

Review

Rethinking retrosplenial cortex: Perspectives and predictions

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SUMMARY

The last decade has produced exciting new ideas about retrosplenial cortex (RSC) and its role in integrating diverse inputs. Here, we review the diversity in forms of spatial and directional tuning of RSC activity, temporal organization of RSC activity, and features of RSC interconnectivity with other brain structures. We find that RSC anatomy and dynamics are more consistent with roles in multiple sensorimotor and cognitive processes than with any isolated function. However, two more generalized categories of function may best characterize roles for RSC in complex cognitive processes: (1) shifting and relating perspectives for spatial cognition and (2) prediction and error correction for current sensory states with internal representations of the environment. Both functions likely take advantage of RSC's capacity to encode conjunctions among sensory, motor, and spatial mapping information streams. Together, these functions provide the scaffold for intelligent actions, such as navigation, perspective taking, interaction with others, and error detection.

INTRODUCTION

The retrosplenial cortex (RSC) in both primates and rodents fits the classic definition of an association cortex with more modern terminology referring to it as a “hub” based on a diverse and broad afferent and efferent connectivity.^{1–5} The past decade has seen a surge in experimental work examining neural dynamics associated with RSC, revealing robust tuning to a host of action, visual stimulus, and location and orientation variables.^{6–33} In parallel, blood-oxygen-level-dependent (BOLD) signals in human functional magnetic resonance imaging (fMRI) work have revealed modulation by distance, orientation, perspective, and strength of memory recall.^{34–48}

Although primarily characterized in this capacity, RSC function clearly extends beyond location and orientation related coding in the service of navigation. Numerous studies implicate the region in mnemonic processing, including both the encoding and retrieval of sequence-based or “episodic” memories. Temporal reorganization of RSC interactions with thalamus accompanies dissociative states in rodents and humans, further highlighting the fact that an understanding of RSC function demands an understanding of the temporal structure of its activity.⁴⁹ Finally, RSC is a component of the default mode network (DMN), a system of brain regions that exhibit activation during offline states wherein agents can engage in picturing, reciting, or predicting actions and outcomes in the real or hypothetical past, present, and future.⁵⁰ The apparent role of RSC in these

seemingly disparate operations indicates that a more unified and higher-level theory regarding a functional role for this region is needed. Thus, a central question raised in this review is how future research can utilize fresh perspectives on RSC function (e.g., predictive coding) to generate new theories, testable hypotheses, and experiments to understand the neural codes through which RSC supports an extensive list of behaviors?

This review necessarily reflects advancements along a number of lines of research and conceptualizations of RSC function. We recognize that these advancements are often difficult to connect to each other. In light of that, we begin with a consideration of RSC anatomy and then take on the current knowledge regarding spatial and temporal dynamics of RSC neurophysiology. These features of RSC structure and dynamics can be interpreted to imply a host of specific functions for RSC, all of which may have credibility. However, we propose that these specific functions can be grouped more generally as RSC functions non-exclusively related to (1) perspective taking, the ability to change mental viewpoints and reference frames and (2) stimulus prediction and error correction based on the integrated series of sensory stimuli, locations, orientations, and actions that together define contextual and episodic memories (Figure 1). We view these functions as complementary to each other, which together provide the spatial and temporal facets of interacting with and detecting changes in our environment. As a highly interconnected hub of the brain, we feel it is important to state that



Figure 1. Summary of the computations and functions of RSC

Those with stars (*) have limited experimental evidence, but we propose these based on the outcomes from the literature and describe in detail in the text. Topological mappings include routes, trajectories, and graph-based spatial knowledge. Prospective coding includes predicting the upcoming changes in perceptual input and comparing the current input to those predictions. The two broad computations provide testable hypotheses about reference frame translation and comparator models of RSC function. Ultimately, they both allow for intelligent actions, such as navigation and interacting with others, as well as detecting changes in the environment and errors in our expectations of those changes.

ascribing any function to RSC is best considered in the context of the network in which it participates.

RSC ANATOMY

RSC afferent/efferent circuitry in rodents

The RSC stands as a major hub for interconnectivity among multiple cortical and subcortical brain regions.¹ As discussed below, the specific character of such interconnectivity is undetermined such that it can either be considered a region serving to fully integrate all inputs or as a point of intersection between more specialized and semi-independent input/output circuitries of distinct neuron sub-populations (Figure 2). Afferent sources include the anterior thalamus (ATN), latero-dorsal thalamus (LD), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), posterior parietal cortex (PPC), primary (V1) and higher-order visual cortices, claustrum (CLA), septal nucleus, subiculum (SUB), pre-subiculum (PrS), post-subiculum (PoS), parasubiculum (PaS), and post-rhinal cortex (PoR).^{2–5,51–54} The list of brain regions receiving output from RSC is overlapping, similarly long, and includes AT, PrS, PoS, PaS, SUB, medial entorhinal cortex (MEC), PPC, ACC, V1, CLA, and secondary motor cortex (M2). Recognized anterior to posterior and granular versus dysgranular

divisions of the region are related to differences in their afferent sources and efferent targets, but divisions in proposed function based on these anatomical features are not the subject of the current review (see Vann et al.⁵⁵ for review). We note that all subregions of RSC are highly interconnected with each other.⁵⁶

RSC is clearly unique in the extent to which it is positioned to integrate sensory and motor systems with output from regions such as ATN and SUB that encode orientation and location in an environment. Yet, the forms by which a diverse set of afferents can be integrated are many and the precise nature of RSC input-output connectivity remains to be defined. In considering theories of RSC function, it is unclear whether this structure should be conceived as having a single, more generalized function versus multiple functions carried out by distinct circuits that share a common modulation by RSC neuron ensembles. The extremes of this contrast are schematized in Figure 2 where inputs to RSC range along two continua. In the “mixed” scheme, afferents from extrinsic sources target RSC neurons in random fashion to form an even distribution of their synaptic terminals among individual RSC neurons. At an opposite “discrete” connectivity extreme, the distributions of afferents from different sources to RSC neurons are highly specific and biased toward different projection-specific sub-populations of RSC neurons.

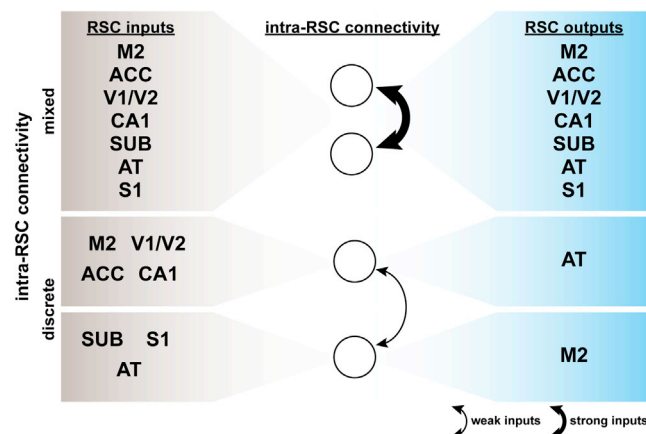


Figure 2. Theoretical extremes of RSC interconnectivity

RSC, as a whole, is home to a diverse and extensive set of afferents and efferents, yet the cellular-level structuring of these inputs and outputs remains to be determined. Here, two extremes of connectivity structure are considered. In the mixed configuration, RSC functions to fully integrate all afferent sources through convergence of afferents onto individual cells and through strong intra-RSC connectivity (bold black arrow). Here, a fixed relationship between specific RSC inputs and outputs is absent. Below, two hypothetical circuits reflect an alternative discrete anatomical configuration. In this scheme, RSC is composed of sets of heterogeneous semi-independent circuits wherein different, weakly interconnected sub-populations of its neurons are biased with respect to specific sets of inputs and outputs. In the mixed model, homogeneous connectivity distributions may maximize encoding of highly complex forms of context through conjunctive encoding or mixed selectivity of place, orientation, environmental structure, visual stimuli, and actions. Under the discrete model, heterogeneous, semi-independent circuits may allow RSC to play multiple specific roles in spatial cognition and memory that vary across time. These independent circuits may nevertheless share reliance on one or more specific forms of information such as head orientation.

Along a second continuum, we consider the extent to which intrinsic (RSC-RSC) afferents are distributed to different projection-specific sub-populations of RSC. Thus, at one extreme, one can envision RSC as operating under a mixed-selectivity model wherein the different forms of information reaching the region are fully integrated and overlapping across the network (Figure 2, top) and in which RSC-RSC interconnectivity is dense. This extreme emphasizes integration of many different forms of information across all projection-specific subtypes of RSC neurons. At the other extreme, RSC could well be composed of highly independent circuits defined by projection-specified sub-populations of RSC neurons differing extensively in the extent to which they gain inputs from different sources (Figure 2, bottom). At this extreme, RSC-RSC interconnectivity is less dense, yielding semi-independent circuitry that shares the space of RSC.

One way to determine the nature of RSC's role in integrating information is to consider the extent to which different projection sub-groups of RSC neurons (for example RSC to AT or RSC to M2) overlap in the density of inputs from different RSC afferent sources including other RSC neurons.⁵⁷ For example, RSC forms specific outputs to the M2 region that are direct, or mediated indirectly, by projections to the PPC or the anteromedial thalamus; these RSC neurons receive direct inputs from M2 itself.⁵⁸ For either extreme, the role of RSC as a hub for intersecting circuitry might be to modulate all circuits according to a single common signal such as head direction (HD), self-motion

(e.g., linear and angular velocities), or environmental location. Alternatively, the common signal shared by circuits intersecting in RSC could take the form of RSC populations conjunctively tuned to a large number of variables such as head orientation or location relative to environmental boundaries, proximity and orientation to walls, distance traveled, self-motion, and/or proximity to specific landmarks.⁵⁷

RSC circuitry in humans

In humans, much of the challenge with RSC circuitry lies in pinning down its precise location, which differs depending on its anatomical, histological, and functional definitions (Figure 3). Anatomically, the splenium of the corpus callosum makes up the anterior boundary and the parieto-occipital sulcus (POS) provides the posterior boundary (Figure 3A).^{55,59} There are no clear gross anatomical boundaries with precuneus, parahippocampal cortex (PHC), or posterior cingulate cortex,^{59,60} although the cingulate isthmus is typically included as part of RSC.⁶¹

Histological studies indicate that RSC is actually a relatively small sub-region of cingulate gyrus in the human, in contrast to the large cortical area it occupies in the rodent (Figure 3B). Granular RSC is located in Brodmann areas (BAs) 29a-c in anterior RSC (corresponding to ventral in the rodent), whereas dysgranular cortex is found in BA30 in the posterior (dorsal) region.^{55,59} Interestingly, histological studies also suggest that much of macaque and human RSC is buried into the sulcus of the corpus callosum and the ventral surface of the cingulate,^{59,65,66} making RSC less of a midline structure than it is often considered to be. When viewing oblique slices of the posterior cingulate gyrus, Morris and colleagues^{61,67} observed that no portion of macaque RSC and only the ventromedial portion of human RSC emerged from the callosal sulcus. Area 30v in the depths of the anterior calcarine sulcus and area 23 in the nearby posterior cingulate are sometimes included in definitions of greater RSC,^{59,67} whereas others disagree with this inclusion.⁵⁵ Unfortunately, cytoarchitecture cannot typically be resolved from standard-resolution MRI, therefore, mapping fMRI activation onto histology is difficult.

Employing functional definitions (Figure 3C) of RSC in human fMRI can circumvent many of these problems; however, this approach restricts interpretation to an a priori function and makes it difficult to identify the underlying anatomical areas. Functional definitions arising from sensitivity to scenes yield a broader “retrosplenial complex,”⁶⁸ which includes regions posterior to BA29 and BA30, instead including POS, lingual gyrus, and calcarine sulcus.^{39,69–73} Other functional and semi-anatomical names for this region include “medial parietal cortex,” “medial place area,” and “posterior medial (or posteromedial) cortex.”

