ACC shares connections with several cortical and subcortical structures, such as the prelimbic and insular cortices (Qadir et al., 2018), mutual connections with the thalamus (Domesick, 1969; Shibata, 1993; Shibata and Naito, 2005), as well as direct connections with the BLA (Bissière et al., 2008; Kita and Kitai, 1990; Ortiz et al., 2019), in line with its role in formation and retrieval of associative memory. While extensive work has shown the involvement of both the thalamus (Ferrara et al., 2017; Han et al., 2008) and the BLA (Helmstetter and Bellgowan, 1994; Vazdarjanova and McGaugh, 1999; see Ressler and Maren, 2019 for a review) in memory formation and retention, as well as a documented interaction between these two structures (Penzo et al., 2015; see Gründemann, 2021), some work is beginning to examine how the ACC interacts with these regions to promote memory. For example, Ortiz et al. (2019) investigated a role for the ACC in contextual fear generalization using a chemogenetic approach to inhibit glutamatergic neurons projecting from the ACC to the BLA (see also Bissière et al., 2008). They demonstrated that inhibiting these neurons attenuated the context generalization induced by either a strong conditioning protocol or the passage of time. This inhibition did not impact freezing to the conditioning context, demonstrating a specific role for the ACC-BLA pathway in fear generalization rather than fear more broadly.

Ongoing work has linked a role for the ACC to social memories. While a detailed analysis is outside the scope of the current review as we are unaware of any work examining the role of the retrosplenial cortex in social memory, ACC activity (Jeon et al., 2010) as well as the ACC-BLA pathway (Allsop et al., 2018) are essential for social fear memory formation, suggesting that social aspects of a memory may recruit ACC activity for memory formation at recent time points. Based on this, future work should examine the specificity of neural and

behavioral responses as a result of social learning over time to have a clearer understanding of the contribution of ACC activity to social memory processes.

2. The role of the retrosplenial cortex in learning and memory

Like the ACC, the retrosplenial cortex is heavily interconnected with brain regions important for learning and memory, including the hippocampus and the thalamus (Sripanidkulchai and Wyss, 1986; Wyss and van Groen, 1992) as well as both the auditory (Todd et al., 2016a) and visual (Vogt and Miller, 1983) cortices. The RSC seems to be especially important for more complex forms of associative learning, including contextual conditioning (Fournier et al., 2019a; Keene and Bucci, 2008; Sigwald et al., 2019; Yamawaki et al., 2019a), TFC (Kwapis et al., 2014, 2015), second order conditioning (Todd et al., 2016b), sensory pre-conditioning (Fournier et al., 2020; Robinson et al., 2014), inhibitory avoidance (Katche and Medina, 2015), and negative patterning (Fournier et al., 2019b). Interestingly, the RSC does not seem to be needed during DFC (Corcoran et al., 2011; Kwapis et al., 2015), in line with theories that suggest the RSC has an especially important role in binding together complex (rather than simple) related stimuli in the environment (de Landeta et al., 2020; Todd and Bucci, 2015).

Some work has begun to investigate the role of the retrosplenial cortex within a larger circuit that supports learning and memory. For example, Yamawaki et al. (2019b) demonstrated that functional connections between the CA1 region of the hippocampus and the RSC as well as between the RSC and the anterior thalamic nucleus regulate contextual fear memory. This work suggests that the RSC is a critical node in a circuit that supports complex memories (see also Yamawaki et al., 2019a; as well as Shepherd and Yamawaki, 2021, for a review).

The RSC can be subdivided into granular and dysgranular regions. While the dysgranular region shares reciprocal connections with regions like the entorhinal and perirhinal cortices, the granular region shares more with the hippocampal formation with most projections stemming from the CA1 and subiculum (Wyss and van Groen, 1992). However, these two subregions are heavily interconnected and communication between the granular and dysgranular regions (see van Groen and Michael Wyss, 1990; 2003) is needed for memory recall (Sigwald et al., 2019). Thus, the cytoarchitecture within RSC might make it especially well-suited for information integration between the hippocampus and cortex (Cowansage, 2018).

