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Authors

Alexander, Andrew S

Place, Ryan

Starrett, Michael J

et al.

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Rethinking retrosplenial cortex: Perspectives and predictions

Andrew S. Alexander[1,6], **Ryan Place**[2,6], **Michael J. Starrett**[3,6], **Elizabeth R. Chrastil**[3,4,7,*], **Douglas A. Nitz**[2,5,7,*]

[1]Department of Psychological and Brain Sciences; Boston University; Boston, MA, 02215; USA

[2]Department of Cognitive Science, University of California, San Diego, La Jolla, CA, 92093; USA

[3]Department of Neurobiology & Behavior, University of California, Irvine, Irvine, CA, 92697; USA

[4]Department of Cognitive Sciences, University of California, Irvine, Irvine, CA 92697; USA

Summary:

The last decade has produced an exciting body of knowledge about the retrosplenial cortex (RSC) that has led to novel insights into RSC circuitry and function as well as clarification of its role as an integrator of multiple brain systems. Still, open questions concerning the computational processes to which RSC contributes remain as does the question of what makes RSC functionally unique. Here, we evaluate the great diversity in forms of spatial and directional tuning of RSC activity, the temporal organization of RSC activity, and the placement, anatomically, of RSC as a nexus point for interactions among a highly diverse set of inputs. We find that RSC anatomy and dynamics are more consistent with a functional role in multiple specific sensorimotor and cognitive processes than with any isolated function. However, we suggest that two more generalized, non-exclusive categories of function can be used to characterize unique roles for retrosplenial cortex circuitry and dynamics in complex cognitive processes. These processes are: *i)* shifting and relating perspectives for spatial cognition and *ii)* stimulus prediction and error correction for current sensory states with internal representations of the environment. The latter function has important implications for the encoding and retrieval of contextual and episodic memories. Both functions likely take advantage of the capacity for RSC neurons to encode conjunctions among sensory, motor, and spatial mapping information streams. Together, these

[*]**Corresponding author:** dnitz@ucsd.edu, chrastil@uci.edu.

[5]Lead contact

[6]These authors contributed equally; order determined by coin flip

[7]Senior authors contributed equally

Author Contributions

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What is the retrosplenial cortex and what does it do? Alexander et al. discuss theories inspired by these questions and highlight their limitations. They propose that retrosplenial activity serves to relate spatial perspectives and to generate predictions about environmental interactions.

Declaration of Interests

The authors declare no conflicts of interest.

functions provide the scaffold for intelligent actions, such as navigation, perspective-taking, and interaction with others, as well as detecting changes in the environment and errors in our expectations of those changes.

Keywords

Perspective taking; Allocentric; Egocentric; Orientation; Episodic Memory; Temporal Sequence; Navigation; Predictive Coding; Spatial Transformation; Network Oscillations

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, 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 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, anterior cingulate cortex, 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 [59] for review). We note that all sub-regions of RSC are highly interconnected with each other [55].

RSC is clearly unique in the extent to which it is positioned to integrate sensory and motor systems with output from regions such as anterior thalamus and subiculum 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. 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 [56]. 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 [57]. 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, 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 [56].

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) [58,59]. There are no clear gross anatomical boundaries with precuneus, parahippocampal cortex (PHC), or posterior cingulate cortex [58,60], 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 (BA) 29a-c in anterior RSC (corresponding to ventral in the rodent), whereas dysgranular cortex is found in BA30 in the posterior (dorsal) region [58,59]. 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 [58,62,63], 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 [61,64] 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 [58,64], whereas others disagree with this inclusion [59]. 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* [65], which includes regions posterior to BA29 and 30, instead including POS, lingual gyrus, and calcarine sulcus [39,66–70]. 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, anterior thalamus, dorsolateral prefrontal cortex (dlPFC), posterior cingulate, and V4, many of which connect through the cingulum bundle [59]. 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 connectivity to occipital regions and vision networks. Anterior/medial areas display connectivity to posterior cingulate, medial prefrontal cortex, and other areas of the default mode network (RSC is often considered part of the default mode network, 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 [69,71,73–75]. High-resolution imaging of local hippocampal connections shows significant functional connectivity with DG/CA4, CA3/2, pre/parasubiculum, and uncus, but not CA1 or subiculum [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, 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 vs. 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 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 acknowledgement 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, parahippocampal cortex, or 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. [73,74] 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., anterior and lateral dorsal thalamus), and the extended hippocampal formation (hippocampus, 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; [78,79,27,7,18]. From a spatial cognition perspective, these observations suggest 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 in order 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 [54,82]. Although linear and angular speed has not yet been associated (or tested to our knowledge) with human RSC activation, fMRI correlates provide indirect evidence for RSC involvement in orienting and tracking functions related to path integration [37,83]. In particular, RSC tracks rotations in place [84], 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 [26,16,18,11]. 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 [85,20,26,86,12,25,22,9]. 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 [87], 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; [88–91,6,30,79]. The preferred receptive field across the EBC ensemble spans the full complement of orientations and distances, generating a signal that could 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 parahippocampal cortex [92], but no recordings in RSC have been attempted to 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 [93,94]. Encoding a spatial layout from a first-person perspective shows enhanced RSC activation compared to encoding from a top-down view, suggesting that RSC could be more important for changes in egocentric head direction than for allocentric location processing [95]. RSC is also sensitive to mirror-reversals in scenes, possibly related

to processing egocentric directions for movement [96]. 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 [97]. 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 to non-self processing, and RSC activation is associated with recalling events that actually happened to oneself compared to imagined events [98], 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 [99–102]. RSC is part of the default mode network, 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 [103]. Finally, recent work demonstrated the presence and potential causal relationship between a slow network oscillation (1–3Hz) 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 [104].

While egocentric coding of self-motion, visual information, and boundaries clearly support spatial cognition and navigation, 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 head direction 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 head direction 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 [105–107]. 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 head direction and for position.

Head direction coding.: Subsets of RSC neurons are sensitive to the heading direction (HD) of the animal relative to environmental boundaries and the layout of prominent landmarks (Figure 4e; [17,79,108–110]). Physiologically distinct cell-types in superficial RSC may process sustained or transient HD information [111,112] 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 [113]. Using fMRI and virtual environments to study head direction in humans has its limitations [114], but they can help identify regions that are sensitive to head direction. RSC is sensitive to changes in global heading direction in humans [44,115,116] and to encoding rotation [84], as well as direction changes in abstract spaces [117]. 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 [17,39,118].

Spatial position coding.: One fMRI study found that RSC codes for allocentric location in humans, although sensitivity to head direction was limited [70], but a more recent study found sensitivity to both location and heading [119]. 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 [120,121]. 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 tasks[122] and during virtual navigation with two-photon calcium imaging [20,21,25,33,12,22]. Similar responsivity has been observed in freely moving studies in rodents [6,30,24], 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 [7,31,8,23,10,123]. These 'route-centered' firing patterns were initially observed in PPC in animals traversing labyrinthian mazes but have now been reported in RSC and other cortical areas [124,125]. Tuning to route space has also been observed in some hippocampal CA1 neurons and in entorhinal cortex [126–130] 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 (Figure 4g–h). Thus, ensembles of route position encoding neurons enable precise reconstruction of the animal's position within a route of a particular shape[131] (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 [65,132]. 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 [133] and it is sensitive to boundary extension illusions [134], 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 [67,135] or when stitching multiple views together into a sense of place [136].

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 [137–140]. Furthermore, RSC is not particularly sensitive to the navigational affordances of a scene[141], 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 [142]. 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 [143,144]. 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 [28,31,20,24,145,13,29]. Together, these findings suggest that RSC extrapolates location information beyond the visual input [65,132], consistent with a route-centered coordinate frame, but there are some findings from the scene literature which 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 [127,146–149]. 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 [124,146], 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 space[8] (Figure 4g–h). 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 [72]. For example, RSC activity tracks object positions along a route, and is sensitive to route direction [150]. 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 locations [151]. In non-spatial domains, RSC codes information about structure within social networks, consistent with mapping topological structure [152]. 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 [153–155]. 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 heading direction, 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 head direction system and extended hippocampal formation emerges from intrinsic connectivity even in the absence of sensory drive [156–160].

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, head direction 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 [154,161,162,153]. These mappings serve to align egocentric viewpoints with their associated allocentric locations (e.g. Figure 5A,B,C,D). 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 [91,6,30,163]. 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 [7,8,22,25,12,24].

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 [164–167]. In RSC, this conjunctive coding can manifest as EBCs that are modulated by specific allocentric head directions, which directly resemble responses in the transformation layer of the network described above (Figure 4e, bottom).

Further, inactivation of RSC causes angular drift of head direction neurons relative to visual landmarks, providing evidence for a role of RSC in anchoring of allocentric perspectives to sensory information during navigation [162,168]. 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 [169,170,80,171–180]

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 [181–183,90,184,185]. 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 medial entorhinal cortex, 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., 186]and to navigating from a first-person perspective after looking at a top-down (allocentric) perspective [121,e.g., 187]. RSC activity also supports allocentric head direction coding that can be used for first-person navigation [44,118,e.g., 188]. Similarly patients with damage to the inferior parietal cortex, posterior cingulate cortex, and RSC have demonstrated difficulty integrating information across egocentric and allocentric frames [189–193]. 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 (Figure 5E,F) 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 frame[47] 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 [194], 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[195], but not in others[196–198]. However, RSC is functionally connected to the hippocampus during early retrieval of different perspectives, particularly when taking atypical observer perspectives[199], 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 to imagined events leads to anterior RSC activation[98], 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 amongst neural populations (see excellent work examining this exact question in flies in [200–202]) 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 [203]. 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 simplistic [56] given that RSC is recruited during both "what" and "where" information encoding and retrieval in rats [204]. 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 processing [19] whereas a transformation model places greater emphasis on the role of RSC in mediating between parietal and medial temporal lobe (MTL) representations [154]. 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 [205,206]. 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 feed-forward 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 ERC and SUB [207,208] as well as projections to secondary motor cortices [57,209,210], 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 [211], 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 [212]. 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 [213]. 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 [214–216]. 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.

RSCs 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 [172], 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 minute inter-trial intervals [217]. 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., (2017) 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-vs-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 [219]. Investigations into RSC activity found increased RSC BOLD responses correlated with faster recall of responses tied to discrete item cues [220], whereas decreased glucose metabolism in RSC has been associated with temporal disorientation amongst Alzheimer's patients [221]. 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 [222]. 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 learning [19] 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[223]. Taken together, HPC and RSC may each represent one level of a predictive coding hierarchy in the human brain [224]. 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 amongst 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 [225,226]. RSC is implicated in successful recognition memory retrieval but not encoding[227–229]. In a human fMRI study of default mode network regions implicated in episodic memory retrieval, significant functional connectivity was observed between MTL and RSC but not between MTL and other default mode networks. Further, RSC but not posterior cingulate cortex showed evidence of mediating MTL connectivity with other cortical default mode network regions [230]. This connectivity underscores the functional importance of RSC as a hub for information processing. Moreover, the extent of this mediation tacked with episodic retrieval success, indicating a link between RSC network functionality and episodic memory. One caveat of these results is that the study focused on healthy older adults, whose functional connectivity may differ from younger cohorts.

The process of consolidating episodic memories, which involves systems-level changes in how representations are instantiated in the brain between initial encoding and successful long-term retrieval, might better explain such RSC-MTL network dynamics. Further literature review and meta-analytic investigations may prove useful in understanding the frequency in which RSC has been an *a priori* target of study in addition to co-activating with other regions of interest when studying familiarity and recollection[231] or episodic memory more generally. Research investigating how RSC and MTL regions differentially support episodic memory across encoding and retrieval will also be crucial. Figure 7A shows hypothetical brain networks during encoding and short-term retention of episodic spatiotemporal context information as well as during long-term retrieval and reinstantiation of this information (Figure 7B). In the former, RSC plays a more passive role, relying on HPC for newly established, context-bound episodic memories. In the latter, RSC retrieves and actively represents bound spatiotemporal contexts and episodic memories in addition to but independent of HPC; this would enable RSC to provide more direct, top-down influence on low-level sensory regions [19,see 225]. Such network reconfiguration in the service of increasingly stable memories that are less susceptible to the effects of interference and focal damage refers to the process of systems consolidation, although this term has become somewhat more divisive of late [see 211]. Thus, Figure 7 represents a simplified visualization of how RSC might serve as a high-level prediction node specifically for well-established memories.

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 [209,232,233]. 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 [208]. 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 orbitofrontal cortex via basal ganglia structures [234] further suggests a role for RSC in reward-based reinforcement and decision making. Such mechanisms may drive similar behavior in humans [235].

Lesions and Case Studies.: Insults to human RSC and the surrounding regions have produced amnestic effects including reduced or non-existent memory for episodic details from stories as well as deficits in autobiographical memory, a syndrome termed retrosplenial amnesia [236,237]. Only a handful of additional cases of retrosplenial amnesia have been reported since [238–241], 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 [242].

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 [176]. 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 [80,243] or after maze rotations, when locally available movements conflict with distally anchored senses of space or direction [174]. Merging visual cues from multiple environments is also found to increase IEG expression in RSC during radial-arm maze performance [244]. RSC lesions also most noticeably impaired T-maze alternation during darkness, where only vestibular sources remained available to guide spatial movement patterns [176]. T-maze navigation in darkness, or conditions that favor egocentric strategies, are accompanied by increased IEG expression in RSC [178,180].

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 judgements 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 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 [206,213,245,246]. Notably, a wealth of research has identified temporal codes in HPC that relate ongoing [247–249] and temporally disjoint experiences [250–253], which have been found to predict forthcoming behaviors and are causatively linked to spatial working memory [252,254–259]. While RSC oscillations and neural populations are often found to shadow HPC dynamics during awake exploratory behavior, specific subtypes of RSC neurons (e.g. egocentric boundary cells) 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 medial temporal lobe areas [260–264]. Curiously, stimulation of this same region fails to produce any noticeable effect on perception, sensation, or autobiographical detail as reported by subjects [265]. 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 [266]. In humans, slower 1–5 (~3) Hz theta - outside the traditional 4–8 Hz cutoff for humans - has been compared to higher 4–12 (~8) Hz theta observed in rodents[267–269], although this is not always the case [261,262]. 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 [270], and the cyclic changes in synaptic plasticity is theorized to support encoding and retrieval of episodic memories [271]. 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) [272,273]. 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 [104,274].

