What is the function of the human retrosplenial cortex?

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I, Stephen Auger, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

The retrosplenial cortex (RSC) comprises Brodmann areas 29/30 and is an integral part of a brain system that is engaged by spatial navigation, scene processing, recollection of the past and imagining the future. Damage involving the RSC in humans can result in significant memory and navigation deficits, while the earliest metabolic decline in Alzheimer's disease is centred upon this region. The precise function of the RSC, however, remains elusive.

In this thesis I sought to determine the key contribution of the RSC in a series of six studies that each comprised behavioural and functional magnetic resonance imaging (fMRI) experiments. Specifically, I discovered that the RSC is acutely responsive to landmarks in the environment that maintain a fixed, permanent location in space, and moreover is sensitive to the exact number of permanent landmarks in view. Using a virtual reality environment populated with entirely novel 'alien' landmarks I then tracked the *de novo* acquisition of landmark knowledge and observed the selective engagement of the RSC as information about landmark permanence accrued. In three further studies I established the parameters within which the RSC operates by contrasting permanent landmarks in large- and small-scale space, by comparing landmark permanence with orientation value, and by investigating permanence in non-spatial domains. In parallel lines of inquiry, I uncovered evidence that a fully functional RSC may be a prerequisite for successful navigation, while also characterising RSC interactions with other brain regions, such as the hippocampus, that could have importance for constructing reliable representations of the world.

Together my findings provide new insights into the role of the RSC in a range of cognitive functions. The RSC's processing of permanent predictable features may represent a key building block for spatial and scene representations that are central to navigation, recalling past experiences and imagining the future.

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List of Abbreviations

ACC – anterior cingulate cortex

AThal – anterior thalamus

DCM – dynamic causal modelling

DLPFC – dorsolateral prefrontal cortex

DTI – diffusion tensor imaging

fMRI – functional magnetic resonance imaging

FWE – family-wise error

GLM – general linear model

gPPI - generalized psychophysiological interaction

HC - hippocampus

HRF – haemodynamic response function

IEG – immediate-early gene

ITC – inferior temporal cortex

MTL – medial temporal lobe

MVB – multivariate Bayes

MVPA – multi-voxel pattern analysis

PHC – posterior parahippocampal cortex

POS – parieto-occipital sulcus

PPI – psychophysiological interaction

ROI – region of interest

RSC – retrosplenial cortex

RSComp – retrosplenial *complex*

SBSOD – Santa Barbara Sense of Direction Scale

SPM – statistical parametric mapping

SVM – support vector machine

TOS – transverse occipital sulcus

VBM – voxel-based morphometry

Chapter 1: General Introduction

1.1 Overview

Why study the retrosplenial cortex (RSC)? The RSC is linked, both anatomically and functionally, with numerous areas of the cerebral cortex and also to subcortical structures (Kobayashi and Amaral, 2000, 2003, 2007; Vann et al., 2009; Epstein and Vass, 2014). Such wide-ranging connectivity hints at a central role in information processing. Through its interactions within this network RSC engagement is associated with key cognitive functions including episodic memory, scene processing, spatial navigation and imagining future or fictitious events. Indeed, RSC is often the 'brightest blob' in functional magnetic resonance imaging (fMRI) studies of these functions (Spreng et al., 2009). Moreover, lesions to this region result in amnesia and navigational deficits (Maguire, 2001a), and the earliest pathology in Alzheimer's dementia is centered on RSC (Pengas et al., 2012).

Despite its potential importance for a range of key cognitive functions, RSC has often been overlooked in favour of its more 'famous' neighbours such as the hippocampus (Vann et al., 2009). By way of an example, in the year before I started my PhD (2010), for every one reference to "retrosplenial" in PubMed listed papers, there were more than ninety three mentions of "hippocampus". It is perhaps not surprising then that little is known about what precise purpose the RSC serves. The key aim of the work presented in this thesis was to put some 'flesh on the bones' of our understanding of RSC function. I set out to try and establish its specific contribution to the wide range of cognitive functions with which it has been associated. In so doing, I hoped also to inform models of memory and navigation more generally, and perhaps to throw some new light on why such functions are compromised in conditions such as Alzheimer's dementia.

In this first chapter I will summarise what is currently known about the RSC. I begin by describing the anatomy of the RSC and its connectivity with other parts of the brain. I then consider RSC function, first in terms of how its neurons behave and then by examining the effects of disruptions brought about by lesions and other pathologies. Following this, I review findings from imaging studies before outlining the prevailing theories of RSC function. Finally, I provide a brief overview of the thesis and each of the experiments I conducted.

1.2 Anatomy

The RSC gets its name from its anatomical location directly behind the splenium of the corpus callosum (its most posterior part). There is a remarkable amount of variation in the region's size and histological characteristics across different species, from flying foxes to hedgehogs, lemurs, kangaroos and, of course, humans. By way of an example, in Korbinian Brodmann's original cytoarchitectural comparisons of the cerebral cortex, he estimated that whereas the area makes up roughly 0.3% of the entire cortical surface in humans, in rabbits it comprises at least 10% (Brodmann, 1909). This diversity raises intriguing questions about why such variation might have emerged. It also makes it difficult to set out a universally appropriate classification, and so precise anatomical descriptions of the region often vary. This thesis will use the most commonly applied definition of Brodmann areas 29 and 30 (Figure 1).

