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The Retrosplenial Cortical Role in Encoding Behaviorally Significant Cues

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The retrosplenial cortex (RSC) has recently begun to gain widespread interest because of its anatomical connectivity with other well-known memory structures, such as the hippocampus and anterior thalamus, and its role in spatial, contextual, and episodic memory. Although much of the current work on the RSC is focused on spatial cognition, there is also an extensive literature that shows that the RSC plays a critical role in a variety of conditioning tasks that have no obvious spatial component. Many of these studies suggest that the RSC is involved in identifying and encoding behaviorally significant cues, particularly those cues that predict reinforcement or the need for a behavioral response. Consistent with this idea, recent studies have shown that RSC neurons also encode cues in spatial navigation tasks. In this article, we review these findings and suggest that the encoding of cues is an important component of the RSC contribution to many forms of learning.

Keywords: retrosplenial, hippocampus, learning, context, navigation

The role of the retrosplenial cortex (RSC) has been a subject of study since the 1970s, but it has only recently begun to gain widespread interest from the neurobiology of learning and memory community. Much of the current interest arises from the observation that the RSC shares functional similarities and anatomical interconnections with the more well-studied hippocampus. The RSC is reciprocally interconnected with the hippocampal system via the subicular complex, anterior thalamus, and entorhinal cortex (for reviews, see Aggleton et al., 2010; Bucci & Robinson, 2014), and RSC lesions impair spatial navigation (Harker & Whishaw, 2002; Keene & Bucci, 2009; Sutherland, Whishaw, & Kolb, 1988; Vann & Aggleton, 2002), contextual memory (Keene & Bucci, 2008b; Kwapis, Jarome, Lee, & Helmstetter, 2015; Robinson, Poorman, Marder, & Bucci, 2012), and episodic memory (Bowers, Verfaellie, Valenstein, & Heilman, 1988; Valenstein et al., 1987). There is also a growing body of rodent neurophysiology and human functional MRI (fMRI) data on the RSC role in spatial navigation (Alexander & Nitz, 2015, 2017; Cho & Sharp, 2001; Maguire, 2001; Miller, Vedder, Law, & Smith, 2014), and the RSC plays a central role in the default mode network, which supports constructive memory processes (Hassabis, Kumaran, Vann, & Maguire, 2007; Schacter & Addis, 2007). Given current interest in the RSC role in navigation and memory, including current work in our laboratory, this literature will surely continue to grow. However, there is also an extensive but largely separate body of data indicating that the RSC plays a critical role in processing behaviorally significant cues, even in tasks that have no obvious spatial component. We believe these findings will be critical for understanding the underlying contribution of the RSC to a wide variety of learning and memory situations, including spatial and contextual memory. In this article, we review these findings and discuss new data on how this cue processing function might fit into a broader account of RSC functions.

Findings from Discriminative Avoidance and Approach Model Systems

Perhaps the most extensive and systematic research on the role of the RSC was done by Michael Gabriel and colleagues using an instrumental discriminative avoidance model system (for review, see Gabriel, 1993). In this task, subjects (rabbits) were placed in a large activity wheel and two different pure tone auditory stimuli (0.5 s) were delivered: one tone, the conditional stimulus (CS+), was followed 5 s later by a footshock, which could be avoided by taking a step in the wheel, whereas the other tone, the CS–, predicted no reinforcement. Using this model system, and a formally similar water-rewarded discriminative approach task, Gabriel and colleagues (Gabriel, 1993) performed numerous lesion and neuronal recording studies to identify the neural circuitry supporting this form of instrumental learning, which includes the anterior cingulate cortex, RSC, and their interconnected thalamic nuclei, the mediodorsal thalamus and anterior nuclear group, respectively. Unfortunately, much of this literature does not appear in search results because the phrase "posterior cingulate cortex" was used to describe the target area (Brodmann's Areas 29b, 29c, and 29d) rather than "retrosplenial cortex," which is more commonly used in the rodent literature.

These studies typically involved recording tone-evoked multiunit activity in control and lesion subjects throughout learning, including recordings during the naïve state prior to learning, during each of the daily training sessions and during asymptotic performance after the task has been well learned. With learning, multiunit activity in these regions begins to discriminate between the

