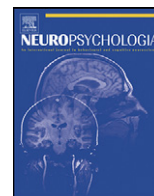




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Understanding retrosplenial amnesia: Insights from animal studies

John P. Aggleton*

School of Psychology, Cardiff University, Tower Building, Park Place, Cardiff, Wales CF10 3AT, UK

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ABSTRACT

Bilateral damage in the posterior cingulate region can induce anterograde amnesia. Identifying the potential contributions of the various areas within this heterogeneous region has, however, largely depended on animal research. Within the posterior cingulate region the retrosplenial cortex stands out by virtue of its dense interconnections with the hippocampal formation and anterior thalamic nuclei. Consistent with these connections is the finding from lesion studies in animals that the retrosplenial cortex is necessary for navigation and spatial learning, and that these functions occur in close conjunction with the hippocampal formation and anterior thalamus. Suggested functions include the creation and maintenance of scenes, linked to the switching between scenes based on different frameworks (e.g. egocentric versus allocentric). More fine-grain analyses suggest that there are functional distinctions between the subregions within the retrosplenial cortex, though these subregions are likely to then act as a coordinated unit. Other studies reveal that the retrosplenial cortex is highly sensitive to damage in distal sites, including damage to sites that do not have direct retrosplenial connections. The resultant retrosplenial dysfunctions, which include decreases in metabolic activity and a loss of plasticity, may contribute both to diencephalic and temporal lobe amnesias as well as to Alzheimer's disease.

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1. Introduction

It has long been appreciated that the posterior cingulate region (areas 23, 29, 30, 31), and the retrosplenial cortices (areas 29, 30) in particular, may have an important role in memory. Initial evidence for this view came from neuropsychological studies suggesting that bilateral damage to this region is sufficient to induce anterograde amnesia (Ironsides & Guttmacher, 1929; Maguire, 2001b; Valenstein et al., 1987). Confirming this link has, however, proved very difficult. While the posterior cingulate region can be damaged by various neurological conditions e.g. tumours, arteriovenous malformations, infarction and haemorrhages, it is uncertain whether these conditions ever produce damage that is demonstrably confined to the retrosplenial cortex. Indeed, examination of the study that coined the term 'retrosplenial amnesia' (Valenstein et al., 1987) reveals that the authors could not exclude the presence of damage in the fornix, the stria terminalis, or adjacent cortical regions within the posterior cingulate area. Furthermore, the potential for disruption to adjacent tracts such as the cingulum bundle and the fornix means that damage in the retrosplenial region can disconnect sites outside this area. For these reasons, delineating the extent of retrosplenial pathology is critical, though made extremely difficult due to the location and shape of the retrosplenial cortex. It is, there-

fore, not surprising that in patient group studies it remains difficult to exclude a contribution from other posterior cingulate areas, as well as the fornix (e.g. Rudge & Warrington, 1991; Valenstein et al., 1987), and even the hippocampus (Gainotti, Almonti, Betta, & Silveri, 1998).

In recent years, numerous functional magnetic resonance imaging (fMRI) studies in normal subjects have added weight to the notion that the retrosplenial cortex is of especial importance for memory (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Maguire, 2001a; Svoboda, McKinnon, Levine, 2006). Even so, there is still the pervasive problem of distinguishing retrosplenial cortex (areas 29, 30) from the adjacent posterior cingulate cortex (areas 23, 31). While it is reasonable to expect that techniques such as fMRI will continue to improve their anatomical resolution, and so better delineate retrosplenial cortex, it remains the case that this information will not reveal whether the retrosplenial cortex is necessary for normal memory. This information comes from studying the impact of retrosplenial cortex pathology.

The lack of patients with confirmed pathology restricted to the retrosplenial cortex means that studies with other animals can offer unique insights into the importance of this specific area for learning and memory. In parallel, our understanding of the connectivity of areas 29 and 30 (e.g. Kobayashi & Amaral, 2003; Kobayashi & Amaral, 2007) has depended on axonal transport studies with animals. Such anatomical studies have been integral in reinforcing the view that the retrosplenial cortex

* Tel.: +44 2920 874563; fax: +44 2920 874858.
E-mail address: aggleton@cf.ac.uk.

occupies a pivotal position in the network of structures supporting episodic memory (Aggleton & Brown, 2006).

In this review the focus will almost entirely be on studies with rodents. Lesion studies with nonhuman primates remain very scarce and are hampered because in the primate brain the retrosplenial cortex occupies an inaccessible, deep position close to the back of the splenium (Kobayashi & Amaral, 2000). In contrast, the rodent retrosplenial cortex occupies almost all the dorsal midline cortex caudal to the level of the body of the fornix. Not only is this area directly accessible, but in the rat the retrosplenial cortex extends over half the length of the entire cerebrum making it one of the largest cortical areas in this species. Consequently there have been numerous lesion and electrophysiological studies of the area, complemented by anatomical tracing studies. A review of these rodent studies shows that this area is specialised for spatial navigation and learning, leading to hypotheses about the ways in which the demands of spatial navigation might spill over into broader aspects of human memory, and so contribute to amnesia.

Two related issues will also be considered. The first is whether the various subregions within the retrosplenial cortex have different functional properties. Again, this is information that at present can only come from animal studies. The second concerns growing evidence that retrosplenial cortex dysfunction is a pervasive aspect of amnesic syndromes brought about by damage to either the medial temporal lobe or the medial diencephalon, i.e. conditions where there is no direct retrosplenial cortex damage. There is now good reason to believe that the retrosplenial cortex is unusually sensitive to the loss of its afferents from either of these areas, and so retrosplenial dysfunction may contribute significantly to almost all anterograde amnesias. It should finally be noted that in this review the term amnesia will be used to refer to anterograde amnesia, and any discussion relating to retrograde amnesia will be specified.

2. Anatomical considerations

It is vital to clarify certain anatomical issues that have, in the past, confused and held back comparative research into retrosplenial cortex function. Most important, is the need to appreciate that in the rodent brain the arrangement of the posterior cingulate region is different to that in primates in a number of key respects. In the human brain the retrosplenial cortex is composed of areas 29 and 30 (Brodmann, 1909), and forms part of the posterior cingulate region along with areas 23 and 31. In the rat brain, however, there are no direct counterparts for areas 23 and 31, and so the entire posterior cingulate cortex should be designated retrosplenial cortex (Vogt & Peters, 1981; Van Groen & Wyss, 1990). As a consequence, the term posterior cingulate cortex for the rodent brain is potentially misleading.