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 memory [275]. Stronger theta-gamma PAC in HPC and cortical regions is linked to increased contextual memory performance and working memory demands respectively [276,277], and specific gamma frequencies coupled to theta phases across MTL subregions have been used to indicate the strength of temporal coordination [278,279].

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 [264], and is linked to coordinated activity between posteromedial sites and MTL regions as well as lateral parietal structures including angular gyrus [262,263]. 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 frequencies and maximal spiking phases, with RSC low-to-high gamma abruptly transitioning at theta peaks, shadowing similar patterns observed in CA1 [272] (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 [280], along with RSC's EBCs (described above), tend to fire at earlier theta-phases than the general population [6,281] (Figure 8A). Similarly, CA1 firing to preferred odors has been found to lock to early theta-phases in response to the presentation of sequences of discrete odor-events [218]. 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. EBC's) 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 time scales (100s of ms). Yet, RSC-HPC interactions may also coordinate memory consolidation and transformation across much longer time scales. RSC has been viewed as a key region in systems consolidation, under the various flavors of multiple trace theory [282,283,284,214,285–288]. 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 [42,186,289,290]. 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 to newly learned pairs [291]. One study involving rats showed that anterior RSC was necessary for representing object recognition ("what"), whereas dorsal HPC was not [204]. In this study, the GABA agonist, muscimol, interfered with memory performance 24 hours 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 scenes [292] 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 [293]. Although other consolidation theories (e.g. synaptic homeostasis)[294] 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 [253,295,296]. SWRs have been directly linked to memory performance [256,297], 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 [298], 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 [299]. As with slower rhythmic LFP activity, RSC high-frequency oscillations and firing rate fluctuations are often coherent with hippocampal SWRs, but like other cortical areas, RSC firing responses are complex, with neurons demonstrating a range of excitation and inhibition at SWR onsets [272,300,301]. Studies have found RSC neuronal responses to precede HPC SWR's during slow wave sleep, with peak RSC inhibition time-locked to SWR onsets [302,303]. Another recent study, however, found decreased thalamic input to superficial RSC inhibitory neurons in the seconds preceding HPC SWRs [304], 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 to 20 times respectively [249,295].

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 [305]. 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, like those that are found to represent aspects of an environment (e.g., EBC's or head-direction cells), might shed light on systems mechanisms that underlie memory use in spatial exploration.

Evaluating 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[73,75]. 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-allocentric 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-allocentric 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 hippocampus, 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 hippocampus 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[168]. 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 [40,43,119,142], there are stunningly few human navigation or episodic memory neuroimaging studies containing hypothesis-driven tests of RSC function that is distinct from the hippocampus 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 hippocampus 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 *i)* the potentially separable functions of dysgranular versus granular RSC, *ii)* computation across superficial and deep layers of RSC, and *iii)* 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 *i)* location and orientation must be translated into action, *ii)* updating of landmark locations and orientations relative to the environment are necessary for task performance, and *iii)* 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 *i)* translation between egocentric and allocentric frames of reference [154], *ii)* retrieval of well-learned spatiotemporal contexts [222], *iii)* reconstruction of past episodes as well as the construction of prospective episodes [306,307], *iv)* relevance for successful recognition memory [227–229], and *v)* 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[59]: "What does the retrosplenial cortex 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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References

1. Sporns O, Honey CJ & Kötter R. Identification and Classification of Hubs in Brain Networks. PLOS ONE 2, e1049 (2007).
2. Sugar J, Witter MP, van Strien NM & Cappaert NLM The retrosplenial cortex: intrinsic connectivity and connections with the (para)hippocampal region in the rat. An interactive connectome. Front. Neuroinformatics 5, 7 (2011).
3. van Groen T. & Michael Wyss J. Connections of the retrosplenial granular a cortex in the rat. J. Comp. Neurol 300, 593–606 (1990). [PubMed: 2273095]
4. Van Groen T. & Wyss JM Connections of the retrosplenial granular b cortex in the rat. J. Comp. Neurol 463, 249–263 (2003). [PubMed: 12820159]
5. Wyass JM & Van Groen T. Connections between the retrosplenial cortex and the hippocampal formation in the rat: A review. Hippocampus 2, 1–11 (1992). [PubMed: 1308170]
6. Alexander AS et al. Egocentric boundary vector tuning of the retrosplenial cortex. Sci. Adv 6, eaaz2322 (2020).
7. Alexander AS & Nitz DA Retrosplenial cortex maps the conjunction of internal and external spaces. Nat. Neurosci 18, 1143–1151 (2015). [PubMed: 26147532]
8. Alexander AS & Nitz DA Spatially Periodic Activation Patterns of Retrosplenial Cortex Encode Route Sub-spaces and Distance Traveled. Curr. Biol. CB 27, 1551–1560.e4 (2017). [PubMed: 28528904]
9. Chang H. et al. Coordinated activities of retrosplenial ensembles during resting-state encode spatial landmarks. Philos. Trans. R. Soc. B Biol. Sci 375, 20190228 (2020).
10. Chinzorig C. et al. Rat Retrosplenial Cortical Involvement in Wayfinding Using Visual and Locomotor Cues. Cereb. Cortex 30, 1985–2004 (2020). [PubMed: 31667498]

11. Clancy KB, Orsolic I. & Mrsic-Flogel TD Locomotion-dependent remapping of distributed cortical networks. Nat. Neurosci 22, 778–786 (2019). [PubMed: 30858604]
12. Fischer LF, Mojica Soto-Albors R, Buck F. & Harnett MT Representation of visual landmarks in retrosplenial cortex. eLife 9, e51458 (2020).
13. Franco LM & Goard MJ A distributed circuit for associating environmental context with motor choice in retrosplenial cortex. Sci. Adv (2021) doi:10.1126/sciadv.abf9815.
14. Hattori R, Danskin B, Babic Z, Mlynaryk N. & Komiyama T. Area-Specificity and Plasticity of History-Dependent Value Coding During Learning. Cell 177, 1858–1872.e15 (2019). [PubMed: 31080067]
15. Hattori R. & Komiyama T. Context-dependent persistency as a coding mechanism for robust and widely distributed value coding. Neuron (2021) doi:10.1016/j.neuron.2021.11.001.
16. Hennestad E, Witoelar A, Chambers AR & Vervaeke K. Mapping vestibular and visual contributions to angular head velocity tuning in the cortex. Cell Rep. 37, 110134 (2021).
17. Jacob P-Y et al. An independent, landmark-dominated head-direction signal in dysgranular retrosplenial cortex. Nat. Neurosci 20, 173–175 (2017). [PubMed: 27991898]
18. Keshavarzi S. et al. Multisensory coding of angular head velocity in the retrosplenial cortex. Neuron S0896–6273(21)00846–1 (2021) doi:10.1016/j.neuron.2021.10.031.
19. Makino H. & Komiyama T. Learning enhances the relative impact of top-down processing in the visual cortex. Nat. Neurosci 18, 1116–1122 (2015). [PubMed: 26167904]
20. Mao D, Kandler S, McNaughton BL & Bonin V. Sparse orthogonal population representation of spatial context in the retrosplenial cortex. Nat. Commun 8, 243 (2017). [PubMed: 28811461]
21. Mao D. et al. Hippocampus-dependent emergence of spatial sequence coding in retrosplenial cortex. Proc. Natl. Acad. Sci. U. S. A 115, 8015–8018 (2018). [PubMed: 30012620]
22. Mao D, Molina LA, Bonin V. & McNaughton BL Vision and Locomotion Combine to Drive Path Integration Sequences in Mouse Retrosplenial Cortex. Curr. Biol. CB 30, 1680–1688.e4 (2020). [PubMed: 32197086]
23. Miller AMP, Mau W. & Smith DM Retrosplenial Cortical Representations of Space and Future Goal Locations Develop with Learning. Curr. Biol. CB 29, 2083–2090.e4 (2019). [PubMed: 31178316]
24. Miller AMP, Serrichio AC & Smith DM Dual-Factor Representation of the Environmental Context in the Retrosplenial Cortex. Cereb. Cortex 31, 2720–2728 (2021). [PubMed: 33386396]
25. Minderer M, Brown KD & Harvey CD The Spatial Structure of Neural Encoding in Mouse Posterior Cortex during Navigation. Neuron 102, 232–248.e11 (2019). [PubMed: 30772081]
26. Powell A. et al. Stable Encoding of Visual Cues in the Mouse Retrosplenial Cortex. Cereb. Cortex 30, 4424–4437 (2020). [PubMed: 32147692]
27. Rancz EA et al. Widespread Vestibular Activation of the Rodent Cortex. J. Neurosci 35, 5926–5934 (2015). [PubMed: 25878265]
28. Smith DM, Barredo J. & Mizumori SJY Complimentary roles of the hippocampus and retrosplenial cortex in behavioral context discrimination. Hippocampus 22, 1121–1133 (2012). [PubMed: 21630374]
29. Sun W. et al. Context value updating and multidimensional neuronal encoding in the retrosplenial cortex. Nat. Commun 12, 6045 (2021). [PubMed: 34663792]
30. van Wijngaarden JB, Babl SS & Ito HT Entorhinal-retrosplenial circuits for allocentric-egocentric transformation of boundary coding. eLife 9, e59816 (2020).
31. Vedder LC, Miller AMP, Harrison MB & Smith DM Retrosplenial Cortical Neurons Encode Navigational Cues, Trajectories and Reward Locations During Goal Directed Navigation. Cereb. Cortex N. Y. N 1991 (2016) doi:10.1093/cercor/bhw192.
32. Vélez-Fort M. et al. A Circuit for Integration of Head- and Visual-Motion Signals in Layer 6 of Mouse Primary Visual Cortex. Neuron 98, 179–191.e6 (2018). [PubMed: 29551490]
33. Voigts J. & Harnett MT Somatic and Dendritic Encoding of Spatial Variables in Retrosplenial Cortex Differs during 2D Navigation. Neuron 105, 237–245.e4 (2020). [PubMed: 31759808]
34. Auger SD, Mullally SL & Maguire EA Retrosplenial Cortex Codes for Permanent Landmarks. PLoS ONE 7, e43620 (2012).

35. Auger SD, Zeidman P. & Maguire EA Efficacy of navigation may be influenced by retrosplenial cortex-mediated learning of landmark stability. Neuropsychologia 104, 102–112 (2017). [PubMed: 28802770]
36. Auger SD & Maguire EA Retrosplenial Cortex Indexes Stability beyond the Spatial Domain. J. Neurosci 38, 1472–1481 (2018). [PubMed: 29311139]
37. Chrastil ER, Sherrill KR, Hasselmo ME & Stern CE There and back again: Hippocampus and retrosplenial cortex track homing distance during human path integration. J Neurosci 35, 15442–15452 (2015). [PubMed: 26586830]
38. Lambrey S, Doeller C, Berthoz A. & Burgess N. Imagining being somewhere else: Neural basis of changing perspective in space. Cereb. Cortex 22, 166–174 (2012). [PubMed: 21625010]
39. Marchette SA, Vass LK, Ryan J. & Epstein RA Anchoring the neural compass: coding of local spatial reference frames in human medial parietal lobe. Nat. Neurosci 17, 1598–1606 (2014). [PubMed: 25282616]
40. Marchette SA, Vass LK, Ryan J. & Epstein RA Outside looking in: Landmark generalization in the human navigational system. J. Neurosci 35, 14896–908 (2015). [PubMed: 26538658]
41. Nau M, Navarro Schröder T, Frey M. & Doeller CF Behavior-dependent directional tuning in the human visual-navigation network. Nat. Commun 11, 3247 (2020). [PubMed: 32591544]
42. Patai EZ et al. Hippocampal and retrosplenial goal distance coding after long-term consolidation of a real-world environment. Cereb. Cortex 29, 2748–2758 (2019). [PubMed: 30916744]
43. Peer M. & Epstein RA The human brain uses spatial schemas to represent segmented environments. Curr. Biol 31, 4677–4688.e8 (2021). [PubMed: 34473949]
44. Shine JP, Valdés-Herrera JP, Hegarty M. & Wolbers T. The human retrosplenial cortex and thalamus code head direction in a global reference frame. J. Neurosci 36, 6371–6381 (2016). [PubMed: 27307227]
45. Sulpizio V, Boccia M, Guariglia C. & Galati G. Functional connectivity between posterior hippocampus and retrosplenial complex predicts individual differences in navigational ability. Hippocampus 26, 841–847 (2016). [PubMed: 27013151]
46. Sulpizio V, Committeri G, Lambrey S, Berthoz A. & Galati G. Role of the human retrosplenial cortex/parieto-occipital sulcus in perspective priming. NeuroImage 125, 108–119 (2016). [PubMed: 26484830]
47. Sulpizio V, Committeri G, Lambrey S, Berthoz A. & Galati G. Selective role of lingual/parahippocampal gyrus and retrosplenial complex in spatial memory across viewpoint changes relative to the environmental reference frame. Behav. Brain Res 242, 62–75 (2013). [PubMed: 23274842]
48. Sulpizio V, Galati G, Fattori P, Galletti C. & Pitzalis S. A common neural substrate for processing scenes and egomotion-compatible visual motion. Brain Struct. Funct 225, 2091–2110 (2020). [PubMed: 32647918]
49. Vesuna S. et al. Deep posteromedial cortical rhythm in dissociation. Nature 586, 87–94 (2020). [PubMed: 32939091]
50. Raichle ME The brain's default mode network. Annu. Rev. Neurosci 38, 433–447 (2015). [PubMed: 25938726]
51. Shibata H, Kondo S. & Naito J. Organization of retrosplenial cortical projections to the anterior cingulate, motor, and prefrontal cortices in the rat. Neurosci. Res 49, 1–11 (2004). [PubMed: 15099698]
52. Sripanidkulchai K. & Wyss JM Thalamic projections to retrosplenial cortex in the rat. J. Comp. Neurol 254, 143–165 (1986). [PubMed: 3794004]
53. van Groen T. & Wyss JM Connections of the retrosplenial dysgranular cortex in the rat. J. Comp. Neurol 315, 200–216 (1992). [PubMed: 1545009]
54. Vogt BA & Miller MW Cortical connections between rat cingulate cortex and visual, motor, and postsubicular cortices. J. Comp. Neurol 216, 192–210 (1983). [PubMed: 6863602]
55. Shibata H, Honda Y, Sasaki H. & Naito J. Organization of intrinsic connections of the retrosplenial cortex in the rat. Anat. Sci. Int 84, 280 (2009). [PubMed: 19322631]

