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The separate and combined properties of the granular (area 29) and
dysgranular (area 30) retrosplenial cortex

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Abstract:

Retrosplenial cortex contains two principal subdivisions, area 29 (granular) and area 30 (dysgranular). Their respective anatomical connections in the rat brain indicate that area 29 is the primary recipient of hippocampal and parahippocampal spatial and contextual information while area 30 is the primary interactor with current visual information.

Lesion studies and measures of neuronal activity in rodents indicate that retrosplenial cortex helps to integrate space from different perspectives, e.g., egocentric and allocentric, providing landmark and heading cues for navigation and spatial learning. It provides a repository of scene information that, over time, becomes increasingly independent of the hippocampus. These processes, reflect the interactive actions between areas 29 and 30, along with their convergent influences on cortical and thalamic targets. Consequently, despite their differences, both areas 29 and 30 are necessary for an array of spatial and learning problems.

Keywords: Landmark, Memory, Navigation, Space, Thalamus

1. Introduction

A brief consideration of retrosplenial cortex (areas 29, 30) properties reveals an intriguing conundrum. Retrosplenial cortex is one of the largest cortical regions in the rodent brain, yet there is a marked reduction in its relative size in the human brain, where posterior cingulate areas 23 and 31 additionally appear, along with the emergence of the adjacent precuneus. Despite its resulting compactness, the human retrosplenial cortex is closely linked with a variety of cognitive processes, with abnormalities in this area being one of the precursors to Alzheimer's disease (Vann et al., 2009; Vanneste et al., 2021). In contrast, it has sometimes proved a challenge to identify cognitive functions that critically depend on the rodent retrosplenial cortex, despite its large extent. Rather, retrosplenial cortex lesions in rodents often have relatively mild consequences in comparison to some of the sites with which it is closely interconnected (Nelson et al., 2015; Mitchell et al., 2018).

As in the primate brain, the rodent retrosplenial cortex is traditionally subdivided into two major areas. These consist of a ventral subdivision (area 29, 'granular') and a dorsal subdivision (area 30, 'dysgranular'). There is, however, considerable variation in how area 29 has been further subdivided by anatomists (Sugar et al., 2011; Vogt & Paxinos, 2014). In this analysis, to help combine findings from different sources, we will treat the granular subdivision (area 29) as if it were a single area.

Retrosplenial cortex is increasingly envisaged as an interface for medial temporal (viewpoint independent) and parietal (egocentric) information, their interaction enabling spatial cognition and episodic memory (e.g., Vann et al., 2009; Alexander & Nitz, 2015; Bicanski & Burgess, 2018). Some of its learning-related attributes take time to emerge, but then contribute to the long-term retention of spatial information. The challenge is to determine how these interactive actions occur and how areas 29 and 30, separately and together, make this possible. For these reasons, the current analysis focusses on the

anatomical, behavioural, and cellular properties of both retrosplenial areas. An emergent theme is that area 30 is primarily concerned with current external (mainly visual) stimuli while area 29 is primarily concerned with both visual and nonvisual cues, the latter including interoceptive signals, relating to past and present spatial and navigational information. For these reasons, one focus is on the complex inter-relationships that areas 29 and 30 have with the hippocampal formation and parahippocampal region as these connections are often presumed to give vital support to the cognitive functions of the retrosplenial cortex. Another focus is on the extensive retrosplenial-thalamic interactions (Sripanidkulchai & Wyss, 1986; Van Groen et al., 1993; Shibata, 1998). While the anterior thalamic nuclei are often seen as principal subcortical partners of areas 29 and 30, an array of other thalamic nuclei contribute to retrosplenial function. Throughout, distinctions between areas 29 and 30 should be tempered with the knowledge that there are multiple, reciprocal connections between these two areas (Shibata et al., 2009).

2. Area 29 versus area 30

2.1 From anatomy to electrophysiology

The cytoarchitectonic border between areas 29 and 30 is immediately apparent in Nissl-stained sections of the rodent brain. Probably the most visible change concerns the appearance of layer II (in area 29 the cells are more closely packed and more densely stained than in area 30). Meanwhile, the terms granular (area 29) and dysgranular (area 30) relate to the status of layer IV.

Arguably the most striking difference in the connections of areas 29 and 30 in the rodent brain concerns their respective hippocampal formation inputs (Figure 1), which terminate in area 29. Similarly in the nonhuman primate, the hippocampal formation preferentially targets area 29 (Aggleton et al., 2012). [Note, the terms hippocampal formation and ‘hippocampal’ refer to the dentate gyrus, CA fields, and subiculum (Burwell & Witter, 2020), while ‘hippocampus’ does not include the subiculum.)] The dorsal subiculum is the principal source of these hippocampal-retrosplenial projections in the rat. These direct efferents terminate densely in layer II and superficial layer III across area 29,

contrasting with much lighter terminations in area 30 (Figures 1, 2). The dense hippocampal inputs to area 29 also contrast with the almost complete lack of direct return projections from retrosplenial cortex to the hippocampal formation (Figure 2) (Sugar et al., 2011). Consequently, return retrosplenial influences are indirect, not only via the parahippocampal region but also via the anterior thalamic nuclei (Prasad & Chudasama, 2013).

At least 50% of the rat dorsal subiculum neurons that project to area 29 bifurcate to innervate the medial mammillary bodies (Kinnavane et al., 2018). These bifurcating projections create an immediate affinity between the medial mammillary bodies and area 29. A further population of dorsal subiculum cells projects to the anteromedial and anteroventral thalamic nuclei, these same thalamic nuclei receiving dense medial mammillary body inputs alongside their reciprocal connections with both areas 29 and 30 (Figure 3). While the functional significance of these various subiculum efferents is only slowly emerging (Yamawaki et al., 2019a; Nelson et al., 2020), the subiculum is known to contain neurons with a variety of spatial properties, including boundary-vector cells, place cells, barrier- or perimeter-related cells, neurons with grid-like patterns of activity, and cells that code for the axis of travel (Lever et al., 2009; Brotons Mas et al., 2010; Olson et al., 2017; O'Mara & Aggleton, 2019; Poulter et al., 2021). Lesion studies indicate that hippocampal spatial information influences area 30 (Mao et al., 2018), potentially via area 29 or the anterior thalamic nuclei.

Along with its subiculum inputs, there is a smaller population of CA1 projections to retrosplenial cortex that again preferentially target area 29 (Figure 2) (Yamawaki et al., 2019b). These projections are inhibitory, with GABAergic CA1 neurons terminating in layer I of area 29, where they help regulate the excitatory inputs from the anterior thalamic nuclei, many of which terminate in the same layer of area 29 (Yamawaki et al., 2019b). In this way they contrast with the glutamatergic subiculum projections that directly excite area 29 pyramidal cells (Yamawaki et al., 2019a; Gao et al., 2021). In addition, area 29 in the rat also receives the large majority of the direct parahippocampal

projections from the postsubiculum and presubiculum that reach retrosplenial cortex (Van Groen & Wyss, 1990b,c).