Integration of information to form a memory is essential during learning itself and during retrieval to elicit the learned response. Consistent with a role in integration, learning that requires integrating complex information before conditioning is RSC-dependent. For example, Fournier et al. (2020) used a sensory preconditioning procedure, in which two neutral stimuli were paired before one of them was later paired with a UCS. While controls learned to respond to the pre-conditioned cue, this effect was eliminated when electrolytic or neurotoxic lesions of the RSC preceded the preconditioning phase (see also Robinson et al., 2012). Further, activity in the RSC is important during both memory acquisition and memory retrieval. In line with this, Fournier et al. (2019a) demonstrated that both context fear acquisition and retrieval were impaired following damage to the RSC (see also Sigwald et al., 2020). The RSC is additionally needed for acquisition and retrieval of trace fear memory as well as trace fear extinction. Kwapis et al. (2015) demonstrated that infusions of the protein synthesis inhibitor anisomycin into the RSC immediately prior to conditioning reduced later recall of trace, but not delay, fear memory.

Additionally, the RSC spans a large portion of the brain and receives distinct inputs across the anterior-posterior axis. These RSC subregions have been separately targeted to gain a thorough understanding of *how* information is connected during learning for subsequent recall. When neural activity is selectively disrupted during the discrete CS-UCS period (including the trace interval) during trace fear acquisition, rather than the entire session, Trask et al. (2021) found selective effects during auditory and context fear memory. Here, optogenetic inhibition of the anterior portion of the RSC (aRSC) during the training trials of CS-UCS acquisition reduced later freezing to the CS, while the same inhibition of the posterior portion of the RSC (pRSC) reduced later freezing to the context, mirroring work that found a role for the anterior RSC in the "what" components of object recognition memory (de Landeta et al., 2020). This pattern of results is likely attributable to the findings that relative to the anterior region of the RSC, the pRSC shares more dense connections with regions like the hippocampus (Corcoran et al., 2016; Sugar et al., 2011; see Wyss and van Groen, 1992, for a review) and entorhinal cortex (Burwell and Amaral, 1998; Kononenko and Witter, 2012), which are important for spatial and contextual memory, whereas the aRSC seems to preferentially connect with the ACC (Sugar et al., 2011).

Follow-up experiments have demonstrated that optogenetic inhibition of either anterior or posterior regions in the RSC during CS retrieval reduces responding elicited by an auditory CS (Trask et al., submitted). This was the case when retrieval occurred 24 h or 6 weeks following conditioning. These results, along with those reported in Fournier et al. (2019a), suggest that (unlike the ACC) the contributions of the RSC seem largely invariable over time. This is in line with results reported by Cowansage et al. (2014) who found that reactivation of neurons originally active during conditioning increased fear responding at both recent and more remote time points. Together, these results suggest that while the anterior and posterior RSC encode distinct aspects of the memory, information binding during memory consolidation within the RSC makes both regions equally important for memory recall (Cowansage, 2018).

Recent work suggests a role for the RSC in promoting systems consolidation, the process by which a memory transfers from hippocampal dependence to hippocampal independence (Winocur and Moscovitch, 2011). de Sousa et al. (2019) demonstrated that stimulation of RSC "engram" neurons can seemingly drive the systems consolidation process. Here, they tagged the ensemble of RSC neurons active during context fear learning and demonstrated that optogenetic stimulation of these cells during either sleep or light anesthesia appeared to accelerate systems consolidation. Following RSC stimulation, the context fear memory showed two features characteristic of remote memory: it generalized to a novel context and engaged the ACC. Thus, this work indicates that the RSC may function, in part, to promote or control the transfer of information from the HF to the ACC during systems consolidation, ultimately producing generalized or "gist-like" memories (see Fig. 1).