56. Ekstrom AD, Huffman DJ & Starrett M. Interacting networks of brain regions underlie human spatial navigation: A review and novel synthesis of the literature. J. Neurophysiol 118, 3328–3344 (2017). [PubMed: 28931613]
57. Yamawaki N, Radulovic J. & Shepherd GM G. A Corticocortical Circuit Directly Links Retrosplenial Cortex to M2 in the Mouse. J. Neurosci 36, 9365–9374 (2016). [PubMed: 27605612]
58. Kobayashi Y. & Amaral DG Macaque monkey retrosplenial cortex: I. three-dimensional and cytoarchitectonic organization. J. Comp. Neurol 426, 339–65 (2000). [PubMed: 10992242]
59. Vann SD, Aggleton JP & Maguire EA What does the retrosplenial cortex do? Nat. Rev. Neurosci 10, 792–802 (2009). [PubMed: 19812579]
60. Pruessner JC Entorhinal and parahippocampal cortex from high-resolution MR images: Considering the variability of the collateral sulcus. Cereb. Cortex 12, 1342–1353 (2002). [PubMed: 12427684]
61. Morris R, Paxinos G. & Petrides M. Architectonic analysis of the human retrosplenial cortex. J. Comp. Neurol 421, 14–28 (2000). [PubMed: 10813770]
62. Braak H. Pigment architecture of the human telencephalic cortex. Cell Tissue Res. 204, 431–440 (1979). [PubMed: 527027]
63. Vogt BA, Vogt LJ, Perl DP & Hof PR Cytology of human caudomedial cingulate, retrosplenial, and caudal parahippocampal cortices. J. Comp. Neurol 438, 353–376 (2001). [PubMed: 11550177]
64. Morris R, Petrides M. & Pandya DN Architecture and connections of retrosplenial area 30 in the rhesus monkey (macaca mulatta). Eur. J. Neurosci 11, 2506–2518 (1999). [PubMed: 10383640]
65. Epstein RA Parahippocampal and retrosplenial contributions to human spatial navigation. Trends Cogn. Sci 12, 388–96 (2008). [PubMed: 18760955]
66. Epstein RA & Kanwisher N. A cortical representation of the local visual environment. Nature 392, 598–601 (1998). [PubMed: 9560155]
67. Park S. & Chun MM Different roles of the parahippocampal place area (PPA) and retrosplenial cortex (RSC) in panoramic scene perception. NeuroImage 47, 1747–1756 (2009). [PubMed: 19398014]
68. Silson EH, Steel AD & Baker CI Scene-selectivity and retinotopy in medial parietal cortex. Front. Hum. Neurosci 10, 1–17 (2016). [PubMed: 26858619]
69. Silson EH et al. A Posterior–Anterior Distinction between Scene Perception and Scene Construction in Human Medial Parietal Cortex. J. Neurosci 39, 705–717 (2019). [PubMed: 30504281]
70. Vass LK & Epstein RA Abstract representations of location and facing direction in the human brain. J. Neurosci 33, 6133–42 (2013). [PubMed: 23554494]
71. Vogt BA, Vogt L. & Laureys S. Cytology and functionally correlated circuits of human posterior cingulate areas. NeuroImage 29, 452–466 (2006). [PubMed: 16140550]
72. Peer M, Brunec IK, Newcombe NS & Epstein RA Structuring knowledge with cognitive maps and cognitive graphs. Trends Cogn. Sci 25, 37–54 (2021). [PubMed: 33248898]
73. Chrastil ER et al. Converging meta-analytic and connectomic evidence for functional subregions within the human retrosplenial region. Behav. Neurosci 132, 339–355 (2018). [PubMed: 30321025]
74. Burles F, Umiltá A, McFarlane LH, Potocki K. & Iaria G. Ventral—Dorsal Functional Contribution of the Posterior Cingulate Cortex in Human Spatial Orientation: A Meta-Analysis. Front. Hum. Neurosci 12, 190 (2018). [PubMed: 29867414]
75. Chrastil ER Heterogeneity in human retrosplenial cortex: A review of function and connectivity. Behav. Neurosci 132, 317–338 (2018). [PubMed: 30160506]
76. Dalton MA, McCormick C. & Maguire EA Differences in functional connectivity along the anterior-posterior axis of human hippocampal subfields. NeuroImage 192, 38–51 (2019). [PubMed: 30840906]
77. Li P. et al. Structural and functional brain network of human retrosplenial cortex. Neurosci. Lett 674, 24–29 (2018). [PubMed: 29530816]

78. Chen LL, Lin LH, Barnes CA & McNaughton BL Head-direction cells in the rat posterior cortex. II. Contributions of visual and ideothetic information to the directional firing. Exp. Brain Res 101, 24–34 (1994). [PubMed: 7843299]

79. Cho J. & Sharp PE Head direction, place, and movement correlates for cells in the rat retrosplenial cortex. Behav. Neurosci 115, 3–25 (2001). [PubMed: 11256450]

80. Cooper BG, Manka TF & Y J. Finding your way in the dark: The retrosplenial cortex contributes to spatial memory and navigation without visual cues. Behav. Neurosci 115, 1012–1028 (2001). [PubMed: 11584914]

81. Elduayen C. & Save E. The retrosplenial cortex is necessary for path integration in the dark. Behav. Brain Res 272, 303–307 (2014). [PubMed: 25026093]

82. Yamawaki N, Radulovic J. & Shepherd GM G. A Corticocortical Circuit Directly Links Retrosplenial Cortex to M2 in the Mouse. J. Neurosci. Off. J. Soc. Neurosci 36, 9365–9374 (2016).

83. Wiener M, Michaelis K. & Thompson JC Functional correlates of likelihood and prior representations in a virtual distance task. Hum. Brain Mapp 37, 3172–3187 (2016). [PubMed: 27167875]

84. Chrastil ER, Sherrill KR, Hasselmo ME & Stern CE Which way and how far? Tracking of translation and rotation information for human path integration. Hum. Brain Mapp 37, 3636–3655 (2016). [PubMed: 27238897]

85. Zhuang J. et al. An extended retinotopic map of mouse cortex. eLife 6, (2017).

86. Campbell MG, Attinger A, Ocko SA, Ganguli S. & Giocomo LM Distance-tuned neurons drive specialized path integration calculations in medial entorhinal cortex. Cell Rep. 36, (2021).

87. Sherrill KR et al. Functional connections between optic flow areas and navigationally responsive brain regions during goal-directed navigation. NeuroImage 118, 386–396 (2015). [PubMed: 26054874]

88. Wang C. et al. Egocentric coding of external items in the lateral entorhinal cortex. Science 362, 945–949 (2018). [PubMed: 30467169]

89. Hinman JR, Chapman GW & Hasselmo ME Neuronal representation of environmental boundaries in egocentric coordinates. Nat. Commun 10, 2772 (2019). [PubMed: 31235693]

90. LaChance PA, Todd TP & Taube JS A sense of space in postrhinal cortex. Science 365, eaax4192 (2019).

91. Gofman X. et al. Dissociation between Postrhinal Cortex and Downstream Parahippocampal Regions in the Representation of Egocentric Boundaries. Curr. Biol 29, 2751–2757.e4 (2019). [PubMed: 31378610]

92. Kunz L. et al. A neural code for egocentric spatial maps in the human medial temporal lobe. Neuron 109, 2781–2796.e10 (2021). [PubMed: 34265253]

93. Gauthier B. & van Wassenhove V. Time Is Not Space: Core Computations and Domain-Specific Networks for Mental Travels. J. Neurosci 36, 11891–11903 (2016). [PubMed: 27881776]

94. Persichetti AS & Dilks DD Perceived egocentric distance sensitivity and invariance across scene-selective cortex. Cortex 77, 155–163 (2016). [PubMed: 26963085]

95. Gomez A, Cerles M, Rousset S, R??my C. & Baciu M. Differential hippocampal and retrosplenial involvement in egocentric-updating, rotation, and allocentric processing during online spatial encoding: an fMRI study. Front. Hum. Neurosci 8, 150 (2014). [PubMed: 24688464]

96. Dilks DD, Julian JB, Kubilius J, Spelke ES & Kanwisher N. Mirror-image sensitivity and invariance in object and scene processing pathways. J. Neurosci 31, 11305–12 (2011). [PubMed: 21813690]

97. Peer M, Salomon R, Goldberg I, Blanke O. & Arzy S. Brain system for mental orientation in space, time, and person. Proc. Natl. Acad. Sci. U. S. A 112, 11072–7 (2015). [PubMed: 26283353]

98. Summerfield JJ, Hassabis D. & Maguire EA Cortical midline involvement in autobiographical memory. NeuroImage 44, 1188–200 (2009). [PubMed: 18973817]

99. Davey CG, Allen NB, Harrison BJ, Dwyer DB & Yücel M. Being liked activates primary reward and midline self-related brain regions. Hum. Brain Mapp 31, 660–8 (2010). [PubMed: 19823984]

100. Johnson SC et al. Neural correlates of self-reflection. Brain 125, 1808–1814 (2002). [PubMed: 12135971]
101. Johnson SC et al. The cerebral response during subjective choice with and without self-reference. J. Cogn. Neurosci 17, 1897–906 (2005). [PubMed: 16356327]
102. Schmitz TW, Rowley HA, Kawahara TN & Johnson SC Neural correlates of self-evaluative accuracy after traumatic brain injury. Neuropsychologia 44, 762–73 (2006). [PubMed: 16154166]
103. Guterstam A, Björnsdotter M, Gentile G. & Ehrsson HH Posterior cingulate cortex integrates the senses of self-location and body ownership. Curr. Biol 25, 1416–1425 (2015). [PubMed: 25936550]
104. Vesuna S. et al. Deep posteromedial cortical rhythm in dissociation. Nature 586, 87–94 (2020). [PubMed: 32939091]
105. O'Keefe J. & Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 34, 171–175 (1971). [PubMed: 5124915]
106. Taube JS, Muller RU & Ranck JB Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. J. Neurosci. Off. J. Soc. Neurosci 10, 420–435 (1990).
107. Hafting T, Fyhn M, Molden S, Moser M-B & Moser EI Microstructure of a spatial map in the entorhinal cortex. Nature 436, 801–806 (2005). [PubMed: 15965463]
108. Chen LL, Lin LH, Green EJ, Barnes CA & McNaughton BL Head-direction cells in the rat posterior cortex. I. Anatomical distribution and behavioral modulation. Exp. Brain Res 101, 8–23 (1994). [PubMed: 7843305]
109. Lozano YR et al. Retrosplenial and postsubicular head direction cells compared during visual landmark discrimination. Brain Neurosci. Adv 1, 2398212817721859 (2017).
110. Angelaki DE et al. A gravity-based three-dimensional compass in the mouse brain. Nat. Commun 11, 1855 (2020). [PubMed: 32296057]
111. Brennan EK et al. Thalamus and claustrum control parallel layer 1 circuits in retrosplenial cortex. eLife 10, e62207 (2021).
112. Brennan EKW, Sudhakar SK, Jedrasiak-Cape I, John TT & Ahmed OJ Hyperexcitable Neurons Enable Precise and Persistent Information Encoding in the Superficial Retrosplenial Cortex. Cell Rep. 30, 1598–1612.e8 (2020). [PubMed: 32023472]
113. Tsitsiklis M. et al. Single-Neuron Representations of Spatial Targets in Humans. Curr. Biol 30, 245–253.e4 (2020). [PubMed: 31902728]
114. Taube JS, Valerio S. & Yoder RM Is navigation in virtual reality with FMRI really navigation? J. Cogn. Neurosci 25, 1008–19 (2013). [PubMed: 23489142]
115. Baumann O. & Mattingley JB Medial parietal cortex encodes perceived heading direction in humans. J. Neurosci 30, 12897–12901 (2010). [PubMed: 20881108]
116. Do T-TN, Lin C-T & Gramann K. Human brain dynamics in active spatial navigation. Sci. Rep 11, 13036 (2021). [PubMed: 34158525]
117. Viganò S, Rubino V, Buiatti M. & Piazza M. The neural representation of absolute direction during mental navigation in conceptual spaces. Commun. Biol 2021 41 4, 1–7 (2021).
118. Shine JP & Wolbers T. Global and Local Head Direction Coding in the Human Brain http://biorxiv.org/lookup/doi/10.1101/2021.10.11.463872 (2021) doi:10.1101/2021.10.11.463872.
119. Persichetti AS & Dilks DD Distinct representations of spatial and categorical relationships across human scene-selective cortex. Proc. Natl. Acad. Sci. U. S. A 201903057 (2019) doi:10.1073/pnas.1903057116.
120. Dhindsa K. et al. Examining the role of the temporo-parietal network in memory, imagery, and viewpoint transformations. Front. Hum. Neurosci 8, 709 (2014). [PubMed: 25278860]
121. Zhang H, Copara M. & Ekstrom AD Differential recruitment of brain networks following route and cartographic map learning of spatial environments. PloS One 7, e44886 (2012).
122. Dean HL & Platt ML Allocentric Spatial Referencing of Neuronal Activity in Macaque Posterior Cingulate Cortex. J. Neurosci 26, 1117–1127 (2006). [PubMed: 16436597]
123. Sato N, Sakata H, Tanaka YL & Taira M. Navigation-associated medial parietal neurons in monkeys. Proc. Natl. Acad. Sci 103, 17001–17006 (2006). [PubMed: 17068129]