While area 29 overwhelmingly receives the direct hippocampal inputs to retrosplenial cortex, along with many parahippocampal inputs, area 30 in the rat brain appears to be especially critical for processing visual stimuli. Initial evidence came from the discovery that area 30 in the rat is reciprocally connected with visual areas 17 and 18b (area 29 is only lightly connected with area 18b, and not with area 17) (Van Groen & Wyss 1990a, 1992a, 2003) (Figure 2). These inputs from visual cortical areas are most concentrated in caudal area 30 (Van Groen & Wyss, 1992a). Posterior parietal cortex is also connected with the retrosplenial cortex, but these connections are more associated with rostral area 30 (Olsen et al., 2016).

Further area 29 and 30 connectivity differences extend to their respective thalamic links (Figure 3). While area 29 in the rat brain is more closely connected with the anterodorsal and anteroventral nuclei, area 30 is more closely connected with the anteromedial thalamic nucleus (Sripanidkulchai et al., 1986; Van Groen & Wyss, 1990, 1992a,b, 2003; Lomi et al., 2021). These same studies show that the lateral dorsal thalamic nucleus is interconnected with both areas 30 and 29, but preferentially projects to area 30. The lateral dorsal nucleus receives inputs from cortical visual areas 17 and 18, with further inputs from a variety of subcortical sites also strongly associated with visual signalling, including the superior colliculus and lateral geniculate nuclei (Thompson & Robertson, 1987a,b).

The lateral posterior thalamic nucleus innervates both areas 29 and 30 but again has a particular affinity with rat area 30 (Kamishina et al., 2009). This thalamic nucleus is regarded as the rodent homologue of the pulvinar. It is seen as a key visual nucleus, receiving visual inputs from both cortical area 17 (V1) and other dorsal stream cortical areas, as well as receiving subcortical inputs from the superior colliculus and dorsolateral geniculate nucleus, resulting in multiple maps of visual space within this thalamic nucleus (Roth et al., 2016; Bennett et al., 2019). It is thought that the lateral posterior

nucleus not only provides distributed information from visual scenes but, like the dorsolateral geniculate nucleus, its projections carry locomotion signals (Roth et al., 2016). One suggestion is that lateral posterior efferents help to signal changes in visual scene not predicted by the animal's own actions (Roth et al., 2016).

Information concerning the corresponding connections in the adult mouse brain is provided by the Allen Mouse Brain Connectivity Atlas (2011), a comprehensive database of axonal projections in the mouse brain (for details see Kuan et al., 2015). Each mouse receives an injection into a *source* brain region of enhanced green fluorescent protein (EGFP) expressing adeno-associated virus (AAV), which acts as an anterograde tracer (see connectivity.brain-mpa.org). Next, the axonal projections are systematically imaged using a TissueCyte 1000 serial two-photon tomography system (Oh et al., 2014). The viral anterograde tracer used in these experiments is of equivalent sensitivity to biotinylated dextran amine (Wang et al., 2014). The Allen Atlas divides retrosplenial cortex into three areas. The 'ventral' retrosplenial cortex corresponds to granular retrosplenial cortex, i.e., area 29. Area 30 has been subdivided between the 'dorsal' and 'agranular' retrosplenial cortex, corresponding to the medial dysgranular and the most lateral dysgranular part of area 30, respectively.

The regions of interest, i.e., those areas containing tracer injections, comprised the various thalamic nuclei known to be interconnected with retrosplenial cortex, as well as area 17, extrastriate cortical areas associated with visual processes, and retrosplenial cortical areas. The focus was on those cases where at least 50% of the injected tracer was restricted to the region of interest (Figure 4). With respect to retrosplenial afferents, both area 17 and the extrastriate cortex (except for the latero-intermediate and the antero-lateral visual areas where data were not available) have axonal terminations in both areas 29 and 30, i.e., there was no strong preference for area 30, unlike the rat. Meanwhile, viral injections into area 29 led to denser tracer signals in the visual areas than injections in area 30. Additionally, unlike the thalamic connections in the rat brain outlined above, there is evidence that area 29 has denser input to the anteromedial thalamic nucleus than area 30 (Figure 4).

These apparent anatomical discrepancies with the rat brain suggest that in the mouse there may be a greater balance with respect to the visual cortical interactions with areas 29 and 30. It should, of course, be remembered that some connectional and functional differences will inevitably exist between the rat and mouse brain (Ellenbroek & Youn, 2016). When making these species comparisons an added complication concerns how area 30 is subdivided in the Allen Atlas, an approach not favoured in rat studies.

Returning to the rat brain, its thalamic connections provide valuable insights into the nature of retrosplenial head-direction cells. It has long been known that the anterodorsal and lateral dorsal thalamic nuclei contain numerous head-direction cells (Mizumori & Williams, 1993; Taube, 1995; 2007), while the anteroventral nucleus contains a smaller population of this same cell type (Tsanov et al., 2011). Such head-direction cells aid navigation as their activity distinguishes the direction an animal is facing, often independent of absolute location, thereby providing compass-like information (Taube, 2007).

There is, however, a critical difference between the anterodorsal and lateral dorsal thalamic nuclei. The anterodorsal nucleus receives vital head-direction information directly from the lateral mammillary nucleus (Blair et al., 1999) which, in turn, receives ascending vestibular (e.g., head velocity) signals (Bassett & Taube, 2001; Vann & Aggleton, 2004). The anterodorsal nucleus is strongly interlinked with area 29 (Figure 3), potentially providing area 29 with interoceptive cues. In contrast, the lateral dorsal nucleus does not receive direct lateral mammillary body inputs. Consequently, its head-direction signals involve additional routes (Dudchenko et al., 2019). One clue comes from how the lateral dorsal nucleus receives visual inputs from cortical areas 17 and 18 as well as from subcortical sites including the superior colliculus and lateral geniculate nuclei (Thompson & Robertson, 1987a,b).

Despite the differences in their thalamic inputs, retrosplenial head-direction cells are found in similar proportions across both areas 29 and 30 (Chen et al., 1994; Cho & Sharp,

2001). Like anterior thalamic head-direction cells, they show anticipatory activation, ahead of the postsubiculum (Cho & Sharp, 2001). Their potential importance is signified by how retrosplenial lesions can disrupt the use of direction information (Pothuizen et al., 2008; Elduayen & Save, 2014). In addition to environmental visual stimuli, the activity of these retrosplenial cells is modulated by angular head velocity and running speed (Lozano et al., 2017), consistent with the interplay of interoceptive and exteroceptive information. Given these diverse inputs, it might be supposed that retrosplenial cortex has a critical role in helping to maintain and co-register head-direction (and other spatial) signals derived from different sensory sources (Roth et al., 2016). More specifically, head-direction cells that are initially driven by internal cues (via the lateral mammillary nucleus) will strongly influence the anterodorsal nucleus and, thence, mainly area 29. In contrast, visual influences on retrosplenial head-direction signalling will occur via both cortical and subcortical routes, the latter including the lateral dorsal and lateral posterior nuclei, which project to both areas 29 and 30, but in the rat prefer area 30. These retrosplenial areas then provide an important route for additional visual information to reach head-direction cells in the anterodorsal nucleus, a conclusion supported by how retrosplenial lesions disturb visual landmark control over anterodorsal head-direction cells but spare directional stability from changing self-movement cues (Clark et al., 2010).