There is little direct anatomical work on RSC connectivity in humans. Most of the circuitry work is taken from macaques; this has been reviewed in depth by Vann and colleagues and includes hippocampal regions, ATN, dorsolateral prefrontal cortex (dlPFC), posterior cingulate, and V4, many of which connect through the cingulum bundle.⁵⁵ As an alternative approach to determine circuitry of RSC, researchers often use functional connectivity—a method of determining correlated activity using fMRI—as a proxy for communication between brain regions (Figure 3D). RSC functional connectivity shows heterogeneity across the region, with the most posterior/lateral areas of RSC tending to have increased

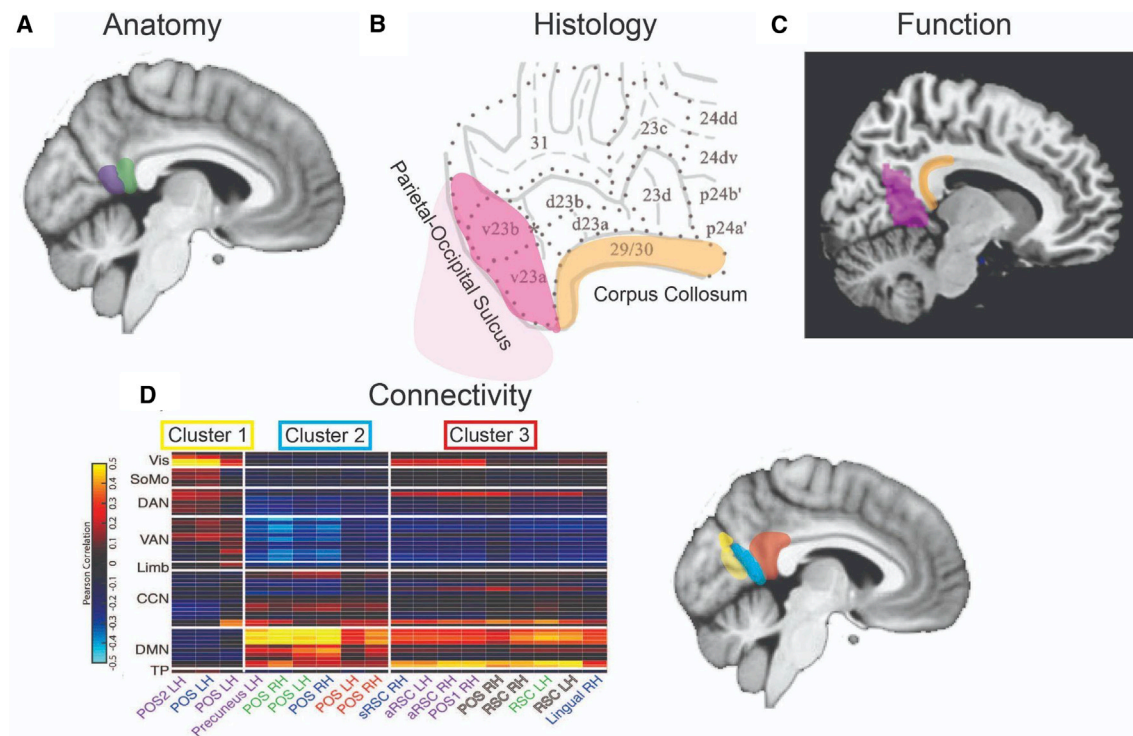


Figure 3. Differing ways to define the anatomy and connectivity of human RSC

(A) Anatomical definition of RSC based on locations of gyri and sulci. Shown in green is the cingulate isthmus, typically considered part of RSC. Shown in purple is the remainder of anatomical RSC, with the posterior border at the POS. Together these form the anatomically defined RSC. Note that these regions do not have a clearly defined cutoff on the superior border or anterior extent.

(B) Flat map of the histology of the posterior medial parietal cortex and posterior cingulate (modified from Vogt et al.⁶²). Retrosplenial cortex defined by BA 29/30 is highlighted in orange. Note that RSC is actually on the ventral surface of the cingulate cortex, in the callosal sulcus.

(C) The functionally defined retrosplenial complex from a recent study, based on scene-sensitive localizers, highlighted in magenta (modified from Peer et al. ⁶³). Comparing (B) and (C), there is very little overlap between the two regions. For illustration purposes, we have included the portion of the functional definition that is located in posterior cingulate into (B), although the functional region extends into the POS and the occipital lobe. We have also added the approximate location of the histological definition in (C). Comparing (A)–(C), there is overlap between the purple region of (A) and portions of (C), and some but not total overlap between the green region in (A) and the histological definition in (B).

(D) Differences in functional connectivity across the RSC region (modified from Chrastil et al.⁶⁴). Seed regions (listed along the bottom with left or right hemisphere, e.g., POS_L) were grouped into three clusters based on their resting state functional connectivity profiles with canonical networks. Approximate locations of the seeds are shown to the right, although there is some variability and overlap. Locations of seeds in cluster 1 were broadly located in the POS and into occipital lobe, those in cluster 2 were broadly located in the anterior bank of POS, and those in cluster 3 were broadly located in in parietal cortex around posterior cingulate and histological RSC. Vis, visual network; SoMo, sensory-motor network; DAN, dorsal attention network; VAN, ventral attention network; LIMB, limbic network; CCN, cognitive control network; DMN, default mode network; TP, temporal-parietal network; POS, parieto-occipital sulcus.

connectivity to occipital regions and vision networks. Anterior/medial areas display connectivity to posterior cingulate, medial prefrontal cortex, and other areas of the DMN (RSC is often considered part of the DMN, although its connectivity with the network is continuous with posterior cingulate). This differing connectivity with the RSC region also appears to be related to the cognitive functions associated with it, with anterior regions more related to episodic memory and posterior regions associated with spatial functions.^{62,64,72,74,75} High-resolution imaging of local hippocampal connections—including CA1/2/3/4 and dentate gyrus (DG) subfields—shows significant functional connectivity with DG/CA4, CA3/2, PrS/PA5, and uncus, but not CA1 or SUB.⁷⁶ Using diffusion imaging to identify the white matter tracts themselves, Li et al.⁷⁷ found that BA30 has strong connections to visual regions, hippocampus (HPC), and thalamus, whereas BA29 connects more to auditory regions, but both have strong connections with prefrontal cortex.

Although human fMRI cannot reach the cellular granularity of rodent studies, one question is whether we can test the degree of overlapping versus unique circuitry in RSC using functional connectivity. Using a seed-based region of interest (ROI) method, every seed will be perfectly correlated with itself. However, it is possible to break up RSC into subregions to determine the mutual connectivity across subregions. This has not been tested to the best of our knowledge. The anatomical gradient of connectivity (Figure 3D) suggests that large-scale overlap is unlikely. However, this conjecture must also be tempered with the acknowledgment that functional connectivity only shows correlations and not the afferent/efferent nature of the connections. The lack of consensus in the human anatomy makes mapping the RSC areas in fMRI studies onto the histologically defined areas difficult. Between the inclusion of area 23 and functional definitions, it is possible—or indeed probable—that findings attributed to RSC in human fMRI imaging are actually located in posterior cingulate, PHC, or

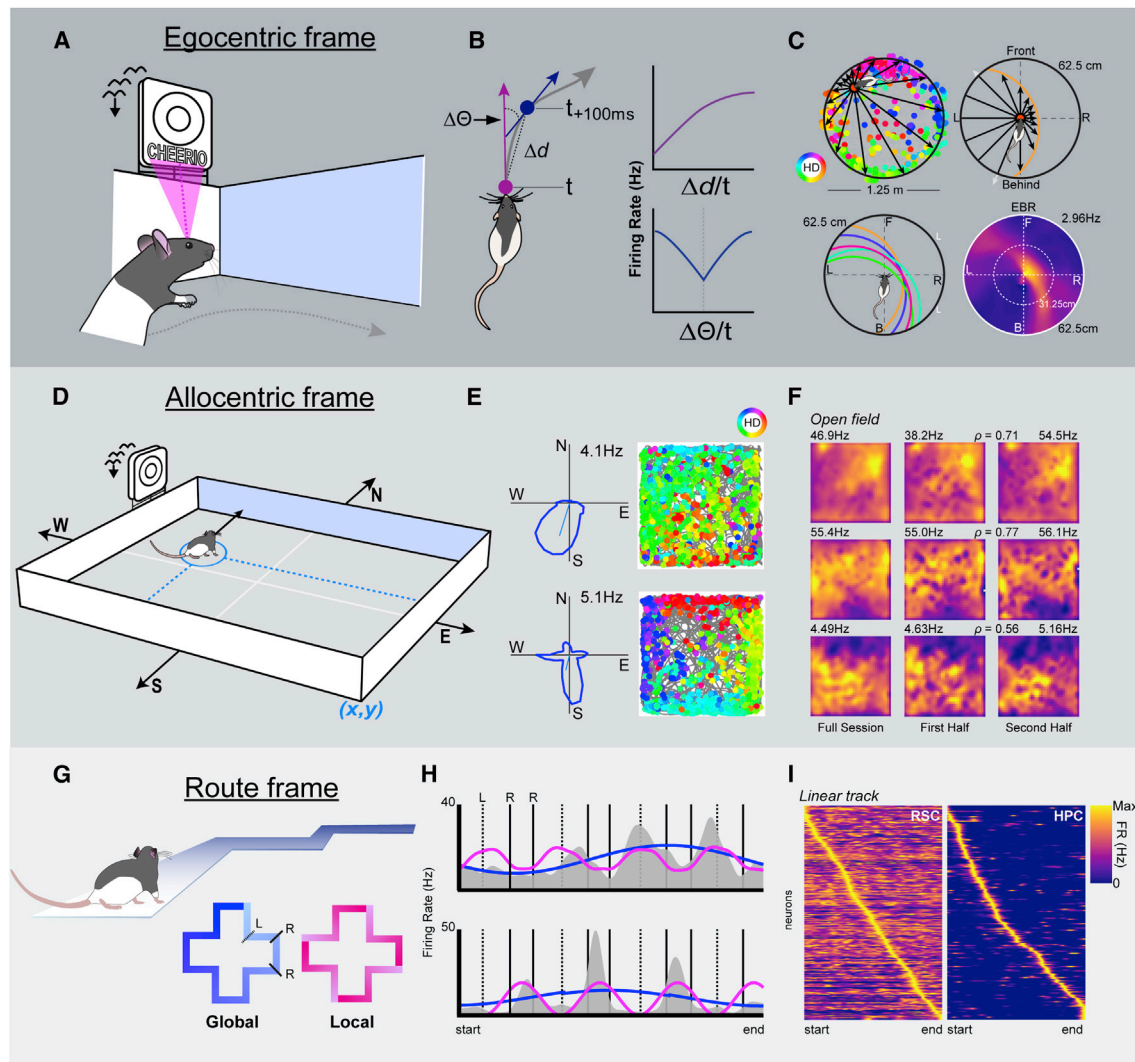


Figure 4. Egocentric, allocentric, and route-centered activity correlates of retrosplenial cortex

(A–C) The egocentric reference frame.

(A) Landmarks and boundaries have distinct egocentric relationships relative to the agent as it moves through space. While paused, the “Cheerio” sign is to the left of the rat and the boundary is in front of the animal. As the animal moves along its future path (gray dashed line), the sign will move behind the animal and the boundary will be to its left.