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cues, with greater firing in response to the CS+ than the CS– (see Figure 1). These studies identified a highly plastic, rapid learning system that encoded the predictive value of the auditory tone cues during the earliest stages of learning, including the medial geniculate nucleus, basolateral amygdala, medial dorsal thalamus, and anterior cingulate cortex (Poremba & Gabriel, 1997a, 1997b). Multiunit activity in these regions began to preferentially encode the CS+ immediately at the outset of training, even before subjects exhibited significant behavioral evidence of learning. In contrast, preferential encoding of the CS+ generally developed more slowly in the RSC and the interconnected anterior thalamic nuclei and only appeared after many training trials (Gabriel & Orona, 1982). The temporal characteristics of this plasticity led Gabriel to characterize these as rapid and slow learning systems, centered on the anterior cingulate cortex and the RSC, respectively. The idea is that rapid plasticity in the anterior system could promote highly flexible fast learning, particularly in emergency conditions such as aversive learning, whereas the slower plasticity of the RSC system was specialized for encoding the reliable regularities of the environment, which only become apparent through repeated experiences. The effects of lesion studies were consistent with this idea: Damage to components of the rapid learning system impaired performance during the initial stages of learning but allowed subjects to eventually reach normal levels of asymptotic performance (Gabriel, Kubota, Sparenborg, Straube, & Vogt, 1991; Gabriel, Sparenborg, & Kubota, 1989). In contrast, lesions of the slow learning system had no effect on the initial acquisition of the avoidance response: Subjects learned normally, but performance dropped off after the subjects reached asymptote (Gabriel, Sparenborg, & Stolar, 1987). Interestingly, the RSC is probably not the final repository for the associative memory, because lesions of the anterior thalamic component of this circuit made after extensive overtraining do not impair behavior (Hart, Poremba, & Gabriel, 1997).

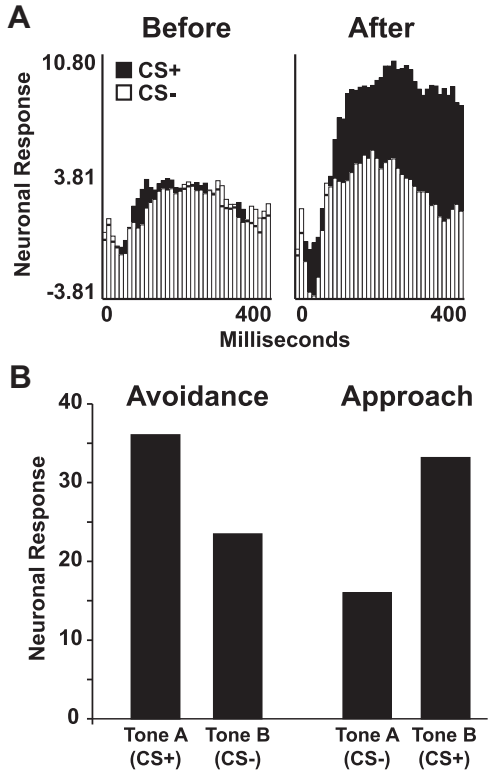

Figure 1. Neuronal responses to auditory cues during discriminative approach and avoidance learning. (A) Tone-evoked multiunit neuronal responses to the auditory cues are shown in the form of *z* scores normalized to pretone baseline, with 400 ms of firing data shown in 10-ms time bins (Smith et al., 2002). Before learning, RSC neurons respond equally to auditory cues of different tonal frequencies (left). After learning, neuronal firing in response to the predictive tone (CS+, black bars) is significantly greater than to the nonpredictive tone (CS–, white bars). (B) RSC neuronal responses are shown for subjects trained to perform the approach and avoidance tasks on alternating days (Freeman et al., 1996). Note that RSC neurons preferentially respond to the reinforcement-predictive auditory cue in both tasks, regardless of differences in tonal frequency, hedonic value (appetitive vs. aversive) and response requirements (approach or avoidance). RSC = retrosplenial cortex; CS = conditional stimulus.

Gabriel used the term "significance coding" to describe the fact that neurons within this region were highly sensitive to the behavioral relevance of the cues (Gabriel, Foster, Orona, Saltwick, & Stanton, 1980). That is, the neural responses did not encode the hedonic value of the cues, nor did they encode the reinforcing stimulus or the specific behavioral response that was required. Instead, the neurons seemed to be sensitive to the cues as predictors of reinforcement and the need for a behavioral response. For example, subjects could be trained to perform appetitive and aversive versions of the task on alternating days. In that situation, RSC neurons preferentially responded to a cue that predicted an impending footshock and the need for a locomotor response during the avoidance task, and on alternating days, they also preferentially responded to a cue that predicted water reward for licking a drinking spout (Figure 1B; Freeman, Cuppernell, Flannery, & Gabriel, 1996). RSC neurons also responded to other task events that had predictive value, such as the insertion of a drinking spout that signaled the opportunity to respond in the appetitive task (Smith, Freeman, Nicholson, & Gabriel, 2002).