As in the primate brain, the rat retrosplenial cortex can be subdivided into a 'granular' area 29 and a 'dysgranular' area 30 (Vogt, Vogt, & Farber, 2004). In this region, the term granular refers to the prominent layer II—a layer of densely packed, small pyramidal cells. The rodent area 29 has been variously subdivided (Jones, Groenewegen, & Witter, 2005). Influential examples include designating either two (Van Groen & Wyss, 1990) or three (Vogt & Peters, 1981) subregions in granular area 29. In this review I will refer to the two principal subregions within the granular area 29 described by Van Groen and Wyss (1990, 2003). As a consequence the retrosplenial cortex contains subarea granular a (Rga) and subarea granular b (Rgb), along with the dysgranular (Rdg or area 30) retrosplenial cortex (Fig. 1). The dysgranular retrosplenial cortex (Rdg) is dorsal and lateral to the granular subregions, while Rga is largely confined to the caudal half of area 29 (Fig. 1). These specific retrosplenial subdivisions will be used in this review as they have been adopted in the majority of studies that have attempted to compare the functions of retrosplenial cortex subareas. Importantly, these three subregions (Rdg, Rga, Rgb) show clear connectivity differences from each other (Van Groen & Wyss, 1990, 1992, 2003).

Studies into the connectivity of the rodent retrosplenial cortex serve to underline the likely role of this region in memory and its potential involvement in amnesia. Most relevant are the dense, reciprocal retrosplenial connections with the hippocampal formation and the anterior thalamic nuclei (Van Groen & Wyss, 1990, 1992, 2003; Wyss & van Groen, 1992). Both areas are notable as they are, respectively, regarded as key sites in the aetiology of temporal lobe and diencephalic amnesia. Furthermore, disconnection studies with rats indicate that the hippocampus and retrosplenial cortex, and the anterior thalamic nuclei and retrosplenial cortex, are interdependent in that they work together to support spatial learning (Sutherland & Hoising, 1993). This interdependence is intriguing as the hippocampus and anterior thalamic nuclei are themselves directly and reciprocally interconnected (Aggleton & Saunders, 1997), and also appear to function interdependently (Warburton, Morgan, Baird, Muir, & Aggleton, 2001). The implication is that the retrosplenial cortex must have some added contribution to the anterior thalamic–hippocampal mnemonic processes, presumably via connections that are not shared with the hippocampus or anterior thalamic nuclei (Vann, Aggleton, & Maguire, 2009).

A final anatomical issue concerns the location of the retrosplenial cortex with respect to its major white matter tract, the cingulum bundle. While the cingulum bundle forms part of the route for the connections of the retrosplenial cortex with other cortical areas as well as with the thalamus (Domesick, 1970; Mufson & Pandya, 1984), the retrosplenial cortex is not the only region to contribute fibres to this tract (Mufson & Pandya, 1984). The fact that the cingulum runs immediately under the granular retrosplenial cortex leaves it very vulnerable to conventional lesion methods, e.g. radiofrequency, electrolytic, or aspiration. Any inadvertent dam-

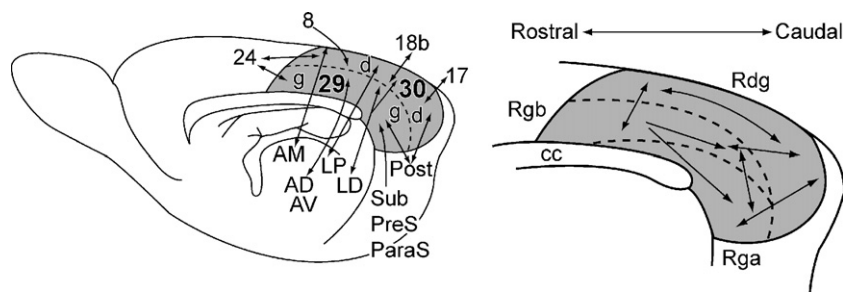


Fig. 1. Schematic diagrams showing the main connections of the rat retrosplenial (areas 29 and 30) cortex. *Left:* Principal extrinsic connections, along with evidence of different patterns of connectivity for the granular (Rga and Rgb) and dysgranular (Rdg) subdivisions. *Right:* Principal intrinsic connections within the retrosplenial cortex (data adapted from Shibata et al., in press). *Abbreviations:* AD anterior dorsal thalamic nucleus; AM, anterior medial thalamic nucleus; AV, anterior ventral thalamic nucleus; LD, laterodorsal thalamic nucleus; LP, lateroposterior thalamic nucleus; ParaS, parasubiculum; Post, postsubiculum; PreS, presubiculum; Sub, subiculum; All other numbers refer to area designations.

age to the underlying cingulum bundle is likely to disconnect the entire retrosplenial cortex even if the lesion itself spares parts of the retrosplenial cortex. In addition, cingulum bundle damage has the potential to disconnect sites that do not include the retrosplenial cortex. As might be expected, surgeries deliberately targeting the cingulum bundle result in spatial memory deficits in rats (Neave, Nagle, Sahgal, & Aggleton, 1996; Neave, Nagle, & Aggleton, 1997; Warburton, Aggleton, & Muir, 1998) and emphasise the need for caution as any tract damage may disconnect fibres of passage. This need is underlined by studies that compared cytotoxic versus radiofrequency lesions of the retrosplenial cortex in mice (Meunier & Destrade, 1988, 1997). Both studies found lesion effects that were attributed to the additional impact of cingulum bundle damage in the cases with radiofrequency lesions. For these reasons, the present review will focus wherever possible on the outcome of cytotoxic lesions of the retrosplenial cortex.

3. The behavioural impact of retrosplenial cortex lesions—modelling amnesia

As has been repeatedly noted, testing animals for anterograde amnesia is fraught with problems (Aggleton & Pearce, 2001). People suffering from anterograde amnesia show severe problems with tests of episodic memory and typically perform poorly on tests of recognition memory, so creating two potential routes for behavioural models of amnesia. There are, however, intrinsic problems with both approaches. First, there are specific difficulties in testing episodic memory in animals. Most critically, we are unable to confirm whether animals possess the ability to search actively and recollect specific past experiences (Suddendorf & Busby, 2003), yet this ability is seen as the essence of episodic memory. There is, however, mounting evidence to suggest that some analogous process might occur in animals (Clayton, Bussey, & Dickinson, 2003; Dere, Kart Teke, Huston, & De Souza Silva, 2006). Less controversial is the demonstration that animals can learn key attributes of episodic memory (the what? where? and when? of an event), and recent ingenious studies have shown that rats, as well as some birds, are able to learn these attributes in combination (Babb & Crystal, 2006; Clayton et al., 2003; Dere et al., 2006; Eacott, Easton, & Zinkivskay, 2005; Iordanova, Good, & Honey, 2008). These demonstrations of 'episodic-like' memory reinforce the value of comparative studies of amnesia and leave the way open for researchers to examine these attributes singly or in combination (Aggleton & Pearce, 2001). An important consideration is that the contribution of a region may only emerge when these attributes are combined, either in pairs or as all three together (Eacott & Norman, 2004; Iordanova, Burnett, Aggleton, Good, & Honey, *in press*). Thus, a null result for just a single attribute need not provide a sufficiently rigorous test.