(B) Egocentric self-motion sensitivity in RSC.^{6,18,78} Left, schematic of change in angular heading ($\Delta\theta$) and distance (Δd) as the agent moves along a trajectory through space (gray line). Displacement is egocentric because it is measured as the difference in these variables between self-position 2 and self-position 1 (pink and blue dots). Right top, a schematic neuron with a linear relationship between firing rate and speed. Right bottom, a schematic neuron with a linear relationship between firing rate and both clockwise and counterclockwise angular speed.

(C) Egocentric boundary coding of RSC.^{6,30} Top left, in background, trajectory plot with locations of spikes for a single neuron color coded by the rat's head direction according to the legend on left. For a single spike in the foreground (enlarged in orange), the boundaries are mapped relative to the animal's current heading (single and multiple spikes are top right and bottom left, respectively). Bottom right, an egocentric boundary rate map for this RSC neuron shows that it is activated when any environmental boundary is to the right of the animal and slightly ahead of it.

(D–F) The allocentric reference frame.

(D) The agent has a distinct spatial position (blue circle) and heading (black arrow) relative to the landmarks and boundaries that define the external environment.

(E) Two RSC neurons (rows) with significant allocentric head direction modulation.^{5,17,79} Left plots depict polar tuning plots. Right plots are the trajectory of the animal (gray) and with positions at the time of spikes indicated by colored circles. Colors correspond to the head direction of the animal at the time of the spike colored according to the legend above. The bottom neuron is sensitive to both the egocentric position of boundaries (see trajectory plot) and the allocentric heading of the animal simultaneously.

(F) Activation of three RSC neurons (rows) during open-field exploration is spatially reliable but does not resemble HPC place cells.^{6,24} Left column, rate map for the full session. Middle and right column, first and second half of the session, respectively.

(G–I) The route-centric reference frame.

(G) Animal position is considered relative to the space within a route, regardless of the route's position in the external world.

(H) Mean firing rates of two RSC neurons that exhibit complex firing patterns within a plus-shaped route schematized on bottom left. Each activation pattern possesses repetitive firing peaks (fit in pink line) that map onto the same track segments within a local topology (in G the bottom right graded pink schematic) and

(legend continued on next page)

POS. Due to this difficulty and the lack of clear definitions in previous studies, we will refer to the broad region as RSC for the remainder of this review. A major challenge for the future of human research on RSC is to generate a consensus delineation of the region and to re-examine the literature to have a clearer idea of the exact locations of the signal peaks. Meta-analytic approaches that use coordinates (e.g., Chrastil et al.⁶⁴ and Burles et al.⁷⁴) have facilitated a better understanding of the mapping of function onto anatomical locations within RSC and have demonstrated functional differences across the anterior-posterior axis, although distributed and heterogeneous functions still pose a challenge.

SPATIAL REFERENCE FRAMES, TRANSFORMATIONS, AND PERSPECTIVE TAKING

The extensive focus on spatial cognition and navigation with respect to RSC function has been informed by RSC's anatomical position as an interface between regions of neocortex involved in sensorimotor processing and spatial processing in peripersonal space (e.g., PPC), thalamic areas that process head orientation tuning (e.g., ATN and LD), and the extended hippocampal formation (HPC, entorhinal cortex, and subicular complex). This positioning suggests that RSC has access to numerous forms of spatial information and could mediate between them.

We begin by reviewing RSC neuron activation correlates as they relate to encoding locations or orientations within a spatial coordinate system (i.e., a reference frame). To organize the discussion, we focus first on neural activation relating to "egocentric" coordinate frames, wherein activity tuning reflects an environmental feature's position within a sensory space (such as the retina or whisker fields of a rodent) or the actions of the animal (e.g., turning left in the context of a navigational task). Following this, we discuss tuning of activity to locations and/or orientations in "allocentric" (or non-egocentric) coordinate frames (e.g., viewpoint invariant encoding of environmental position in reference frames defined by external features such as boundaries). Finally, we consider the potential for computations related to transformations and conjunctions between the two, for example, a "route-centric" coordinate frame that appears to reflect the conjunction of egocentrically and allocentrically organized spatial information. We conclude this section by analyzing the prominent theory of RSC function in computing transformations between spatial coordinate systems and propose the potential for a more generalized role of RSC in multiple forms of perspective taking. Perspective taking may take advantage of overlapping input/output circuitries in RSC, allowing the animal to use multiple frames of reference when interacting with the environment, but is not exclusively tied to egocentric-allocentric spatial transformations.

Egocentric coordinate frame

The egocentric coordinate frame can be defined by changes to the position of sensory stimuli with respect to ourselves as we

move about the world (Figure 4A). Self-motion as sensed by the vestibular system, optic flow, proprioception, and/or motor efference copy can all also be considered to be anchored in egocentric frames of reference.

Self-motion

RSC possesses a number of neurons sensitive to movement-related variables. As in many other regions, multiple studies have reported large percentages of RSC neurons with modulation of firing rate reflecting the linear and angular movement speed of the animal (Figure 4B).^{7,18,27,78,79} From a spatial cognition perspective, these observations suggest that RSC may contribute to "path integration," a computation thought to be used in some forms of navigation and spatial mapping in which animals can iteratively track and integrate changes to linear and angular displacement to self-locate. Indeed, lesion or inactivation of the region results in navigation deficits in darkness in which path integration is required.^{80,81} Of course, RSC tuning to linear and angular movement may also function to mediate actions themselves through projections to the M2 sub-region of frontal cortex.^{54,58} Although linear and angular speed has not yet been associated (or tested to the best of our knowledge) with human RSC activation, fMRI correlates provide indirect evidence for RSC involvement in orienting and tracking functions related to path integration.^{37,82} In particular, RSC tracks rotations in place,⁸³ consistent with the animal literature on turn sensitivity.

Visual processing

RSC also appears important for integrating self-motion and position signals with visual information present in the environment. Stimuli that mimic or enhance optic flow information can bidirectionally modulate (i.e., enhance or suppress) the response to linear and/or angular speed.^{11,16,18,26} Moreover, portions of RSC possess retinotopy (i.e., sensitivity to egocentric position), which may generate landmark-anchored responses and enhanced coding of spatial position during virtual navigation tasks.^{9,12,20,22,25,26,84,85} Finally, imaging of RSC efferents to visual cortex revealed tuning to learned visual stimuli that, through reentrant connections, contributes to responses in visual cortex itself.¹⁹ Human fMRI shows functional connectivity between RSC and regions that process optic flow information during first-person navigation,⁸⁶ further supporting the importance of RSC in visual processing.

Egocentric bearing and distance

It is possible that abstraction of egocentric self-motion or sensory signals is critical for the formation of egocentric boundary vector cells (EBCs) in RSC. Originally dubbed "direction-dependent place fields" and recharacterized in recent work, EBCs possess egocentric receptive fields that respond whenever any boundary occupies a preferred distance and direction relative to the animal itself (Figure 4C).^{6,30,79,87–90} The preferred receptive field across the EBC ensemble spans the full complement of orientations and distances, generating a signal that could

an overarching gain modulation (fit in blue line) that simultaneously tracks position within the full track space reflecting the global topology⁸ (in G the bottom left graded blue schematic).

(I) RSC (top left) and HPC (top right) putative principal neurons possess spatially reliable firing patterns during track running that can be used to decode spatial position within a route.^{7,20,23} In freely moving animals, RSC neurons exhibit non-zero firing patterns along the majority of the full track space, while HPC neurons tend to exhibit singular activity peaks with negligible activity in all other locations.

theoretically be used to guide behavior given current affordances or to map environment shape (among many possible uses). In support of a sensory origin, EBC receptive fields tend to possess contralateral biases in receptive field orientation, stability across novel or differently shaped environments, and in some cases can be disrupted when physical boundaries are removed. Interestingly, RSC EBCs persist in the absence of visual or whisker-related sensory information and in some, but not all, cases respond to objects inserted within the bounds of the traversable environment.³⁰ Collectively, these data suggest that an individual EBC can be driven by multiple sensory modalities (e.g., tactile and visual) and support the hypothesis that a function of RSC in spatial cognition could be to learn the association between prominent sensory signals such as boundaries and environmental locations.

So far, evidence for EBC-like coding in humans has only been found in PHC,⁹¹ but no recordings in RSC have been attempted to the best of our knowledge. However, there is evidence that RSC is tuned to other egocentric perspective information in humans. For example, RSC has been shown to be sensitive to egocentric distance to locations and to objects in a scene.^{92,93} Encoding a spatial layout from a first-person perspective shows enhanced RSC activation compared with encoding from a top-down view, suggesting that RSC could be more important for changes in egocentric HD than for allocentric location processing.⁹⁴ RSC is also sensitive to mirror-reversals in scenes, possibly related to processing egocentric directions for movement.⁹⁵ RSC is active when judging which of a pair of places, events, or people is closer to oneself, with some anterior-posterior differences depending on spatial or person modality.⁹⁶ Although these egocentric distance judgments and scene-related features are not about boundaries per se, these egocentric relationships provide meaning about location and navigability.

Oneself

Another aspect of egocentric processing and reference frames is simply the idea of oneself, including the physical body, pain, emotional pain, and self-image. Human RSC is sensitive to self-referential processing compared with non-self-processing, and RSC activation is associated with recalling events that actually happened to oneself compared with imagined events,⁹⁷ which could also have implications for episodic memory. Likewise, RSC and posterior cingulate activation is more related to judgments about oneself and to self-reference than to other types of judgments, such as subjective preference.^{98–101} RSC is part of the DMN, a network of brain regions involved in self-referential processing, as well as many episodic and future thinking functions.⁵⁰ In an out-of-body teleportation illusion, RSC activity reflected self-location, while nearby posterior cingulate mediated both self-location and sense of body ownership.¹⁰² Finally, recent work demonstrated the presence and potential causal relationship between a slow network oscillation (1–3 Hz) in RSC and dissociative behavior in both mice and in humans experiencing dissociative seizures, suggesting that temporal organization of RSC activity patterns plays a critical role in linking sense of self to the physical body.⁴⁹

While egocentric coding of self-motion, visual information, and boundaries clearly support spatial cognition and naviga-

tion, processing of more abstract egocentric information such as sense of self may reflect a more general binding function of RSC. Given RSC's back projections to visual processing regions and the HD system, conjunctive processing of these spatial variables could associate spatial signals and provide “downstream” structures with expected viewpoints or locations to mediate (1) error correction of hippocampal allocentric processing and/or (2) predictive coding in sensory processing regions. In this way, egocentric tuning of locations and orientations can be considered consistent with both perspective taking and in the prediction functions we consider below.

Allocentric coordinate frame

An allocentric coordinate frame is defined by the relative positions of features in the external environment (Figure 4D). In non-human animals, place cells, grid cells, and HD cells have been observed within broader spatial processing circuitry and among other forms of spatial and directional tuning that, altogether, can be considered to form a distributed cognitive map.^{103–105} Typically, these neurons possess receptive fields that are anchored, in a viewpoint-invariant manner, within the allocentric reference frame defined by environmental boundaries and distal visual cues. RSC possesses sensitivity to allocentric space by coding for HD and for position.

Head direction coding

Subsets of RSC neurons are sensitive to the HD of the animal relative to environmental boundaries and the layout of prominent landmarks (Figure 4E).^{17,79,106–108} Physiologically distinct cell types in superficial RSC may process sustained or transient HD information^{109,110} for multiple environmental locations having different views for the same orientation. HD cells have not yet been found in human RSC, although they have been found in medial temporal regions.¹¹¹ Using fMRI and virtual environments to study HD in humans has its limitations,¹¹² but they can help identify regions that are sensitive to HD. RSC is sensitive to changes in global HD in humans^{44,113,114} and to encoding rotation,⁸³ as well as direction changes in abstract spaces.¹¹⁵ Furthermore, Marchette et al. found that posterior RSC is sensitive to local heading features.³⁹ Similar sensitivity to local heading orientation has been reported in rodents and manifests as multimodal directional tuning in multi-compartment environments that is anchored to prominent visual landmarks.¹⁷ The presence of both forms of heading information within the region indicates that RSC may mediate registration of location in both local and global coordinate systems.^{17,39,116}

Spatial position coding

One fMRI study found that RSC codes for allocentric location in humans, although sensitivity to HD was limited,⁷³ but a more recent study found sensitivity to both location and heading.¹¹⁷ Another study found that performing an allocentric pointing task requiring judgment of relative direction from imagined headings led to increased RSC activity compared with a pointing-in-place task.^{118,119} Furthermore, RSC integrates locations across a segmented space into a single map, with sensitivity to distances between locations.⁴³ These findings suggest that RSC is recruited for additional allocentric processing beyond mapping location relative to boundaries.