Another component of the significance coding idea is that neural responses should amplify sensory cues that signal important outcomes, such as pain or danger. Consistent with this, RSC firing was sensitive to changes in the salience and probability of the tone cues. After training with a standard 500-ms tone cue, a change to either a shorter (200 ms) or longer (5,000 ms) tone induced a heightened response in the RSC (Sparenborg & Gabriel, 1990), an effect that was particularly prominent in the anterior cingulate cortex. Heightened responses also occurred during test sessions when the predictive tone was infrequent (20% of trials compared with 50% of trials during training; Stolar, Sparenborg, Donchin, & Gabriel, 1989). Thus, manipulations that altered the salience or probability of these cues evoked a heightened neural response. Overall, these findings clearly point to an RSC role in encoding cues on the basis of their predictive value. Less is known about the RSC role in behavioral response output. However, RSC neuronal firing has been shown to ramp up to the time when subjects initiate an avoidance or approach response, which may function as a "go" signal sent to the motor systems of the brain (Kubota, Wolske, Poremba, Kang, & Gabriel, 1996; Smith et al., 2002).

Findings From Other Learning Tasks

In the time since the Gabriel research program, an extensive body of work has accumulated on the RSC role in a variety of conditioning tasks. An exhaustive review of this work is beyond the scope of this article, but many of the findings have reinforced the idea that the RSC is critical for processing behaviorally significant cues. Overall, the data suggest that the RSC is not needed for simpler forms of learning, but it becomes engaged when the task becomes more complex and cue–outcome relationships become more difficult for subjects to discern. For example, the RSC and related thalamic structures do not appear to be necessary for Pavlovian eyeblink or fear conditioning when the CS and US overlap in time (i.e., delay conditioning; Gabriel et al., 1996; Kwapis et al., 2015), but the RSC is needed for the acquisition and extinction fear conditioning with a trace interval between the CS and US (i.e., trace conditioning; Kwapis et al., 2015). It has been proposed that trace conditioning relies on explicit memory whereas delay conditioning does not (Weike, Schupp, & Hamm, 2007), so this finding may suggest an RSC role in explicit memory for cue–outcome associations (Kwapis, Jarome, Lee, Gilmartin, & Helmstetter, 2014). However, one study has failed to find an RSC role in trace eyeblink conditioning (Weible, McEchron, & Disterhoft, 2000), and another has shown that the RSC is needed for the retrieval of a remote delay-conditioned fear memory (Todd, Mehlman, Keene, DeAngeli, & Bucci, 2016).

In trace-conditioning tasks, the trace interval creates added difficulty in discerning cue–outcome relationships. The RSC can also be engaged by tasks for which cue–outcome relationships are difficult to discern because of the presence of two or more potentially important cues. For example, the RSC is required for reversal of a dual cue discriminative eyeblink response, even without a trace interval (Berger, Weikart, Bassett, & Orr, 1986). RSC lesions also impair feature negative discrimination learning (Keene & Bucci, 2008a; Robinson, Keene, Iaccarino, Duan, & Bucci, 2011), in which subjects must learn that a given cue (e.g., a tone) predicts reinforcement when it is presented alone but that same cue predicts no reinforcement when presented along with a second cue (e.g., a light). Similarly, RSC lesions impaired the ability to respond appropriately to compound cues formed by combining elemental cues that individually require incongruent behavioral responses (Nelson, Hindley, Haddon, Vann, & Aggleton, 2014). The discriminative avoidance task described in the previous section also fits this general framework because it involves two cues that must be disambiguated. Consistent with this, RSC lesions impaired a visuospatial conditional discrimination involving two different cues, each requiring a different response (go-left or go-right; Bussey, Muir, Everitt, & Robbins, 1997).

Although the above findings highlight the RSC sensitivity to the relationship between cues and reinforcement or behavioral response requirements (i.e., cue–outcome and cue–response contingencies), another body of work has shown that the RSC is needed for the ability to spontaneously form associations among neutral stimuli. Specifically, lesions or DREADD inactivation of the RSC impair sensory preconditioning (Robinson, Adelman, Mogul, Ihle, & Davino, 2018; Robinson et al., 2014), in which subjects are initially exposed to repeated pairing of two neutral stimuli (e.g., a tone and a light) without any reinforcement. During the subsequent conditioning phase, one of the cues (e.g., the light) is paired with reinforcement. The subjects are then tested with the second cue (the tone, which was never paired with reinforcement): Responding to the tone indicates that subjects must have formed an association between the light and tone during the initial preconditioning phase. On the basis of these findings and the observation that the RSC is critical for contextual memory processes (Keene & Bucci, 2008b; Kwapis et al., 2015; Robinson et al., 2012), Bucci and colleagues proposed a theoretical account in which a key contribution of the RSC is to generate stimulus–stimulus associations between neutral stimuli, resulting in the formation and storage of a configural representation of the context (Bucci & Robinson, 2014; Todd & Bucci, 2015). The observation that contextual fear memory is prevented in subjects that do not have sufficient time to explore the context prior to delivery of the shock (the immediate shock deficit) is consistent with this idea (Todd, DeAngeli, Jiang, & Bucci, 2017), as is the apparent tendency for the RSC to become engaged when subjects must deal with multiple cues as described above. However, it is worth noting that much of the currently available data are agnostic as to whether the RSC generates coherent configural representations or simply encodes individual cues that are strongly associated with a particular context (Bar & Aminoff, 2003). Preliminary neurophysiological evidence from our laboratory suggests that RSC ensembles do encode contexts (Miller, Serrichio, Tse, Shi, & Smith, 2017), but careful manipulation of contextual variables will be needed to fully resolve this issue.