124. Nitz DA Tracking route progression in the posterior parietal cortex. Neuron 49, 747–756 (2006). [PubMed: 16504949]
125. Kaefer K, Nardin M, Blahna K. & Csicsvari J. Replay of Behavioral Sequences in the Medial Prefrontal Cortex during Rule Switching. Neuron 106, 154–165.e6 (2020). [PubMed: 32032512]
126. Frank LM, Brown EN & Wilson M. Trajectory Encoding in the Hippocampus and Entorhinal Cortex. Neuron 27, 169–178 (2000). [PubMed: 10939340]
127. Derdikman D. et al. Fragmentation of grid cell maps in a multicompartment environment. Nat. Neurosci 12, 1325–1332 (2009). [PubMed: 19749749]
128. Singer AC, Karlsson MP, Nathe AR, Carr MF & Frank LM Experience-Dependent Development of Coordinated Hippocampal Spatial Activity Representing the Similarity of Related Locations. J. Neurosci 30, 11586–11604 (2010). [PubMed: 20810880]
129. Rubin A. et al. Revealing neural correlates of behavior without behavioral measurements. Nat. Commun 10, 1–14 (2019). [PubMed: 30602773]
130. Moore JJ, Cushman JD, Acharya L, Popeney B. & Mehta MR Linking hippocampal multiplexed tuning, Hebbian plasticity and navigation. Nature 599, 442–448 (2021). [PubMed: 34671157]
131. Nitz D. Parietal cortex, navigation, and the construction of arbitrary reference frames for spatial information. Neurobiol. Learn. Mem 91, 179–185 (2009). [PubMed: 18804545]
132. Epstein RA & Baker CI Scene Perception in the Human Brain. Annu. Rev. Vis. Sci 5, 373–397 (2019). [PubMed: 31226012]
133. Epstein RA & Higgins JS Differential parahippocampal and retrosplenial involvement in three types of visual scene recognition. Cereb. Cortex 17, 1680–93 (2007). [PubMed: 16997905]
134. Park S, Intraub H, Yi D-J, Widders D. & Chun MM Beyond the edges of a view: Boundary extension in human scene-selective visual cortex. Neuron 54, 335–342 (2007). [PubMed: 17442252]
135. Park S, Chun MM & Johnson MK Refreshing and integrating visual scenes in scene-selective cortex. J. Cogn. Neurosci 22, 2813–22 (2010). [PubMed: 19929756]
136. Robertson CE, Hermann KL, Mynick A, Kravitz DJ & Kanwisher N. Neural representations integrate the current field of view with the remembered 360° panorama in scene-selective cortex. Curr. Biol 26, 2463–2468 (2016). [PubMed: 27618266]
137. Harel A, Kravitz DJ & Baker CI Deconstructing visual scenes in cortex: Gradients of object and spatial layout information. Cereb. Cortex 23, 947–957 (2013). [PubMed: 22473894]
138. Kamps FS, Julian JB, Kubilius J, Kanwisher N. & Dilks DD The occipital place area represents the local elements of scenes. NeuroImage 132, 417–424 (2016). [PubMed: 26931815]
139. Park S. et al. Parametric Coding of the Size and Clutter of Natural Scenes in the Human Brain. Cereb. Cortex 25, 1792–1805 (2015). [PubMed: 24436318]
140. Walther DB, Chai B, Caddigan E, Beck DM & Fei-Fei L. Simple line drawings suffice for functional MRI decoding of natural scene categories. Proc. Natl. Acad. Sci. U. S. A 108, 9661–6 (2011). [PubMed: 21593417]
141. Bonner MF & Epstein RA Coding of navigational affordances in the human visual system. Proc. Natl. Acad. Sci. U. S. A 114, 4793–4798 (2017). [PubMed: 28416669]
142. Walther DB, Caddigan E, Fei-Fei L. & Beck DM Natural scene categories revealed in distributed patterns of activity in the human brain. J. Neurosci 29, 10573–81 (2009). [PubMed: 19710310]
143. Aminoff EM & Tarr MJ Associative processing is inherent in scene perception. PloS One 10, e0128840 (2015).
144. Bar M. & Aminoff E. Cortical analysis of visual context. Neuron 38, 347–358 (2003). [PubMed: 12718867]
145. Carstensen LC, Alexander AS, Chapman GW, Lee AJ & Hasselmo ME Neural responses in retrosplenial cortex associated with environmental alterations. iScience 24, 103377 (2021).
146. Nitz DA Spaces within spaces: rat parietal cortex neurons register position across three reference frames. Nat. Neurosci 15, 1365–1367 (2012). [PubMed: 22960933]
147. Chrastil ER & Warren WH From cognitive maps to cognitive graphs. PLoS ONE 9, e112544 (2014).

148. Dabaghian Y, Brandt VL & Frank LM Reconceiving the hippocampal map as a topological template. eLife 3, e03476 (2014).

149. Rueckemann JW, Sosa M, Giocomo LM & Buffalo EA The grid code for ordered experience. Nat. Rev. Neurosci 22, 637–649 (2021). [PubMed: 34453151]

150. Schinazi VR & Epstein RA Neural correlates of real-world route learning. NeuroImage 53, 725–735 (2010). [PubMed: 20603219]

151. Takahashi N, Kawamura M, Shiota J, Kasahata N. & Hirayama K. Pure topographic disorientation due to right retrosplenial lesion. Neurology 49, 464–469 (1997). [PubMed: 9270578]

152. Peer M, Hayman M, Tamir B. & Arzy S. Brain coding of social network structure. J. Neurosci 41, 4897–4909 (2021). [PubMed: 33903220]

153. Bicanski A. & Burgess N. A neural-level model of spatial memory and imagery. eLife 7, (2018).

154. Byrne P, Becker S. & Burgess N. Remembering the past and imagining the future: a neural model of spatial memory and imagery. Psychol Rev 114, 340–375 (2007). [PubMed: 17500630]

155. Clark BJ, Simmons CM, Berkowitz LE & Wilber AA The retrosplenial-parietal network and reference frame coordination for spatial navigation. Behav. Neurosci 132, 416–429 (2018). [PubMed: 30091619]

156. Dragoi G. & Tonegawa S. Preplay of future place cell sequences by hippocampal cellular assemblies. Nature 469, 397–401 (2011). [PubMed: 21179088]

157. Peyrache A, Lacroix MM, Petersen PC & Buzsáki G. Internally organized mechanisms of the head direction sense. Nat. Neurosci 18, 569–575 (2015). [PubMed: 25730672]

158. Trettel SG, Trimper JB, Hwaun E, Fiete IR & Colgin LL Grid cell co-activity patterns during sleep reflect spatial overlap of grid fields during active behaviors. Nat. Neurosci 22, 609–617 (2019). [PubMed: 30911183]

159. Gardner RJ, Lu L, Wernle T, Moser M-B & Moser EI Correlation structure of grid cells is preserved during sleep. Nat. Neurosci 22, 598–608 (2019). [PubMed: 30911185]

160. Farooq U. & Dragoi G. Emergence of preconfigured and plastic time-compressed sequences in early postnatal development. Science (2019) doi:10.1126/science.aav0502.

161. Lever C, Burton S, Jeewajee A, O'Keefe J. & Burgess N. Boundary Vector Cells in the Subiculum of the Hippocampal Formation. J. Neurosci 29, 9771–9777 (2009). [PubMed: 19657030]

162. Bicanski A. & Burgess N. Environmental anchoring of head direction in a computational model of retrosplenial cortex. J. Neurosci 36, 11601–11618 (2016). [PubMed: 27852770]

163. Alexander AS et al. Adaptive integration of self-motion and goals in posterior parietal cortex. Cell Rep. 38, (2022).

164. Andersen RA & Mountcastle VB The influence of the angle of gaze upon the excitability of the light- sensitive neurons of the posterior parietal cortex. J. Neurosci 3, 532–548 (1983). [PubMed: 6827308]

165. Andersen RA, Essick GK & Siegel RM Encoding of spatial location by posterior parietal neurons. Science 230, 456–458 (1985). [PubMed: 4048942]

166. Andersen RA, Snyder LH, Li CS & Stricanne B. Coordinate transformations in the representation of spatial information. Curr. Opin. Neurobiol 3, 171–176 (1993). [PubMed: 8513228]

167. Pouget A. & Sejnowski TJ Spatial Transformations in the Parietal Cortex Using Basis Functions. J. Cogn. Neurosci 9, 222–237 (1997). [PubMed: 23962013]

168. Clark BJ, Bassett JP, Wang SS & Taube JS Impaired Head Direction Cell Representation in the Anterodorsal Thalamus after Lesions of the Retrosplenial Cortex. J. Neurosci 30, 5289–5302 (2010). [PubMed: 20392951]

169. Pohl W. Dissociation of spatial discrimination deficits following frontal and parietal lesions in monkeys. J. Comp. Physiol. Psychol 82, 227–239 (1973). [PubMed: 4632974]

170. Whishaw IQ, Maaswinkel H, Gonzalez CL & Kolb B. Deficits in allothetic and idiothetic spatial behavior in rats with posterior cingulate cortex lesions. Behav. Brain Res 118, 67–76 (2001). [PubMed: 11163635]

171. Harker KT & Whishaw IQ Impaired Spatial Performance in Rats with Retrosplenial Lesions: Importance of the Spatial Problem and the Rat Strain in Identifying Lesion Effects in a Swimming Pool. J. Neurosci 22, 1155–1164 (2002). [PubMed: 11826144]

172. Vann SD & Aggleton JP Extensive cytotoxic lesions of the rat retrosplenial cortex reveal consistent deficits on tasks that tax allocentric spatial memory. Behav. Neurosci 116, 85–94 (2002). [PubMed: 11895186]

173. Vann SD, Kristina Wilton LA, Muir JL & Aggleton JP Testing the importance of the caudal retrosplenial cortex for spatial memory in rats. Behav. Brain Res 140, 107–118 (2003). [PubMed: 12644284]

174. Vann SD & Aggleton JP Testing the importance of the retrosplenial guidance system: effects of different sized retrosplenial cortex lesions on heading direction and spatial working memory. Behav. Brain Res 155, 97–108 (2004). [PubMed: 15325783]

175. Vann SD & Aggleton JP Selective dysgranular retrosplenial cortex lesions in rats disrupt allocentric performance of the radial-arm maze task. Behav. Neurosci 119, 1682–1686 (2005). [PubMed: 16420172]

176. Pothuizen HHJ, Aggleton JP & Vann SD Do rats with retrosplenial cortex lesions lack direction? Eur. J. Neurosci 28, 2486–2498 (2008). [PubMed: 19032585]

177. Keene CS & Bucci DJ Damage to the retrosplenial cortex produces specific impairments in spatial working memory. Neurobiol. Learn. Mem 91, 408–414 (2009). [PubMed: 19026755]

178. Pothuizen HHJ, Davies M, Albasser MM, Aggleton JP & Vann SD Granular and dysgranular retrosplenial cortices provide qualitatively different contributions to spatial working memory: evidence from immediate-early gene imaging in rats. Eur. J. Neurosci 30, 877–888 (2009). [PubMed: 19712100]

179. Aggleton JP Understanding retrosplenial amnesia: Insights from animal studies. Neuropsychologia 48, 2328–2338 (2010). [PubMed: 19800900]

180. Czajkowski R, Zglinicki B, Rejmak E. & Konopka W. Strategy-Specific Patterns of Arc Expression in the Retrosplenial Cortex and Hippocampus during T-Maze Learning in Rats. Brain Sci. 10, 854 (2020). [PubMed: 33202708]

181. Wilber AA, Clark BJ, Forster TC, Tatsuno M. & McNaughton BL Interaction of egocentric and world-centered reference frames in the rat posterior parietal cortex. J. Neurosci. Off. J. Soc. Neurosci 34, 5431–5446 (2014).

182. Peyrache A, Schieferstein N. & Buzsáki G. Transformation of the head-direction signal into a spatial code. Nat. Commun 8, 1752 (2017). [PubMed: 29170377]

183. Sarel A, Finkelstein A, Las L. & Ulanovsky N. Vectorial representation of spatial goals in the hippocampus of bats. Science (2017) doi:10.1126/science.aak9589.

184. Jercog PE et al. Heading direction with respect to a reference point modulates place-cell activity. Nat. Commun 10, 2333 (2019). [PubMed: 31133685]

185. Mallory CS et al. Mouse entorhinal cortex encodes a diverse repertoire of self-motion signals. Nat. Commun 12, 671 (2021). [PubMed: 33510164]

186. Wolbers T. & Büchel C. Dissociable retrosplenial and hippocampal contributions to successful formation of survey representations. J. Neurosci. Off. J. Soc. Neurosci 25, 3333–3340 (2005).

187. Sherrill KR et al. Hippocampus and retrosplenial cortex combine path integration signals for successful navigation. J. Neurosci 33, 19304–19313 (2013). [PubMed: 24305826]

188. Marchette SA, Vass LK, Ryan J. & Epstein RA Anchoring the neural compass: coding of local spatial reference frames in human medial parietal lobe. Nat. Neurosci 17, 1598–1606 (2014). [PubMed: 25282616]

189. Hashimoto R, Tanaka Y. & Nakano I. Heading Disorientation: A New Test and a Possible Underlying Mechanism. Eur. Neurol 63, 87–93 (2010). [PubMed: 20090342]

190. Hashimoto R. & Nakano I. The Card Placing Test: a new test for evaluating the function of the retrosplenial and posterior cingulate cortices. Eur. Neurol 72, 38–44 (2014). [PubMed: 24853605]

191. Ino T. et al. Directional Disorientation Following Left Retrosplenial Hemorrhage: a Case Report with FMRI Studies. Cortex 43, 248–254 (2007). [PubMed: 17405670]

192. Katayama K, Takahashi N, Ogawara K. & Hattori T. Pure Topographical Disorientation Due to Right Posterior Cingulate Lesion. Cortex 35, 279–282 (1999). [PubMed: 10369100]

193. Suzuki K, Yamadori A, Hayakawa Y. & Fujii T. Pure Topographical Disorientation Related to Dysfunction of the Viewpoint Dependent Visual System. Cortex 34, 589–599 (1998). [PubMed: 9800092]

194. Buckner RL & Carroll DC Self-projection and the brain. Trends Cogn. Sci 11, 49–57 (2007). [PubMed: 17188554]

195. St. Jacques PL, Carpenter AC, Szpunar KK & Schacter DL Remembering and imagining alternative versions of the personal past. Neuropsychologia 110, 170–179 (2018). [PubMed: 28633886]

196. Bukowski H. The Neural Correlates of Visual Perspective Taking: a Critical Review. Curr. Behav. Neurosci. Rep 2018 53 5, 189–197 (2018).