There is evidence for allocentric position coding at the single-unit level in both rodents and primates in both head-fixed target detection tasks¹²⁰ and during virtual navigation with two-photon calcium imaging.^{12,20–22,25,33} Similar responsivity has been observed in freely moving studies in rodents,^{6,24,30} although the form of location-related firing varies widely between these experimental conditions. Specifically, spatial responses seem to resemble hippocampal place fields in calcium imaging experiments using head-fixed mice (Figure 4I), while this is only rarely the case in freely moving rats (Figure 4F). This disparity likely arises from some combination of differences between calcium versus extracellular electrophysiological recording dynamics, the absence versus presence of vestibular information during movement through an environment, and/or interspecies differences. In addition, the nature of rodent virtual reality experiments on linear tracks conflates environmental location with a specific viewpoint-dependent scene at a given location, such that these setups do not match data collected in the real world. Manipulations of environmental features such as distal landmark rotations have not yet been conducted to verify that these position-related activation patterns are truly anchored to the allocentric coordinate frame. In addition to landmark manipulations, an exploration of activation given distinct approach angles to the same position in space would be useful for assessing allocentric modulation in virtual tasks in both rodents and humans. Taken together, there is evidence for an allocentric coordinate frame in RSC, but it is not unequivocal, and there are still significant gaps to determine under what conditions RSC encodes spatial relationships for specific local viewpoint-dependent reference frames versus viewpoint-independent location in a global reference frame.

Route-centered coordinate frame, spatial context, and topological mappings

RSC also reflects position within the space of a well-known trajectory.^{7,8,10,23,31,121} These “route-centered” firing patterns were initially observed in PPC in animals traversing labyrinthine mazes but have now been reported in RSC and other cortical areas.^{122,123} Tuning to route space has also been observed in some hippocampal CA1 neurons and in entorhinal cortex,^{124–128} in which case it has sometimes been referred to as “path equivalent” encoding of location. Tuning to route location in RSC is characterized as complex fluctuations in firing rate for single neurons that are reliable within the space of a route and independent of specific egocentric actions (Figures 4G and 4H). Thus, ensembles of route position encoding neurons enable precise reconstruction of the animal’s position within a route of a particular shape¹²⁹ (Figure 4I). The key difference in route representations between PPC and RSC seems to hinge on the influence of allocentric information. PPC neurons reflecting position along a route, itself an allocentric space, are largely invariant to the position of the maze in the allocentric space defined by environmental boundaries. Subsets of RSC cells with sensitivity to route progress can be either invariant to or drastically modulated by environmental positioning of the route. This property of RSC route representations is thought to reflect a possible function of the region in interrelating and transforming spatial position across multiple coordinate systems (see corresponding section below).

Similarly, human RSC is also involved in situating a landmark as a place in the larger environmental context.^{68,130} RSC requires access to memory for this process, such that it retrieves spatial and conceptual information associated with external and internal views of the landmark, but it does not require familiarity with the landmarks to relate different views.⁴⁰ Furthermore, RSC has preferential activation for a scene in a larger context, such as a labeled location,¹³¹ and it is sensitive to boundary extension illusions,¹³² which expand the scene beyond what is visible. Relatedly, RSC treats different views of a scene as being the same when viewed from continuous movement^{70,133} or when stitching multiple views together into a sense of place.¹³⁴

Scene perception as route context

In light of these findings, an interpretation of RSC’s known scene selectivity in terms of navigational routes could be appropriate. Situating a scene into the broader environmental context could facilitate learning a trajectory, such that a navigator could associate a location with other ones nearby. Does the scene perception literature support this idea? In opposition to this idea, human RSC is broadly sensitive to environmental layout and global scene properties, without necessarily associating any objects or contextual details into the space.^{135–138} Furthermore, RSC is not particularly sensitive to the navigational affordances of a scene,¹³⁹ which could speak against either egocentric or route-centered reference frames. On the other hand, low-level visual information is not solely responsible for its response to scenes, indicating that RSC also processes other contextual information.¹⁴⁰ In addition, RSC is sensitive to objects that have a strong contextual relationship—whether spatial or non-spatial in context—indicating a broader role of building contextual associations in RSC.^{141,142} In rodents, RSC neurons exhibit multi-selective sensitivity to numerous contextually linked variables including sensory information, actions, and value. Accordingly, RSC population activity can be used to accurately decode spatial context.^{13,20,24,28,29,31,143} Together, these findings suggest that RSC extrapolates location information beyond the visual input,^{68,130} consistent with a route-centered coordinate frame, but there are some findings from the scene literature that do not fully mesh with this interpretation. A conclusive test of route-centered representations conducted in humans is critical to tease apart the subtleties of RSC tuning to routes of known shape.

Topological mappings

Recent experimental data and theoretical formulations call for a reconsideration of the fundamental nature of the “cognitive map,” specifically, the extent to which it should be considered to be strictly metric versus topological and more reflective of spatial information as described in graph theory.^{125,144–147} In some ways, route-centered representations might be thought of as topological mapping of trajectory features. This interpretation is consistent with the reported adaptation of route-position-dependent firing of PPC neurons to changes in the scale of a route or route components^{122,144} but has yet to be tested for RSC neurons. A rodent study examining RSC route representations on routes with recurrent structure seems to support this hypothesis. Here, RSC route cells were observed to exhibit periodic spatial fields that mapped to both local and global topological features of the route space⁸ (Figures 4G and 4H).

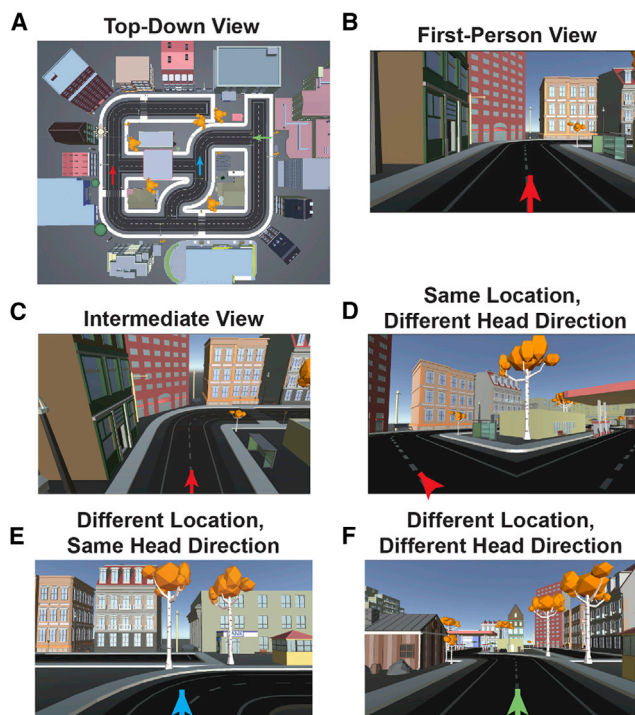


Figure 5. The viewpoint and reference frame problem

There are many features that could be informative to navigating in a complex environment, and multiple frames of reference that navigators can shift between.

(A) The top-down (largely allocentric) view of locations as marked at the ends of the colored arrows.

(B) The first-person (largely egocentric) view from one location and head direction (red arrow).

(C) An intermediate view between the top-down view in (A) and first-person view in (B) (red arrow).

(D) The same location as (B) and (C) but a different head direction.

(E) A different location (blue arrow) but same head direction as the red arrow in (A).

(F) A different location and different head direction (green arrow), although the original location (red arrow) is visible. As a navigator moves through the environment, predictive coding provides information about what they will see at different locations and headings, with the potential to compare the prediction with the visual stimulus. Landmarks of various sizes and permanence are seen throughout the environment, with varying egocentric distances and directions. We note that all views of an environment are technically egocentric, even top-down views. However, those such as in (A) will facilitate building an allocentric representation, whereas first-person views tend to facilitate egocentric representations.

Further, the distribution of periodicity shifted between mazes with different geometric structure, indicating that RSC route-centric firing flexibly adapted to routes with different topologies.

Although human neuroscience has limited evidence of this topological question, some studies suggest that RSC can track an allocentric location along a route while updating egocentric movement, consistent with a topological mapping.⁶³ For example, RSC activity tracks object positions along a route and is sensitive to route direction.¹⁴⁸ RSC activity is also associated with the Euclidean distance to a target location during path integration.³⁷ In addition, lesions lead to an inability to take routes to known locations or place them on a map of their city, while sparing the recognition and identification of the loca-

tions.¹⁴⁹ In non-spatial domains, RSC codes information about structure within social networks, consistent with mapping topological structure.¹⁵⁰ Taken together, both the human and animal literature suggest that RSC could process this intermediate route representation as well as topology, but there are neither direct tests nor firm evidence to determine one way or the other.

Reference frame transformations/perspective shifting

We have now laid out three potential frames of reference that have purported RSC involvement. Yet, RSC is not typically considered to be the seat of any of these reference frames. Instead, it is often considered to be a center for transformation between them, likely due to their co-occurrence in RSC. For example, an influential theory (called the BBB model) of RSC function proposes that the region facilitates transformations between egocentric and allocentric coordinate systems.^{151–153} We now turn to this question, weighing the evidence for different types of transformations. Figure 5 provides an overview of potential transformations and lays out the potential problem of reference frame transformations. Although potential transformations include the BBB model's top-down (largely allocentric) views/representations to first-person (egocentric) views/representations, transformations could also occur between different first-person views at the same location, first-person views in different locations, first-person views with the same HD, views in-between top-down and first-person, etc. The myriad of potential transformations suggests that RSC may be involved in shifting between perspectives more broadly. Yet, we will also question the current evidence for such transformations and consider what would be strong evidence for this theory.

What is a reference frame transformation?

While there exists neuroanatomical and experimental support for the BBB model, interpretation requires further consideration of what “transformation” actually means. Confusion may arise as the term is sometimes used to indicate a complete derivation of allocentric receptive fields from egocentric sensory information, but support for this definition is lacking as activation in the HD system and extended hippocampal formation emerges from intrinsic connectivity even in the absence of sensory drive.^{154–158}

The more scaled-back definition of transformation, but the one for which there is more support within this literature, refers to an alignment of egocentric information with these already encoded/preconfigured allocentric representations. Specifically, the BBB models of RSC function in spatial transformation feature a role for the region in rotationally aligning egocentric and allocentric perspectives. In this operationalization, HD information (HD cells) is combined with first-person viewpoint information (i.e., EBCs or egocentric object receptive fields) in RSC to construct directionally modulated boundary representations that reciprocally map between EBCs and allocentric boundary vector cells of the extended hippocampal formation.^{151,152,159,160} These mappings serve to align egocentric viewpoints with their associated allocentric locations (e.g., Figures 5A–5D). Thus, in sensory-driven mode, egocentric viewpoints are utilized to rotate and align extant allocentric representations. In an internally driven mode facilitating imagery or recall, these models rotate allocentric directional or place memories into their associated egocentric viewpoints. Any or all such transformations can also function

in the service of location or viewpoint predictions and associated error correction in line with our second proposed general function for RSC.