Recent Findings on the RSC Role in Processing Navigational Cues

Conditioning tasks involving explicit cues are not the only domain in which the RSC is involved. The RSC has also been implicated in processing navigational cues, and much of this literature has come from studies of human subjects (for review, see Miller et al., 2014). RSC lesions frequently cause impairments in spatial navigation and a striking feature of this deficit is the inability to use landmarks to construct routes to goal locations (Ino et al., 2007; Kim, Aminoff, Kastner, & Behrmann, 2015; Maguire, 2001; Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997). fMRI studies in healthy subjects show RSC involvement when subjects view visual scenes containing prominent landmarks (Morgan, Macevoy, Aguirre, & Epstein, 2011), especially when subjects were asked to make spatial judgments about the scenes (Epstein, Parker, & Feiler, 2007; Wolbers, Weiller, & Büchel, 2004). The RSC even appears to preferentially encode permanent features of the environment rather than temporary moveable objects, which would be less useful for navigation (Auger, Mullally, & Maguire, 2012; Auger, Zeidman, & Maguire, 2015). RSC lesions are known to impair navigation in rodents (Harker & Whishaw, 2002; Keene & Bucci, 2009; Sutherland et al., 1988; Vann & Aggleton, 2002), and as with humans, some observations suggest an RSC role in the use of navigational cues. For example, in some maze studies, rats with RSC lesions were only impaired when inconsistencies between intra- and extramaze cues were introduced to the task (Nelson, Powell, Holmes, Vann, & Aggleton, 2015; Pothuizen, Aggleton, & Vann, 2008; Vann & Aggleton, 2004). Others have found that RSC inactivation had little effect on radial maze performance until access to visual cues was removed by testing the rats in darkness (Cooper, Manka, & Mizumori, 2001;

Cooper & Mizumori, 1999). The RSC is known to contain head direction cells (Cho & Sharp, 2001), and a recent study found that some RSC neurons simultaneously exhibit two opposing directional preferences in an environment with two distinctive orienting cues, suggesting a unique RSC sensitivity to landmarks (Jacob et al., 2017).

Findings from our laboratory have also provided indirect support for the idea that RSC neurons encode navigational cues (Smith, Barredo, & Mizumori, 2012, Figure 2). We trained rats on a blocked alternation task, in which they approached one location for chocolate milk reward for the first half of each daily training session and then they switched to a different location for the second half. Rats learn this task, reaching an asymptote of approximately 84% correct in 6.7 sessions, on average. In solving this task, rats invariably employed a "win–stay" strategy: Even after reaching asymptotic performance, they repeatedly went to the first location as long as rewards continued to be dispensed there, and they only switched to the new location after failing to get a reward at the initial location (Figure 2A). Thus, in addition to being a reinforcing stimulus, the rats used the reward as an important navigational cue that instructs the rat to return to the same location on the next trial. Consistent with this idea, a large number of RSC neurons (~45%) selectively responded to either the east or west reward. These responses were not simply a response to the chocolate milk reward per se (because they were selective for one reward location or the other), nor were they purely spatial (large changes in firing rate occurred at the time of the reward even when the rat's position did not change). Instead, these responses were driven by the co-occurrence of the reward and the specific location where it was obtained. We have seen these responses throughout the rostro-caudal extent of the RSC granular b region, suggesting that this is a very large-scale signal involving many neurons. Remarkably, this phenomenon emerged on the very first day of training (Figure 2C) before the rats had shown clear behavioral evidence of learning (performance was not statistically different from chance performance). This suggests that encoding the reward location is a primary concern for the RSC at the outset of learning and the win–stay approach that rats took suggests that this was related to the fact that the reward location is potentially useful as a cue. However, this finding was serendipitous and our interpretation is hypothetical, as this task was not designed to test hypotheses about navigational cues and we could not isolate the dual roles of the reward as a navigational cue and a reinforcing stimulus.