A second route for testing features of amnesia has been to assess recognition memory. There has, however, been much debate over the merit of this approach (for opposing views see Aggleton & Brown, 1999; Squire, Wixted, & Clark, 2007). Clearly, if a loss of recognition memory is intrinsic to the definition of amnesia then the debate has been pre-empted. More useful is to focus on the critical issue of whether patients can suffer a severe loss of episodic memory i.e. are 'amnesic', yet retain seemingly intact recognition. While this issue remains contentious (Aggleton & Brown, 2006; Squire et al., 2007; Wixted, 2007; Yonelinas et al., 2002), there are both individual and group studies that provide strong evidence for disproportionate deficits in episodic memory in the context of little or no apparent recognition memory problems (Aggleton & Shaw, 1996; Aggleton et al., 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Tsivilis et al., 2008; Vann et al., 2008; Yonelinas et al., 2002). One interpretation of these patients, which typically have more focal pathology than most amnesics, is that

they rely on spared 'familiarity-based' recognition to solve recognition tasks (Aggleton & Brown, 2006; Vann, Tsivilis et al., 2009; Yonelinas et al., 2002; but see Squire et al., 2007). In contrast, these same cases show impaired 'recollective-based' recognition, alongside marked deficits in episodic memory. Further, support for this dual-process explanation comes from a patient with temporal cortex damage that provides the double dissociation, i.e. impaired familiarity-based recognition but spared recollective-based recognition (Bowles et al., 2007).

If there are independent mechanisms for familiarity and recollective-based recognition (Aggleton & Shaw, 1996; Eichenbaum, Yonelinas, & Ranganath, 2007; but see Squire et al., 2007; Wixted, 2007) then there are serious pitfalls when using recognition as a substitute for episodic-like memory in animals. The most obvious pitfall is the considerable evidence that rats have access to familiarity information (Brown & Aggleton, 2001), coupled with the parsimonious assumption is that they typically rely on this information when solving tests of recognition memory. As a consequence, tests of object recognition do not provide a benchmark test for animal models of amnesia—rather they focus on an aspect of cognition that is often but not always lost in amnesia (familiarity-based recognition). This account does not, however, mean that rats might not have a process analogous to recollective-based recognition (Eichenbaum et al., 2007), rather any separation of these putative processes will require special testing procedures (Fortin, Wright, & Eichenbaum, 2004) that have yet to be applied to the retrosplenial cortex.

A further issue concerns the distinction between working memory and reference memory when applied to animal learning. The term 'working memory' has a somewhat different connotation to that used with human research. For animals, working memory refers to that information which is required within a given trial, but may prove misleading for subsequent trials or sessions (Honig, 1978; Olton, Becker, & Handelmann, 1979). An example is reinforced T-maze alternation, where the rat must remember the last (sample) run, but ignore the information prior to the last sample run. Reference memory, in contrast, refers to the learning of associations that are constant across sessions, e.g. that the sample run is always reinforced. Using these definitions, it can be shown that spatial working memory in rats can last for hours (Bartus et al., 1985). One consequence is that rodent working memory should not be seen as directly comparable to human short-term memory or working memory. A second consequence is that it may be appropriate to use tests of 'working memory' when assessing attributes of amnesia in animals even though working memory is intact in many human amnesics. A further consequence of these definitions is that tests of object recognition for animals need not be assumed to tax working memory. This is because any object recognition task using trial-unique stimuli (new test objects every trial) will have no added demand for the animal to distinguish between the present trial and previous trials, i.e. the relevant information can be held across trials with little or no impact on performance (except for the potential build-up of common elements or features across objects).

A final factor when considering the impact of retrosplenial lesions in animals is the extent of retrosplenial cortex damage. There has been a common tendency to spare the most caudal retrosplenial cortex in lesion studies, though it is now clear that this region is important for spatial learning (Vann & Aggleton, 2004; Vann, Brown, & Aggleton, 2000; Vann, Wilton, Muir, & Aggleton, 2003) and has distinct connections (Van Groen & Wyss, 1992; Shibata, Honda, Sasaki, & Naito, *in press*; Fig. 1). As might be expected, lesions that spare the caudal retrosplenial cortex are less disruptive than more complete lesions that involve the full rostro-caudal extent of the area (Vann et al., 2003; Vann & Aggleton, 2002; Vann & Aggleton, 2004a). These differences in lesion extent may help to explain some of the null effects reported after retrosple-

nal cortex lesions (e.g. Bussey, Everitt, & Robbins, 1997; Bussey, Muir, Everitt, & Robbins, 1997; Neave, Lloyd, Sahgal, & Aggleton, 1994) and are the most likely explanation (Aggleton & Vann, 2004) for some of the apparent discrepancies between studies that have been attributed by some to strain effects (Harker & Whishaw, 2004). One consequence is that great care needs to be taken when comparing across research groups that employ different lesion sizes or surgical methods. A final factor that may alter the impact of retrosplenial cortex lesions on spatial memory is the extent of pre-surgical and post-surgical training (Cain, Humpartzoomian, & Boon, 2006; Lukoyanov, Lukoyanova, Andrade, & Paula-Barbosa, 2005).

The next three sections will consider the what? where? and when? attributes of episodic memory, and examine how they are affected by retrosplenial cortex lesions. The relatively few studies that have looked at combinations of these attributes will also be considered. At present it appears that no study has looked at the impact of retrosplenial cortex damage on a task that combines all three attributes.

4. Object recognition—what?

Tests of object recognition have been used to address the ‘what?’ attribute of episodic-like memory. The attraction is that such tasks not only test object identity but also involve one-trial learning, and so capture a further feature often attributed to episodic and episodic-like memory. This use of object recognition tasks should, however, be treated with care as outline above. Furthermore, the notion of one-trial learning has to be considered carefully. While the experimenter may define a test session as a single trial, e.g. 5 min exposure to a novel object, for the rat this period might be more accurately considered as multiple trials comprising discrete bouts of object exploration.

Several studies have described the impact of cytotoxic retrosplenial cortex lesions on spontaneous tests of object recognition. None of these studies has found evidence that retrosplenial cortex damage impairs performance (Parron & Save, 2004; Vann & Aggleton, 2002; Ennaceur, Neave, & Aggleton, 1997). Likewise, lesions of the cingulum bundle do not appear to disrupt spontaneous object recognition (Ennaceur et al., 1997). One limitation with these studies is that they all use spontaneous exploration as a behavioural measure, and there appear to be no reports on the effect of retrosplenial lesions on tests of object recognition that use a reinforced delayed nonmatching-to-sample rule (Steckler, Drinkenburg, Sahgal, & Aggleton, 1998).