These complex, diverse afferent routes for head-direction information accord with the recent proposal of a distinction between ‘traditional’ head-direction cells (e.g., in the anterodorsal thalamic nucleus) and a second group of ‘sensory’ head-direction cells driven by polarising visual features within the environment (Dudchenko et al., 2019). Preliminary evidence for different classes of head-direction cells can be seen in a recording study of areas 29 and 30 (Jacob et al., 2017). In that study, some area 30 head-direction cells reversed their preferred directionality when rats walked between two chambers or even when within a single chamber, the ‘bidirectional cells’ seemingly driven by shared visual landmarks (Jacob et al., 2017). (As area 29 was only recorded in one rat the apparent lack of ‘bidirectional cells’ in this area requires further investigation). In contrast, ‘traditional’ head-direction cells in the anterodorsal thalamic

nucleus maintain a single preferred direction (Dudchenko & Zinyuk, 2005), as if controlled by internal cues. As the firing of these area 30 bidirectional head-direction cells (Jacob et al., 2017) can be maintained in the dark there may still be multi-modal drivers, perhaps reflecting convergence from different thalamic and cortical sites on area 30 or the presence of area 29 and area 30 interconnections (Figures 2, 3). The presence of different classes of directional cells in other brain sites closely connected with retrosplenial cortex (e.g., Olson et al., 2017; Kornienko et al., 2018) increases the opportunity for similar cells in this cortical area. The concept of two, partially independent classes of head-direction cells (Dudchenko et al., 2019) has the added attraction that it helps to explain why lesions targeting ‘traditional head-direction’ sites, such as the lateral mammillary nucleus often have only minor, transient effects on spatial tasks (e.g., Vann, 2005; Dillingham & Vann, 2019) – reflecting how other populations of head-direction cells may still operate (Dudchenko et al., 2019).

It has been observed that the head-direction signal often relies on environmental landmarks, but for this to be effective the brain needs to distinguish those markers that are stable and those that can shift position. Both human neuroimaging (Auger et al., 2012; Epstein & Vass, 2014) and rodent electrophysiology (Lozano et al., 2017) strongly suggest that retrosplenial cortex attends to stable landmarks. Two-photon imaging of area 30 in mice further indicates that these landmark representations reflect the integration of visual, motor, and spatial information (Fischer et al., 2020). As already noted, some ‘bidirectional cells’ in area 30 respond to matching local visual landmarks, e.g., pairs of cues set at 180° , thereby disengaging local from global orientation signals (Jacob et al., 2017). Contrasts between traditional head-direction and bidirectional cells may then help to identify those ‘landmarks’ that are stable and those that change position.

These retrosplenial functions stand in contrast with postrhinal cortex. It has recently been shown that, like retrosplenial cortex, postrhinal cortex receives direct inputs from cortical area V1 alongside subcortical visual areas, including those from the lateral posterior (pulvinar) area which, in turn, receives inputs from the superior colliculus (Beltramo & Scanziano, 2019). That same research showed how visual neurons in postrhinal cortex

are sensitive to moving objects (Beltramo & Scanziano, 2019), potentially having an important role in the rapid detection of threatening stimuli. Despite its many visual inputs, postrhinal cortex does not appear to control visual landmark information in the head-direction system (Peck & Taube, 2017), providing a contrast with retrosplenial cortex.

Area 29 versus area 30

2.2 Lesion studies

A limited number of studies have examined the consequences of permanent lesions centered in either area 29 or 30, with the further limitation that these two areas have not been directly compared in the same experiment (Table 1). Selective area 30 lesions were sufficient to impair radial-arm maze foraging but only when this spatial working memory task became reliant on distal visual cues, following rotation of the arms to disrupt intra-maze cues (Vann & Aggleton, 2005). In a separate study, area 30 lesions impaired acquisition of a spatial location task when direction of travel provided inconsistent information (Hindley et al., 2014b), indicative of an inability to effectively use visual landmark cues. To further examine visual processing, rats were tested on a spontaneous cross-modal object recognition task (Hindley et al., 2014a). Both rats with area 30 lesions and rats with area 29 + 30 lesions were included. Area 30 lesions selectively impaired recognition when the object was sampled in the dark and then tested for familiarity discrimination in the light. As no deficit was seen when the sampling and test conditions remained constant, whether dark or light, the selective deficit suggests a difficulty in integrating the different sensory impressions of the same object. The combined (areas 29 and 30) lesioned rats also failed the dark to light cross-modal problem, but this impairment was less selective (Hindley et al., 2014a).

Meanwhile, some studies have compared area 29 lesions with combined area 29 and 30 lesions (Pothuizen et al., 2010). Both lesions resulted in similar deficits during acquisition of the radial-arm maze task, affecting performance in the light and in the dark. Further testing in parallel T-mazes suggested that area 29 lesions (like area 30 lesions) particularly disrupt spatial working memory when intra-maze cues are removed

(Pothuizen et al., 2010). Meanwhile, in a study of lesions within subareas of area 29 (Rga versus Rgb), only lesions in Rgb disrupted delayed matching-to-position in a water-maze (Van Groen et al., 2004). Lastly, the loss of area 29 deep pyramidal cells following administration of MK801 marginally affected the acquisition of contextual fear conditioning, but seemingly had a greater effect on subsequent retention or expression after conditioning (Sigwald et al., 2020).

Despite the shortage of studies that have directly compared area 29 with area 30 lesions (Table 1), most findings support the idea that area 30 is particularly concerned with visual aspects of the scene, hence, deficits emerge after maze rotation, which taxes distal visual cues (Vann & Aggleton, 2005). This function extends beyond distal spatial cues as contributions were found for cross-modal matching of near objects (Hindley et al., 2014a), where the integration component in the light was of particular importance. With the marked preference that dorsal hippocampal projections have for area 29, it is noticeable that area 29 lesions were sufficient to disrupt spatial learning whether in the light or dark (Pothuizen et al., 2010) and, unlike area 30 lesions, impaired initial radial-arm maze learning in the light (Vann & Aggleton, 2005; see Table 1). Nevertheless, the loss of area 30 is sufficient to disrupt some hippocampal-dependent spatial tasks (Table 1).

It is also helpful to consider the few behavioral studies that have attempted to disconnect specific inputs to or from retrosplenial cortex. An early study that employed crossed permanent unilateral lesions in rats trained on the Morris water maze (Sutherland & Hoising, 1993) found evidence for the importance of both retrosplenial – hippocampal and retrosplenial – anterior thalamic interactions for spatial learning. Other disconnection studies support the idea that retrosplenial cortex can act as a way-station, helping to link the hippocampal formation with the anterior thalamic nuclei (Dumont et al., 2010).