In order to conclusively determine whether RSC neurons encode navigational cues, we developed a T maze task in which the reward location was explicitly cued by a flashing light, which served as a beacon that the rats learned to approach for a chocolate milk reward (Figure 3; Vedder, Miller, Harrison, & Smith, 2017). At the start of each trial, the rat was placed on the stem of the maze facing away from the choice point. As soon as the rat turned around to approach the choice point, the experimenter turned on one of the two flashing light cues to indicate the reward location for that trial (right or left). Right and left trials were randomly intermixed, and the light remained on until the rat arrived at the reward location and consumed the reward. We chose to use a beacon, rather than one or more landmarks, because the light has an unambiguous onset time and we could be confident that the rats would attend to this highly salient cue. Additionally, onset of the light cue occurred

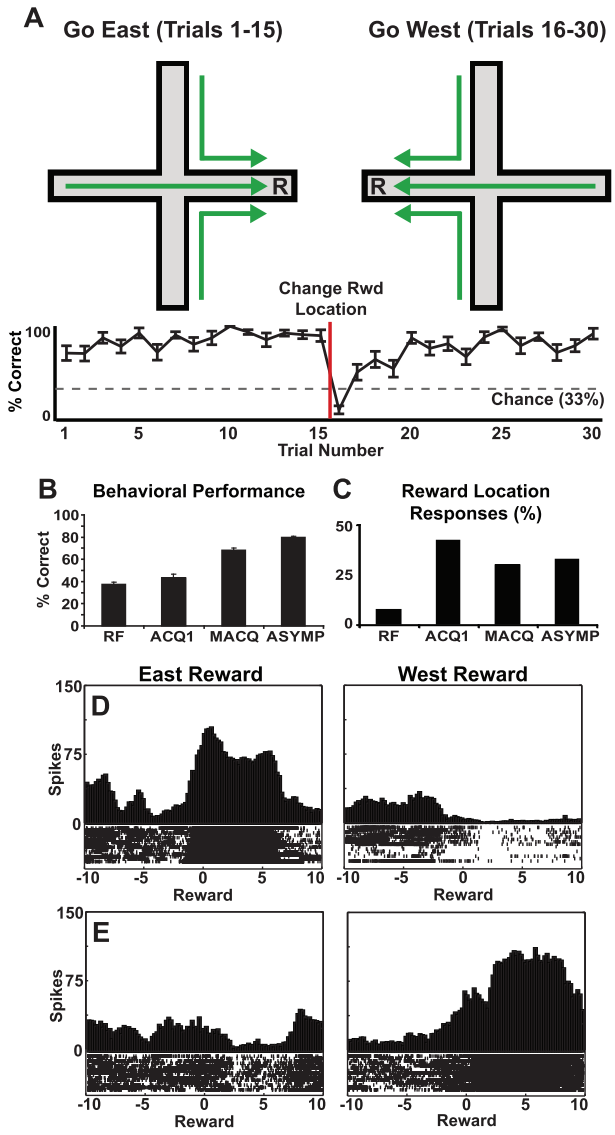

Figure 2. RSC responses during blocked alternation. (A) Rats were trained to approach the east arm for reward for the first 15 trials of each daily training session and the west arm for the next 15 trials. Each day, the rats were given a 30-s lights-out period after Trial 15 to indicate that the reward location was about to shift to the west arm. However, even in well-trained subjects (>80% correct overall), the rats never learned to use the lights-out cue to shift their responding. Instead, they invariably went to the old (east) reward location until no reward was found there, and only then did they shift to the west arm. (B) Average behavioral performance is shown for a baseline recording session prior to learning (pretraining foraging for randomly placed rewards, RF), the first training session (Day1), the session midway through acquisition (Mid), and during asymptotic performance (Asymp). (C) The percentage of RSC neurons that exhibited a significant response that was selective for both the receipt of the reward and the location (east or west) at each of the same training stages as in Plot B. (D–E) Two examples of RSC neurons that selectively responded to one reward location are shown in the form of peri-event time histograms showing 10 s of firing data before and after the receipt of the reward at Time 0, with trial-by-trial rasters below each histogram. The neuron in Plot D fired selectively for rewards received at on the east arm, whereas the neuron in Plot E fired on the west arm. RSC = retrosplenial cortex. See the online article for the color version of this figure.