A different picture emerges when rats are tested on the spontaneous recognition of familiar objects that are placed in novel spatial configurations (‘associative recognition’). Now rats with extensive retrosplenial cortex lesions (Vann & Aggleton, 2002) fail to detect the novel spatial configuration as they do not spend additional time exploring the spatially re-arranged objects. In this ‘object-in-place’ task (Dix & Aggleton, 1999) rats need to link specific objects with specific locations. In an ‘object location’ task (Dix & Aggleton, 1999) the rat need only notice that there is an object in a novel location, i.e. there is no requirement to link a specific object with its particular location. Again, there is evidence that the loss of retrosplenial cortex impairs the ability to respond to the repositioning of an object (Ennaceur et al., 1997; Parron & Save, 2004). These object-in-place and object-location deficits are informative as they suggest that there may be something special about the involvement of the retrosplenial cortex in tests of associative recognition.

5. Spatial learning—where?

Behavioural analyses of retrosplenial cortex lesions have largely focussed on tests of navigation and spatial learning. There are several reasons for this focus. One is that the anatomical connections

of the area link it to regions (hippocampus, anterior thalamus) known to be vital for spatial memory. Another reason is that electrophysiological recording studies have directed attention to this domain as approximately 10% of the cells in the rat retrosplenial cortex can be classified as ‘head-direction’ cells (Chen, Lin, Green, Barnes, & McNaughton, 1994; Cho & Sharp, 2001). These cells have the property that they can distinguish the direction that the animal is facing independent of its location i.e. they act like a compass. Such head-direction cells are equally distributed across the dysgranular and granular retrosplenial cortices (Chen et al., 1994). A third reason is that human cases of unilateral retrosplenial region damage can display a selective deficit in spatial orientation (Aguirre & D’Esposito, 1999; Epstein, 2008; Maguire, 2001b; Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997). Such patients may recognise familiar, neighbourhood landmarks yet still be unable to find their way in the same environment. Consequently, these patients with unilateral retrosplenial cortex damage do not know which direction to take and often fail to learn new routes (Epstein, 2008; Maguire, 2001b; Vann, Aggleton et al., 2009).

Rats with retrosplenial cortex lesions have been tested on an array of standard spatial learning tasks using the water-maze, radial-arm maze, and T-maze. In the water-maze deficits are found for both the reference memory version (Harker & Whishaw, 2002; Lukoyanov et al., 2005; Sutherland & Hoesing, 1993; Sutherland, Whishaw, & Kolb, 1988; Vann & Aggleton, 2002; Vann et al., 2003; Warburton et al., 1998; Whishaw, Maaswinkel, Gonzalez, & Kolb, 2001) where the escape platform occupies a constant position across sessions, and the working memory version (Harker & Whishaw, 2004; Sutherland et al., 1988; Vann et al., 2003) where the platform position is fixed within a session but moves across sessions. A component of the initial reference memory deficit may be a tendency for greater thigmotaxis, i.e. swimming close to the side walls (Lukoyanov et al., 2005). Acquisition of the standard radial-arm maze task (do not revisit a previously entered arm within a session) is sometimes (Cooper & Mizumori, 2001; Vann & Aggleton, 2002, 2004a), but not always affected (Pothuizen, Aggleton, & Vann, 2008; Vann & Aggleton, 2004a; Vann et al., 2003) by retrosplenial cortex lesions. This apparent inconsistency is strongly associated with the extent of retrosplenial sparing in the various studies (Vann et al., 2003; Vann & Aggleton, 2004a).

Much more consistent is the finding that retrosplenial cortex lesions, even if they are incomplete, impair eight-arm radial maze performance when the rat is interrupted after the first four choices so that the arms of the maze are rotated before the trial is completed. Now the remaining, correct (unvisited) arms occupy the same spatial location with respect to distal room cues, but the use of intra-maze cues is nullified and the rat is further challenged by the additional delay and disruption. Every study using this rotation manipulation has produced a clear lesion-induced deficit (Pothuizen et al., 2008; Vann & Aggleton, 2002, 2004a, 2004b, 2005; Vann et al., 2003, 2004). A notable feature is that the impairment can emerge even if prior acquisition performance appears normal (Pothuizen et al., 2008; Vann & Aggleton, 2004a, 2005; Vann et al., 2003). Attempts to distinguish the various demands of maze rotation on performance point to the conflict in spatial cue information as being critical (Vann & Aggleton, 2004a, 2004b), a finding consistent with other lesion evidence that the retrosplenial cortex is associated with spatial strategy switching (Pothuizen et al., 2008; Wesierska, Adamska, & Malinowska, 2009).

Given the sensitivity of the radial-arm maze task (especially the rotation condition) and water-maze tasks, it might be supposed that T-maze alternation would also be sensitive to retrosplenial cortex lesions. The first study to use this task (Markowska, Olton, Murray, & Gaffan, 1989) did, indeed, find very severe deficits but the lesions were made by aspiration, and cytotoxic lesions of a similar extent failed to find a T-maze alternation deficit in either standard

acquisition or after interposed delays between sample and test run (Aggleton, Neave, Nagle, & Sahgal, 1995). In contrast, cingulum bundle lesions impaired both acquisition and subsequent performance (Aggleton et al., 1995), suggesting that damage to this tract contributed to the findings of Markowska et al. (1989). This pattern of results was repeated in later studies that again found no clear acquisition deficit on T-maze alternation after cytotoxic retrosplenial cortex lesions (Aggleton et al., 1995; Neave et al., 1994) but a deficit after cingulum bundle damage (Neave et al., 1996, 1997; Warburton et al., 1998; see also Meunier & Destrade, 1997). One possible explanation is that the retrosplenial null effects reflect incomplete lesions, but a more complete lesion still only produced a borderline T-maze alternation acquisition deficit (Pothuizen et al., 2008). Another explanation is that the retrosplenial cortex contributes differentially to multiple forms of spatial learning (Vann, Aggleton et al., 2009) and that T-maze alternation can be solved by multiple strategies e.g. allocentric alternation, egocentric alternation, intra-maze cue alternation, and direction alternation (Dudchenko, 2001; Futter & Aggleton, 2006). Consequently, the lesion always leaves sufficient ways for the rat to solve and perform the task, and so has only a relatively mild effect. This explanation is consistent with the impact of rotation on radial-arm maze alternation, where a suboptimal strategy is unmasked. Further support comes from a study that tried to isolate systematically the cues used for T-alternation (Pothuizen et al., 2008). Here, the effects of retrosplenial cortex damage were only clearly exposed when the rats were forced to rely on directional alternation (Pothuizen et al., 2008), a strategy that might rely on head-direction information.