3. Similar molecular mechanisms promote memory formation in the ACC and RSC

While there are subtle differences in the way in which ACC and RSC promote storage and maintenance of long-term associative memory, they appear to rely on largely overlapping molecular mechanisms. Although much work remains to fully characterize the molecular mechanisms that support memory in both regions, the work to date indicates that the ACC and RSC rely on many of the same molecular players as other memory-relevant structures, like the hippocampus and amygdala. The unique roles that the ACC and RSC play in complex and remote memory may therefore stem from their circuit-level connections, rather than changes at the molecular level. While the RSC seems to be connected with areas critical for spatial memory formation and retrieval, the ACC seems to be more preferentially connected to regions that promote memory formation of specific elements (Kita and Kitai, 1990; Ortiz et al., 2019; Shibata and Naito, 2005) irrespective of context. Below, we review the shared molecular mechanisms of memory formation and storage within both the ACC and RSC. Specifically, we examine the role of glutamatergic receptors, protein synthesis, and gene expression in both regions as they pertain to memory formation.

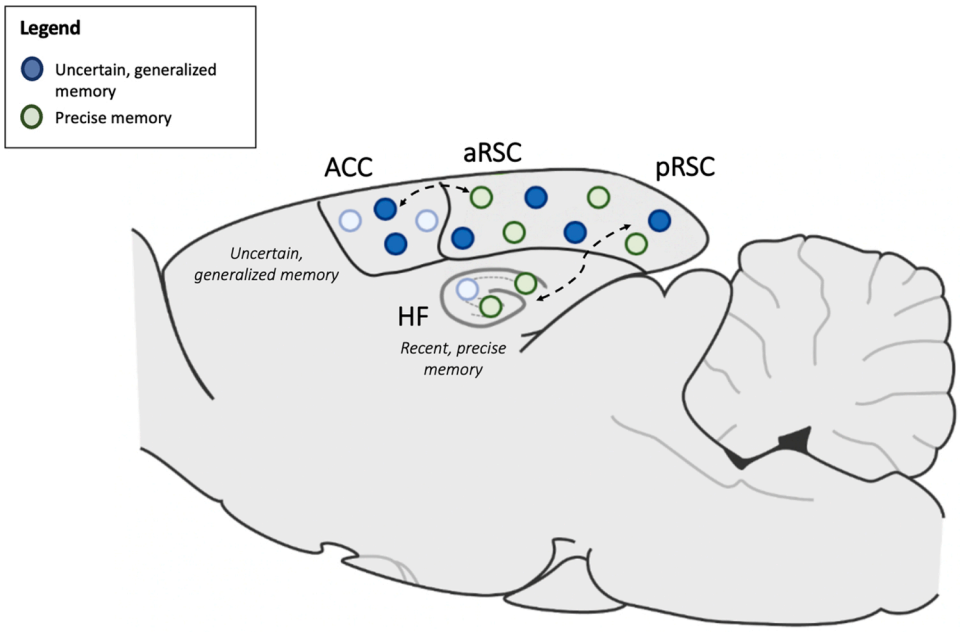

Fig. 1. Proposed circuit-level model of the types of memory supported by each subregion along the anterior cingulate-retrosplenial cortical axis. Precise fear memories tested at recent timepoints from conditioning often require RSC-HF synchronization. The requirement for HF activity to recall memories is transient and decreases over time, a phenomenon linked to systems consolidation. During this time, the memory becomes less precise and requires ACC activity. The RSC is optimally positioned to trigger the transition of hippocampal-dependent to ACC-dependent memories through its reciprocal connectivity and the ongoing requirement for RSC activity in complex forms of memory.

3.1. Glutamate receptors

Glutamate receptors are critically important to memory formation and long-term storage of the memory, as well as the processes through which memories can become labile at later retrieval sessions. Activation and trafficking of glutamatergic NMDA and AMPA receptors during conditioning are essential to memory acquisition, consolidation, and reconsolidation (Ferrara et al., 2019; Jarome et al., 2011; Johansen et al., 2011). The synaptic presence of glutamate receptors as well as glutamatergic receptor activation is thought to represent alterations in synaptic strength that ultimately contribute to the cellular basis of memory (LeDoux, 2014).