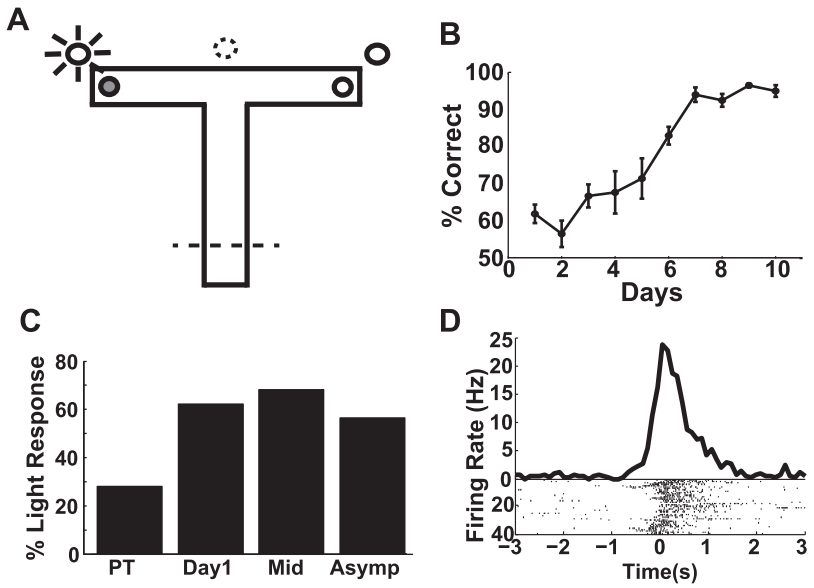

Figure 3. RSC responses during a cued T maze task. (A) Rats were trained to approach a flashing light cue positioned over the right or left reward location (left reward trial is illustrated). The rat was placed on the stem of the maze facing away from the choice point and the light was illuminated as soon as the rat turned around and took a step forward (dashed line). Before regular training sessions began, we recorded baseline responses to a light cue positioned at the choice point (dashed circle), which was illuminated during half of the trials in a random manner. This light was only used during this pretraining session and it did not predict the reward locations, which were also randomly selected. (B) Rats learned this task in 6.4 training sessions, on average, and reached an asymptote of 94% correct. (C) The percentage of RSC neurons that exhibited a significant response to the light cue are shown for each training stage (pretraining, PT, the first training session, the session mid-way to asymptote, Mid, and asymptotic performance, Asymp). (D) An example RSC neuron that responded to the onset of the light cue (Time 0) is shown in the form of a peri-event time histogram along with a raster display. RSC = retrosplenial cortex. Adapted from "Retrosplenial Cortical Neurons Encode Navigational Cues, Trajectories and Reward Locations During Goal Directed Navigation," by L. C. Vedder, A. M. P. Miller, M. B. Harrison, & D. M. Smith, 2017, *Cerebral Cortex, 27*, pp. 3716–3717. Copyright 2017 by Oxford University Press. Adapted with permission.

several seconds before the rat arrived at the reward so we could distinguish responses to the navigational cue and the reward.

Nearly 30% of RSC neurons responded to the light cue even before it had acquired any predictive value (i.e., during a pretraining session in which the light was randomly presented at the choice point on half the trials). This large initial response was likely because of the high salience of the flashing light cue. However, the percentage of light-responsive neurons more than doubled to 63% on the very first day of training and remained high for the rest of the training sessions (Figure 3C). Thus, the RSC emitted a massive response to the critical predictive cue at the very earliest stages of learning, similar to the reward location responses of the previous experiment. Interestingly, these neuronal responses did not distinguish between the left and right light positions but instead responded equally to both. This was unexpected given the RSC role in the discrimination tasks, and the reasons for this are not known. However, this may have occurred because the left and right lights were equally predictive of reinforcement and both required the same kind of locomotor approach response, unlike the cues in a discrimination task which predict different outcomes and require different behavioral responses. Nevertheless, these results clearly confirm that RSC neurons encode navigational cues, consistent with the findings of fMRI and lesion studies described at the beginning of this section.

Interestingly, we also found that RSC neurons exhibited the same kind of responses to the reward locations that we observed in the previous study (Figure 4B). However, unlike the previous study, these responses did not suddenly emerge on the first day of training. Instead, they gradually increased in prevalence throughout learning (Figure 4A). This difference is particularly striking because the stimuli that evoked the response (0.2 ml of chocolate milk delivered to a metal cup at the end of the maze arm) were the same in both experiments. This comparison suggests that whenever a particular stimulus can serve as a navigational cue, regardless of whether it is an explicit cue, such as the light, or a more abstract cue, such as the reward location in a win–stay task, it evokes a large and rapid response in the RSC. When the same stimuli are not useful as navigational cues, the RSC may still encode them but not as rapidly or robustly (Figure 4C).

Lastly, we found that individual RSC neurons frequently exhibited discrete responses to several different stimuli and task events. For example, the neuron illustrated in Figure 4D emitted a burst of spikes at the start of the trial, when the rat was placed on the stem of the maze, another burst after the cue light was illuminated, and

a third burst as the rat arrived at the reward location (with the last burst selective for the right reward location). We only used one explicit cue in this task (the light), but this tendency toward "multiresponsivity" was quite common, with approximately 67% of RSC neurons exhibiting at least two separately identifiable responses. This may suggest that RSC neurons would be predisposed to encode multiple cues, consistent with the RSC role in encoding contexts (Bucci & Robinson, 2014; Todd & Bucci, 2015). In the instrumental discrimination studies described above, RSC neurons responded to both the predictive and nonpredictive tones, and the discrimination resulted from the fact that firing was increased in response to the predictive tone (Figure 1A).