Evidence for an involvement in navigation as well as spatial memory comes from lesion evidence that the retrosplenial cortex is needed for path-integration based on idiothetic cues (Whishaw et al., 2001; Cooper, Manka, & Mizumori, 2001). Path integration (dead-reckoning) describes the ability to compute a direct route back to the start of path without retracing the actual route taken. For this ability the rat updates its current position using idiothetic cues so that it can calculate a bearing back to the start of its route. As a consequence path integration can occur in the dark.

A resulting issue is whether navigation problems provide a more parsimonious account of the spatial learning deficits reported after retrosplenial cortex lesions i.e. the rats can learn the location but do not know how to get there. In fact, a consideration of the available evidence (see below) shows that while navigation deficits occur they cannot explain all spatial learning deficits. Furthermore, effective navigation requires learning as the animal updates its position and will benefit from previously learnt arrays of spatial cues. Consequently, any distinction between spatial learning and navigation is likely to be relative rather than absolute. There is, for example, evidence that retrosplenial cortex inactivation impairs navigation in novel testing situations, as well as in the dark (Cooper et al., 2001). These deficits have been interpreted as reflecting the interplay between mnemonic processes and accurate navigation (Cooper & Mizumori, 1999; Cooper et al., 2001).

One way to approach this navigation versus learning problem is to isolate particular component attributes of navigation and determine the impact of retrosplenial cortex lesions. A test in the water-maze that required rats to learn a constant swim trajectory in the dark (fixed heading angle and distance) found no deficit after retrosplenial lesions (Zheng et al., 2003). In a similar 'landmark' test in the water-maze rats were trained to find a hidden escape platform that was at a constant direction and distance from a visible beacon that changed its absolute position on every trial (Vann & Aggleton, 2004a, 2004b). Rats with extensive retrosplenial cortex lesions were still able to solve this task, i.e. they could still learn a set direction that remained constant over every trial. The use of direction information was then tested in a different way by reinforcing T-maze alternation in two parallel T-mazes placed side-by-side

(Pothuizen et al., 2008). While retrosplenial lesioned rats could solve the alternation task in the light, a clear impairment emerged when tested in the dark when performance was thought to rely almost entirely on direction (fixed heading) alternation (Pothuizen et al., 2008). Other relevant evidence comes from the finding that rats with complete retrosplenial cortex lesions are unimpaired on performing an egocentric discrimination (Vann & Aggleton, 2002). The conclusion is that the retrosplenial cortex is important not for discerning a particular direction, but for linking that direction with past experience. This interplay between navigation and memory echoes the conclusions of Cooper et al. (2001).

A second way to approach this navigation versus learning issue is to consider spatial tasks with little or no navigational demands. An example is the object-in-place task where the objects to be explored remain in constant view to the rat. Rats with retrosplenial lesions are impaired on this task (Vann & Aggleton, 2002) and its variants (Ennaceur et al., 1997; Parron & Save, 2004), even though the navigational demands are minimal. Related evidence comes a study reporting impaired contextual fear conditioning following retrosplenial cortex lesions (Keene & Bucci, 2008a, 2008c). Here, again, the problem involves a spatial context but has potentially little or no navigational demands. Another task that might be usefully employed in future studies is the annular water maze (Brun et al., 2002) where rats can only swim in a ring of water. Learning the location of a submerged platform is revealed on probe trials where the platform is removed, and in which the rats pause over the learnt location. This task involves learning a spatial location but minimises navigational demands as the rats can only adopt a single route.

The conclusion, therefore, is that retrosplenial cortex lesions often impair both spatial learning and navigation, and this should not be surprising given their interplay. At the same time, the impact of retrosplenial cortex lesions does not appear to be confined to one particular class of spatial information and can be masked by the availability of alternate strategies that can be used to solve many spatial memory tasks. It is also possible to conclude that many of these spatial functions occur in close conjunction with the hippocampus and the anterior thalamic nuclei. This view is not only consistent with the connectivity of the region but receives direct support from disconnection studies that have examined spatial learning in the Morris water maze (Sutherland & Hoesing, 1993). Such findings place the retrosplenial cortex even more centrally in the neuroanatomy of anterograde amnesia as they bring together key regions for temporal lobe and diencephalic amnesia.

6. Temporal learning—when?

While there is clear need to examine the importance of the retrosplenial cortex for the 'when?' attribute of episodic-memory, this does not yet appear to have happened. Research is required using several different approaches. One approach is to look at temporal order e.g. the ability to discriminate between recent and less recent stimuli (e.g. Barker, Bird, Alexander, & Warburton, 2007), though this approach is potentially confounded by presumed differences in trace strength. Another approach concerns the ability to use time of day as a contextual property in a conditional learning task (Iordanova et al., 2008, in press). A third approach is to examine the importance of the retrosplenial cortex for temporal duration learning, though some rodent studies indicate that this form of temporal learning need not be hippocampal dependent (Dietrich & Allen, 1998; Kyd, Pearce, Haselgrove, Amin, & Aggleton, 2007; Meck, 1988) and, hence, may also not rely on the retrosplenial cortex.

7. Other classes of learning

Despite the understandable focus on spatial learning, a small number of studies have assessed the impact of retrosplenial cortex

lesions in rodents on other forms of learning. Retrosplenial cortex lesions do not appear to affect the acquisition of a visual discrimination or its reversal (Bussey, Muir, et al., 1997). Indeed, in the same study there was some evidence that the same lesions facilitated acquisition of an 8-pair concurrent visual discrimination (Bussey, Muir, et al., 1997), though it should be noted that the lesions spared the more caudal parts of the area i.e. those retrosplenial regions that receive most visual inputs (Van Groen & Wyss, 1992). More complete retrosplenial cortex lesions also failed to affect a simple visual discrimination (Keene & Bucci, 2008b). In contrast, there is evidence that retrosplenial lesions can induce deficits on more complex tasks. Late stages of learning a visuospatial conditional task (if visual stimulus A select right lever, if visual stimulus B select left lever) were mildly impaired (Bussey, Muir, et al., 1997). Likewise, lesion-induced deficits were found in the acquisition of a compound 'feature negative task' (Keene & Bucci, 2008b) where a tone might signal food but that same tone in combination with a visual stimulus predicts no food.

A number of studies have examined the impact of retrosplenial cortex damage on fear conditioning and avoidance learning. As has already been noted, retrosplenial cortex lesions can impair the acquisition of contextual conditions (Keene & Bucci, 2008a, 2008c). In contrast, fear conditioning to a tone appears unaffected (Keene & Bucci, 2008a, 2008c). This pattern of results fits with the notion that the retrosplenial cortex aids conditioning within visual scenes, especially as these impairments are unlikely to reflect more general problems in processing emotion-evoking stimuli as retrosplenial lesions need not disrupt passive avoidance or freezing behaviour (Keene & Bucci, 2008a, 2008c; Lukoyanov & Lukoyanova, 2006). Unfortunately, the situation appears less resolved as Lukoyanov and Lukoyanova (2006) reported that retrosplenial cortex lesions need not disrupt contextual fear conditioning, though it has been suggested that this null result is due to spared caudal retrosplenial tissue (Keene & Bucci, 2008c). It was also reported that retrosplenial lesions can disrupt two-way active avoidance (Lukoyanov & Lukoyanova, 2006), where a deficit in contextual learning could even aid performance.