Activation of glutamate receptors within the ACC and RSC are some of the most well-characterized molecular processes underlying memory formation and retention. Surface expression of the GluN2B subunit is critical for memory formation in the hippocampus due to a change in its phosphorylation state and similarly is required for long-term potentiation (LTP) in the ACC and context fear memory formation (Einarsson and Nader, 2012; Plattner et al., 2014; Wang et al., 2009; Zhao et al., 2005). Inhibition of GluN2B activity prevents context fear memory retention, and this receptor activity is required during conditioning for context fear retention when tested one or three days later (Einarsson and Nader, 2012; Zhao et al., 2005), suggesting NMDARs mediate contextual fear memory in the ACC through potentiation of synapses. In the RSC, NMDAR activity is required for recent and remote context fear memory retention, but not in the ACC at remote time points, identifying an important distinction between the ACC and RSC for remote memory retrieval (Corcoran et al., 2011). Further, GluN2A-containing, but not GluN2b-containing NMDAR activity may drive the necessity for RSC NMDAR activity during memory recall (Corcoran et al., 2011). NMDA activity in the RSC is also essential for extinction learning, with context fear extinction requiring GluN2B subunit activity in the RSC (Corcoran et al., 2013). This suggests potentially divergent roles for NMDAR subunit activity in the RSC in different memory processes that are distinct from their roles in the ACC.

Further, antagonism of AMPARs in the ACC impairs remote but not recent fear memory retrieval and is involved in systems reconsolidation, a process by which additional brain regions are recruited to help maintain a memory after fear retrieval. Specifically, Einarsson et al. (2015) show that ACC AMPARs are essential for generalized fear expression and are critical for both systems consolidation and reconsolidation. In the ACC, AMPARs are upregulated following TFC (Toyoda et al., 2007). This upregulation is essential for TFC and can be inhibited with GluN2B receptor blockade, suggesting that NMDAR activity regulates changes in AMPAR state that are essential for memory formation (Descalzi et al., 2012). Together with previous data discussed, GluN2B-containing NMDA receptors may contribute to memory processes linked to generalization and synaptic potentiation (measured with AMPA receptor synaptic presence) to a greater extent than that seen in the RSC. While little is known about AMPA receptor trafficking and activity in the RSC, it is possible that there are different temporal profiles for AMPA trafficking and synaptic presence when compared to the ACC, such that earlier time points of potentiation may be evident to match the necessity for glutamate receptor activity for memory processes at recent and remote time points. Further, unlike the ACC, these processes may be more sensitive to changes in GluN2A-containing NMDA receptors, indicating a necessity for synaptic potentiation and plasticity in the RSC for precise memories at recent time points, as well as generalized memories at remote time points. These differences in NMDA sensitivity may be due to distinct inputs to the ACC and RSC promoting not only the time-dependent nature of these brain regions but the role of these regions in memory precision over time.

3.2. Protein synthesis

Memory consolidation is characterized by a transient window in which memories require *de novo* protein synthesis, and the formation of a memory can be disrupted with protein synthesis inhibition (or another amnesic agent) within this "consolidation window" (Abel and Lattal, 2001; Bourtchouladze et al., 1998; Desgranges et al., 2008; Kwapis et al., 2011). A similar process is engaged during memory reactivation, in which the presentation of new information makes the established memory temporarily labile and modifiable (García-DeLaTorre et al., 2009; Nader et al., 2000). This phenomenon has been termed reconsolidation and can be used to assess the necessity of brain regions for persistent memory storage, as sites sensitive to reconsolidation effects are thought to require retrieval-dependent plasticity. The general finding is that interrupting protein synthesis during memory consolidation or reconsolidation produces an amnesia-like effect, with experimental animals showing reduced memory relative to controls. Together,

an understanding of brain regions that require protein synthesis-dependent plasticity during consolidation and reconsolidation can indicate where memories are permanently stored and change over time, which is believed to be a critical factor driving the transition from precise to generalized memories.