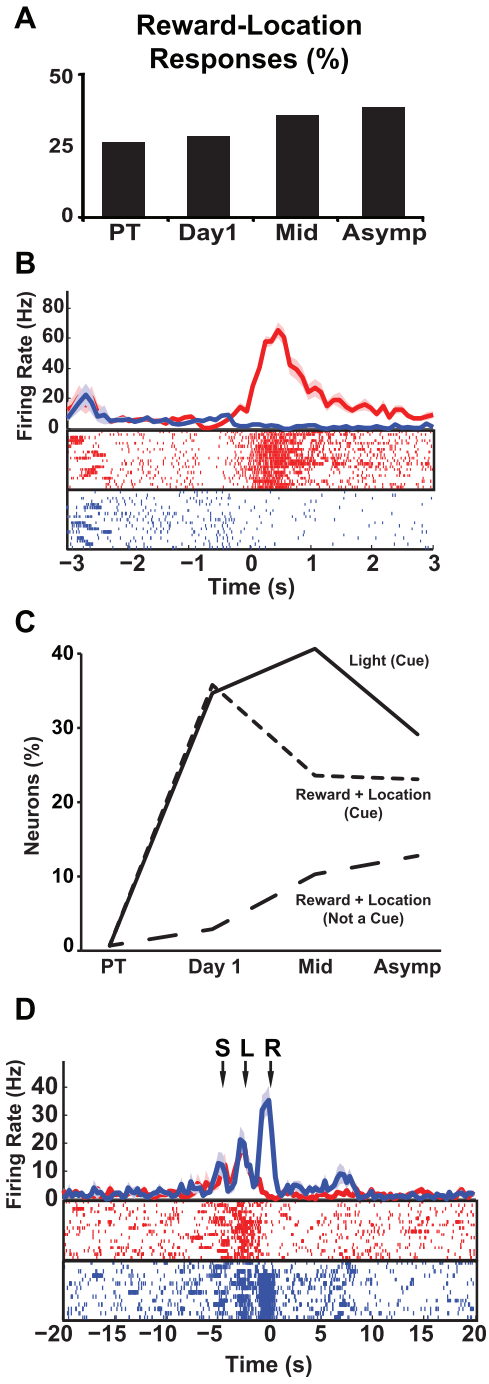

Figure 4. Other RSC responses from the cued T maze task. (A) The percentage of RSC neurons that exhibited a significant response that was selective for both the receipt of the reward and the location (left or right) is shown for each training stage (pretraining, PT, the first training session, the session mid-way to asymptote, Mid, and asymptotic performance, Asymp). Note that these responses did not emerge immediately on the first day of training. (B) An example neuron with a reward-location response is shown in the form of a peri-event time histogram with a raster display. Trials with the reward on the right are shown in blue (lower raster), whereas trials with the reward on the left are shown in red (upper raster). Left and right trials were randomly intermixed and they are only separated in the raster for illustration. (C) The percentage of RSC neurons that encode an explicit navigational cue, such as the light cue, increases dramatically on the first day of training (solid line). In the blocked alternation study, in which rats used a win-stay strategy (see Figure 2), the reward and its location may have served as an important navigational cue and similarly rapid encoding was seen (fine dashed line). In contrast, the reward location could not be used as a cue in the light cued T maze study because the current reward did not indicate the location for the upcoming reward which randomly switched from one trial to the next. Under these conditions, the responses did not show a sudden increase early in training (coarse dashed line). Data are expressed as the increase in the percentage of neurons at each stage of training relative to the pretraining baseline. (D) An example neuron that exhibited significant responses to three separate task events is shown in the form of a peri-event time histogram aligned to receipt of the reward (Time 0). Additional events are indicated by arrows (S = trial start, L = light onset and R = reward). RSC = retrosplenial cortex. See the online article for the color version of this figure. Adapted from "Retrosplenial Cortical Neurons Encode Navigational Cues, Trajectories and Reward Locations During Goal Directed Navigation" by L. C. Vedder, A. M. P. Miller, M. Harrison, & D. M. Smith, 2017, *Cerebral Cortex, 27*, pp. 3716, 3717. Copyright 2017 by Oxford University Press. Adapted with permission. See the online article for the color version of this figure.