197. Schmidt D. et al. Visuospatial working memory and changes of the point of view in 3D space. NeuroImage 36, 955–968 (2007). [PubMed: 17493835]

198. St. Jacques PL, Szpunar KK & Schacter DL Shifting visual perspective during retrieval shapes autobiographical memories. NeuroImage 148, 103–114 (2017). [PubMed: 27989780]

199. Iriye H. & St. Jacques PL How visual perspective influences the spatiotemporal dynamics of autobiographical memory retrieval. Cortex 129, 464–475 (2020). [PubMed: 32599462]

200. Fisher YE, Lu J, D'Alessandro I. & Wilson RI Sensorimotor experience remaps visual input to a heading-direction network. Nature 576, 121–125 (2019). [PubMed: 31748749]

201. Kim SS, Hermundstad AM, Romani S, Abbott LF & Jayaraman V. Generation of stable heading representations in diverse visual scenes. Nature 576, 126–131 (2019). [PubMed: 31748750]

202. Lu J. et al. Transforming representations of movement from body- to world-centric space. Nature 601, 98–104 (2022). [PubMed: 34912123]

203. Todd TP & Bucci DJ Retrosplenial Cortex and Long-Term Memory: Molecules to Behavior. Neural Plasticity vol. 2015 e414173 https://www.hindawi.com/journals/np/2015/414173/ (2015).

204. de Landeta AB, Pereyra M, Medina JH & Katche C. Anterior retrosplenial cortex is required for long-term object recognition memory. Sci. Rep 10, 4002 (2020). [PubMed: 32152383]

205. Clark A. Perceiving as Predicting. in Perception and Its Modalities (eds. Stokes D, Matthen M. & Biggs S) 23–43 (Oxford University Press, 2014). doi:10.1093/acprof:oso/9780199832798.003.0002.

206. Rao RPN & Ballard DH Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. Nat. Neurosci 2, 79–87 (1999). [PubMed: 10195184]

207. Kobayashi Y. & Amaral DG Macaque monkey retrosplenial cortex: II. Cortical afferents. J. Comp. Neurol 466, 48–79 (2003). [PubMed: 14515240]

208. Kobayashi Y. & Amaral DG Macaque monkey retrosplenial cortex: III. Cortical efferents. J. Comp. Neurol 502, 810–833 (2007). [PubMed: 17436282]

209. Olson JM, Li JK, Montgomery SE & Nitz DA Secondary Motor Cortex Transforms Spatial Information into Planned Action during Navigation. Curr. Biol 30, 1845–1854.e4 (2020). [PubMed: 32302586]

210. Rounds EL, Alexander AS, Nitz DA & Krichmar JL Conjunctive coding in an evolved spiking model of retrosplenial cortex. Behav. Neurosci 132, 430–452 (2018). [PubMed: 29863371]

211. Yonelinas AP, Ranganath C, Ekstrom AD & Wiltgen BJ A contextual binding theory of episodic memory: systems consolidation reconsidered. Nat. Rev. Neurosci 20, 364–375 (2019). [PubMed: 30872808]

212. Buzsáki G. & Tingley D. Space and Time: The Hippocampus as a Sequence Generator. Trends Cogn. Sci 22, 853–869 (2018). [PubMed: 30266146]

213. Mehta MR, Barnes CA & McNaughton BL Experience-dependent, asymmetric expansion of hippocampal place fields. Proc Natl Acad Sci U A 94, 8918–8921 (1997).

214. Kwapis JL, Jarome TJ, Lee JL, Gilmartin MR & Helmstetter FJ Extinguishing trace fear engages the retrosplenial cortex rather than the amygdala. Neurobiol. Learn. Mem 113, 41–54 (2014). [PubMed: 24055593]

215. Todd TP, Meyer HC & Bucci DJ Contribution of the retrosplenial cortex to temporal discrimination learning. Hippocampus 25, 137–141 (2015). [PubMed: 25348829]
216. Trask S, Pullins SE, Ferrara NC & Helmstetter FJ The anterior retrosplenial cortex encodes event-related information and the posterior retrosplenial cortex encodes context-related information during memory formation. Neuropsychopharmacology 46, 1386–1392 (2021). [PubMed: 33580135]
217. Powell AL et al. The retrosplenial cortex and object recency memory in the rat. Eur. J. Neurosci 45, 1451–1464 (2017). [PubMed: 28394458]
218. Terada S, Sakurai Y, Nakahara H. & Fujisawa S. Temporal and Rate Coding for Discrete Event Sequences in the Hippocampus. Neuron 94, 1248–1262.e4 (2017). [PubMed: 28602691]
219. Bowers D, Verfaellie M, Valenstein E. & Heilman KM Impaired acquisition of temporal information in retrosplenial amnesia. Brain Cogn. 8, 47–66 (1988). [PubMed: 3166818]
220. Mesulam MM, Nobre AC, Kim Y-H, Parrish TB & Gitelman DR Heterogeneity of Cingulate Contributions to Spatial Attention. NeuroImage 13, 1065–1072 (2001). [PubMed: 11352612]
221. Hirono N. et al. Hypofunction in the posterior cingulate gyrus correlates with disorientation for time and place in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 64, 552–554 (1998). [PubMed: 9576555]
222. Hsieh L-T & Ranganath C. Cortical and subcortical contributions to sequence retrieval: Schematic coding of temporal context in the neocortical recollection network. NeuroImage 121, 78–90 (2015). [PubMed: 26209802]
223. Hindy NC, Ng FY & Turk-Browne NB Linking pattern completion in the hippocampus to predictive coding in visual cortex. Nat. Neurosci 19, 665–667 (2016). [PubMed: 27065363]
224. Barron HC, Auksztulewicz R. & Friston K. Prediction and memory: A predictive coding account. Prog. Neurobiol 192, 101821 (2020).
225. Goddard E, Contini EW & Irish M. Exploring Information Flow from Posteromedial Cortex during Visuospatial Working Memory: A Magnetoencephalography Study. J. Neurosci 42, 5944–5955 (2022). [PubMed: 35732493]
226. Haque RU, Inati SK, Levey AI & Zaghloul KA Feedforward prediction error signals during episodic memory retrieval. Nat. Commun 11, 6075 (2020). [PubMed: 33247100]
227. Daselaar SM, Fleck MS & Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. J. Neurophysiol 96, 1902–1911 (2006). [PubMed: 16738210]
228. Daselaar SM et al. Posterior midline and ventral parietal activity is associated with retrieval success and encoding failure. Front. Hum. Neurosci 3, 13 (2009). [PubMed: 19680466]
229. Yonelinas AP, Otten LJ, Shaw KN & Rugg MD Separating the brain regions involved in recollection and familiarity in recognition memory. J. Neurosci. Off. J. Soc. Neurosci 25, 3002–3008 (2005).
230. Kaboodvand N, Bäckman L, Nyberg L. & Salami A. The retrosplenial cortex: A memory gateway between the cortical default mode network and the medial temporal lobe. Hum. Brain Mapp 39, 2020–2034 (2018). [PubMed: 29363256]
231. Yonelinas AP Components of episodic memory: the contribution of recollection and familiarity. Philos. Trans. R. Soc. Lond. Ser. B 356, 1363–1374 (2001). [PubMed: 11571028]
232. Barthas F. & Kwan AC Secondary motor cortex: where 'sensory' meets 'motor' in the rodent frontal cortex. Trends Neurosci. 40, 181–193 (2017). [PubMed: 28012708]
233. Stevenson RF, Reagh ZM, Chun AP, Murray EA & Yassa MA Pattern Separation and Source Memory Engage Distinct Hippocampal and Neocortical Regions during Retrieval. J. Neurosci 40, 843–851 (2020). [PubMed: 31748377]
234. Monko ME & Heilbronner SR Retrosplenial Cortical Connectivity with Frontal Basal Ganglia Networks. J. Cogn. Neurosci 33, 1096–1105 (2021). [PubMed: 34428786]
235. Gahnstrom CJ & Spiers HJ Striatal and hippocampal contributions to flexible navigation in rats and humans. Brain Neurosci. Adv 4, 2398212820979772 (2020).
236. Gainotti G, Almonti S, Di Betta AM & Silveri MC Retrograde amnesia in a patient with retrosplenial tumour. Neurocase 4, 519–526 (1998).

237. Valenstein E. et al. RETROSPLENIAL AMNESIA. Brain 110, 1631–1646 (1987). [PubMed: 3427404]
238. Maeshima S. et al. Retrosplenial Amnesia without Topographic Disorientation Caused by a Lesion in the Nondominant Hemisphere. J. Stroke Cerebrovasc. Dis 23, 441–445 (2014). [PubMed: 23608367]
239. Meng D, Alsaeed M, Randhawa J. & Chen T. Retrosplenial Stroke Mimicking Transient Global Amnesia. Can. J. Neurol. Sci 48, 884–885 (2021). [PubMed: 33431103]
240. Osawa A, Maeshima S. & Kunishio K. Topographic Disorientation and Amnesia due to Cerebral Hemorrhage in the Left Retrosplenial Region. Eur. Neurol 59, 79–82 (2008). [PubMed: 17934287]
241. Song L, Constanthin P, Lin N, Tian Y. & An L. Injury to the human retrosplenial cortex: Two cases and a review of the literature. Trends Med. 20, (2020).
242. Vargha-Khadem F. et al. Developmental amnesia: Effect of age at injury. Proc. Natl. Acad. Sci 100, 10055–10060 (2003). [PubMed: 12904585]
243. Cooper BG & Mizumori SJY Retrosplenial cortex inactivation selectively impairs navigation in darkness. NeuroReport 10, 625–630 (1999). [PubMed: 10208601]
244. Amin E, Pearce JM, Brown MW & Aggleton JP Novel temporal configurations of stimuli produce discrete changes in immediate-early gene expression in the rat hippocampus. Eur. J. Neurosci 24, 2611–2621 (2006). [PubMed: 17100849]
245. Friston K. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci 11, 127–138 (2010). [PubMed: 20068583]
246. Hawkins J, George D. & Niemasik J. Sequence memory for prediction, inference and behaviour. Philos. Trans. R. Soc. B Biol. Sci 364, 1203–1209 (2009).
247. Foster DJ & Wilson MA Hippocampal theta sequences. Hippocampus 17, 1093–1099 (2007). [PubMed: 17663452]
248. O'Keefe J. & Recce ML Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3, 317–330 (1993). [PubMed: 8353611]
249. Skaggs WE, McNaughton BL, Wilson MA & Barnes CA Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus 6, 149–172 (1996). [PubMed: 8797016]
250. Davidson TJ, Kloosterman F. & Wilson MA Hippocampal Replay of Extended Experience. Neuron 63, 497–507 (2009). [PubMed: 19709631]
251. Karlsson MP & Frank LM Awake replay of remote experiences in the hippocampus. Nat. Neurosci 12, 913–918 (2009). [PubMed: 19525943]
252. Pfeiffer BE & Foster DJ Hippocampal place-cell sequences depict future paths to remembered goals. Nature 497, 74–79 (2013). [PubMed: 23594744]
253. Wilson MA & McNaughton BL Reactivation of hippocampal ensemble memories during sleep. Science 265, 676–679 (1994). [PubMed: 8036517]
254. Fernández-Ruiz A. et al. Long-duration hippocampal sharp wave ripples improve memory. Science 364, 1082–1086 (2019). [PubMed: 31197012]
255. Girardeau G, Benchenane K, Wiener SI, Buzsáki G. & Zugaro MB Selective suppression of hippocampal ripples impairs spatial memory. Nat. Neurosci 12, 1222–1223 (2009). [PubMed: 19749750]
256. Jadhav SP, Kemere C, German PW & Frank LM Awake Hippocampal Sharp-Wave Ripples Support Spatial Memory. Science (2012) doi:10.1126/science.1217230.
257. Johnson A. & Redish AD Neural Ensembles in CA3 Transiently Encode Paths Forward of the Animal at a Decision Point. J. Neurosci 27, 12176–12189 (2007). [PubMed: 17989284]
258. Singer AC, Carr MF, Karlsson MP & Frank LM Hippocampal SWR Activity Predicts Correct Decisions during the Initial Learning of an Alternation Task. Neuron 77, 1163–1173 (2013). [PubMed: 23522050]
259. Wang Y, Romani S, Lustig B, Leonardo A. & Pastalkova E. Theta sequences are essential for internally generated hippocampal firing fields. Nat. Neurosci 18, 282–288 (2015). [PubMed: 25531571]