Protein synthesis also seems to play an important role in memory processing along the ACC-RSC axis. Inhibiting protein synthesis (through anisomycin infusions) in the ACC immediately after training blocks expression of a recently acquired memory (Einarsson and Nader, 2012; Zhang et al., 2011). Similarly, protein synthesis inhibition in the ACC after retrieval impairs reconsolidation at both recent and remote time points, associated with precise and generalized memory respectively (Einarsson and Nader, 2012). Inhibiting protein synthesis in the RSC has a similar deleterious effect on memory, with anisomycin infusions into the RSC before training impairing expression of both recent trace and context fear memory (Katche et al., 2013b; Kwapis et al., 2015). Interestingly, protein synthesis inhibition given 12 h following inhibitory avoidance training impairs memory during a test at seven days but not two days later (Katche et al., 2013a) suggesting that peaks of protein synthesis many hours after acquisition may be uncoupled from recent memory retrieval and tied to more remote memory maintenance. Together with findings demonstrating that protein synthesis inhibitors in the RSC given before training impacts memory performance for a relatively recently-acquired (i.e., 24-hr) memory that is typically precise, this might suggest that ongoing protein synthesis in the RSC is necessary for the maintenance of long-term memories, such as generalized memories.

3.3. Immediate early gene expression

Certain immediate early genes (IEGs) have been associated not only with memory expression, but also play important roles in memory consolidation and reconsolidation. *Zif268* is a zinc finger protein believed to be essential for transcription. The IEG *Zif268* (or *Erg-1*) is critical for both the consolidation (Bozon et al., 2003a) and reconsolidation of memory (Bozon et al., 2003b; Lee et al., 2006). Further, the presence of *Zif268* has been suggested as a proxy measure for the engagement of reconsolidation-like memory updating (Lee, 2010; Lee et al., 2004). Blocking ZIF268 expression in the lateral amygdala disrupts consolidation (Maddox et al., 2011; Malkani et al., 2004) and reconsolidation (Maddox et al., 2011) of fear learning, demonstrating a necessity for this increase in activity during active memory processing.

Expression of certain IEGs within the ACC and RSC also seems to be important during associative memory formation and retrieval and can indicate the mechanisms by which memory is formed and stored in these cortical regions. For example, Frankland et al. (2004) demonstrated that increased *Zif268* expression within the ACC was observed following retrieval of a remote contextual fear memory (acquired one month prior to testing), but not a recent memory (acquired one day prior to testing), suggesting transcriptional activity is required during these time points. Similarly, *cFos* expression, commonly used as a marker of cellular activity, is elevated in the ACC following trace, but not delay, fear conditioning (Han et al., 2003), consistent with behavioral reports of impairments in trace, but not delay conditioning following ACC inactivation. *cFos* expression is also increased in the RSC following context fear acquisition and step-down inhibitory avoidance training (Katche and Medina, 2015; Robinson et al., 2012; Sigwald et al., 2019). Collectively, these results support the numerous behavioral results showing activity in the RSC and ACC is required for distinct aspects of memory during acquisition, consolidation, and recall.

Arc, a cytoskeletal protein essential for supporting glutamatergic receptor synaptic expression, is required for synaptic potentiation underlying memory formation (Chowdhury et al., 2006; Guzowski et al., 2000; Shepherd et al., 2006; Wall and Corrêa, 2018). Arc protein is upregulated in the ACC following inhibitory avoidance training (Zhang et al., 2011). Arc expression is also increased in the ACC when mice are exposed to a novel context one or fourteen days following CFC, and selectively increases to the training context at remote time points (Cullen et al., 2015). Similarly, following contextual fear acquisition, *Arc* gene expression is upregulated in the RSC (Robinson et al., 2012). Together, these results demonstrate that many of the same transcripts involved in hippocampal or amygdalar memory formation also support ACC- and RSC-dependent memory.