Perhaps most informative are those studies selectively targeting the hippocampal projections to retrosplenial cortex as these will principally involve area 29. Using chemogenetic silencing, evidence emerged that the dense glutamatergic retrosplenial

projections from the subiculum can be subdivided into two components with subtly different roles (Yamawaki et al., 2019a). While vGlut1+ projections may be principally involved in processing recent context memories, the parallel vGlut2+ projections aid the long-lasting storage of fear-inducing context memories (Yamawaki et al., 2019a). Meanwhile, disruption of the inhibitory CA1 projections to retrosplenial cortex during task acquisition resulted in enhanced contextual fear conditioning (Yamawaki et al., 2019b). This action was opposed by the anterior thalamic projections to retrosplenial cortex, which impaired contextual fear conditioning when silenced. It was concluded that the inhibitory CA1 pathway to area 29 normally suppresses, while the excitatory anterior thalamic pathway to area 29 enhances the expression of context memories (Yamawaki et al., 2019b). Further details on these important interactions comes from a recent optogenetic study showing how anterior thalamic and dorsal hippocampal projections recruit the same population of area 29 pyramidal cells (layer III), which are distinct from those influenced by the claustrum and anterior cingulate cortex (Brennan et al., 2021). The anterior thalamic inputs include information about speed of head rotation (Brennan et al., 2021).

Area 29 versus area 30

2.3 Activation studies

One class of evidence comes from comparing immediate-early gene expression in areas 29 and 30 in rats (Pothuizen et al., 2009). Following performance of a spatial working memory task (radial-arm maze foraging), *c-fos* and *zif268* expression increased in area 29, irrespective of whether the task was in the light or dark. In contrast, area 30 activations only occurred when the task was performed in the light. Furthermore, positive correlations were seen between *c-fos* expression in area 30 and performance of the spatial memory task when performed in the light (Pothuizen et al., 2009), reinforcing this association. Other immediate-early imaging studies found evidence for the long-term recruitment of retrosplenial cortex in mice that had been trained 30 days previously to learn the location of a specific arm in a radial maze (Maviel et al., 2004).

It is known that retrosplenial cortex lesions can impair the acquisition of contextual fear conditioning (Keene & Bucci, 2008a,c). Building on these behavioral findings has been the development of techniques in the mouse to place *c-fos* activated retrosplenial neurons under optical control. These studies have revealed ‘engram-like’ neuronal populations in retrosplenial cortex. One of the first such studies showed the apparent reinstatement of a specific context used in a fear conditioning paradigm following stimulation of retrosplenial *c-fos* activated neurons (Cowensage et al., 2014). The resulting retrosplenial effect on behavior (freezing) then became independent of hippocampal inactivation over time (Cowensage et al., 2014). As the optical stimulation was via a skull window, the intervention largely targeted area 30 (Cowensage et al., 2014). In follow-up optogenetic studies using contextual fear conditioning (involving distinctive odours) activation of area 30 neuronal ensembles one day after learning promoted characteristics consistent with enhanced engagement of neocortical areas during retrieval, as well as contextual generalization and decreased hippocampal dependence (de Sousa et al., 2019).

Complementary analyses have used *in vivo* 2-photon imaging to record neuronal activity patterns in area 30. In one such study, mice were trained on the spatial Morris water maze task while *c-fos* tagged neurons were visualised (Czajkowski et al., 2014). A repetitive pattern of cell activation was recorded in area 30, suggesting that an experience-dependent memory trace is both formed and retained in this area (Czajkowski et al., 2014). A related analysis also examined *c-fos* active neurons in area 30 of mice (Milczarek et al., 2018). An important element was the long-term tracking of these neuronal ensembles for several weeks after acquiring the spatial task (reference memory learning in a radial-arm maze in the light). A context-specific pattern of neuronal activity was identified, which was reinstated on subsequent task retrieval (Milczarek et al., 2018). Furthermore, the stability of this engram-like pattern in area 30 was predictive of task performance, again indicative of an important role in consolidation as well as acquisition.

These activation studies suggest that the expression of *c-fos* may be an intrinsic aspect of the learning processes associated with retrosplenial cortex. With this in mind, it is notable that lesions of the anterior thalamic nuclei, mammillothalamic tract, and

hippocampus all result in profound reductions of *c-fos* activity in both areas 29 and 30 (Jenkins et al., 2004; Albasser et al., 2007; Poirier et al., 2008; Vann & Albasser, 2009). Anterior thalamic lesions also disrupt some forms of retrosplenial plasticity (Garden et al., 2009), while reducing spine density in area 29 (Harland et al., 2014). Together the distal impact of these limbic lesions on retrosplenial cortex might be expected to exacerbate their local actions on learning and memory. These disruptive effects may, however, be asymmetric as retrosplenial cortex lesions have little or no effect on *c-fos* activation in the hippocampal formation (Powell et al., 2018).

Electrophysiological recordings have revealed retrosplenial neuronal responses relating to spatial memory and navigation, in addition to heading direction (Chen et al., 1994). These neuronal responses can also represent goal-directed navigation (Vedder et al., 2017) and complex place cells (Cho & Sharp, 2001). Comparisons of retrosplenial place cells with hippocampal place cells reveal some informative differences (Cho & Sharp, 2001; Smith et al., 2012). Many retrosplenial place responses appear to be direction dependent (Cho & Sharp, 2001) and, when running in a cross-maze, retrosplenial place cells emerged as training progressed while some hippocampal place cells were evident from the beginning of training (Smith et al., 2012). Hippocampal cells also typically had smaller place fields and showed greater differentiation of the rewarded locations within the maze (Smith et al., 2012). Nevertheless, retrosplenial place cells also exhibit responses linked to the reward (Smith et al., 2012). Indeed, a high proportion of retrosplenial cells respond to task relevant cues, but unlike hippocampal neurons most respond to more than one task-related attribute (Vedder et al., 2016). These different, but related, patterns help to explain how both structures contribute to contextual conditioning in a complementary manner.

One repeating feature is how retrosplenial activity is closely linked to task learning (Gabriel, 1993). This attribute is, for example, seen with training on a continuous T-maze alternation task (Miller et al., 2019). Here, it was also found that retrosplenial neuronal activity not only increasingly discriminated between components of the maze but also reflected trajectory to the rewarded arm of the maze (Miller et al., 2019). Consequently,

it became possible to use retrosplenial activity to predict turn choices late in training, so-called ‘splitter cells’ (Vedder et al., 2016; Miller et al., 2019). Furthermore, just as lesion studies have shown the importance of retrosplenial cortex for contextual fear conditioning, retrosplenial neuronal activity can discriminate contexts (Miller et al., 2021), as also seen for the hippocampus. However, in addition, some retrosplenial neurons show higher rates of firing in a preferred context, irrespective of location, revealing two modes of context representation (Miller et al., 2021). Meanwhile, across many of these studies there remains the need to distinguish area 29 and area 30 cell activity. Finally, many spatially sensitive retrosplenial neurons, unlike those in the hippocampal formation, are simultaneously sensitive to allocentric, egocentric, and route-centric frames of reference (Alexander & Nitz, 2015; Alexander et al., 2020).