260. Dastjerdi M. et al. Differential electrophysiological response during rest, self-referential, and non-self-referential tasks in human posteromedial cortex. Proc. Natl. Acad. Sci. U. S. A 108, 3023–3028 (2011). [PubMed: 21282630]
261. Foster BL, Dastjerdi M. & Parvizi J. Neural populations in human posteromedial cortex display opposing responses during memory and numerical processing. Proc. Natl. Acad. Sci. U. S. A 109, 15514–15519 (2012). [PubMed: 22949666]
262. Foster BL, Kaveh A, Dastjerdi M, Miller KJ & Parvizi J. Human Retrosplenial Cortex Displays Transient Theta Phase Locking with Medial Temporal Cortex Prior to Activation during Autobiographical Memory Retrieval. J. Neurosci 33, 10439–10446 (2013). [PubMed: 23785155]
263. Foster BL, Rangarajan V, Shirer WR & Parvizi J. Intrinsic and Task-Dependent Coupling of Neuronal Population Activity in Human Parietal Cortex. Neuron 86, 578–590 (2015). [PubMed: 25863718]
264. Foster BL & Parvizi J. Resting oscillations and cross-frequency coupling in the human posteromedial cortex. NeuroImage 60, 384–391 (2012). [PubMed: 22227048]
265. Foster BL & Parvizi J. Direct cortical stimulation of human posteromedial cortex. Neurology 88, 685–691 (2017). [PubMed: 28100728]
266. Buzsáki G. Theta Oscillations in the Hippocampus. Neuron 33, 325–340 (2002). [PubMed: 11832222]
267. Jacobs J. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. Philos. Trans. R. Soc. B Biol. Sci 369, 20130304 (2014).
268. Watrous AJ et al. A comparative study of human and rat hippocampal low-frequency oscillations during spatial navigation. Hippocampus 23, 656–661 (2013). [PubMed: 23520039]
269. Herweg NA, Solomon EA & Kahana MJ Theta Oscillations in Human Memory. Trends Cogn. Sci S1364661319302943 (2020) doi:10.1016/j.tics.2019.12.006.
270. Hyman JM, Wyble BP, Goyal V, Rossi CA & Hasselmo ME Stimulation in Hippocampal Region CA1 in Behaving Rats Yields Long-Term Potentiation when Delivered to the Peak of Theta and Long-Term Depression when Delivered to the Trough. J. Neurosci 23, 11725–11731 (2003). [PubMed: 14684874]
271. Hasselmo ME What is the function of hippocampal theta rhythm?—Linking behavioral data to phasic properties of field potential and unit recording data. Hippocampus 15, 936–949 (2005). [PubMed: 16158423]
272. Alexander AS, Rangel LM, Tingley D. & Nitz DA Neurophysiological signatures of temporal coordination between retrosplenial cortex and the hippocampal formation. Behav. Neurosci 132, 453–468 (2018). [PubMed: 30070554]
273. Lomi E. et al. Evidence for two distinct thalamocortical circuits in retrosplenial cortex. Neurobiol. Learn. Mem 185, 107525 (2021).
274. Safaryan K. & Mehta MR Enhanced hippocampal theta rhythmicity and emergence of eta oscillation in virtual reality. Nat. Neurosci 24, 1065–1070 (2021). [PubMed: 34183867]
275. Lisman JE & Jensen O. The Theta-Gamma Neural Code. Neuron 77, 1002–1016 (2013). [PubMed: 23522038]
276. Tamura M, Spellman TJ, Rosen AM, Gogos JA & Gordon JA Hippocampal-prefrontal theta-gamma coupling during performance of a spatial working memory task. Nat. Commun 8, 2182 (2017). [PubMed: 29259151]
277. Tort ABL, Komorowski RW, Manns JR, Kopell NJ & Eichenbaum H. Theta–gamma coupling increases during the learning of item–context associations. Proc. Natl. Acad. Sci 106, 20942–20947 (2009). [PubMed: 19934062]
278. Colgin LL Theta–gamma coupling in the entorhinal–hippocampal system. Curr. Opin. Neurobiol 31, 45–50 (2015). [PubMed: 25168855]
279. Jensen O. & Colgin LL Cross-frequency coupling between neuronal oscillations. Trends Cogn. Sci 11, 267–269 (2007). [PubMed: 17548233]
280. Poulter S, Lee SA, Dachtler J, Wills TJ & Lever C. Vector trace cells in the subiculum of the hippocampal formation. Nat. Neurosci 24, 266–275 (2021). [PubMed: 33349710]

281. Kitanishi T, Umaba R. & Mizuseki K. Robust information routing by dorsal subiculum neurons. Sci. Adv 7, eabf1913 (2021).
282. Nadel L. & Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr. Opin. Neurobiol 7, 217–227 (1997). [PubMed: 9142752]
283. Gilboa A. & Moscovitch M. No consolidation without representation: Correspondence between neural and psychological representations in recent and remote memory. Neuron 109, 2239–2255 (2021). [PubMed: 34015252]
284. Sutherland RJ, Lee JQ, McDonald RJ & Lehmann H. Has multiple trace theory been refuted? Hippocampus 30, 842–850 (2020). [PubMed: 31584226]
285. Kwapis JL, Jarome TJ, Lee JL & Helmstetter FJ The retrosplenial cortex is involved in the formation of memory for context and trace fear conditioning. Neurobiol. Learn. Mem 123, 110–116 (2015). [PubMed: 26079095]
286. de Sousa AF et al. Optogenetic reactivation of memory ensembles in the retrosplenial cortex induces systems consolidation. Proc. Natl. Acad. Sci 116, 8576–8581 (2019). [PubMed: 30877252]
287. Czajkowski R. et al. Encoding and storage of spatial information in the retrosplenial cortex. Proc. Natl. Acad. Sci 111, 8661–8666 (2014). [PubMed: 24912150]
288. Yamawaki N, Corcoran KA, Guedea AL, Shepherd GMG & Radulovic J. Differential Contributions of Glutamatergic Hippocampal→Retrosplenial Cortical Projections to the Formation and Persistence of Context Memories. Cereb. Cortex N. Y. NY 29, 2728–2736 (2019).
289. Hirshhorn M, Grady C, Rosenbaum RS, Winocur G. & Moscovitch M. Brain regions involved in the retrieval of spatial and episodic details associated with a familiar environment: an fMRI study. Neuropsychologia 50, 3094–3106 (2012). [PubMed: 22910274]
290. Winocur G. & Moscovitch M. Memory Transformation and Systems Consolidation. J. Int. Neuropsychol. Soc 17, 766–780 (2011). [PubMed: 21729403]
291. Hussin AT, Abbaspoor S. & Hoffman KL Retrosplenial and hippocampal synchrony during retrieval of old memories in macaques. 2021.05.28.446142 https://www.biorxiv.org/content/10.1101/2021.05.28.446142v1 (2021) doi:10.1101/2021.05.28.446142.
292. Epstein RA, Parker WE & Feiler AM Where Am I Now? Distinct Roles for Parahippocampal and Retrosplenial Cortices in Place Recognition. J. Neurosci 27, 6141–6149 (2007). [PubMed: 17553986]
293. Troiani V, Stigliani A, Smith ME & Epstein RA Multiple Object Properties Drive Scene-Selective Regions. Cereb. Cortex 24, 883–897 (2014). [PubMed: 23211209]
294. Tononi G. & Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res. Bull 62, 143–150 (2003). [PubMed: 14638388]
295. Nádasdy Z, Hirase H, Czurkó A, Csicsvari J. & Buzsáki G. Replay and Time Compression of Recurring Spike Sequences in the Hippocampus. J. Neurosci 19, 9497–9507 (1999). [PubMed: 10531452]
296. Stark E. et al. Pyramidal Cell-Interneuron Interactions Underlie Hippocampal Ripple Oscillations. Neuron 83, 467–480 (2014). [PubMed: 25033186]
297. Girardeau G, Cei A. & Zugaro M. Learning-Induced Plasticity Regulates Hippocampal Sharp Wave-Ripple Drive. J. Neurosci 34, 5176–5183 (2014). [PubMed: 24719097]
298. Logothetis NK et al. Hippocampal–cortical interaction during periods of subcortical silence. Nature 491, 547–553 (2012). [PubMed: 23172213]
299. Nir Y. et al. Regional Slow Waves and Spindles in Human Sleep. Neuron 70, 153–169 (2011). [PubMed: 21482364]
300. Jadhav SP, Rothschild G, Roumis DK & Frank LM Coordinated Excitation and Inhibition of Prefrontal Ensembles during Awake Hippocampal Sharp-Wave Ripple Events. Neuron 90, 113–127 (2016). [PubMed: 26971950]
301. Nitzan N. et al. Propagation of hippocampal ripples to the neocortex by way of a subiculum-retrosplenial pathway. Nat. Commun 11, 1947 (2020). [PubMed: 32327634]
302. Karimi Abadchi J. et al. Spatiotemporal patterns of neocortical activity around hippocampal sharp-wave ripples. eLife 9, e51972 (2020).

303. Opalka AN, Huang W, Liu J, Liang H. & Wang DV Hippocampal Ripple Coordinates Retrosplenial Inhibitory Neurons during Slow-Wave Sleep. Cell Rep. 30, 432–441.e3 (2020). [PubMed: 31940487]

304. Chambers AR, Berge CN & Vervaeke K. Cell-type-specific silence in thalamocortical circuits precedes hippocampal sharp-wave ripples. 2021.05.05.442741 Preprint at 10.1101/2021.05.05.442741 (2021).

305. Branco T, Clark BA & Häusser M. Dendritic Discrimination of Temporal Input Sequences in Cortical Neurons. Science 329, 1671–1675 (2010). [PubMed: 20705816]

306. Ranganath C. & Ritchey M. Two cortical systems for memory-guided behaviour. Nat. Rev. Neurosci 13, 713–726 (2012). [PubMed: 22992647]

307. Ritchey M. & Cooper RA Deconstructing the Posterior Medial Episodic Network. Trends Cogn. Sci 24, 451–465 (2020). [PubMed: 32340798]

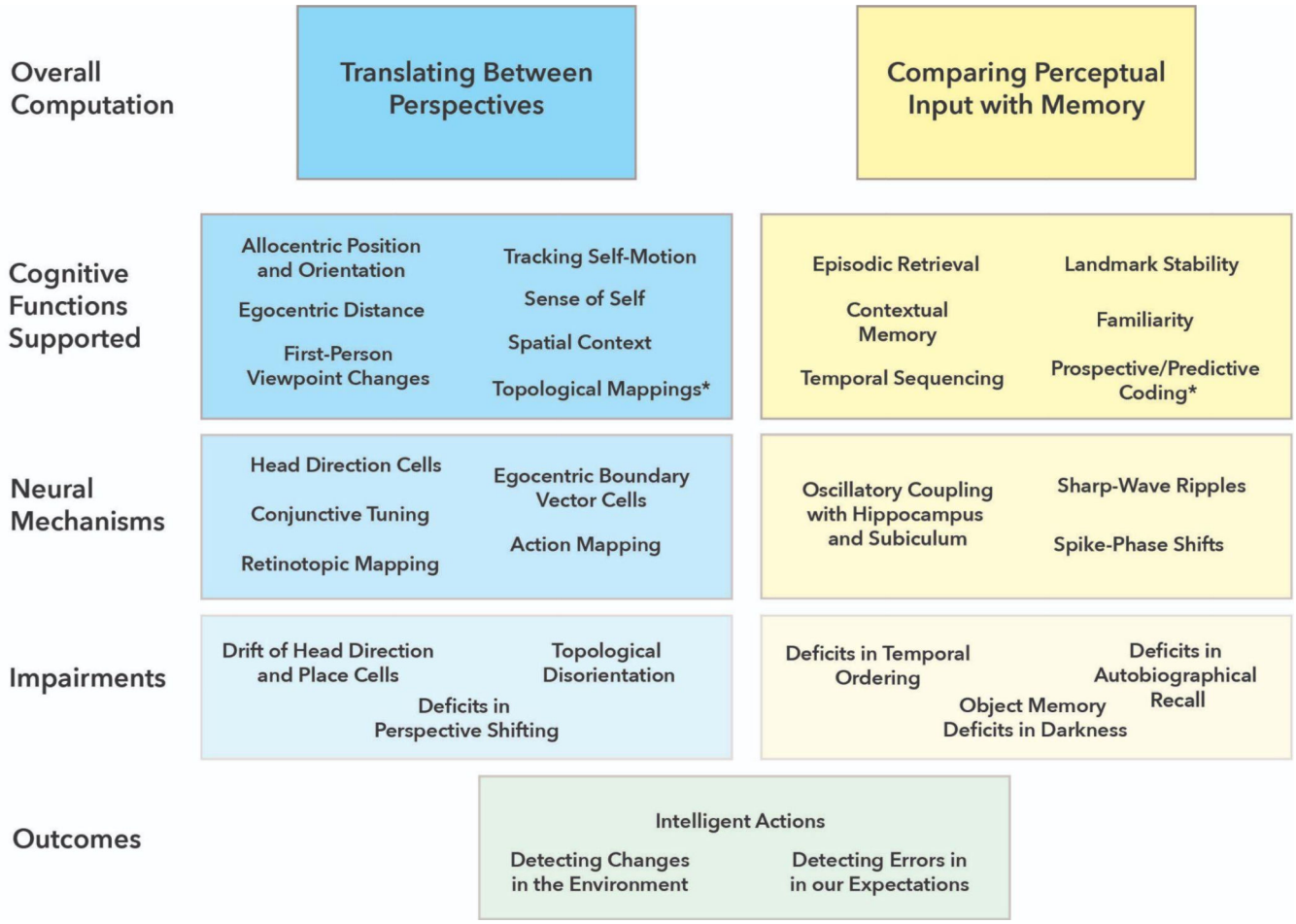

Figure 1. Summary of the computations and functions of RSC.

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.