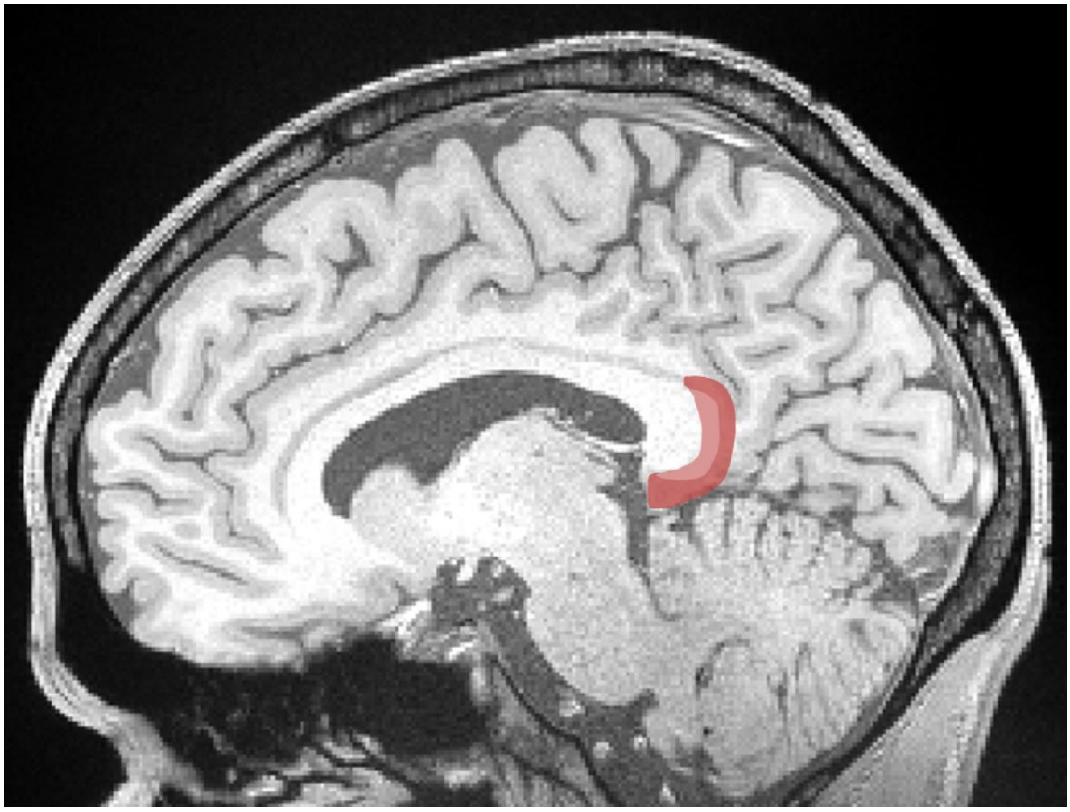

Figure 1 Location of RSC. A schematic diagram showing the locations of Brodmann areas 29 (lighter red) and 30 (darker red) on a sagittal midline section of an MRI scan of my brain.

Rather than there being distinct boundaries between the two sub-regions (area 29 and 30), the change is more gradual. This is especially true for humans, where RSC

cytoarchitecture is relatively poorly differentiated compared to lower order mammals (Brodmann, 1909). Moving from area 29 to 30 there is a progressive thickening of the cortex and increasing definition of the individual layers (Figure 2), hence it is often referred to as "transitional" cortex (Fatterpekar et al., 2002). In non-human primates, there are four distinctive cortical layers in lateral parts of area 29 and this transitions towards the 'usual' six in area 30 (Kobayashi and Amaral, 2000).

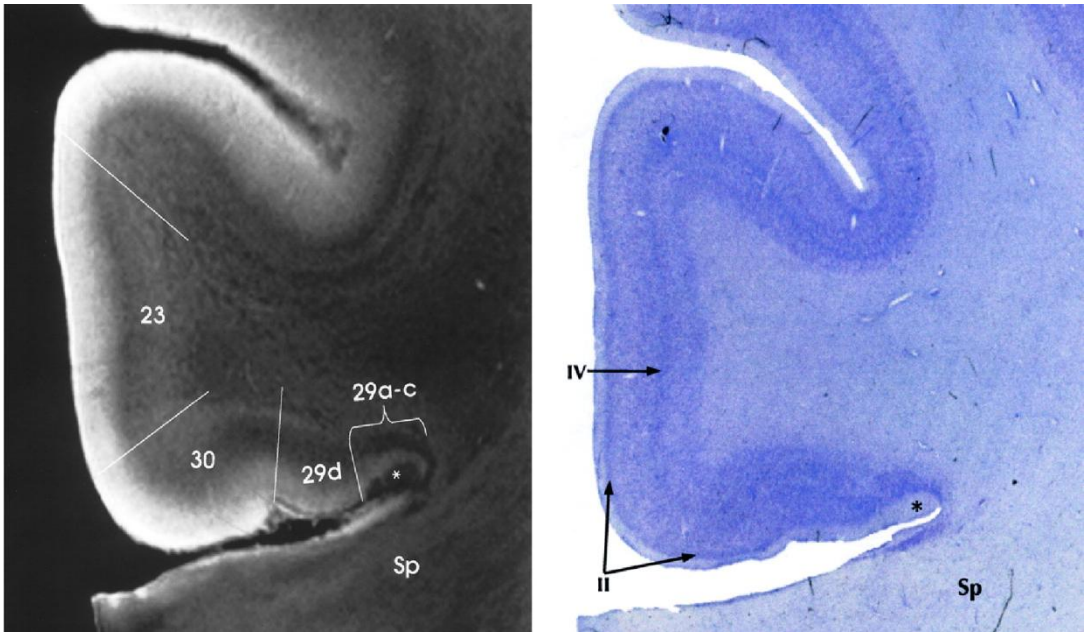

Figure 2 RSC Cytoarchitecture. 9.4T MR microscopy of excised human RSC (left) and Nissl stained image of the same sample (right) showing the "transitional" nature of RSC. Moving from area 29 (a-c and d) to 30 there is progressive thickening of the cortex. * shows prominent myelination in a thick layer I. Sp indicates the splenium of the corpus callosum. 6.25x magnification. (From Fatterpekar et al., 2002 with permission from AJNR).