Support for egocentric-allocentric transformations

Theoretical support for this model stems from the neuroanatomical connectivity patterns discussed above. RSC has overlapping connections to both parietal regions and visual cortex (known for egocentrically mapped somatotopic and retinotopic information) and to the greater hippocampal formation (home to representations of location and orientation in allocentric spaces). Experimental evidence for this model of RSC as an egocentric-allocentric transformation circuit is mounting but still tenuous. However, a few pieces of data support the above model beyond neuroanatomical connectivity. First, EBCs described above have now been reported in several structures, including RSC and parietal cortex.^{6,30,90,161} These cells were predicted in the BBB model as “parietal window” cells and provide first-person viewpoint information by coding for the egocentric direction and distance to external features in the environment. Second, many studies have shown that RSC possesses neurons with spatial receptive fields sensitive to specific combinations of egocentric and allocentric variables.^{7,8,12,22,24,25} These conjunctive responses are critical for networks designed to interface across spatial coordinate systems and resemble gain fields as reported in pioneering work exploring reference frame transformations for sensorimotor control.^{162–165} In RSC, this conjunctive coding can manifest as EBCs that are modulated by specific allocentric HDs, which directly resemble responses in the transformation layer of the network described above (Figure 4E, bottom).

Further, inactivation of RSC causes angular drift of HD neurons relative to visual landmarks, providing evidence for a role of RSC in anchoring of allocentric perspectives to sensory information during navigation.^{160,166} Similarly, variability in RSC activation becomes better accounted for by position relative to landmarks rather than self-motion over repeated exposures to a virtual reality environment.¹² This is consistent with a role for RSC in using egocentric signals to anchor allocentric representations as the animal learns important spatial interrelationships through experience. Finally, RSC dysfunction produces behavioral deficits in tasks requiring animals to utilize egocentric and/or allocentric navigational strategies.^{80,167–178}

While these experimental findings lend support for the proposed role of RSC in facilitating spatial transformations, there are important caveats to consider. Namely, conjunctive egocentric-allocentric representations, thought to be critical evidence of a role for RSC in interfacing across disparate spatial reference frames, have been observed in numerous structures beyond the region.^{89,179–183} Thus, conjunctive reference frame representations cannot be considered a unique property of RSC, an indication that the coordinate transformation is distributed. Critically, there is little evidence of RSC inactivation impacting boundary-anchored responses in downstream regions such as MEC, despite this being a natural prediction arising from the models described above.³⁰

There is indirect support for the role of RSC in reference frame transformations in humans. For example, RSC activity is related to route learning from an egocentric viewpoint (e.g., Wolbers and Büchel¹⁸⁴) and to navigating from a first-person perspective after

looking at a top-down (allocentric) perspective (e.g., Sherrill et al.¹⁸⁵; Zhang et al.¹¹⁹). RSC activity also supports allocentric HD coding that can be used for first-person navigation (e.g., Shine and Wolbers¹¹⁶; Marchette et al.³⁹; Shine et al.⁴⁴). Similarly patients with damage to the inferior parietal cortex, posterior cingulate cortex, and RSC have demonstrated difficulty integrating information across egocentric and allocentric frames.^{186–190} However, not all of these cases were consistent with regard to reported deficits in, or preservation of, the ability to use maps or viewpoint-based information in isolation. There were also discrepancies with regard to the effect of RSC-specific damage on remote versus recent memory for space. Thus, there is a need for additional evidence directly implicating the transformation process.

Proposed broader perspective-taking function

There is more evidence in humans, however, that changing viewpoints to different locations within the first-person perspective (Figures 5E and 5F) involves RSC. In contrast to the transformation between egocentric and allocentric reference frames as has been proposed previously, this more general perspective taking function could also include a shift between two different allocentric or two different egocentric perspectives. For example, Lambrey and colleagues showed that mentally rotating one’s viewpoint to the position of an avatar or an arrow resulted in activation of RSC/POS.³⁸ In a series of experiments, Sulpizio et al. showed that RSC activity is related to the amount of viewpoint change relative to the environmental frame⁴⁷ and that RSC activity is modulated by the magnitude of a viewpoint shift.⁴⁶ These findings indicate that RSC has a role in orienting and processing view-based information from a first-person perspective, but they do not provide any indication that RSC is used for allocentric location or transformation between egocentric and allocentric reference frames.

These findings also take the transformation idea a step further, suggesting that perhaps RSC is involved in perspective taking more broadly. Computing other viewpoints and perspectives is central to retrospective, prospective, and counterfactual thinking,¹⁹¹ and a more general perspective taking function would expand RSC’s role beyond the spatial domain to include memory, prediction, planning, and social cognition. Here, the evidence is somewhat mixed. RSC showed activation related to changes in visual perspective in one study,¹⁹² but not in others.^{193–195} However, RSC is functionally connected to the HPC during early retrieval of different perspectives, particularly when taking atypical observer perspectives,¹⁹⁶ suggesting that RSC could be important for visualizing viewpoints that require extensive transformation. On the other hand, recalling events that really happened to the participant compared with imagined events leads to anterior RSC activation,⁹⁷ suggesting that RSC might be more related to one’s own viewpoint. It is also important to consider that few of these perspective-taking studies have examined activation related to the degree or the direction of the shift.

Falsifying the transformation hypothesis

With these data from both rodents and humans in mind, it is important to ask what a spatial transformation would look like at a mechanistic level among neural populations (see excellent work examining this exact question in flies in Fisher et al.,¹⁹⁷

Kim et al.,¹⁹⁸ and Lu et al.¹⁹⁹) and what evidence would be needed to validate, falsify, or differentiate this proposed RSC function from others associated with the region. The lack of direct evidence supporting the transformation hypothesis may be due, in part, to the challenge of defining exactly what a transformation involves in terms of a neural code. For example, is the binding, storage, and subsequent recall of concurrently occurring egocentric and allocentric spatial signals sufficient to be dubbed a spatial transformation or does the term require a continuous and active computation such as that observed within sensory processing streams? Without a clear definition of a transformation, the problem is ill-posed, and attempts at falsification will be unlikely to yield unequivocal results.

Complementary or potentially competing hypotheses should also be explored. For instance, RSC is implicated in the encoding of episodic memory (discussed next) and is anatomically positioned to associate hippocampal formation output with concurrent sensory context.²⁰⁰ Could experimental evidence for RSC facilitating spatial transformations reflect a more general role of the region in binding contextually rich sensory information with HPC output? Perhaps RSC computation is better verbalized as a predictor or comparator rather than a translator or an associator? Evaluating the transformation hypothesis will require clever and carefully designed experimental paradigms that directly test predictions derived from not only the BBB model, but also other models of RSC computations.

Overall, RSC has been shown to be sensitive to numerous spatial reference frames. In addition to the well-known egocentric and allocentric codings, we posit that a route-centered coordinate frame could also be part of RSC's reference frame repertoire, which would allow for trajectory planning and updating. The coexistence of multiple spatial systems has led to the theory that RSC could transform between them, based on conjunctive coding. Although we find there is ample indirect evidence to support this idea, a direct test still needs to be conducted. We also suggest that a more general perspective taking function could underlie these transformations, which could expand RSC function beyond the spatial domain and into realms that include prospection and counterfactual thinking.

TEMPORAL ORGANIZATION, EPISODIC MEMORY, AND PREDICTION

While spatial models do not preclude RSC from supporting other neural codes, strict interpretations from these models may be overly simplistic⁵⁷ given that RSC is recruited during both “what” and “where” information encoding and retrieval in rats.²⁰¹ How might conceptualizing RSC as a comparator or predictor rather than a translator or transformer generate novel, testable hypotheses about RSC neural mechanisms and cognition? We argue that prediction places greater emphasis on the top-down role of RSC driving sensory processing¹⁹ whereas a transformation model places greater emphasis on the role of RSC in mediating between parietal and medial temporal lobe (MTL) representations.¹⁵² By considering RSC through the lens of episodic memory alongside spatial processing, we propose a second generalized, non-exclusive category of RSC function—that of a critical node in a predictive coding hierarchy.

In this section we will highlight research in episodic memory which paints RSC as a critical node in a predictive coding hierarchy across spatial and non-spatial domains. We summarize findings linking RSC to established and reliable self-referential memories that incorporate a specific context and temporal structure of events. We begin with a brief introduction to predictive coding before making the case that it may manifest behaviorally as memory for temporal sequences. We go on to discuss how such temporal structure is crucial for establishing the rich spatiotemporal contexts necessary for episodic memory, thus transitively linking prediction to both spatial and episodic memory. In the latter portion of this section, we review literature on single-cell and population dynamics within and between RSC, MTL, early visual cortex, the dorsal visual stream, and higher-order areas associated with decision making and motor planning. We argue that such mechanisms are consistent with a plausible neural instantiation of predictive coding. How these dynamics differ prior to and after consolidation are also addressed. We posit that this establishes a framework in which RSC is central to predicting bottom-up perceptual information from memory to plan and guide behavior as in traditional models of predictive coding. In these models, predictions percolate in a top-down fashion to sensory processing regions. These processing regions then provide bottom-up error signals that are used to resolve discrepancies between predicted and actual perceptual signals.^{202,203} In this rendering, we view RSC as a contributor of top-down signals that reflect conjunctions among multiple forms of sensory, motor, and spatial information. Thus, the “predictive” signal is one that matches, or does not, the full situational context provided by the environment and the organism's locations and actions within it. Further, such predictive signaling varies and is organized across time to reflect the remembered succession of states of the environment.

An argument for predictive coding

A predictive coding model is somewhat analogous to product development: a manufacturer designs and builds a prototype and gives it to a sample of target consumers or a focus group where they receive specific notes on facets of the product that end-users believe need to change, resulting in a final product that most closely realizes what the consumers actually want. In this analogy, the manufacturer represents RSC and the prototype represents a prediction from RSC about the state of the world that influences early sensory processing codes. The product testing notes are feedforward error signals from those sensory areas (product testers) that carry any residual sensory information that was not expected based on RSC predictions (i.e., the notes only describe how the prototype failed to meet consumer expectations and take for granted how it succeeded). This design-test feedback cycle is iterative, and the final product is a modified and updated RSC prediction that better coordinates local sensory region predictive codes to reduce future discrepancies. Incorporating these principles of predictive coding may help to explain general RSC computations in both spatial and non-spatial domains, particularly with regard to a lack of dependence on RSC for allocentric representation. Given the hub-like connectivity of RSC, including major efferent and afferent connections to entorhinal cortex and SUB^{204,205} as

well as projections to secondary motor cortices,^{58,206,207} this region seems well positioned both in the sense that it is at the top of a cortical visual perception hierarchy and in terms of being able to rapidly affect meaningful behavior via prediction or error correction.

Temporal organization in service of prediction

Episodic memory involves retrieving specific details that are associated with a specific context. A context can be an environment, a location, a date, or even a state of mind,²⁰⁸ and the spatial context we have discussed so far is insufficient for defining episodic memory. Richer spatiotemporal contexts provide a powerful constraint for structuring episodes in memory, i.e., temporal organization.²⁰⁹ Making predictions requires having knowledge of what will happen next in a sequence—a unidirectional association of events. Predictive shifts in spatial HPC place codes have been shown to result from animals traversing stereotyped paths, such as repeated episodes of running laps on a rectangular track.²¹⁰ Thus, a neural code for temporal organization, which is a sequence of many linked temporal associations, in and of itself can be considered a form of predictive coding. Here, we consider findings that link RSC to temporal sequence memory. In general, RSC is found to modulate behavior in response to durations ranging from seconds to minutes.^{211–213} We hypothesize that expanding known RSC spatial coding schemes (described above) to the temporal domain might support the stable event predictions that have been observed in RSC population dynamics.