A characteristic of some of these findings is how aspects of retrosplenial neuronal activity resemble those of the hippocampal formation but typically emerge later in training. Consequently, this pattern echoes with the slow-learning retrosplenial system first conceptualised by Gabriel and colleagues (Gabriel, 1993; Gabriel & Talk, 2001), who showed how training-induced activity in retrosplenial cortex gradually emerges to a variety of non-spatial cues that signal appetitive or aversive outcomes. Even so, retrosplenial neuronal responses to relevant spatial and non-spatial cues can sometimes be seen from the earliest stages of training (Smith et al., 2018), leading to questions concerning why these different temporal profiles may occur (Smith et al., 2018).

A notable discovery is that many retrosplenial neurons can be categorised as ‘egocentric boundary vector cells’ (Alexander et al., 2020). These cells are particularly frequent in area 30, potentially reflecting the combination of occipital (visual) and parietal influences on this area. The spatial fields of these cells are active when environmental boundaries occur at a particular orientation and distance to the animal. This spatial signal, which is encoded in egocentric coordinates, is independent of self-motion and context invariant. Consequently, these egocentric vector codes could enable spatial system transformations and support the anchoring and utilization of allocentric representations (Alexander &

Nitz, 2015; Alexander et al., 2020). Furthermore, some of these neurons are synchronized with hippocampal theta oscillations (Alexander et al., 2020).

Two-photon calcium imaging has afforded further insights. Mao et al. (2017) reported that the superficial layers of both area 29 and area 30 contain place cells very similar to those first described for the hippocampus. In head-fixed mice running on a linear treadmill containing tactile cues, retrosplenial neurons exhibited narrowly tuned place fields. Positionally tuned responses persisted, albeit less stably when tactile stimuli were removed. Place fields were similarly preserved when the experiment was repeated in the dark, i.e., in the absence of visual input. Finally, changing the position along the linear treadmill at which the animal was rewarded had little effect on the position where neurons responded. In a follow-up study Mao et al. (2018) showed that the place field responses in area 30 critically depend on hippocampal inputs.

It is at present unclear how retrosplenial place field neurons relate to ‘border cells’ originally described in medial entorhinal cortex (Solstad et al., 2008) and recently reported in rats for both area 29 and 30 following tetrode recordings (van Wijngaarden et al., 2020; see also Campbell et al., 2020). Unlike typical medial entorhinal border cells, these retrosplenial cells had multiple firing fields on each of four available walls, with a variety of preferred distances from the walls. Interestingly, border cells maintained their spatial tuning both in darkness and when the physical walls, i.e., tactile cues, were removed (Solstad et al., 2008). Van Wijngaarden et al. (2020) further established that retrosplenial border cells were invariant to rotations of the global environment under which allocentric cells shift their response fields, implying they were egocentric. The finding that inhibition of the medial entorhinal cortex disrupted border coding in retrosplenial cortex, but not *vice versa*, indicates a transformation from allocentric to egocentric representation. Additional evidence for such a coordinate system transformation again comes from the study by Alexander et al. (2020) who showed that many area 30 neurons respond to boundaries at a specific orientation and location relative to the animal itself. These results support the conclusion by Alexander and Nitz (2015) that retrosplenial cortex maps the conjunction of egocentric and allocentric space. A

further imaging study (Fischer et al., 2020) reinforced the idea that the local integration of visual, motor, and spatial information within area 30 provides landmark representations, while electrophysiological studies further emphasise the likely importance of medial entorhinal – retrosplenial interactions (Campbell et al., 2020).

In a study using 2-photon cellular imaging in awake head-fixed mice, a remarkable 40% of neurons in caudal area 30 responded to large-field gratings (Powell et al., 2020). By comparison only 6% of cells responded in rostral area 30, reflecting how caudal area 30 is more strongly interconnected with visual areas 17 and 18b (Van Groen & Wyss, 1992). Just as informative was the finding of a retinotopic map of visual space in caudal area 30, which was stable over weeks (Figure 5A, B) (Powell et al., 2020). This constitutes an egocentric representation of visual space very similar to that in visual cortex, from which it is presumably inherited. [Visual responses in area 29 were not tested by Powell et al. (2020), in part due to the difficulty of accessing this area for two-photon imaging.] The visual responses in area 30 were as spatially selective as those measured in V1, whereas selectivity for orientation and direction of drifting gratings amounted to only about half that of V1 (Powell et al., 2020). Interestingly, while in V1 all directions of visual motion are equally represented, in retrosplenial cortex there is a significant bias in directional preference toward naso-temporal motion, corresponding to the direction of visual flow that occurs when the animal is moving forward (Powell et al., 2020).

Consistent with this final finding, Powell et al. (2020) also revealed that retrosplenial neuronal responses are strongly modulated by locomotion, both in the absence or presence of visual stimulation (Figure 5C, D). Meanwhile it has previously been shown that sensory processing by V1 neurons is modulated by locomotion signals (Niell & Stryker, 2010; Keller et al., 2012; Dipoppa et al., 2018). Nevertheless, in retrosplenial cortex the firing rates of a significantly greater percentage of cells than in V1 are either positively or negatively correlated with the (spontaneous) run speed of the mouse on a treadmill in darkness (Powell et al., 2020). Among visually responsive cells, similar numbers of cells exhibited either suppression or facilitation to a drifting grating by the

animal's running; with a subset of parvalbumin-positive inhibitory interneurons being particularly strongly suppressed during locomotion (Powell et al., 2020).

A recent study by Mao et al. (2020) provides further insight into how the combination of visual and locomotion signals may drive sequential, place cell-like activity in retrosplenial cortex. Using a virtual reality (VR) visual display in combination with a linear treadmill they imaged head-fixed mice (thus removing vestibular self-motion cues). Locomotion of the mouse on the belt was yoked to the updating of the virtual 'tunnel' of visual textures, providing self-motion cues through optic flow but not positional cues. After a fixed travel distance on the treadmill the display turned black, and the animal received a reward. In line with their earlier study (Mao et al., 2017), retrosplenial neurons responded sequentially as a function of location in the VR environment (but not as a function of position on the belt). To test whether retrosplenial neuronal responses represent the integration of optic flow signals or distance travelled on the treadmill the VR flow speed was varied relative to the running speed on the belt; VR position tuning was found to be largely unaffected changing VR gain (Mao et al., 2020). When four identical landmarks were added to the VR scene at fixed locations, a minority of neurons responded repeatedly at fixed positions along the VR 'tunnel' relative to the positions of the landmarks. These results show that retrosplenial neurons encode both an internal representation of (visual) space and external stimuli (Mao et al., 2020); in other words, the results are consistent with retrosplenial cortex providing an active intermediary between brain regions generating different forms of spatial maps, e.g., egocentric and allocentric representations (Byrne et al., 2007; Alexander & Nitz, 2015).