Within RSC a distinction is often made between so called 'granular' area 29 and 'dysgranular' area 30 because of differences in the respective densities of the band of neurons in a "granule cell layer" subjacent to layer I (Aggleton, 2010). Given the atypical laminar structure of RSC, this granule cell layer has been labelled in various ways as "layer II-IV" (Vogt and Pandya, 1987) and "layer III (IV)" (Vogt, 1976; Morris et al., 1999) in primates or layer II in rats (Aggleton, 2010). Rodent granular area 29 can be further subdivided into two parts (29a and 29b) based upon its connectivity (van Groen and Wyss, 1990). 29a is sometimes further divided (Vogt and Peters, 1981) and in humans too, some classifications partition RSC into as many as five different areas (Braak, 1979); but this is rarely necessary for the purposes of studying RSC function in humans. However the subregions are defined, they are all densely interconnected with one another (Shibata et

al., 2009; Sugar et al., 2011). It is also worth noting that in primates RSC, together with areas 23 and 31, comprise a wider posterior cingulate region (Vogt et al., 1995), whereas rats have no direct equivalent of areas 23 and 31 so the entire posterior cingulate cortex is labelled RSC (Vogt and Peters, 1981; van Groen and Wyss, 1990).

An important anatomical difference between the rodent and primate RSC is its accessibility. In rats it occupies almost the entire dorsal midline caudal to the fornix (Aggleton, 2010), which makes it directly accessible for electrophysiological and lesion studies (Figure 3A). In humans and other primates, it lies much deeper in the midline of the brain and very close to large draining blood vessels which presents numerous problems for studying the function of the region (Figure 3B).

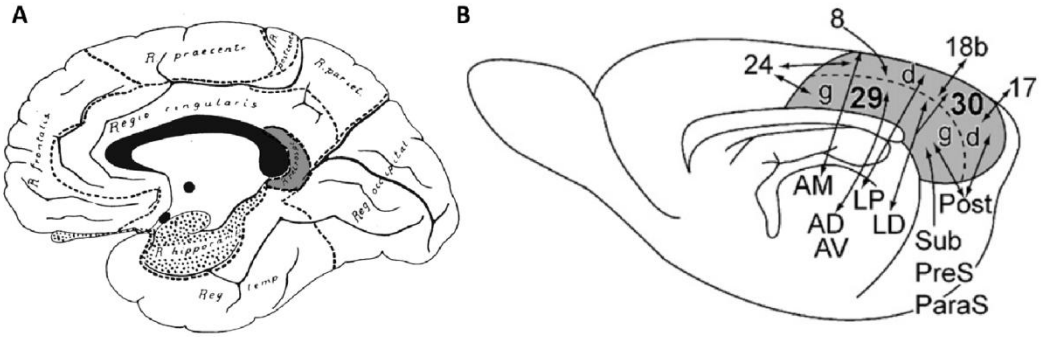

Figure 3 Human and rat RSC. Grey shaded areas show the RSC in humans (A) and rats (B). Rat RSC occupies almost the entire dorsal midline caudal to the fornix, whereas in humans (and other primates) it is much less accessible, deep in the middle of the brain. (A from Brodmann, 1909, now in the public domain; B from Aggleton, 2010 with permission from Elsevier).

Surgery in non-human primates is problematic, especially when trying to make precise lesions, while in humans focal lesions to the RSC rarely occur. A common pathology involving the RSC in humans is strokes; however, these are rarely focal to the RSC and often also compromise tissue outwith areas 29 and 30. The amount of brain tissue between RSC and the surface of the head decreases the signal-to-noise ratio for scalp recording techniques (electroencephalography, magnetoencephalography), and also precludes transcranial magnetic stimulation. FMRI does not have this issue, and is therefore the most commonly used methodology for studying RSC function in humans.

1.3 Connectivity

Very few RSC anatomical tracer studies have been conducted in humans, but work in macaque monkeys and rats indicate that RSC is densely interconnected with a wide range of both cortical and subcortical brain regions. In the macaque monkey, RSC sends extensive cortical efferent projections to the dorsolateral prefrontal cortex (particularly areas 46, 9, 10 and 11) and medial temporal lobes (presubiculum, parasubiculum, entorhinal and parahippocampal cortex), as well as areas V4 and 7a (Figure 4A; Kobayashi and Amaral, 2007). It receives inputs from similar regions, most notably the hippocampal formation (entorhinal cortex, subiculum, presubiculum and parasubiculum) and parahippocampal, perirhinal, dorsolateral prefrontal (areas 46, 9, 10 and 11), parietal and occipital (V2) cortex (Figure 4B; Kobayashi and Amaral, 2003; Lavenex et al., 2004). It is also worth noting that RSC shares numerous additional local projections with adjacent areas 23 and 31 (Parvizi et al., 2006). However, these nearby regions have a markedly different pattern of extrinsic connectivity compared to RSC, most notably in the relative absence of projections to the medial temporal lobes.