RSC's role in integrating non-spatial experiences within spatial or temporal frameworks has been established using object-recognition testing in rodents. In addition to displaying compromised object-place memory,¹⁷⁰ RSC-lesioned rats were unable to assign relative temporal positions to objects presented within a continuous sequence; rather, lesioned rats could only appropriately discriminate relative presentation order of objects (i.e., object-recency) between blocks separated by 30 min inter-trial intervals.²¹⁴ The same study found RSC engagement, observed through increased immediate-early gene (IEG) expression, correlated with object-recency discrimination performance for all inter-trial interval durations. RSC was most obviously recruited in assigning order, in space or time, to experiences that were likely to share a common temporal environment. Another study found temporary RSC inactivation disrupted rodents' use of previous trial outcomes to appropriately update left versus right action selections needed to maximize reward.¹⁴

Predictive sequences related to spatial reference frames

RSC activity reflecting progress through a route (described above) yields sequences of firing rate modulations to allocentric or egocentric reference frame conjunctions. This form of representation could also function as a predictive mechanism that amplifies or reduces activity responses in RSC target structures to a sequence of repeated or expected features as one moves through an environment and as one anticipates upcoming turns (Figure 6A). In tasks and experiences lacking extended navigation across space, RSC neurons could exhibit similar variations in activity within a larger sequence of sensory and motor events. The task utilized in Powell et al.²¹⁴ involves encounters with

different objects across time and demands encoding of their temporal sequence. Impairments in task performance with RSC lesions could reflect RSC encoding of object encounter sequences across time that are akin to the encounter sequences of different locations and views across a locomotor trajectory (schematized in Figure 6B). Whether RSC neuronal activity patterns accomplish this has yet to be explicitly shown, but it is known that two-photon calcium imaging can persistently decode long sequences of left versus right movement combinations demanded by the given environment.¹⁴ That is, stable RSC ensembles reflect the planned order of left-right movements, and the active ensemble adjusts in line with perceived environmental changes to reflect a new order of actions.

Human evidence implicating RSC in sequence learning is sparse, yet the available evidence suggests RSC is necessary for encoding the temporal information of novel items.²¹⁶ Investigations into RSC activity found increased RSC BOLD responses correlated with faster recall of responses tied to discrete item cues,²¹⁷ whereas decreased glucose metabolism in RSC has been associated with temporal disorientation among Alzheimer's patients.²¹⁸ Interestingly, one study showed that patterns of multi-voxel fMRI activity in RSC could be used to accurately classify an item's position in a list of object images, independent of the item's identity.²¹⁹ Such RSC indexing could facilitate selective activation of stimulus-identity representations for downstream sequence elements in anticipation of their relevance for upcoming behavior. This fits nicely with results from mice showing that early visual cortex neurons better reflect stimulus properties prior to learning but then become more strongly influenced by top-down modulation from RSC after learning¹⁹ as shown in Figure 7A. Similarly, in HPC, pattern completion has been proposed to facilitate predictive codes that drive patterns of activation in visual cortices.²²⁰ Taken together, HPC and RSC may each represent one level of a predictive coding hierarchy in the human brain.²²¹ It is also possible that the relative utility of HPC and RSC for prediction and memory changes over time through processes such as consolidation.

Prediction in service of episodic memory

Storage of episodic memories in a temporal sequence allows the retrieval of a single instance to recover a series of forthcoming events. Of course, the formation of a sequence of events demands unique events to be encoded among their relative order, but when recalled, the sequence itself can serve to cue expected behaviors and related memories.

Recognition memory retrieval

While no two experienced episodes are ever completely identical, previously formed episodic memories do seem to influence our expectations for ongoing or upcoming events.^{222,223} RSC is implicated in successful recognition memory retrieval but not encoding.^{224–226} In a human fMRI study of DMN regions implicated in episodic memory retrieval, significant functional connectivity was observed between MTL and RSC but not between MTL and other DMNs. Further, RSC but not posterior cingulate cortex showed evidence of mediating MTL connectivity with other cortical DMN regions.²²⁷ This connectivity underscores the functional importance of RSC as a hub for information processing. Moreover, the extent of this mediation tacked with episodic

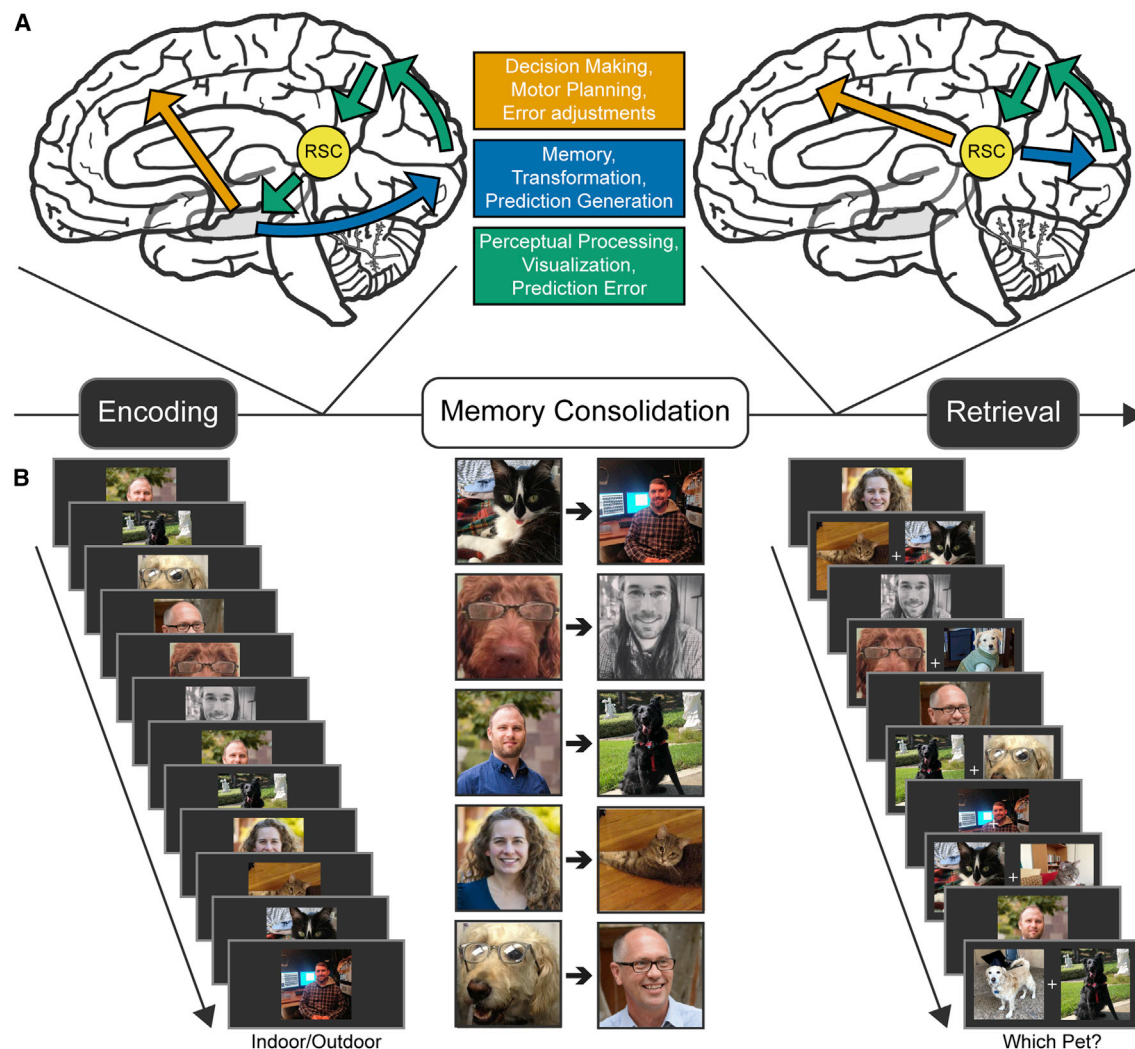


Figure 7. Hypothetical example of how consolidation might alter the role of RSC in a predictive coding hierarchy

(A) Prior to consolidation, RSC is insufficient for a functioning predictive coding hierarchy, necessitating HPC involvement for high-resolution binding of stimulus and event features (left); eventually, reliable representations of stimulus sequences encoded in RSC may be sufficient to reactivate transient representations represented by neuronal populations in early sensory regions (right).

(B) An example of an experimental task to elicit (A); stimuli are displayed in sequence while participants make perceptual judgments (“indoor/outdoor?”) unrelated to the underlying temporal structure (left). Pairs of stimuli that are always shown one after the other in a fixed order are stored and consolidated over a period of time after encoding (middle). During a two-alternative forced choice recollection task, seeing one member of a pair is sufficient to predict what one of the alternatives will be (“which pet?”) and prepare for a behavior response. Together, this figure illustrates how RSC might serve as a high-level prediction node for well-established memories. HPC, hippocampus; RSC, retrosplenial cortex.

Memory and prediction to guide behavior

In addition to being a hub between visual processing streams and MTL regions, RSC is also well situated to coordinate prediction-based behavioral planning and decision making. Rodent RSC has direct and indirect projections to M2, facilitating coordination between sensory information and behavioral action plans.^{206,229,230} Similarly in primates, regions that support planning and enacting movement as well as visuomotor coordination areas are efferents of either RSC, posterior cingulate, or both.²⁰⁵ Were RSC reading out a comparison between predicted and perceived states of the world, it would be well situated for communicating on-the-fly adjustments to motor plans. In a recent study, mice passively navigated a virtual T-maze and

used a joystick to choose a hallway. Importantly, the reward hallway was determined by the wall patterns (a non-spatial context cue), suggesting that RSC activity was modulated by context-driven decision making and action.¹³ In rats, RSC connectivity to the OFC via basal ganglia structures²³¹ further suggests a role for RSC in reward-based reinforcement and decision making. Such mechanisms may drive similar behavior in humans.²³²

Lesions and case studies

Insults to human RSC and the surrounding regions have produced amnesic effects including reduced or non-existent memory for episodic details from stories as well as deficits in autobiographical memory, a syndrome termed retrosplenial amnesia.^{233,234} Only a

handful of additional cases of retrosplenial amnesia have been reported since,^{235–238} emphasizing the need for careful and directed basic research into RSC's participation in human memory function more generally. In developmental amnesics, volumetric loss has been observed in the RSC in addition to HPC and other regions.²³⁹

RSC lesions produce only mild deficits in rodents attempting to solve traditional memory tasks, designed to assess rodents' abilities to utilize memory for allocentric positions (e.g., T-maze, radial-arm maze, or Morris-water maze) under conditions that afford consistent orientation to stable local and distal cues.¹⁷⁴ RSC contributions to memory become clear when distal cues are disabled or misaligned relative to learned local structures and movement patterns. For example, rats with RSC lesions have difficulty assigning recency to the traversal of spatial radial-arm maze segments in darkness^{80,240} or after maze rotations, when locally available movements conflict with distally anchored senses of space or direction.¹⁷² Merging visual cues from multiple environments is also found to increase IEG expression in RSC during radial-arm maze performance.²⁴¹ RSC lesions also most noticeably impaired T-maze alternation during darkness, where only vestibular sources remained available to guide spatial movement patterns.¹⁷⁴ T-maze navigation in darkness, or conditions that favor egocentric strategies, are accompanied by increased IEG expression in RSC.^{176,178}

A failure of RSC to utilize bottom-up prediction error to generate or update sensory prediction might explain impoverished behavior across both spatial and episodic memory tasks. In spatial memory, this could manifest as the inability to navigate a recently altered environment. In episodic memory, behavioral deficits may appear as a failure to assign recency (i.e., to utilize knowledge for the temporal order or structure of episodic traversal). RSC's involvement in retrieving and establishing spatial or temporal structures—or recognizing common features from distinct experiences—is also consistent with a role for abstracting and integrating spatially or temporally separate components. If so, metabolic activity in RSC might be expected to track the difficulty of recognition memory judgments of familiarity.