Finally, a series of studies by Gabriel and colleagues have repeatedly shown that the retrosplenial cortex is involved in discriminative avoidance learning by rabbits (a specific acoustic stimulus predicts a shock that can be avoided by running in a wheel while a different tone is not followed by shock). Electrophysiological studies found discriminative patterns of training-induced activity in retrosplenial cortex that occur at mid and late stages of task acquisition, and that are specific to particular lamina and subregions within the cortical area (Gabriel, Vogt, Kubota, Poremba, & Kang, 1991). Furthermore, retrosplenial cortex lesions in the rabbit appear to affect the late stages of this discriminative avoidance learning i.e. they attenuate the effects of overtraining (Gabriel, 1993). Such findings led to the notion (Gabriel, 1993) of a 'posterior circuit' involving the interactions between retrosplenial cortex and the anterior ventral thalamic nucleus (part of the anterior thalamic nuclei). This posterior circuit is thought to be specialised for the maintenance and retention of the learnt event, with the consequence that it is more dependent on rehearsal and less flexible to changes in stimulus associations (Gabriel, 1993). A similar pattern of findings has since been extended to appetitive discriminations by rabbits (Smith, Freeman, Nicholson, & Gabriel, 2002). Such findings have been interpreted to indicate that the retrosplenial cortex is important for both training-induced increases in attention to significant cues as well as subsequent (late-stage) cue-based retrieval (Gabriel & Talk, 2001). This notion of aiding cue selection is again reflected in the suggestion that retrosplenial lesions in rats disrupt tasks where there is the simultaneous presentation of potentially conflicting information (Keene & Bucci, 2008b).

8. Functional differences within the rodent retrosplenial cortex

As noted in Section 2, the retrosplenial cortex is not uniform. Like the primate brain, the rodent retrosplenial cortex comprises areas 29 and 30 (Rdg), with the rodent area 29 further subdivided into two major divisions (Rga and Rgb, see Fig. 1). These three retrosplenial areas (Rdg, Rga, Rgb) have different patterns of connectivity (Van Groen & Wyss, 1990, 1992, 2003), with Rdg being more interconnected with visual areas while the granular regions (Rga, Rgb) are more connected with structures providing interoceptive information. Consequently it might be predicted that Rdg is more important for visually guided spatial memory/navigation whereas the granular regions would have a greater involvement in navigation reliant on idiothetic cues, e.g. path integration. It is, however, the case that the three areas (Rdg, Rga, Rgb) are interconnected (Shibata et al., *in press*) such that they might also function as an integrated whole (Fig. 1). At the same time, this detailed anatomical study indicates a convergence of intrinsic connections within the caudal retrosplenial cortex (Shibata et al., *in press*), again underlining the importance of including this region in any experimental retrosplenial cortex lesion.

At present, only two lesion studies in rats have tried to examine the importance of the individual subareas within the retrosplenial cortex. In one study, lesions in Rga were compared with lesions in Rgb (Van Groen, Kadish, & Wyss, 2004). Only lesions in Rgb disrupted delayed-matching-to-position in a water-maze. A second study examined the effect of selective Rdg lesions (Vann & Aggleton, 2005), which impaired the use of visual allocentric cues in the radial-arm maze, a finding consistent with predictions based on its connectivity (Van Groen & Wyss, 1992). There is thus preliminary evidence that the subregions within the retrosplenial cortex have different functional specialisations. Additional evidence comes from a study of immediate-early gene expression within the retrosplenial cortex (Pothuizen, Davies, Albasser, Aggleton, & Vann, 2009). That study showed increased retrosplenial activation of the two genes under investigation (*zif268* and *c-fos*) following performance of a spatial working memory task in the radial-arm maze. For the granular regions (Rga and Rgb) this activation was found irrespective of whether the task was performed in the light or the dark, but for the dysgranular region (Rdg) this increased activation was restricted to performance in the light (Pothuizen et al., 2009). This pattern of results not only indicates a functional distinction within the retrosplenial cortex, with the dysgranular region engaged by distal visual stimuli and the granular region engaged by interoceptive cues, but this pattern again accords with what is known about the connectivity of these areas and with the limited number of relevant lesion studies (Vann & Aggleton, 2005).

9. The retrosplenial cortex and distal pathology

Evidence is emerging that retrosplenial cortex dysfunction may be an obligatory feature of both temporal lobe and diencephalic amnesia. As a consequence it may not only be necessary to extend our notions of the functional pathology of these syndromes but also to identify the nature of any additional impact brought about by retrosplenial cortex dysfunction. There is a long history to the idea that distal damage might have covert pathological effects on cortical function (Baron et al., 1992; Finger, Koehler, & Jagella, 2004; Von Monokow, 1911), and in the case of the retrosplenial cortex this evidence comes from brain imaging studies and from investigations into retrosplenial cortex activity following selective limbic damage. The modal finding is that distal damage reduces retrosplenial activity but has little or no impact on cellular structure and cell number, so potentially rendering any pathological effects as 'covert'.

Both PET and fMRI studies of diencephalic amnesia and temporal lobe amnesia reveal that hypoactivity in the retrosplenial/posterior cingulate region is typical in these syndromes (Fazio et al., 1992; Joyce et al., 1994; Paller et al., 1997; Reed et al., 2003). A similar pattern of retrosplenial hypometabolism is consistently found in Alzheimer's disease (Minoshima et al., 1997; Nestor, Fryer, Ikeda, & Hodges, 2003; Nestor, Fryer, Smielewski, Hodges, 2003; Villain et al., 2008). This latter finding is of great potential significance as this posterior cingulate/retrosplenial hypoactivity is often the first metabolic symptom of Alzheimer's disease. Post-mortem studies have also shown decreases in cingulate energy-related genes (Liang et al., 2008; Valla, Berndt, & Gonzalez-Lima, 2001), though these studies have so far focussed on the adjacent area 23, and not areas 29 and 30. It has also been found that cases of Mild Cognitive Impairment show hypoactivity in the posterior cingulate region that is centred in the retrosplenial cortex (Nestor, Fryer, Ikeda, et al., 2003; Nestor, Fryer, Smielewski, et al., 2003). These findings are most informative as Mild Cognitive Impairment is often prodromal to Alzheimer's disease.