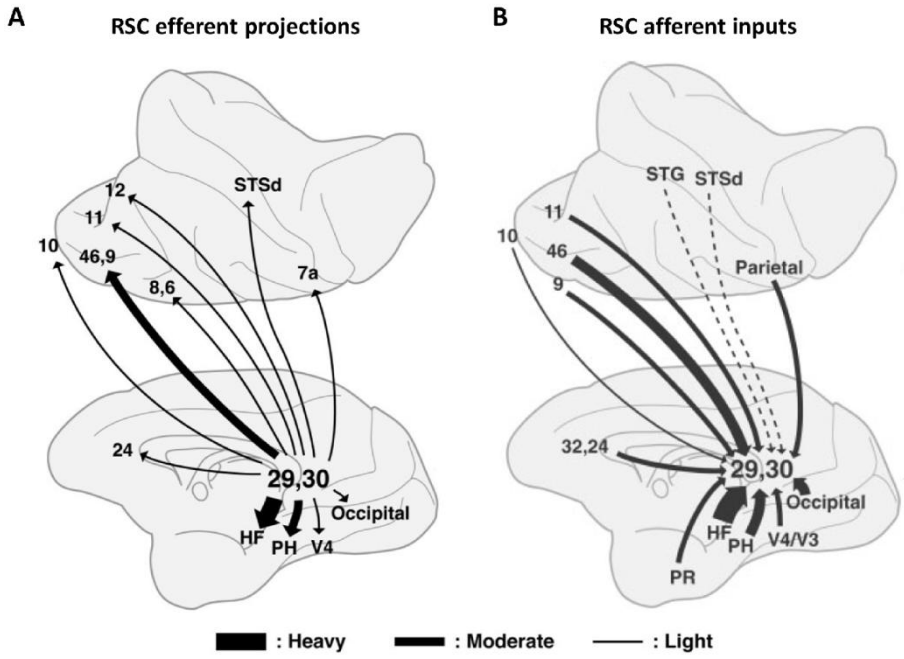

Figure 4 Summary diagram illustrating RSC connectivity in macaques. Major cortical efferent (A) and afferent (B) connections of the RSC (areas 29 and 30). Thick lines represent the heaviest connections with progressively thinner lines indicating less substantial connectivity. Numbers refer to Brodmann areas. HF = hippocampal formation; PH = parahippocampal cortex; PR = perirhinal cortex; V3/4 = visual association cortex; STG = superior temporal gyrus; STSd = dorsal bank of the superior temporal sulcus. (Adapted from Kobayashi and Amaral, 2003, and 2007 with permission from Wiley-Liss Inc).

There are also some differences in the connectivity of the RSC subregions. Area 29 receives a large majority of projections from the hippocampus (both subiculum and presubiculum) and entorhinal cortex (Aggleton et al., 2012). Area 30, on the other hand, is more densely connected to the dorsolateral prefrontal cortex (areas 9 and 46) and local regions (area 23) (Morris et al., 1999). Tracer studies which take subcortical regions into account find that RSC is also densely connected with the thalamus, particularly the anterior ventral and laterodorsal nuclei (Mufson and Pandya, 1984; Morris et al., 1999; Aggleton et al., 2014). Projections from the anterior thalamic nuclei are estimated to comprise approximately 50% of the total thalamic input to RSC, compared to just 17% for the adjacent parts of posterior cingulate cortex (Buckwalter et al., 2008).

RSC connectivity in rodents is broadly similar to that of primates, with dense reciprocal projections existing between the hippocampus (particularly subiculum, presubiculum and postsubiculum) and anterior and laterodorsal thalamic nuclei (van Groen and Wyss, 1990, 1992; Van Groen and Wyss, 2003; Wright et al., 2010). The main difference between rodents and primates is the absence of equivalent connectivity with dorsolateral prefrontal areas that are present in the higher order species. This disparity is particularly noteworthy given that in primates, RSC provides the largest and most direct connections between the medial temporal lobes and dorsolateral prefrontal cortex (Kobayashi and Amaral, 2003). There is also a minor discrepancy in the apparent connectivity between RSC and nucleus reuniens in rodents (van Groen and Wyss, 1992; McKenna and Vertes, 2004), but lack of a comparable reuniens input to primate RSC (Buckwalter et al., 2008). The primate nucleus reuniens and RSC instead appear to provide different parallel disynaptic routes between the prefrontal cortex and hippocampus (Aggleton, 2014).

Having provided a broad overview of RSC anatomy and its connectivity with other brain areas, I will now outline what is known about how the neurons in RSC behave.

1.4 Electrophysiology

As mentioned previously, the anatomy of the RSC in primates makes it difficult to implant electrodes and record single-unit neural activity. There are a few examples of recordings within regions that include RSC, but to date they tend to lack sufficient anatomical precision to ensure that responses genuinely emanate from RSC and not other more

posterior brain areas (e.g. Sato et al., 2006). Rodent RSC by comparison is far more accessible, and consequently the majority of electrophysiological research has been conducted in rats. [Note that I discuss intra-cranial recordings in humans in Section 1.10.1].

Rodent RSC displays rhythmical slow-wave (theta) activity. This activity is generated locally, but also partially depends upon septal inputs (Borst et al., 1987; Talk et al., 2004). The most notable individual cell type within RSC are 'head-direction' cells. These are neurons which act as a type of compass and fire whenever an animal's head is facing in a specific direction (Figure 5). They were first discovered in the postsubiculum of rodents (Taube et al., 1990) and subsequently in the RSC (Chen et al., 1994a,b) and other anatomically connected regions: anterodorsal (Blair and Sharp, 1995; Taube, 1995) and laterodorsal (Mizumori and Williams, 1993) thalamic nuclei and entorhinal cortex (Sargolini et al., 2006). Head direction cells have yet to be found in primate RSC (perhaps owing to the difficulty in recording from the region), but they have been identified in the presubiculum (Robertson et al., 1999).