Remaining Questions and Concluding Remarks

Together, the results reviewed here suggest that the RSC plays a particular role in encoding behaviorally significant cues. This role is apparent in spatial tasks in which the RSC may uniquely encode navigational cues such as landmarks and beacons, and in nonspatial conditioning tasks in which the RSC encodes important predictive cues and cues that may be important components of the context. The specific factors that make a given task critically dependent on the RSC are not fully understood, but the need to process multiple cues or complex contingencies is a common feature of RSC-dependent conditioning tasks, and the capacity to cope with multiple cues is also important for most spatial navigation and contextual memory tasks. This is notably reminiscent of discussions about the factors that lead to hippocampal involvement in various memory, navigation, and nonspatial conditioning tasks (e.g., Fanselow, 2000; McEchron & Disterhoft, 1999; Rudy & Sutherland, 1995). Nevertheless, the tendency of RSC neurons to produce large-scale responses to any task-relevant discrete cue is a remarkably consistent finding, suggesting that the encoding of cues reflects an important component of RSC function.

However, some important questions remain. Several findings suggest that the temporal characteristics of RSC involvement may be quite important, but they remain poorly understood. Findings from the discriminative avoidance model suggest that RSC involvement is limited to the late stages of learning, after subjects reach asymptotic performance, and preliminary data from our laboratory suggest a similar late-stage impairment in spatial alternation (Miller & Smith, 2012). Selective involvement in asymptotic performance is consistent with an RSC role in consolidation of long-term memories, as several findings have suggested (Cowansage et al., 2014; Czajkowski et al., 2014; Freeman & Gabriel, 1999; Katche et al., 2013). However, we have also seen that some RSC neural responses emerge at the very earliest stages of learning (e.g., Figure 3), suggesting a role in rapidly identifying and encoding important cues. Even in the discriminative avoidance model, in which overall RSC responses tended to develop slowly over the course of learning, some RSC cortical layers and their interconnected anterior thalamic nuclei exhibited rapidly developing plasticity (Gabriel & Orona, 1982). Similarly, mixed fast and slow responses were seen in our cued spatial tasks (Figure 4C). Another unresolved issue is that RSC responses appear to be driven by the predictive relationship with reinforcement and the need for a behavioral response in many tasks. However, sensory preconditioning studies convincingly demonstrate an RSC role in encoding neutral cues that have no reinforcement-predictive value at the time of encoding, and the RSC role in contextual memory, in which the association of contextual stimuli occurs spontaneously without the need for reinforcement, is well established.

These two apparent contradictions, rapid versus slow engagement and reinforcement-predictive versus neutral cue processing, may be related to each other. Rapid responses may be driven by reinforcement contingencies, whereas slow responses might reflect the accumulation and consolidation of reliable regularities in the environment that do not involve explicit reinforcement. If so, this suggests a dual role of the RSC that is reflective of the fact that the RSC is both an input structure that carries important sensory information to other limbic memory regions such as the hippocampus (Cooper & Mizumori, 2001) and a likely target for the consolidation of hippocampal-dependent memories (Cowansage et al., 2014; Czajkowski et al., 2014; Katche et al., 2013). Initially, the RSC may rapidly identify and encode cues that have clear reinforcement contingencies and pass this information to the hippocampus (Figure 5), in which such contingencies have been shown to influence hippocampal representations (Smith & Mizumori, 2006; Yeshenko, Guazzelli, & Mizumori, 2004). In contrast, the processing of neutral cues may reflect the slower accumulation and consolidation of neutral stimulus–stimulus associations such as those that define contexts. A comprehensive account of the RSC contribution to memory will need to account for these temporal characteristics as well as the factors that drive the encoding of various kinds of sensory cues.

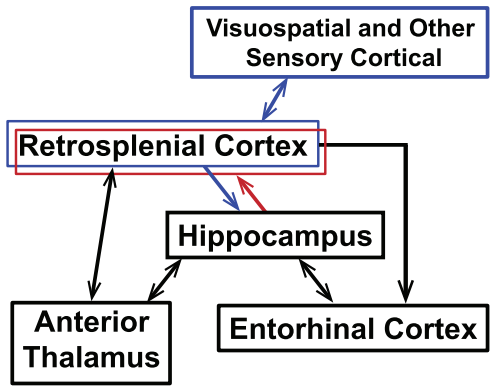

Figure 5. Theoretical model of RSC interactions with the hippocampus. Early in learning, visuospatial and other sensory information arrives at the RSC, where behaviorally significant cues are identified and encoded. Large-scale RSC responses to these predictive cues emerge rapidly (e.g., Figure 3) and may play an important role in establishing or orienting hippocampal representations (blue pathway). In contrast, RSC spatial and contextual representations, which do not rely on reinforcement contingencies, emerge slowly and may reflect consolidation of information from the hippocampus, where such representations are known to emerge rapidly (red pathway). These interactions could arise from relatively direct anatomical pathways via the subiculum or CA1 projections to the RSC (direct arrows) or through more indirect routes involving the anterior thalamus and entorhinal cortex. RSC = retrosplenial cortex. See the online article for the color version of this figure.

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