The most obvious explanation for the retrosplenial hypoactivity in Alzheimer's disease and Mild Cognitive Impairment is that it is due to early pathology within this same region. This account had seemed unlikely as this region has not typically been linked with early pathology in Alzheimer's disease (Braak and Braak, 1991a, 1991b). Recent MRI analyses, however, indicate the presence of retrosplenial atrophy in the very early stages of the disease, which can progress at a similar rate to hippocampal atrophy (Pengas, Hodges, Watson, & Nestor, *in press*; Scahill, Schott, Stevens, Rossor, & Fox, 2002). The implication is that pathological changes *within* the retrosplenial cortex may be crucial for the hypoactivity in dementia. Complementary evidence that temporal lobe atrophy may not be sufficient to induce a retrosplenial/posterior cingulate hypometabolism comes from cases of semantic dementia where the extent of temporal lobe atrophy may be comparable to that in cases of Alzheimer's disease yet retrosplenial hypometabolism is not found (Nestor, Fryer, & Hodges, 2006). This comparison (Nestor et al., 2006) must, however, be treated with caution as it ignores the potential contribution of other atrophy in Alzheimer's disease, e.g. in the anterior thalamus, and assumes equivalent temporal lobe pathology for these different dementias.

An additional explanation is that retrosplenial hypoactivity follows the loss of retrosplenial inputs from specific limbic sites. Evidence for such a deafferentation effect comes from the retrosplenial hypoactivity seen in cases of temporal lobe and diencephalic amnesia (Fazio et al., 1992; Joyce et al., 1994; Paller et al., 1997; Reed et al., 2003). The same mechanism could also occur in Alzheimer's disease as both the hippocampal formation and the anterior thalamic nuclei suffer early pathology in the progression of the disease (Braak & Braak, 1991a, 1991b; Nestor, Fryer, Smielewski, et al., 2003). In addition, there is early atrophy in the cingulum bundle in Alzheimer's disease (Zhang et al., 2007; Villain et al., 2008), the tract that conveys projections to and from the retrosplenial cortex. Not surprisingly, a number of studies have begun to look at the impact of selective, limbic lesions on retrosplenial cortex function in animals to understand better this relationship.

Studies with rats have shown that lesions in the anterior thalamus or in the hippocampus do not produce overt changes in the organisation of the retrosplenial cortex, with typically no changes in the numbers of retrosplenial cells (Albasser, Poirier, Warburton, & Aggleton, 2007; Jenkins, Vann, Amin, & Aggleton, 2004; Poirier & Aggleton, 2009; Van Groen, Vogt, & Wyss, 1993). There may, however, be subtle changes in cell morphology and packing following the loss of neuropil. At the same time, lesions in both the anterior thalamic nuclei and hippocampus produce dramatic reductions in the retrosplenial expression of at least two immediate-early genes (IEG), *c-fos* and *zif268* (Albasser et al., 2007; Jenkins et al.,

2004; Poirier & Aggleton, 2009). These effects, which are found irrespective of lesion method, prior behaviour, or strain of rat, appear shortly after surgery and are probably permanent. In the case of anterior thalamic lesions, the most spectacular decreases in IEG activity (up to 90%) are seen in the superficial layers (II and upper III) of the granular retrosplenial cortex, while hippocampal lesions disrupt immediate-early gene activity more evenly across superficial and deep layers (Albasser et al., 2007; Jenkins et al., 2004; Poirier & Aggleton, 2009). These reductions in retrosplenial IEG expression appear far greater than in any other areas examined (Aggleton, 2008). These findings are significant as IEGs, including *c-fos* and *zif268*, are thought to have key roles in orchestrating long-term neuronal responses to changes in afferent information and, as a consequence, have an integral role in effective learning (Bozon, Davis, & Laroche, 2002; Countryman, Kaban, & Colombo, 2005; Davis, Bozon, & Laroche, 2003; He, Yamada, & Nabeshima, 2002; Tischmeyer & Grimm, 1999). It is also likely that *c-fos* and *zif268* could reflect just the tip of the iceberg, as a plethora of other genes might also be disrupted by retrosplenial deafferentation. Evidence that this is the case comes from a microarray study that identified numerous genes showing altered activity in the retrosplenial cortex following anterior thalamic damage, with a preponderance towards genes involved in energy metabolism (Poirier et al., 2008). Equally striking is the discovery that cutting the mammillothalamic tract in rats also leads to a profound depression of retrosplenial IEG activity (Vann & Albasser, *in press*). The significance of this latter result is that the surgery disconnects the anterior thalamic nuclei but does not directly disconnect retrosplenial cortex i.e. the impact on the later is indirect.

The next question is whether these retrosplenial activity changes associated with distal damage have functional consequences. Evidence that this is the case comes from the disconnection study in rats (Sutherland & Hoising, 1993) that demonstrated the interdependence between the anterior thalamic nuclei and retrosplenial cortex, and between the hippocampus and retrosplenial cortex. Other evidence comes from the finding that anterior thalamic lesions in rabbits not only mimic the disruptive effects of retrosplenial cortex lesions on active avoidance but also block the training induced electrophysiological changes in the retrosplenial cortex that accompanies learning by normal rabbits (Gabriel, 1993).

Finally, a recent study by Garden et al. (2009) provides unique insights as it not only identified a specific retrosplenial dysfunction (loss of long-term depression) brought about by distal (anterior thalamic) damage but this dysfunction could not be merely due to the loss of specific (thalamic) information that is normally required to drive retrosplenial cortex plasticity. In that study rats received unilateral anterior thalamic lesions and several weeks after recovery were sacrificed and retrosplenial brain slices taken (Garden et al., 2009). Electrophysiological recordings showed that the local cortical circuits appeared intact so that the same input stimulation could be used to compare plasticity in slices from either the 'intact' or 'lesioned' hemisphere. While slices from the intact hemisphere showed induction of long-term depression, this was not the case for slice tissue from the 'lesioned' hemisphere (for procedural reasons other forms of plasticity could not be examined). Furthermore, this loss of plasticity was localised to layers II/III, i.e. the same layers that shows the most marked reductions of IEG expression after anterior thalamic damage (Jenkins et al., 2004). Consequently, the study by Garden et al. (2009) provides direct support for the contentious notion of 'covert' or 'hidden' pathology in memory related areas (Bachevalier & Meunier, 1996; Squire & Zola, 1996). That is, cells that appeared superficially intact and normal, yet behave as if functionally damaged as a consequence of distal damage. These results also suggest that in diseases like Alzheimer's disease there is the *combined* impact from both intrinsic

sic retrosplenial pathology and the effect of disconnections from distal sites. The consequent retrosplenial deficits presumably contribute to the cognitive impairments in dementia. For anterograde amnesia the implication is that retrosplenial cortex dysfunction occurs in both temporal lobe and diencephalic amnesias, so helping to merge these two syndromes that have often in the past been seen as distinct entities.