Areas 29 and 30 contain similar densities of head direction cells (8.5% and 8.4% respectively), but they differ in whether or not their activity is modulated by a rat's behaviour (Chen et al., 1994b). Chen et al. (1994b) found that 19% of the head direction cells in area 29 were also sensitive to what a rat is doing (e.g. velocity/direction of locomotion, turning), whereas all cells in area 30 had a seemingly purer representation of head direction which is insensitive to behavioural state.

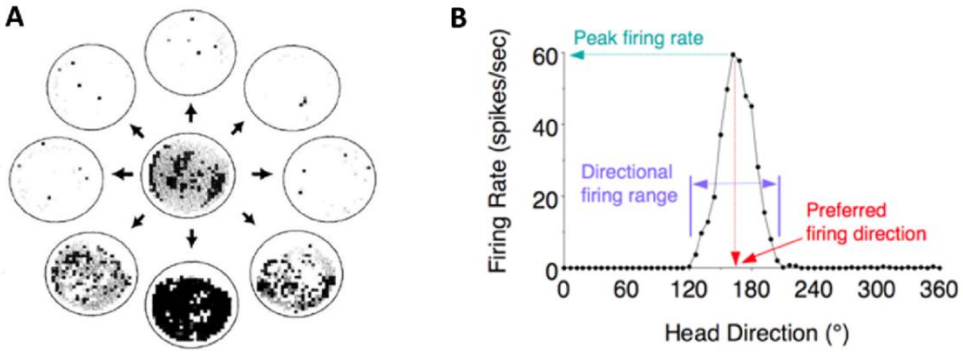

Figure 5 RSC head direction cells. A shows an example firing rate map of an RSC head direction cell. Each circle shows the average firing rate as a function the rat's location within a cylindrical environment. Darker colours correspond to a higher firing rate. The central map shows average firing across a whole recording session, this is surrounded by circles showing the same data but broken down according to which direction the rat's head happened to be facing at the time. B shows an example plot of a neuron's firing rate versus head direction, highlighting three parameters which can be used to characterise head direction cells. (A adapted from Cho and Sharp, 2001; B from scholarpedia.org with permission from Jeffrey Taube).

There is also further diversity in how RSC head direction cells are affected by external cues. The majority of cells are unaffected by rotating visual cues, but for some (about 24%) their preferred firing direction follows an external cue when it is rotated and a further 15% have a variable sensitivity to visual cues (Chen et al., 1994a). There are no reported differences in how neurons in areas 29 and 30 might be influenced by external cues.

This original set of studies by Chen and colleagues was extended, most notably by the work of Cho and Sharp (2001). They found that RSC head direction cells tend to be anticipatory, correlating best with a rat's directional heading 25 msec in the future. This is similar to head direction cells in the anterior thalamus (anticipating by about 23 msec) but not postsubiculum which show no anticipatory behaviour (Taube and Muller, 1998). In addition to 'pure' head direction cells, Cho and Sharp found 19% of RSC cells were broadly responsive to some combination of a rat's location and heading direction in a circular environment. There is also an isolated report of RSC neurons developing responses to context-specific reward locations (i.e. rewards located in specific places only during certain parts of a trial), compared to more generalised contextual responses (e.g. separate responses to places, parts of a trial and rewards) in the hippocampus (Smith et al., 2011).

In summary, electrophysiological recordings in rodents show RSC neurons are responsive to certain spatial information, particularly the direction a rat's head is pointing. However, this only accounts for a minority of cells in the region and it is still unclear what function(s) the vast majority of other neurons might serve. Further clues may be gleaned by examining how lesions to RSC impact upon rodent behaviour.

1.5 Animal lesion studies

Lesions to the rat RSC (both neurotoxic and electrolytic) produce a number of behavioural impairments. The majority of rodent lesion studies investigate the importance of RSC for performing spatial tasks and navigating. Clear deficits can be found on a range of tasks, especially those which require the use of external environmental cues, including: navigating to a hidden platform in a water-maze, both when its location is constant or changes across sessions (Sutherland et al., 1988; Whishaw et al., 2001; Harker and

Whishaw, 2002, 2004; Vann and Aggleton, 2002; Vann et al., 2003; Lukoyanov et al., 2005; Cain et al., 2006) and not returning to a recently visited location in a radial-arm maze (Cooper and Mizumori, 2001; Vann and Aggleton, 2002, 2004; Keene and Bucci, 2009).

However, the spatial deficits produced by RSC lesions can be somewhat variable. This is sometimes related to the size of the lesion and how much residual RSC tissue remains (Vann and Aggleton, 2004). Many studies have left caudal RSC intact, but this appears to be important for performing certain spatial tasks (Vann et al., 2003; Vann and Aggleton, 2004). It is therefore unclear whether or not caudal sparing could account for a relative lack of navigational impairment seen in some RSC lesioned animals (Neave et al., 1994; Bussey et al., 1997). RSC lesions can also produce damage to nearby white matter tracts, most notably the cingulum bundle, which could also account for some of the deficits observed (Warburton et al., 1998). For example, performance on a simple T-maze alternation task had once been considered sensitive to RSC lesions (Markowska et al., 1989), but subsequent work indicated that this may have in fact resulted from more extensive damage to the cingulum bundle (Neave et al., 1994, 1996; Meunier and Destrade, 1997; Neave, 1997; Warburton et al., 1998). It has even been suggested that the species of rat tested can have a significant bearing upon what deficits are produced (Harker and Whishaw, 2002), although this might have in fact reflected differences in lesion extent rather than between species (Pothuizen et al., 2008).