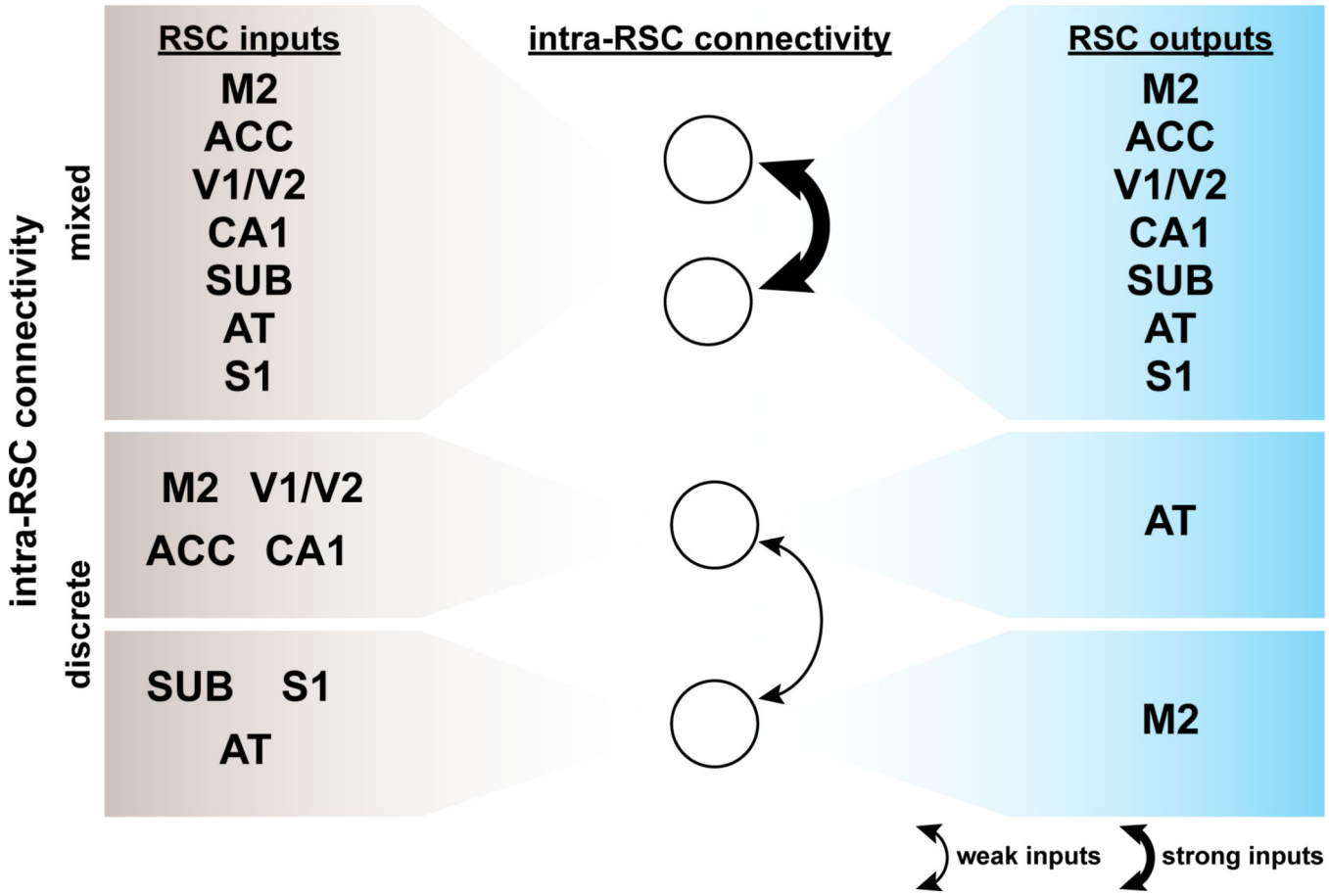

Figure 2. Theoretical extremes of RSC interconnectivity.

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, homogenous 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.

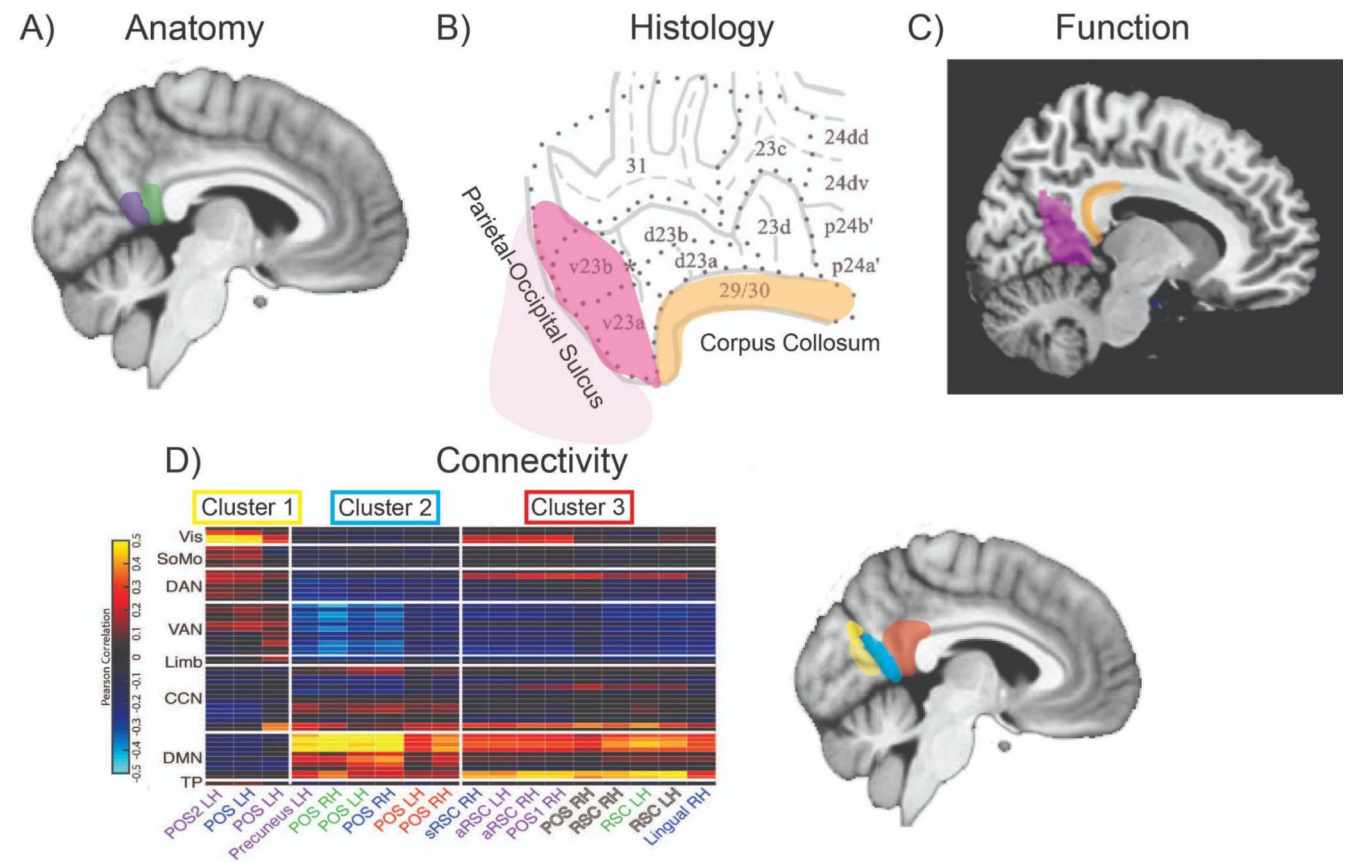

Figure 3. Differing ways to define the anatomy and connectivity of human RSC.

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[71]). 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[72]). 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 panel 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 panel C. Comparing A, B, and 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[73]). Seed regions (listed along the bottom with left or right hemisphere, e.g. POS LH) 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.

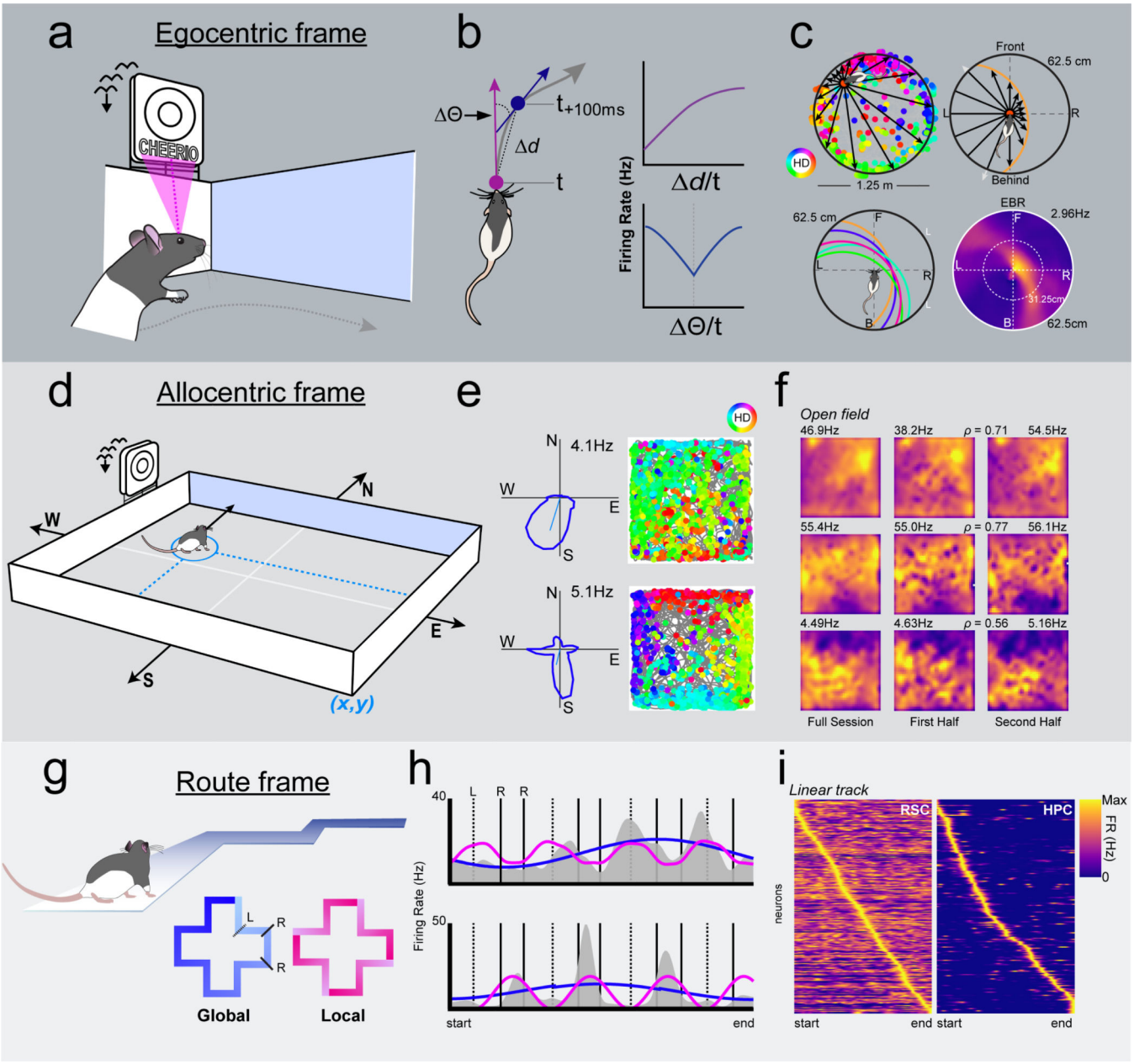

Figure 4. Egocentric, allocentric, and route-centered activity correlates of retrosplenial cortex.

a-c. The egocentric reference frame. 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 (ΔΘ) 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 ratemap for this RSC neuron shows 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. 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[6,17,79]. 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, ratemap 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 4**g** the bottom right graded pink schematic) and an overarching gain modulation (fit in blue line) that simultaneously tracks position within the full track space reflecting the global topology[8] (in 4**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.

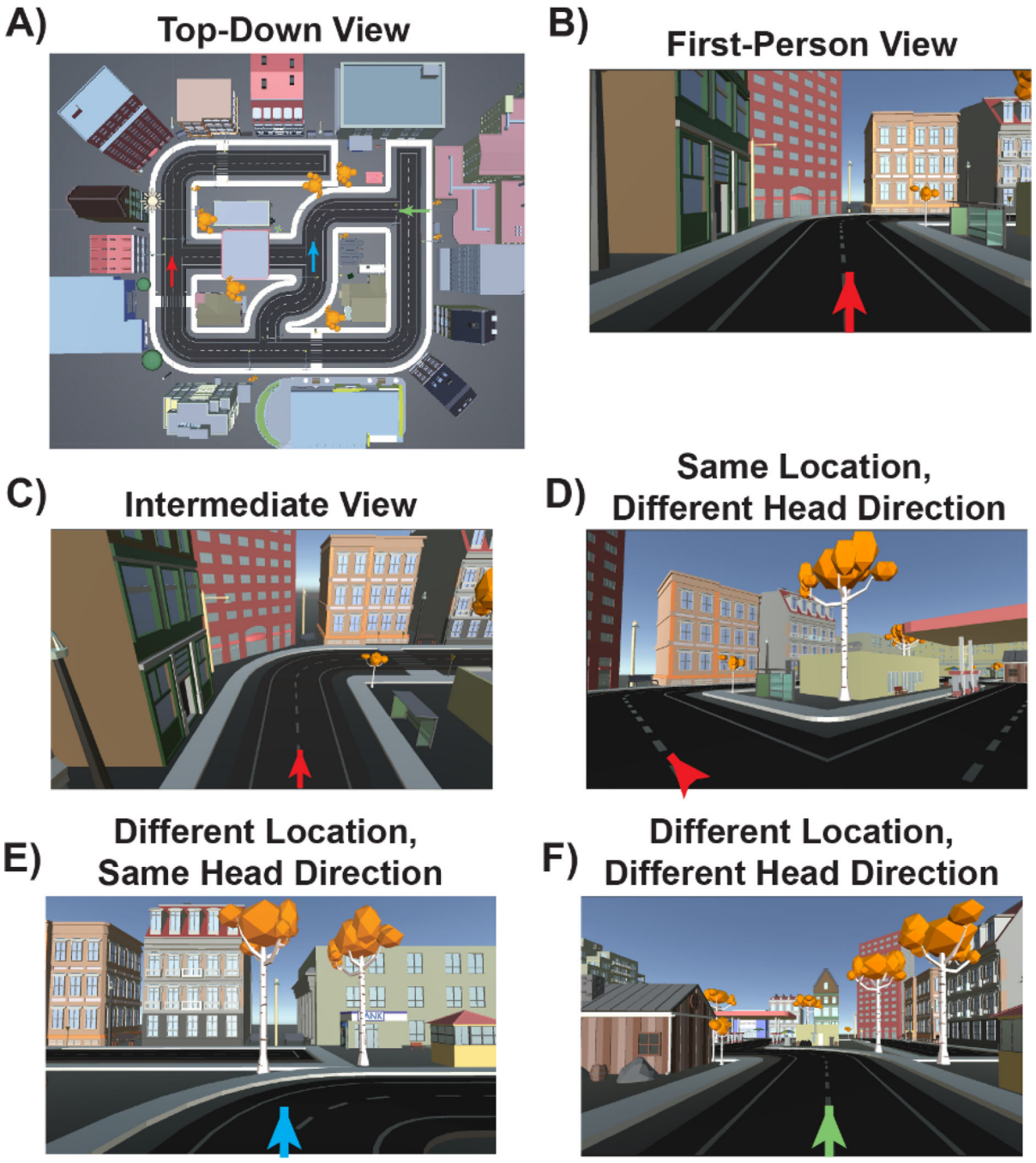

Figure 5. The viewpoint and reference frame problem.