10. Summary and conclusions

There seems little doubt that 'retrosplenial amnesia' exists, and increasing evidence for the importance of this region for memory is now coming from human brain imaging studies as well as neuropsychological investigations of people with bilateral pathology in this region (Vann, Aggleton et al., 2009). The latter evidence shows that damage to the retrosplenial region can produce retrograde amnesia as well as anterograde amnesia (Maguire, 2001b; Vann, Aggleton et al., 2009). At present, animal studies have focussed almost exclusively on the importance of the region for new learning. One result is that the present review has largely been confined to considering anterograde amnesia, leaving retrograde amnesia a topic for future investigation.

It may be most helpful first to summarise what animal studies have told us that could not be determined from human research. One major contribution has come from anatomical studies that have revealed how in the primate brain it is areas 29 and 30 (rather than area 23 or 31) that are predominantly interconnected with the hippocampal formation and anterior thalamic nuclei (Kobayashi & Amaral, 2003, 2007; Mufson & Pandya, 1984; Shibata & Yukie, 2009). While these studies show that other posterior cingulate regions have anterior thalamic and hippocampal connections, it is also clear that the densest connections are with areas 29 and 30—though ultimately we will need to understand how all of these posterior cingulate areas interact to support memory. It has also emerged that these three regions (hippocampus, anterior thalamus, retrosplenial cortex) function in an integrated system. This latter discovery raises the critical question of what is it that the retrosplenial cortex contributes i.e. what is its unique attribute? Again, one of the first clues comes from a consideration of the neuroanatomy of the region. The connections of the retrosplenial cortex with cortical visual and somatosensory areas (occipital and parietal) provide rapid access to visual and somatosensory information, properties that are not shared with the hippocampus and anterior thalamus. In addition, the retrosplenial cortex has direct, reciprocal links with the dorsolateral prefrontal cortex (Morris, Pandya, & Petrides, 1999), so providing a route for the hippocampus and anterior thalamus to interact with prefrontal areas vital for executive function.

Given these anatomical properties it is not surprising that analyses of retrosplenial function in rodents have focussed heavily on its contributions to spatial memory and spatial navigation. Here, there are some direct parallels with functions that have been emerged from human studies (e.g. Epstein, 2008), though with far less anatomical resolution than animal studies. These parallels are important as they underline the value of more fine grain analyses of retrosplenial function in animals. One example is the emerging evidence of functional specialisations *within* areas 29 and 30, evidence that has all come from studies with animals.

Consistent with the diverse pattern of retrosplenial connections, animal studies confirm that the area is involved in multiple aspects of spatial navigation and learning. Consequently, lesion-induced deficits have been observed in memory tasks thought to specifically tax allocentric spatial information, directional information, and path-integration processing. The notion that this area is a convergent point for different streams of information processing has, therefore, emerged as a common theme of theories of retrosple-

nial cortex function. In one model it has been proposed that spatial learning is dependent on two parallel circuits within the tegmentum and diencephalon (Vann & Aggleton, 2004b). The 'lateral' system (dorsal tegmental nucleus of Gudden, lateral mammillary nucleus, anterior dorsal thalamic nucleus) provides head-direction information while the 'medial' system (ventral tegmental nucleus of Gudden, medial mammillary nucleus, anterior medial and anterior ventral thalamic nuclei) provides theta rhythm, which acts back upon the hippocampus. The retrosplenial cortex is notable as it provides one of the first convergent points between these systems, e.g. head direction cells are found across both the granular and dysgranular subregions.

Two related models of retrosplenial function can be derived from this set of anatomical and behavioural properties. The first can be described as 'integrator'. Such models assume that the region is required for specific tasks that demand the integration of different forms of spatial information. This account will explain the connectivity of the region and the lack of a marked lesion impact on many standard spatial memory tests. The problem with this model is the failure, so far, to identify a complex form of spatial memory that is unusually sensitive to retrosplenial cortex damage. Candidates include the flexible use of direction information (Pothuizen et al., 2008), learning the spatial and temporal disposition of items in a scene ('structural' learning), or linking geometric features of a scene with its content. Such forms of learning remain to be tested rigorously.

This same notion of information integration is central to the second set of retrosplenial models. These 'translation' models suppose that the retrosplenial cortex is important for switching between different viewpoints (Bird & Burgess, 2008; Byrne, Becker, & Burgess, 2007). The basic idea is that episodic memory requires a translation between different frames of reference for the event information within specific scenes to be consolidated and retrieved. The most obvious translation is from a viewer-centred (egocentric) frame to a world-centred (allocentric) frame (Byrne et al., 2007). This account of retrosplenial cortex function accommodates the findings from spatial learning studies where it is found that unexpected changes in the demands on spatial strategy selection can expose the impact of retrosplenial lesions (e.g. Pothuizen et al., 2008; Vann & Aggleton, 2004a, 2004b, 2005; Vann et al., 2003, 2004; Wesierska et al., 2009). These findings raise the question of whether these putative translation functions are asymmetric (e.g. just from egocentric to allocentric) or reciprocal. The overarching notion is that the retrosplenial cortex not only enables the rapid creation of distinct, separate spatial scenes but also aids the effective mental navigation through these real or imagined scenes (Vann, Aggleton et al., 2009). It is, therefore, notable that animal studies using very different behavioural paradigms (e.g. avoidance discrimination, feature negative patterning) again conclude that this region is important for effective creation and use of scenes (Keene & Bucci, 2008c). An alternative view is that the retrosplenial cortex is important for extracting relevant cue types when there is cue competition or conflict (Gabriel & Talk, 2001), though a possible shortcoming with this latter description is that it may be too imprecisely worded to derive strong predictions.

A further issue is that retrosplenial cortex damage need not disrupt all tasks that rely on scene information. Parker and Gaffan (1997) reported that monkeys with combined anterior and posterior cingulate ablations showed only a very mild deficit in the acquisition of a series of concurrent visual discrimination in which the monkey is thought to use the combination of the element to be discriminated and its unique background (scene) to solve the task effectively. One potential explanation is that the task does not require a viewer translation or change in strategy (see above) as the monkeys are trained pre-operatively on the task in which they sit still and press a touch screen from a constant perspective. Related

issues concern the finding that the impact of retrosplenial cortex lesions on spatial learning are rarely as severe as those described after either hippocampal or anterior thalamic damage, highlighting the need to understand in much more detail the three-way relationship between these key structures.

It is now clear that there are a closely related family of ideas concerning retrosplenial cortex function and how, as a consequence, damage to this region should disrupt episodic memory. A related prediction is that selective retrosplenial cortex damage (areas 29, 30) will spare familiarity-based recognition in humans. An ongoing task will be to determine the extent to which these overlapping theories of retrosplenial function can be subsumed under one overarching role or whether it makes more sense to assume from the outset that this region will have a number of closely related functions. Evidence from both anatomical and electrophysiological investigations would currently suggest the latter.

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