Other rodent lesion studies have assessed more general amnesic effects. These suggest that RSC may be more important for remote rather than recent memory processes (Haijima and Ichitani, 2008), although sparing of caudal parts of RSC might again have contributed to some residual function (Haijima and Ichitani, 2012). Other studies indicate that inactivation of RSC can interfere with both recent and remote memory processes (Corcoran et al., 2011; Katche et al., 2013).

There is one particular deficit which RSC lesions appear to consistently produce, irrespective of the overall extent of damage. This impairment is revealed with a modified version of an eight-arm radial maze task (Vann and Aggleton, 2002, 2004, 2005; Vann et al., 2003; Pothuizen et al., 2008). Rats start in an octagonal centre chamber with eight arms coming off from its sides. They are required to visit each of the eight arms once in order to retrieve a food pellet. An optimal strategy requires the rats to not re-enter any of

the previously visited arms. RSC lesioned animals are specifically impaired when, after making the first four choices, the maze is rotated by one arm position and the arms are rebaited so that food pellets are now situated in the same locations relative to external room cues as before (but in different arms of the actual maze). Thus, RSC lesions appear to specifically impair a rat's ability to use external cues rather than conflicting intra-maze information. This is consistent with other work which has found RSC to be important for segregating spatial information and selecting which is best to use (Wesierska et al., 2009). However, this apparent strategy selection impairment is not restricted to using external visual cues. Indeed, numerous deficits have also been identified in RSC lesioned rats using directional and self-motion information in the dark (Cooper and Mizumori, 1999; Cooper et al., 2001; Whishaw et al., 2001; Pothuizen et al., 2008), although RSC does not appear to be necessary for more straightforward navigation using idiothetic cues (Zheng et al., 2003).

RSC lesions also produce deficits in more general spatial tasks which do not require any form of active navigation, including associating certain places with aversive and appetitive stimuli (Lukoyanov and Lukoyanova, 2006; Keene and Bucci, 2008a, 2008b, Hindley et al. 2014a). It has also been implicated in integrating information from multiple different types of environmental cue (e.g. auditory, visual) in order to obtain a food reward in some (Keene and Bucci, 2008c; Robinson et al., 2011; Nelson et al., 2014) but not all circumstances (St-Laurent et al., 2009). Rats with a lesioned RSC also appear unable to recognise when an object has changed location (Vann and Aggleton, 2002; Parron and Save, 2004), although as with many navigational deficits, this could in some circumstances be attributed to more extensive lesion damage to the fornix or cingulate cortex which can both impair ability to locate objects (Ennaceur et al., 1997).

An increasing number of attempts are being made to establish whether lesions to specific RSC subregions give rise to different functional deficits. Lesioning area 30 alone makes rats more likely to use a turn-based strategy for a radial-arm maze task, rather than using external visual cues (Vann and Aggleton, 2005) and impairs the use of visual cues to solve spatial problems (Hindley et al., 2014a). This is broadly consistent with the region's greater anatomical connectivity with visual areas (van Groen and Wyss, 1992). Area 30 is also specifically implicated in integrating information across different types of cue (e.g. visual, tactile, olfactory; Hindley et al., 2014b). Area 29b lesions, but not those to 29a,

produce a small impairment on a water-maze task (Van Groen et al., 2004) but otherwise, selective and complete RSC lesions appear to produce quite similar spatial deficits (Pothuizen et al., 2010).

Further insights about RSC function are revealed by the effects of RSC lesions upon the electrophysiological properties of neurons in distant parts of the brain to which it connects. In the anterior thalamus, RSC lesions do not abolish head direction cell firing, but they do reduce the stability of their directional tuning (Clark et al., 2010). These RSC lesions appear to specifically disrupt the influence of salient visual landmarks upon thalamic head direction cell firing, with no equivalent effect upon self-motion cues. Inactivating RSC also affects the stability of hippocampal place cells, but does not abolish them (Cooper and Mizumori, 2001). In certain circumstances, hippocampal oscillations in the 8-12 Hz range can also be influenced by modulations in RSC (Destrade and Ott, 1982), but slow-wave theta rhythmicity (4-7 Hz) in RSC and the hippocampus appear to be independent of one another (Borst et al., 1987; Talk et al., 2004).

Overall, it is difficult to provide a unified account of RSC function based upon the impairments produced by lesions in rodents on subtly different tasks. This ambiguity arises in part from differences in the precise extent of lesions, and also which other brain areas may be included. What is clear is that RSC appears to play some role in processing spatial and environmental cues to assist in tasks which require the use of this information, such as in navigation. It is difficult to be more specific than this given that we cannot know exactly how rodents are performing navigational tasks and which alternative strategies they may adopt to compensate for the loss of RSC function. The interpretation of results is further complicated by the significant anatomical and cognitive differences between rodents and humans. Humans with lesions involving the RSC could therefore provide further insight into the region's contribution to cognition although, as I outline below, this is not without its own limitations.

1.6 Human lesions studies

RSC lesions in humans tend to be the result of either strokes or tumours. The damage therefore usually extends far beyond RSC, and so cannot be regarded as selective when compared with the precise surgeries performed in rodent studies (Figure 6). This lack of

anatomical specificity could have a significant impact upon the nature of any deficits produced. The rodent lesion literature highlights how small differences in the size of RSC lesions and involvement of other tissues could account for key differences in the behaviour they influence (Vann and Aggleton, 2004; Aggleton, 2010). Therefore, caution needs to be exercised when considering whether functions ascribed to RSC from lesion case reports are truly specific to this region.