RSC-hippocampal activity to support temporal coordination and predictive function

Here, we review literature investigating the temporal coordination between RSC and HPC activity during HPC theta oscillations and sharp-wave ripple (SWR) activity bursts. Establishing a temporal dynamic between RSC and other widely known memory regions (e.g., HPC) is critical for understanding RSC's role in organizing memory with primary sensory and motor inputs. It could be argued that temporal coding for episodes or stimuli, in the strictest sense, does not constitute a prediction. However, evidence suggests that, whether by design or epiphenomenal, the very existence of temporal codes gives rise to predictions.^{203,210,242,243} Notably, a wealth of research has identified temporal codes in HPC that relate ongoing^{244–246} and temporally disjoint experiences,^{247–250} which have been found to predict forthcoming behaviors and are causatively linked to spatial working memory.^{249,251–256} While RSC oscillations and neural

populations are often found to shadow HPC dynamics during awake exploratory behavior, specific subtypes of RSC neurons (e.g., EBCs) violate this trend. A similar complex interplay between RSC and HPC is observed within the neural dynamic found to accompany sleep or other “offline” behavioral instances.

Online RSC memory mechanisms

The lion's share of contributions to our understanding of oscillatory dynamics of RSC neural populations come from rodent literature. However, in humans RSC intracranial EEG power fluctuations in the theta and high-gamma bands have been observed across various tasks including autobiographical memory, arithmetic, and non-episodic self-referential declarative memory; theta-phase synchrony has been reported between RSC/posteromedial and MTL areas.^{257–261} Curiously, stimulation of this same region fails to produce any noticeable effect on perception, sensation, or autobiographical detail as reported by subjects.²⁶² Extensive and deliberate study will be required to construct a comprehensive picture of interspecies similarities and differences in RSC function.

Theta oscillation dynamics

The theta rhythm oscillation (4–12 Hz) dominates the oscillatory profile throughout the HPC in rodents, as they actively explore space or objects, during the encoding and retrieval of episodic information.²⁶³ In humans, slower 1–5 (~3) Hz theta—outside the traditional 4–8 Hz cutoff for humans—has been compared with higher 4–12 (~8) Hz theta observed in rodents,^{264–266} although this is not always the case.^{258,259} The rhythm has been linked to mechanisms that support neural plasticity in the HPC, with theta peaks and troughs associated with synaptic potentiation and depression, respectively,²⁶⁷ and the cyclic changes in synaptic plasticity are theorized to support encoding and retrieval of episodic memories.²⁶⁸ Activity organized within single HPC theta cycles allows spike-timing-dependent plasticity mechanisms to link participant neurons, and the temporal structure within individual HPC theta cycles is thought to be crucial for episodic memory formation.

The theta rhythm is prominently observed in the RSC's local field potential (LFP) during awake mobility in rodents, and like EC layer III, RSC theta is largely coherent with theta at the HPC CA1 pyramidal layer. While rat RSC receives several theta-paced inputs that are shared with the HPC (e.g., medial septum, MEC, anterior ventral thalamus) and from the HPC itself, RSC spike outputs are not typically rhythmic like those observed in HPC neurons. Few RSC neurons (~5%) fire rhythmically to a continuous stream of theta cycles, yet many RSC spike activities are modulated relative to CA1 theta (~35% dysgranular RSC, ~65% granular RSC).^{269,270} Thus, it is clear that RSC computations are influenced by the HPC theta rhythm at times, yet there is still potential for RSC neurons to participate in locally generated theta oscillators or slower cortical and HPC rhythms.^{49,271}

RSC spiking and locally generated gamma activity is found to follow similar HPC activity patterns within theta cycles (Figure 8). Gamma frequency oscillations locked to specific theta phases, known as phase-amplitude coupling (PAC), have been proposed to reflect a neural coding scheme for ordering sequences or integrating items within working

Retrosplenial-Hippocampal Theta Dynamics

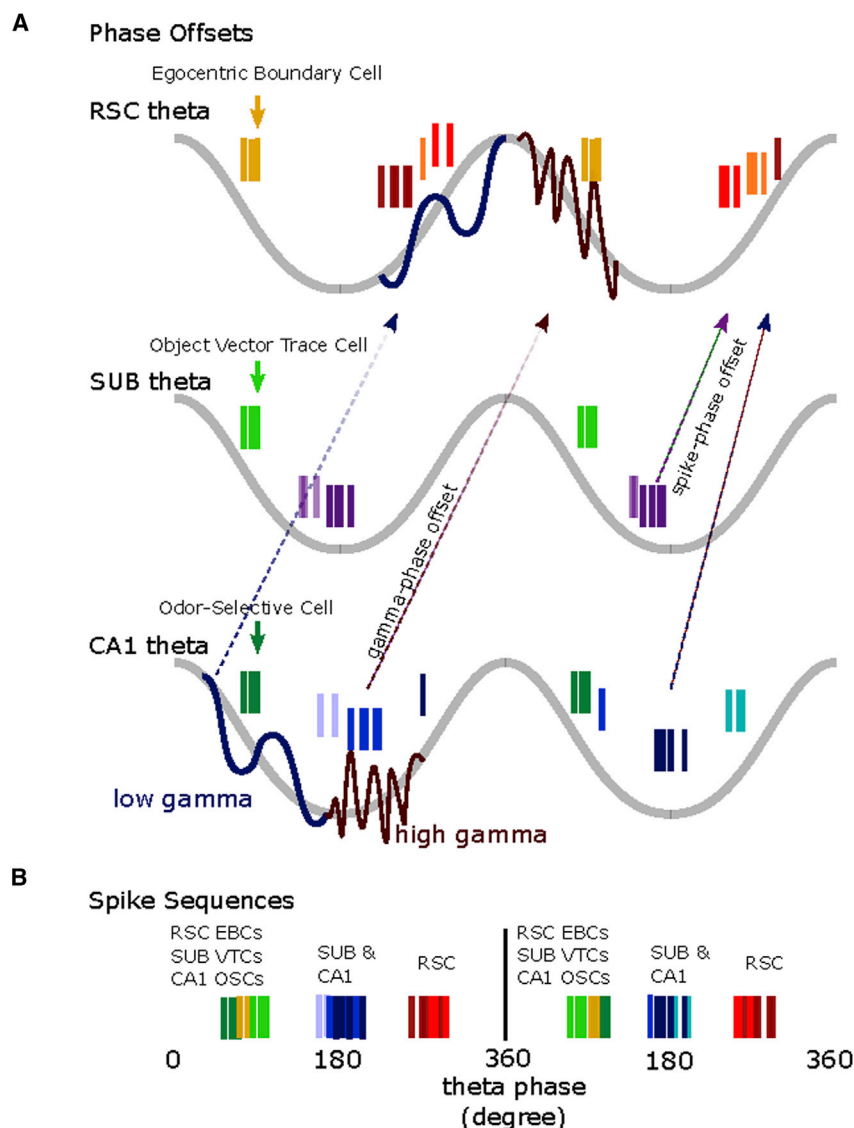


Figure 8. Theta-phase coordination between hippocampus and retrosplenial cortex

(A) Two consecutive theta-cycles (light gray) are depicted for RSC (top), SUB (middle), and CA1 (bottom), which align across all three regions. Gamma rhythm patterning and peak spike probabilities in RSC follow corresponding CA1 dynamics. In RSC (top), distinct theta locations for peak low and high gamma amplitudes are found at ascending and descending phases, respectively, which follows similar CA1 (bottom) peak low-to-high gamma transitions found at theta troughs.²⁶⁹ Peak SUB (purple bars; middle) and HPC spiking (blue bars; bottom) occurs at theta-troughs, whereas peak RSC spiking follows, at ascending theta.^{269,277} Counter to the predicted theta-phase from general spiking, RSC egocentric boundary cells (yellow bars, top), SUB object vector trace cells (green bars, middle), and CA1 odor-selective cells are found to shift spiking to descending early phases during specific behavioral conditions.^{6,215,278}

(B) Spike sequences within individual theta phases start with SUB and RSC responses that are linked to the objects and structures within an environment. Peak SUB and HPC spike probabilities follow, and general RSC spike probabilities conclude the sequence. RSC, retrosplenial cortex; SUB, subiculum; EBC, egocentric boundary cell; VTC, vector trace cell; OSC, object-selective cell.

quencies and maximal spiking phases, with RSC low-to-high gamma abruptly transitioning at theta peaks, shadowing similar patterns observed in CA1²⁶⁹ (Figure 8A).

Spike-phase shifts

Recent evidence has identified subsets of SUB and RSC neurons with spiking locked to early theta phases during encoding of specific environmental structures. SUB neurons found to encode directional relationships to physical objects and their previous locations,²⁷⁸ along with the RSC's EBCs (described above), tend to fire at earlier theta phases than the general population^{6,277} (Figure 8A). Similarly, CA1 firing

memory.²⁷² Stronger theta-gamma PAC in HPC and cortical regions is linked to increased contextual memory performance and working memory demands, respectively,^{273,274} and specific gamma frequencies coupled to theta phases across MTL subregions have been used to indicate the strength of temporal coordination.^{275,276}

Theta-gamma PAC is also found in the RSC. Human posteromedial theta-gamma coupling has been associated with RSC, but only reported during awake rest,²⁶¹ and is linked to coordinated activity between posteromedial sites and MTL regions as well as lateral parietal structures including angular gyrus.^{259,260} As in CA1, one study reported RSC gamma in rats changed in frequency with evolving theta phases, which suggests a temporal coordination between HPC and RSC within theta cycles. Interestingly, RSC gamma ranges and spike probabilities were phase-shifted relative to matching CA1 fre-

to preferred odors has been found to lock to early theta phases in response to the presentation of sequences of discrete odor events.²¹⁵ Such early theta-phase SUB and RSC spiking that reflects proximity and orientation to boundaries and objects and specific sensory signals could conceivably act to coordinate neurons firing at later phases of the theta sequence (Figure 8B). In this case, specific RSC responses (e.g., those of EBCs) lead sequential activity throughout the rest of the HPC-RSC network, which may mechanistically facilitate the integration of RSC top-down information into HPC circuits for predictive processing.

Offline RSC memory mechanisms

The foregoing review of RSC spiking with respect to HPC theta oscillations emphasizes RSC-HPC network interactions on short timescales (100 s of ms). Yet, RSC-HPC interactions may also coordinate memory consolidation and transformation across

much longer timescales. RSC has been viewed as a key region in systems consolidation, under the various flavors of multiple trace theory.^{211,279–285} Such models posit that recent memories rely on HPC for storage and retrieval, while more remote memories show a graded decrease in HPC reliance as complementary memory “traces” are established in the cortex. Increased or emergent RSC activity has been associated with the retrieval of stable episodic memories, whereas increased hippocampal activity is more representative at encoding and during retrieval of nascent episodic memories.^{42,184,286,287} Not yet reviewed preliminary findings from electrophysiological work in non-human primates show distinct activation of RSC during retrieval of object-scene pairs a full year after encoding compared with newly learned pairs.²⁸⁸ One study involving rats showed that anterior RSC was necessary for representing object recognition (what), whereas dorsal HPC was not.²⁰¹ In this study, the GABA agonist, muscimol, interfered with memory performance 24 h later when introduced immediately following a training session, suggesting a time-sensitive involvement of anterior RSC in memory consolidation.