A missing feature of many, but not all (e.g., Cho & Sharp, 2001; Alexander et al., 2020; Lomi et al., 2021) of the cited electrophysiological studies is the inclusion of comparisons between area 29 and 30 properties. One exception (Lomi et al., 2021) analysed the large numbers of nondirectional cells in areas 29 and 30, finding that almost twice as many of the area 29 nondirectional cells are strongly entrained by theta oscillations, with associated differences in their theta characteristics at the level of individual cells, e.g., proportionately more theta-bursting neurons in area 29 (Lomi et al

2021). This latter feature, bursting, might reflect properties of the dense subiculum inputs to area 29 (Anderson & O'Mara, 2003; Simonnet, & Brecht, 2019). Meanwhile, the imaging studies described above typically focus on area 30, often for practical reasons. Area 30 presents the experimenter with accessible cortical tissue on the dorsal surface of the brain. Area 29, in contrast, is deeper and not directly visualised. However, miniature endoscopes using prism lenses now offer the prospect of imaging this area too. Clearly, given the evidence from anatomical tracers it will be particularly valuable to compare visual responsiveness in areas 29 and 30, while also determining hippocampal formation and parahippocampal influences.

3.0 The bigger picture

Several themes repeatedly emerge when comparing areas 29 and 30. Perhaps the most striking stems from how retrosplenial cortex is the recipient of an array of interoceptive and exteroceptive information from both cortical and subcortical sources. This includes afferent head-direction, head rotation, and hippocampal spatial information (especially to area 29), parietal egocentric signals (especially to area 30), and cortical visual information (especially to area 30). Some of these connectional differences may prove to be particularly evident in the rat brain. At the same time, areas 29 and 30 are strategically placed to mediate and integrate this information. Some of this integration may occur directly between areas 29 and 30 (e.g., vestibular and locomotion with visual) while other aspects of sensory integration may principally occur within a given area (e.g., area 30 for visual, egocentric, and locomotor feedback). Given these properties, it is not surprising that retrosplenial cortex is increasingly placed in models that emphasise its role as an interface for medial temporal (viewpoint independent) and parietal (egocentric) information, the combination of which enables key elements of spatial cognition (e.g., Alexander & Nitz, 2015; Bicanski & Burgess, 2018). We would add to such models the direct contributions from multiple thalamic nuclei, which differentially provide interoceptive and exteroceptive information to areas 29 and 30 (Figure 3).

These integrative functions help to explain how retrosplenial cortex lesions can affect spatial learning in both the light (e.g., Vann & Aggleton, 2002) and dark (Cooper &

Mizumori, 1999; Cooper et al., 2001; Elduayen & Save, 2014), with deficits in the light often becoming most apparent when the rat is required to flexibly use an array of cue strategies (Vann & Aggleton, 2005; Pothuizen et al., 2008; Hindley et al., 2014b), e.g., switching between intra-maze cues and extra-maze cues. For these reasons, the conundrum in the Introduction of why rodent retrosplenial cortex is relatively large yet the impact of retrosplenial lesions is often relatively modest can begin to be resolved. Natural foraging by rats (*Rattus norvegicus*) occurs in both the light and dark, where rats must distinguish permanent from transient landmarks, utilising a complex array of visual, olfactory, vibrissae, somatosensory, and vestibular signals. Such real-life conditions create complex, dynamic challenges that match the properties emerging for retrosplenial cortex. In contrast, laboratory studies naturally seek to simplify spatial problems by reducing cue types. This simplified approach unwittingly creates effective solutions in the absence of retrosplenial cortex. It may also be relevant that retrosplenial cortex can aid the separation of overlapping stimuli (Keene & Bucci, 2008b; see also Hindley et al., 2014b; Nelson et al., 2018), a problem often integral to real-world contexts.

A second emerging theme concerns how retrosplenial cortex contributes to both the initial acquisition and long-term retention of spatial memory tasks (Todd & Bucci, 2015). One source of evidence for long-term consolidation comes from studies utilising *c-fos* expression (Maviel et al., 2004; Czajkowski et al., 2014; Milczarek et al., 2018). These same studies indicate that with time there is increasing independence from the hippocampal formation (Maviel et al., 2004; Cowensage et al., 2014; de Sousa et al., 2019). Related evidence from lesion studies again reveals that retrosplenial cortex has greater importance when retrieving remotely (rather than recently) acquired auditory or visual cues involved in fear conditioning (Todd et al., 2016; Jiang et al., 2018; Sigwald et al., 2020). These findings point to a temporal shift in function from the hippocampal formation to retrosplenial cortex that might match changes in glutamatergic signalling (Yamawaki et al., 2019a). We would envisage a parallel shift in thalamic – retrosplenial interactions over this same time.

A challenge is to determine whether these various retrosplenial functions operate separately or jointly to support human episodic memory (Mitchell et al., 2018). Current memory models place considerable emphasis on the integration of contextual information, closely allied to mechanisms of scene construction to aid consolidation and retrieval (e.g., Barry & Maguire, 2019). Retrosplenial cortex is just one of several brain sites that appear to have the properties required for these spatial functions. But, in addition, it is a hub, not just between hippocampal and anterior thalamic sites vital for memory (Vann et al., 2009) but also between medial temporal and frontal cortical sites in the default mode network (Kaboodvand et al., 2018; Smallwood et al., 2021). The challenge is to use the differences between areas 29 and 30 to help reveal individual retrosplenial actions with the goal of understanding their combined effects. This goal is exemplified by the work of David Bucci.

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Figure 1.

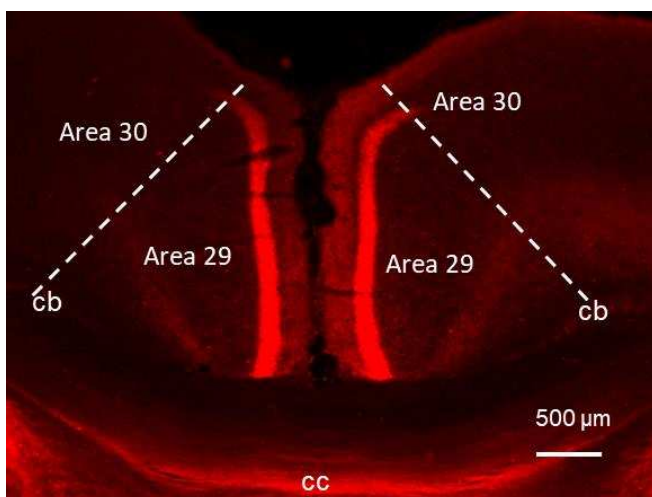


Figure 1. Dorsal subicular termination in area 29 (granular retrosplenial cortex). Photomicrograph of a coronal section of the rat retrosplenial cortex showing terminal label (red signal) restricted to layers II and upper III of granular retrosplenial cortex (area 29) following an injection of AAV5-CaMKIIa-hM4Di(Gi)-mCherry into dorsal subiculum (after Nelson et al., 2020). Abbreviations: cb, cingulum bundle; cc, corpus callosum.

Figure 2.