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 panel A will facilitate building an allocentric representation, whereas first-person views tend to facilitate egocentric representations.

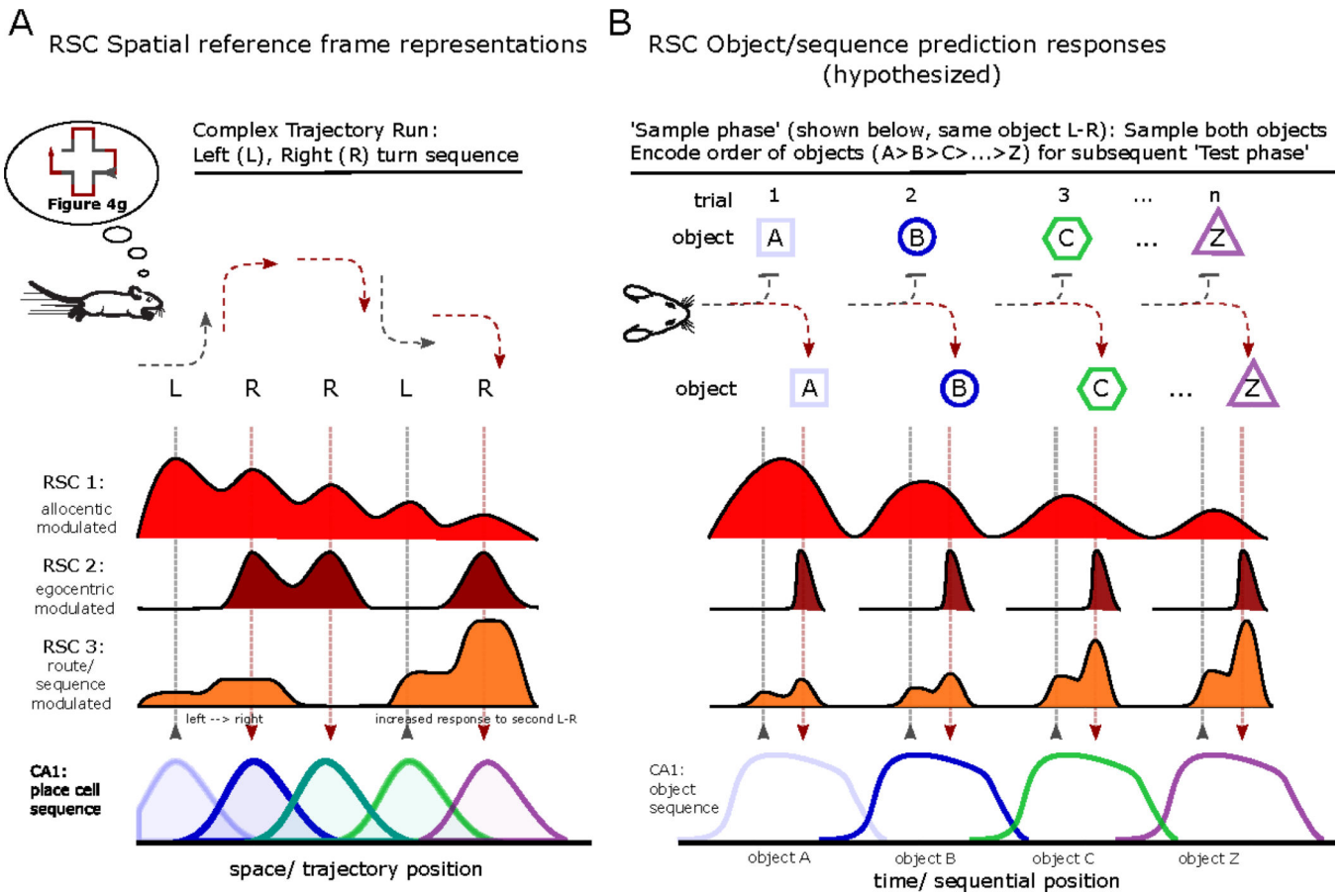

Figure 6. Predictive sequence correlates hypothesized from known spatial reference frame responses.

A. Top: A continuous trajectory running task, requires rats to learn spatial routes with repetitive egocentrically defined (left vs right) movement sequences(inspired by Alexander et al., 2017[8]). Middle: There are known RSC and HPC neuron responses to spatial trajectory running. Three example types of RSC neurons modulated by allocentric, egocentric, and route reference frames. RSC 1 changes response amplitude to each movement position throughout the route's progression. RSC 2 simply responds to all rightward turns. RSC 3 contains a conjunctive response to conjunctions of route progress and turn type sequences, firing for left-right turn combinations with amplitude modulations to route progress (i.e. increased amplitude at second placement of left-right transition). Bottom: Different CA1 place cells respond to each position along the route. **B.** Top: A discrete object sequence task (inspired by Powell et al., 2017[217]) requires the rat to sample same-object pairs in a sequence, making arbitrary left/right 'choices' at each stage. For simplicity here, the depicted rat uses sequentially structured movements for each sample trial, consisting of leftward glances (gray, upward dashes) and rightward movement selections (red, downward arrows). Discrete event responses for RSC and HPC neurons. Middle: Hypothesized object-sequence responses for RSC neurons following properties observed from the corresponding spatial reference frame representation. RSC 1 changes response amplitude to each event within the sequence reflecting the temporal progression of object encounters. RSC 2 responds to egocentric rightward movements or possibly the second of two movement

directions within a trial sequence, since rightward selections follow leftward glances for each trial depicted here. RSC 3 responds to right turn responses that follow leftward glances and increases response amplitude to repeated occurrences of left-right trial structure within the overall sequence of object pair presentations. We note that RSC might also conjunctively encode the identity of each object based on inputs from the visual cortex. Bottom: Inspired by HPC responses to sequences of odors, here different HPC neurons respond to each object within the sequence[218]. RSC = retrosplenial cortex, HPC = hippocampus.

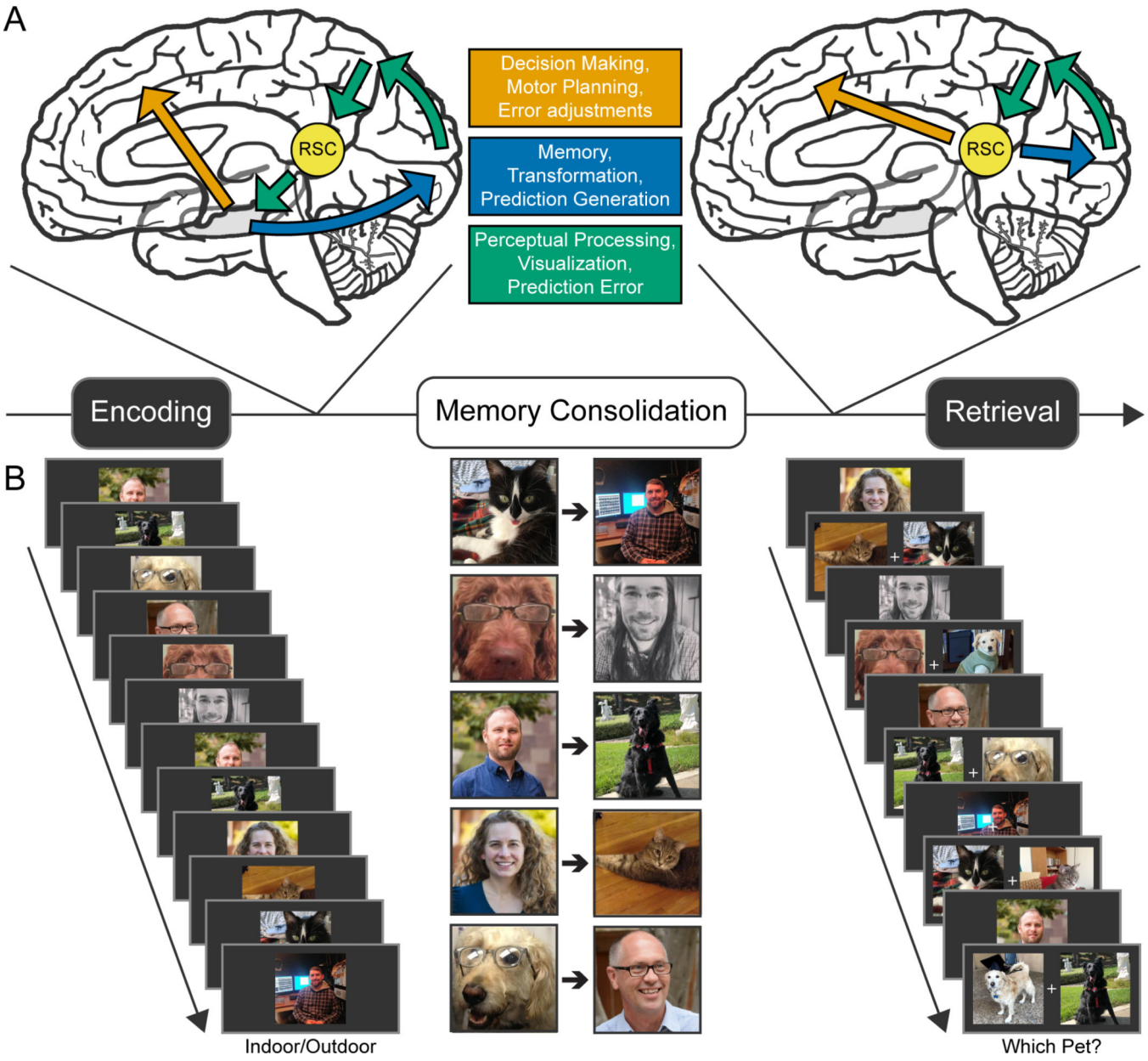

Figure 7. Hypothetical example of how consolidation might alter the role of RSC in a predictive coding hierarchy.

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.

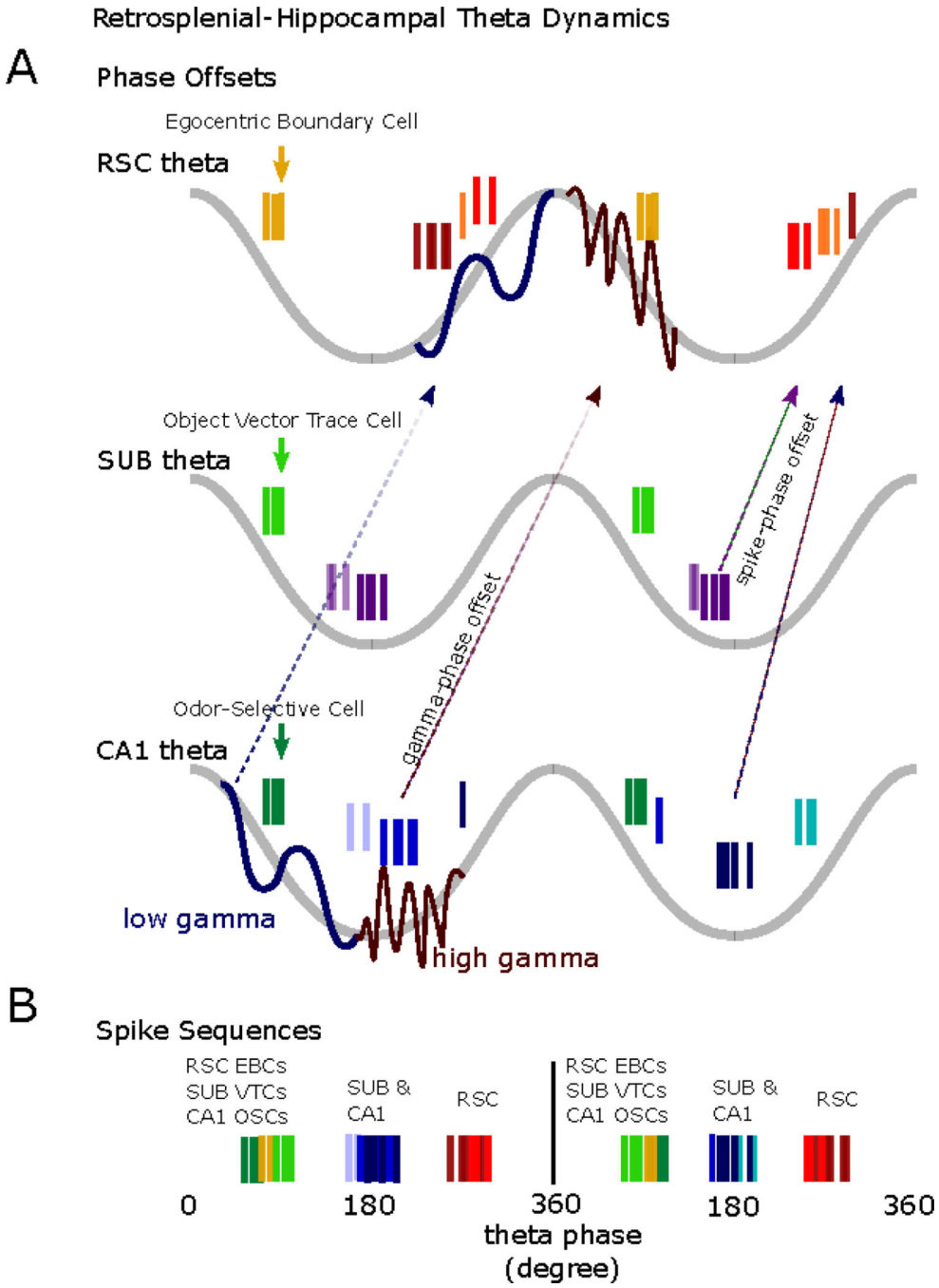

Figure 8. Theta-phase coordination between Hippocampus and Retrosplenial cortex.

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[272]. Peak SUB (purple bars; middle) and HPC spiking (blue bars; bottom) occurs at theta-troughs, whereas peak RSC spiking follows,

at ascending theta[272,281]. 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[6,218,280]. **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.