3.4. Epigenetic mechanisms

Epigenetic mechanisms change gene expression by modifying chromatin structure, rather than affecting the underlying DNA sequence. These dynamic changes can persistently alter the state of a cell, providing a potential mechanism that might contribute to the long-lasting cellular changes necessary for memory formation. The most prominent epigenetic mechanisms involved in memory include DNA methylation and histone modifications (e.g., acetylation, phosphorylation, methylation, etc.). Although there is relatively little research on the involvement of epigenetic processes within the RSC or ACC in associative memory, the evidence to date suggests that epigenetic mechanisms in these cortical regions may contribute to the persistence or long-term storage of remote memories.

One epigenetic mechanism known to play a key role in the cortex is DNA methylation, which is typically associated with gene repression. Research has shown that DNA methylation in the ACC may block the transcription of inhibitory genes, most notably calcineurin (Baumgärte and Mansury, 2012) at remote timepoints. Miller et al. (2010) observed increased methylation at the calcineurin promoter at remote time points (30 days) following CFC, a timepoint at which ACC activity is required for fear generalization. Blocking methylation with a DNA methyltransferase inhibitor (DNMTi) at remote time points blocks context fear memory (Miller et al., 2010), suggesting that methylation in the ACC is essential for remote memory retrieval. Although the authors demonstrated that DNMTi treatment reversed methylation at the calcineurin promoter and prevented the corresponding repression of calcineurin transcription, the use of a general pharmacological inhibitor of methylation likely impacted a number of genes beyond calcineurin. It is therefore difficult to attribute the observed impairment in memory solely to the lack of calcineurin methylation, although it is clear that methylation in the ACC is broadly necessary for remote memory retrieval.

Other studies have shown that epigenetic markers associated with transcriptional activation (trimethylation of histone 3, lysine 4 (H3K4me3) and DNA 5-hydroxymethylation (5-hmc)) are increased at plasticity-related genes in the ACC at remote timepoints. Specifically, both H3K4me3 and 5-hmc occupancy are increased in the coding region of *cFos* (but not *Npas4*) at remote timepoints after context fear conditioning (Webb et al., 2017). Whether other inhibitory genes are also epigenetically repressed in the ACC (or RSC) at remote timepoints is currently unclear. Similarly, it is unknown whether other epigenetic mechanisms, such as histone acetylation also play a role in remote memory storage in the ACC or RSC.

4. Conclusion

We have provided evidence demonstrating a necessity for both the RSC and ACC in memory formation with overlapping molecular mechanisms regulating memory in these regions. However, one major distinction is that the RSC shows a role in maintaining precise memories throughout time (e.g., Cowansage et al., 2014), while the ACC requires a degree of uncertainty or memory imprecision (Cullen et al., 2015; Ortiz et al., 2019). In line with its role in memory generalization, the ACC seems to be critically involved in systems consolidation, commonly studied with a generalized remote memory. At these remote time points, the requirement for the ACC seems to be independent of the hippocampus, a brain region traditionally not necessary for remote systems

consolidation. The RSC is optimally positioned to mediate this transfer of memory from hippocampus-dependence to ACC-dependence and in fact, the RSC has been linked to initiating systems consolidation (Cowansage, 2018; de Sousa et al., 2019).

Overall, the literature currently demonstrates a crucial role for both the anterior cingulate and retrosplenial cortices in associative memory acquisition, consolidation, and retrieval. Interestingly, while the molecular mechanisms that support memory seem to be similar between the two structures, the types of memory they support differs in subtle ways. While the RSC seems to have a broad, time-independent role in information binding of distinct aspects of associative memory, the ACC seems to be especially important for generalized memories, either by time or by strength of the memory. Further, it seems likely that the RSC facilitates the transition between hippocampal-dependent, precise memory to a less precise ACC-dependent memory.

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