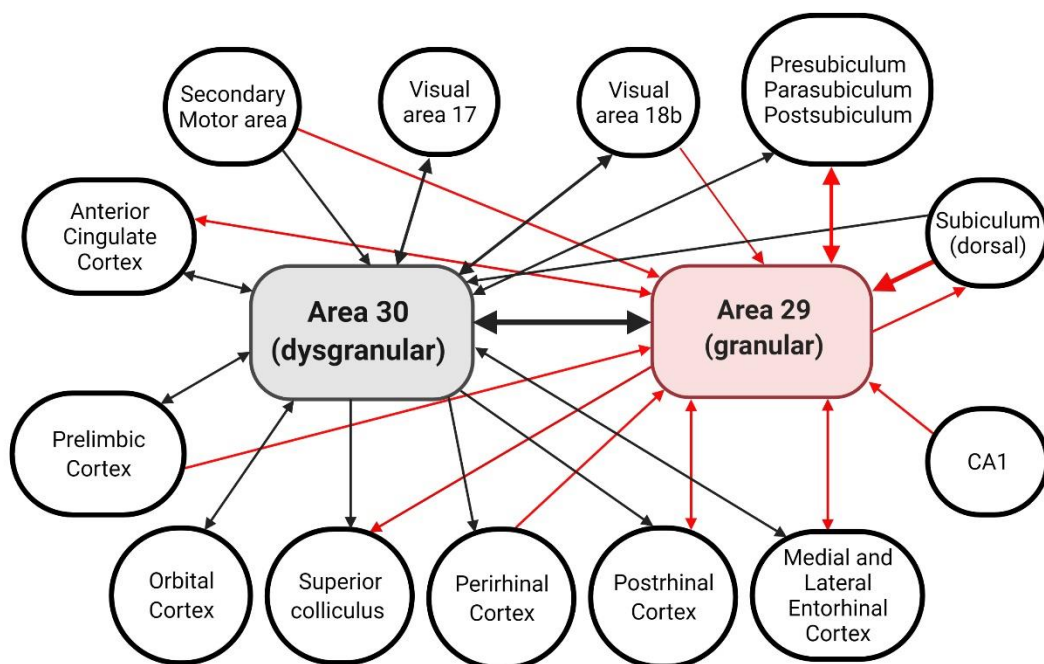


Figure 2. Cortical connectivity of rat areas 29 and 30 (retrosplenial cortex). The figure highlights the many differences between areas 29 and 30, including the greater involvement of area 30 with visual areas. The thickness of the arrows provides an indication of the relative strengths of the connections. The figure was created with *Biorender.com*

Figure 3.

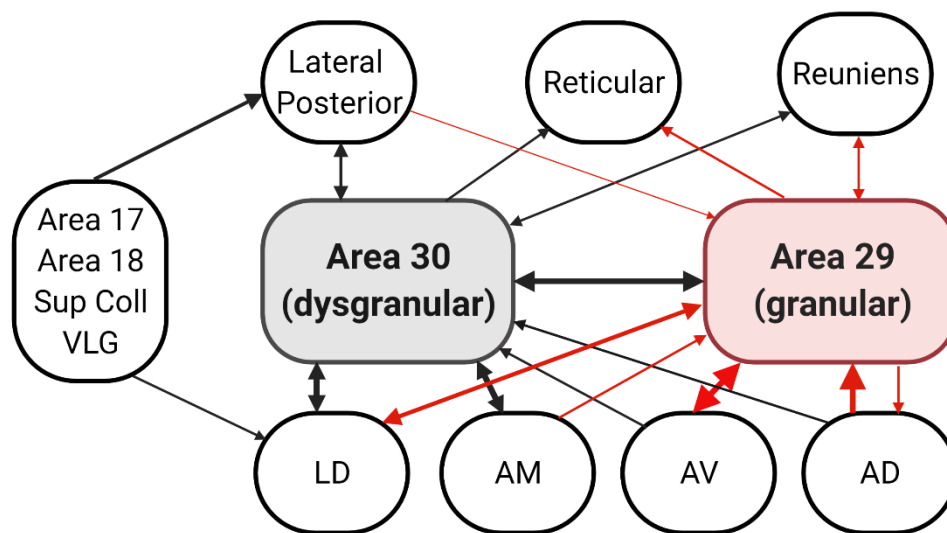


Figure 3. Thalamic connectivity of rat areas 29 and 30 (retrosplenial cortex). The figure highlights the many differences between areas 29 and 30, including the greater involvement of area 30 with thalamic and other subcortical visual areas. Abbreviations: AD, anterodorsal nucleus; AM, anteromedial nucleus; AV, anteroventral nucleus; LD, lateral dorsal nucleus; Sup Coll, superior colliculus; VLG, ventral lateral geniculate. The

thickness of the arrows provides an indication of the relative strengths of the connections.
The figure was created with *Biorender.com*

Figure 4.

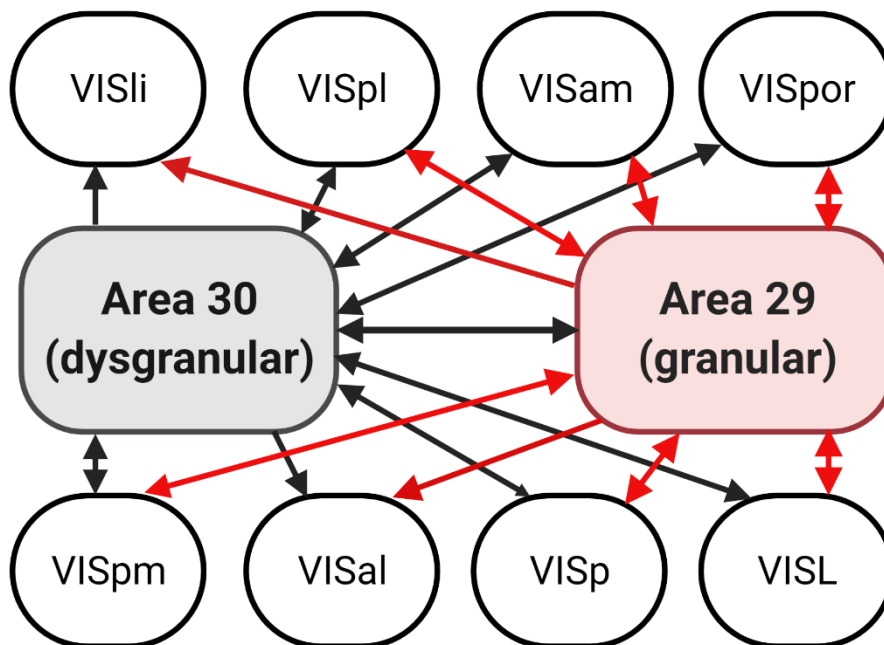


Figure 4. Connectivity of areas 29 and 30 with visual cortical areas in the mouse brain according to the Allen Mouse Connectivity Atlas (2011). A total of 31 cases were used where over 50% of the injection was within the projection source area. The reciprocal connections between area 29 and visual cortical areas appeared denser than the corresponding connections with area 30. Note, no cases with tracer injections in VISli or VISal were found and so their efferents could not be depicted. Abbreviations: VISli: laterointermediate area; VISpl: posterolateral area; VISam: anteromedial area; VISpor: postrhinal area; VISpm: posteromedial visual area; VISal: anterolateral medial area; VISp: Primary visual area (area 17); VISL: lateral visual area. The figure was created with *Biorender.com*