In humans, a central role for RSC within a multiple trace systems consolidation theoretical framework is consistent with studies that have shown preferential RSC activation for familiar scenes²⁸⁹ and tracking of visual landmark permanence^{34,35} as well as the consistency of landmarks or actions.³⁶ Further, RSC is responsive to scenes that scored higher on several object-based dimensions, including place-related, spatially defined, strongly associated with context, fixed in a stable location, larger in real-world size, and further in distance, which together form a “landmark suitability” factor. RSC had a stronger response when a background was present, possibly indicative of a contextual effect.²⁹⁰ Although other consolidation theories (e.g., synaptic homeostasis)²⁹¹ are beyond the scope of this review, advances in understanding RSC functional contributions to consolidation should evaluate compatibility with various systems consolidation theories.

Sharp-wave ripples (SWRs)

Locally generated high-frequency oscillations observed in the HPC, known as SWRs, contain activity bursts that “replay” temporally compressed patterns of place cell rate modulations.^{250,292,293} SWRs have been directly linked to memory performance,^{253,294} with those occurring offline proposed to assist memory consolidation into the neocortex. Notably, fMRI recordings in monkeys find the majority of cortex to ramp up activity in line with HPC SWRs, with subcortical regions jointly decreasing activity,²⁹⁵ and in humans, posterior cingulate—sometimes considered part of the human retrosplenial complex—neurons were among the most numerous in terms of the proportion phase-locked to slow waves during sleep.²⁹⁶ As with slower rhythmic LFP activity, RSC high-frequency oscillations and firing rate fluctuations are often coherent with hippocampal SWRs, but similar to other cortical areas, RSC firing responses are complex, with neurons demonstrating a range of excitation and inhibition at SWR onsets.^{269,297,298} Studies have found RSC neuronal responses to precede HPC SWR’s during slow wave sleep, with peak RSC inhibition time-locked to SWR onsets.^{299,300} Another recent study, however, found decreased thalamic input to superficial RSC inhibitory neurons in the seconds preceding

HPC SWRs,³⁰¹ which should release RSC from local inhibition. While more research is needed to conclude the complex coordination between RSC and HPC during SWRs, the current findings suggest SWRs in the hippocampal system might prime specific RSC networks to integrate long-range cortical connections.

Our understanding of consolidation mechanisms within RSC, and how they relate to HPC, is limited in a similar manner as our knowledge of RSC theta dynamics that underlie “online” retrieval and encoding processes. That is, we have yet to link coordinated HPC–RSC neurophysiology responses to behavior, as we have with HPC SWRs. As noted above, RSC neural activity correlates have been observed in relation to a variety of positional or movement features relative to both the subject and the environment. Neurons and the assemblies they form, of course, coordinate to transmit information at much finer timescales than could be observed by tracking a subject’s position and movement from an outside lens. In the HPC, for example, theta sequences and SWR-coordinated spike activity are found to reflect experiences temporally compressed by factors of 10–20 times, respectively.^{246,292}

While the processes required for downstream neurons to “read” finely timed sequences need further study, investigations into cortical dendritic computations suggest that the sequential order of synaptic inputs can govern the cell’s probability of response.³⁰² RSC neurons’ order of activation, relative to HPC sequential firing, might signify the direction of information flow in circuits composed of RSC and HPC populations, and the change in sequential ordering is indicative of an evolving neural state accompanied by an altered distribution of inputs. For example, RSC neurons with responses timed to precede HPC sequences (i.e., neurons found to fire at the beginning of a theta cycle) could be integrating inputs outside of the HPC and serve to bias the episodic memories or perspectives retrieved in a learned setting. Understanding the temporal activation of specific RSC neuron responses, such as those that are found to represent aspects of an environment (e.g., EBC’s or HD cells), might shed light on systems mechanisms that underlie memory use in spatial exploration.

Evaluating the RSC’s role in prediction

Connecting these neural mechanisms more strongly to memory recall and other behavior will be critical to developing a plausible predictive coding account of RSC function. We need to assess known RSC representations and their temporal coordination with HPC, along with other inputs or output regions, as dictated by anatomical discoveries. Behaviors composed of learning discrete sequences may afford the opportunity to manipulate RSC spike timing relative to perceptions, actions, neural oscillations, and fMRI activations. Experimental paradigms utilizing familiarity ratings to assay episodic memory—as in human fMRI research—should be careful to contrast both the degree of discrepancy between representational predictions and experimental stimuli (e.g., more challenging lure stimuli) as well as successful and unsuccessful recognition. Other potentially fruitful avenues of research, especially in humans where RSC remains more loosely defined, include diffusion-weighted MRI methods and functional connectivity analyses. These tools may reveal how RSC and other brain regions, or even networks, interact and change to better predict an animal’s environment.

CONCLUSIONS, NEXT STEPS, AND THE FUTURE OF RSC

Our review of the literature on RSC reveals a wide range of perspectives concerning how it may best be described anatomically, what its neural dynamics specifically reflect, and, given this, the functional role of RSC in spatial cognition and memory. We have discussed two complementary functions: (1) perspective shifting across a multitude of spatial reference frames and (2) prediction generation derived from the encoding of highly complex spatiotemporal contexts along with prediction updating derived from feedforward sensory error signals. Both functions align nicely with functional distinctions seen in human neuroimaging, such that anterior subregions tend to have more episodic memory functions, whereas posterior subregions tend to have more spatial tuning.^{64,75} These functions also align nicely with rodent neurophysiological work emphasizing fine-scale temporal organization of conjunctive coding of sensory, motor, and spatial information streams.

Perspective taking and prediction go hand-in-hand

RSC neurons display conjunctive tuning to multiple location, orientation, and timing variables and the region is well connected to areas responsible for stimulus-specific sensory representations, long-term memory, planning, and action. These conjunctions across sensory, motor, and spatial information processing streams can in turn form the basis for the interface of spatial representations in different reference frames; this interface is necessary for flexible perspective shifting. These same conjunctions also represent higher-order contextual information that can functionally predict simpler forms of information, such as the presence and egocentrically referenced location of an individual visual stimulus during movement through an environment.

With respect to navigation and encoding of environmental location and structure, one can easily identify multiple, highly specific codes within RSC implied by its individual cell types (e.g., encoding of route position and structure as well as encoding of position and orientation relative to environmental boundaries and landmarks). Each such code points to a role for RSC in representing an extended and richer “cognitive map” of the environment that is inextricably linked to computations necessary for transformations between spatial reference frames. This could take the form of specific bidirectional egocentric-alloentric transformations (e.g., mapping of egocentric scenes based on allocentric position and orientation). In this way, the spatial tuning properties of RSC populations and the diversity of its input/output circuitries are also consistent with the broader idea of perspective taking, such as in first-person versus top-down or differing first-person assessments of location in an environment. Here, the available data support the role of RSC not only in egocentric-alloentric perspective transformations but also in computing perspective from locations not currently occupied by the navigator (Figure 1).

For temporal coding related to episodic memory, we find evidence for a relationship between population-wide oscillations and spiking activity that supports the encoding of sequences and a temporal framework for interaction between HPC, the subicular complex, and cortex. Such encoding of experience across

time can form the basis for perceptual expectations based on prior learning episodes; this process is succinctly explained by models of predictive coding in the brain. Predictive coding, of course, can form a basis for neurophysiological processes related to matching of current sensory input to memory or to inputs from HPC reflecting current environmental location and orientation. In turn, mismatch, or error detection, can trigger the updating of representations as appears to be the case for orientation tuning.¹⁶⁶ A role for RSC in prediction is further supported by its sensitivity to well-learned spatial and non-spatial stimuli, especially during successful recognition memory. Finally, an appealing feature of this predictive coding framework is its potential to explain episodic memory findings “in addition to” spatial results as opposed to simply supplanting classical spatial accounts.

From a functional point of view, one could consider prediction generation to be part of the mechanisms—or “how”—and perspective taking to be part of the contents—or what—of episodic and spatial memory. Alternatively, perspective taking could be considered a type of predictive coding by predicting other spatial, temporal, or social viewpoints. Finally, these generalized functions of RSC—perspective taking and episodic prediction—are also suggestive of RSC contributing to a representation of spatiotemporal “context.” While a singular, unified theory of retrosplenial function may be far off or even improbable, we hope this review has provided some degree of synthesis across diverse and expanding literature on this fascinating region of the brain. An outstanding question, then, is how should future studies approach questions relating to the cognitive, neural, and behavioral correlates of RSC?

Current gaps and what is needed next

Even within a species, we have highlighted a number of critical gaps that remain in our understanding of RSC circuitry and function. To fill those gaps, we need strong theoretically informed tests of RSC function. For example, in humans, although the scene perception literature has a number of studies that distinguish the contributions of RSC from those of other scene-selective cortex,^{40,43,117,140} there are stunningly few human navigation or episodic memory neuroimaging studies containing hypothesis-driven tests of RSC function that is distinct from the HPC or general navigation/memory circuitry. Many of the findings we have uncovered on episodic memory, perception of self, familiarity, or viewpoint have come through looking at the lists of results but were not necessarily the highlighted finding of the paper. RSC is often an afterthought of the HPC and MTL, but it is time for theoretically driven tests of RSC function in humans.

To integrate and reconcile theoretical models of RSC, we need targeted tests of RSC’s anatomy, dynamics, and functional role in cognition. With respect to anatomy, future work in humans should better define the brain areas that should be considered RSC and delineate the afferent and efferent connections specific to humans. In rats, it is expected that modern approaches to circuit tracing and manipulation will resolve questions regarding (1) the potentially separable functions of dysgranular versus granular RSC, (2) computation across superficial and deep layers of RSC, and (3) the extent to which RSC should be viewed as a connection point between specific circuitries or viewed under

more common and generalized conceptions of “association cortices” as integrators of inputs from a very broad range of sources.

With respect to dynamics, future work in humans should address how to better measure changing functional connectivity and neural oscillations during complex behavior, potentially including new imaging modalities or analysis methods (e.g., dynamic functional connectivity). In rodents and humans, more work is needed to consider how RSC neurons operate under conditions wherein (1) location and orientation must be translated into action, (2) updating of landmark locations and orientations relative to the environment are necessary for task performance, and (3) boundary and route shapes vary systematically. For work in head-restrained conditions, work in humans and rodents must attempt to disentangle locations and orientation tuning from specific egocentric viewpoints and integrated distance.

With respect to its functional role in cognition, future work in rodents and humans should make targeted tests that distinguish between various hypotheses of RSC function. Specific testable possibilities include (1) translation between egocentric and allocentric frames of reference,¹⁵² (2) retrieval of well-learned spatio-temporal contexts,²¹⁹ (3) reconstruction of past episodes as well as the construction of prospective episodes,^{303,304} (4) relevance for successful recognition memory,^{224–226} and (5) the generation of predictions based on allocentric and conceptual knowledge, and the comparison of these predictions with incoming perceptual information.

We still have not fully answered the question posed by Vann, Aggleton, and Maguire:⁵⁵ “what does the RSC do?” Indeed, this review and the abundant set of new findings it examines may have opened up more questions about RSC function than they have answered. However, the last decade has produced a substantive and exciting body of knowledge that can move the field toward new insights into RSC circuitry and function and clarify the role of RSC as an integrator of multiple thalamic, hippocampal, and cortical systems.

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AUTHOR CONTRIBUTIONS

Conceptualization, A.S.A., R.P., M.J.S., E.R.C., and D.A.N.; writing – original draft, A.S.A., R.P., M.J.S., E.R.C., and D.A.N.; writing – review & editing, A.S.A., R.P., M.J.S., E.R.C., and D.A.N.; visualization, A.S.A., R.P., M.J.S., E.R.C., and D.A.N.; supervision, E.R.C. and D.A.N., project administration, D.A.N.; funding acquisition, A.S.A., E.R.C., and D.A.N.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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