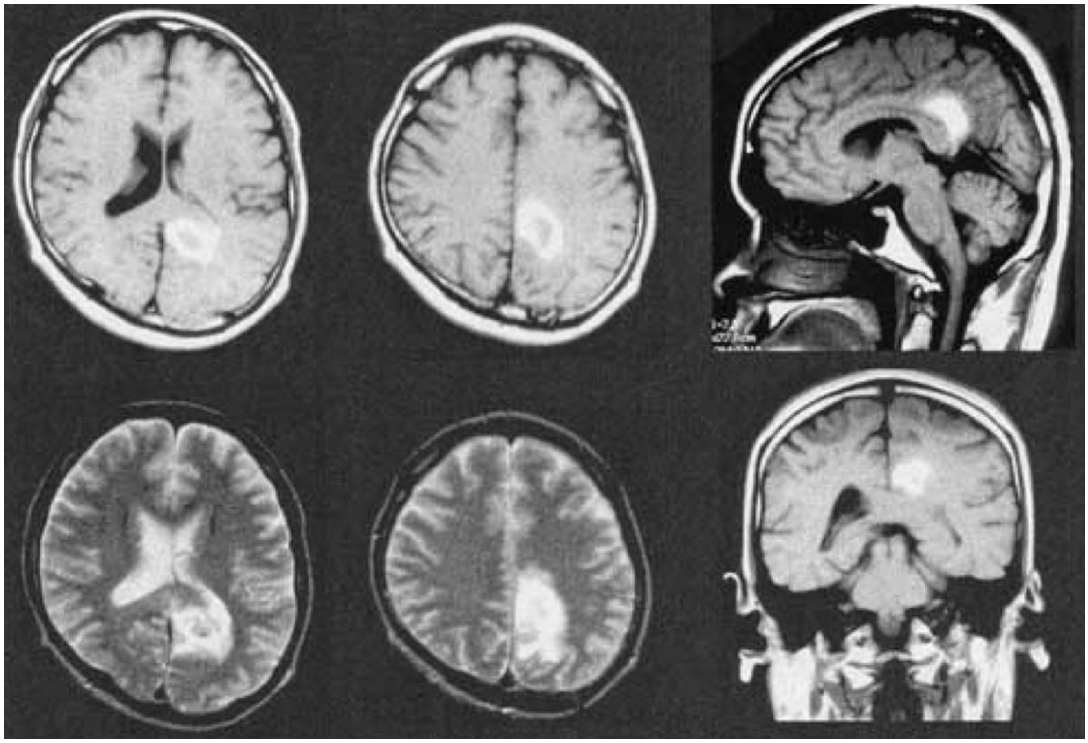

Figure 6 Example of a human RSC lesion. MRI of a subcortical haematoma (axial, sagittal and coronal views) in a patient with spatial disorientation. The lesion includes RSC, but as with many lesions involving this region, there is also extensive pathology to more lateral, superior and posterior areas. (From Maeshima et al., 2001, with permission from Elsevier).

The deficit most commonly associated with lesions of the RSC is a so-called topographic or heading disorientation (Valentine et al., 1987; Obi et al., 1992; Takahashi et al., 1997; Aguirre et al., 1998; Alsaadi et al., 2000; Maguire, 2001a; Greene et al., 2006; Osawa et al., 2006; Ino et al., 2007). Here, patients appear relatively unimpaired at recognising familiar landmarks but are seemingly unable to derive directional information from them in order to navigate or orientate themselves. There is also a more general inability to form new memories (anterograde amnesia) (Valentine et al., 1987; Rudge and Warrington, 1991; Gainotti et al., 1998; Maguire, 2001a; McDonald et al., 2001; Oka et al., 2003; Osawa et al., 2006; Ino et al., 2007; Maeshima et al., 2014) or recall information which was learned before the lesion (retrograde amnesia). The retrograde amnesia tends to be for more

recent memories (Valentine et al., 1987; Takayama et al., 1991; Maguire, 2001a; McDonald et al., 2001; Oka et al., 2003; Osawa et al., 2006), but can extend to events as long as ten years pre-morbidly (Gainotti et al., 1998). These memory deficits can often resolve within a few months, especially if the lesion is unilateral (Maguire, 2001a), with at least some of this recovery seeming to reflect compensation in residual RSC tissue (Ino et al., 2007).

However, as noted previously, these lesions are almost never restricted to just RSC. Most also include damage to adjacent white matter tracts in the splenium of the corpus callosum and cingulum bundle, with some also extending variously to the fornix, medial temporal lobes and posterior cingulate cortex (Rudge and Warrington, 1991; Gainotti et al., 1998; Maguire, 2001a). However, the specificity of the deficit in topographic disorientation and consistency with which it is produced is intriguing, especially as it is also broadly consistent with the type of impairments seen with more precise rodent surgeries.

In recent years, the condition of "developmental topographical disorientation" has been reported. These individuals appear to present with deficits similar to those with lesions to their RSC, but with no obvious structural brain abnormality. There is some evidence that their RSC may be unusually underactive while performing spatial tasks (Iaria et al., 2009), although much more needs to be learned about this condition, and in particular whether it is a true deficit or merely reflects the lower end of the normal spectrum of individual differences in spatial and navigation ability.