Figure 5

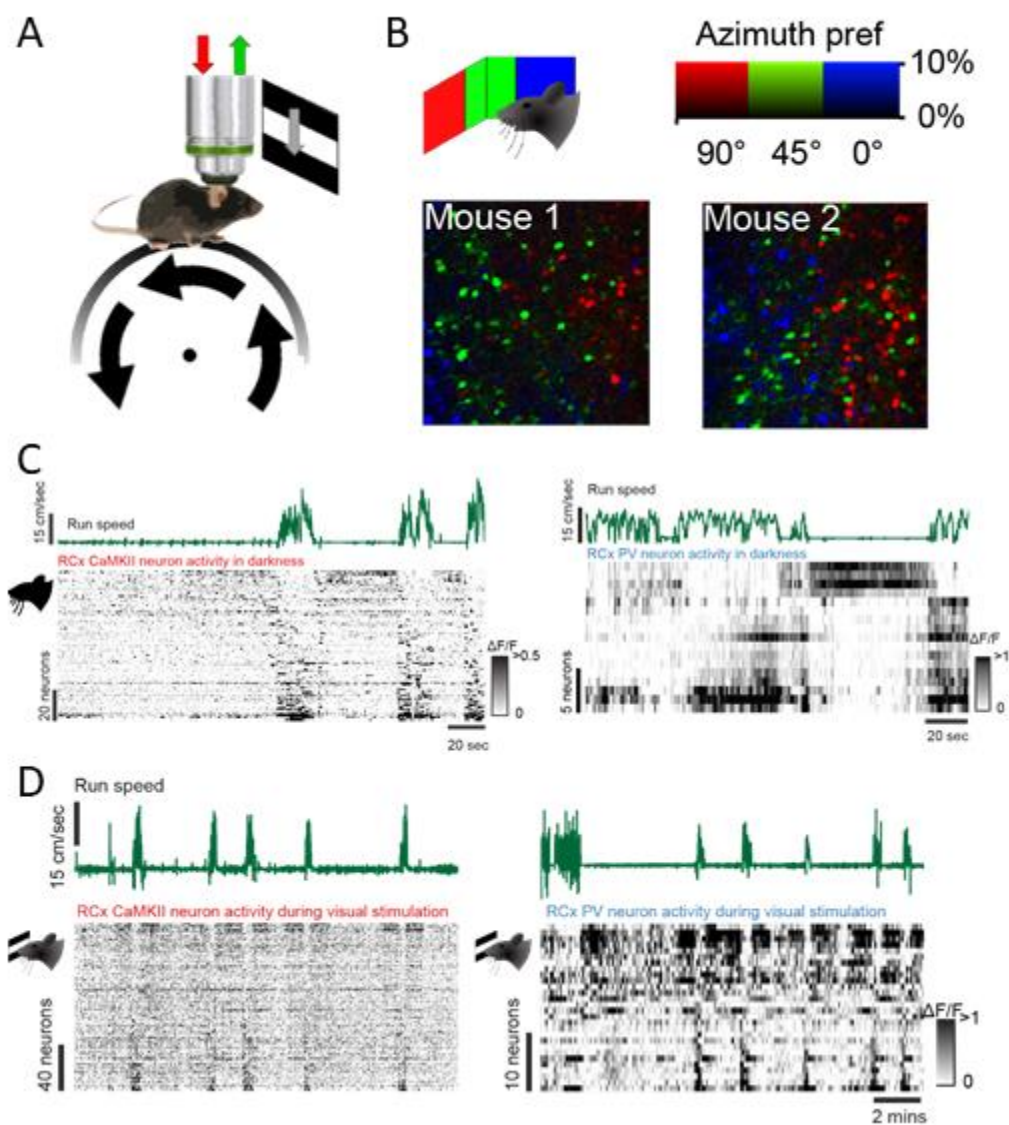


Figure 5: Responses of area 30 neurons to visual stimulation and locomotion.

(A) Setup schematic; two-photon calcium imaging of awake head-fixed mice which were free to run on a custom designed fixed-axis cylindrical treadmill. (B) Visual responses of excitatory (CaMKII positive) neurons expressing GCaMP6f to grating stimuli presented in three different azimuth positions; pixel-wise response maps from two mice shown. (C) Comparison of the activity of excitatory (CaMKII positive) and inhibitory (parvalbumin [PV] positive) area 30 neurons in darkness. Run speed (top), and raster representation of neural activity (below, rows are individual neurons) sorted by run speed correlation. Note

that the activity of some neurons (upper rows) is strongly suppressed while the mouse runs while other neurons (lower rows) are strongly activated. (D) Modulation of the responses of excitatory (CaMKII positive) and inhibitory (PV positive) area 30 neurons to visual stimulation by locomotion. Run speed (top) and raster representation of neural activity (below) during visual stimulation sorted by run speed correlation in excitatory neurons (left) and inhibitory (PV) neurons (right). After Powell et al. (2020).

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<u>Experiment</u>	<u>Area 29</u>	<u>Area 30</u>	<u>Reference</u>
RAM acquisition	X	√	Pothuizen ea. 2010; Vann Aggleton 2005
RAM rotation (distal cues)	X	X	Pothuizen ea. 2010; Vann Aggleton 2005
RAM dark	X		Pothuizen ea. 2010
Xmodal matching		X (dark to light)	Hindley ea. 2014a
Location (dry maze)		X (distal cues)	Hindley ea. 2014b
T-maze alternation	X (acquisition)		Pothuizen ea. 2010
T-maze alternation	X (distal cues)		Pothuizen ea. 2010
Water-maze	X (working memory)		Van Groen ea. 2004
Context fear condit.	X (long retrieval interval)		Sigwall ea. 2020
Context fear condit.	↑ (CA1→29 silencing)		Yamawaki ea. 2019b
Context fear condit.	X (Sub→29 silencing) (vGlut1, vGlut		Yamawaki ea. 2019a
Context fear condit.	X (ATN→29 silencing)		Yamawaki ea. 2019b
RAM light	↑ Fos, Zif	↑ Fos, Zif	Pothuizen ea. 2009
RAM dark	↑ Fos, Zif	~ Fos, Zif	Pothuizen ea. 2009
RAM light		↑ Fos correlate task retrieval	Milczarek ea. 2018
ePhys	HD cells	HD cells	Chen ea. 1994 Cho & Sharp 2001
ePhys	Egocentric boundary vector cells (10%)	Egocentric boundary vector cells (39%)	Alexander ea. 2020
ePhys, Ca ²⁺ imaging	Place cells	Place cells	Cho & Sharp 2001 Mao ea. 2017
ePhys	Nondirectional θ	Fewer nondirectional θ cells, different properties	Lomi ea. 2021

Table 1. Comparisons of granular (area 29) and dysgranular (area 30) retrosplenial cortex. The results refer to the effects of permanent lesions (Pothuizen down to Sigwall), transient lesions (Yamawaki), immediate-early gene activity expression (Pothuizen, Milczarek), neuronal recording (ePhys) and Ca²⁺ imaging (Mao). A blank space reflects the lack of a corresponding study. Abbreviations: ATN, anterior thalamic nuclei; condit., conditioning; ePhys, electrophysiology; HD, head direction; RAM, radial-arm maze; Xmodal, cross-modal; %, percentage of cells in region categorised as egocentric boundary cells; ↑ increased expression or facilitated performance; ~ no change; X impaired performance.