1.7 Neurological disorders

RSC pathology has been associated with a number of neurological conditions, including depression (Ries et al., 2009), autistic spectrum disorders (Weng et al., 2010; Starck et al., 2013), fibromyalgia (Wik et al., 2006), post-traumatic stress disorder (Liberzon et al., 1999; Piefke et al., 2007), schizophrenia (Mitelman et al., 2005; Bluhm et al., 2009) and bipolar disorder (Nugent et al., 2006). However, in most cases these are typically isolated reports with little additional corroborating evidence of RSC involvement. Alzheimer's dementia, on the other hand, has been consistently linked with RSC dysfunction. The prodromal phase of the disease is known as mild cognitive impairment (MCI) and RSC is one of the first brain areas to show pathological changes at this early stage, both atrophic (Pengas et

al., 2010; Tan et al., 2013) and metabolic (Minoshima et al., 1997; Nestor et al., 2003a; Chetelat et al., 2008; Hashimoto and Nakano, 2014; Lee et al., 2014). There are also changes to adjacent white matter tracts, the splenium of the corpus callosum and cingulum (Zhang et al., 2007) and changes to these tracts are linked to hippocampal atrophy (Villain et al., 2008). Dementia-related alterations in RSC grey matter density, glucose metabolism and white matter tracts are all specifically associated with impaired performance at learning routes through a new environment (Pengas et al., 2012). This is particularly relevant given that disorientation is a common early symptom in Alzheimer's dementia and so is consistent with the comparable spatial deficits brought about by lesions to RSC in humans and animals.

Mouse models of Alzheimer's disease show RSC dysfunction to precede overt amyloid plaque aggregation (Poirier et al., 2011). This local RSC dysfunction could reflect pathology originating in the region itself or alternatively from deafferentation of anterior thalamic and/or hippocampal connections, two other brain regions which are themselves implicated in the early stages of the disease (Nestor et al., 2003b). Support for the latter theory comes from rodent studies which investigate how RSC function can be affected by damage to distant connected brain regions, a phenomenon known as diaschisis.

1.8 Disconnection studies

The expression of immediate-early genes (IEG), such as *c-fos* and *zif268*, can be used as a marker of neuronal activity within a brain region (Dragunow and Faull, 1989; Worley et al., 1991). Numerous studies have looked at how lesions within one brain area can affect IEG expression within another. This allows inferences to be made about how a region's function may be altered by deafferentation from some of its inputs. In the RSC, IEG expression is usually induced when rats perform a standard eight arm radial-maze task (see Section 1.5) compared to just running up and down a single arm (Vann et al., 2000). The expression of IEGs in RSC after these tasks is considerably reduced following lesions to both the hippocampus (Albasser et al., 2007) and anterior thalamic nuclei (Jenkins et al., 2002a, 2002b, 2004; Poirier and Aggleton, 2009; Dupire et al., 2013), but not other connected regions (e.g. laterodorsal thalamic nuclei, entorhinal and postrhinal cortex). RSC IEG expression is also reduced by lesions to the mammillothalamic tract (Vann and Albasser, 2009) and Gudden's ventral tegmental nucleus (Vann, 2013). This is interesting

given that neither of these two structures is thought to provide any significant direct input to RSC. These effects are perhaps instead indirectly mediated through the mutually connected anterior thalamic nuclei.

These reductions in RSC IEG expression can be associated with minimal changes in the size, shape, number and general appearance of neurons in the region, suggesting that the pathology brought about by deafferentation can be 'covert' (Jenkins et al., 2004; Albasser et al., 2007), although this is not always the case (Poirier and Aggleton, 2009). Lesions to the anterior thalamic nuclei can bring about a reduction in the density of spines in superficial layers of RSC (Harland et al., 2014). However, whereas spine density in area CA1 of the hippocampus can be recovered by placing rats in enriched housing, no equivalent recovery seems to occur in RSC.

This pattern of anterior thalamic lesions producing changes to the superficial cortical layers of RSC is a common occurrence, particularly in area 29. Six to twelve weeks after lesions to the anterior thalamic nuclei there is up to an 89% reduction in levels of *c-fos* in superficial layers of area 29 (Jenkins et al., 2004). These changes are even evident just 1 week post-surgery, but with longer delays (9-12 months) deeper cortical layers and area 30 are also affected (Jenkins et al., 2004; Poirier and Aggleton, 2009). Both hippocampal and mammillothalamic tract lesions produce more widespread reductions and it is possible that the anterior thalamic nuclei findings reflect lesion sparing (Albasser et al., 2007).

Changes in RSC following anterior thalamus lesions are not limited to IEG expression. Superficial layers of RSC area 29 also show reduced cytochrome oxidase activity following anterior thalamic lesions (Mendez-Lopez et al., 2013). Cytochrome oxidase activity is another marker of neural activity (Wong-Riley, 1989), which seems more closely linked to metabolic *capacity*, i.e. how much activity *can* a neuron sustain rather than how much it necessarily *does*, which IEGs reflect (Sakata et al., 2005). Lesions to the anterior thalamus also cause a direct reduction in synaptic plasticity (long term depression) and $GABA_A$ (but not NMDA or AMPA) transmission within only superficial layers of RSC (Garden et al., 2009). These results are consistent with another study which, following anterior thalamic lesions, found transcriptome changes in RSC for a number of molecules which are involved in neuronal plasticity and one (*gabrd*) which is specifically related to GABAergic

transmission (Poirier et al., 2008). Poirier et al. also found changes in molecules associated with energy metabolism, which mirrors the results of a further study where superficial layers of area 29 were the site of altered expression of genes linked to neural plasticity and metabolism following lesions to the anterior thalamus (Amin et al., 2010). These links to metabolic changes in RSC are especially intriguing given the metabolic pathology present within the region at the earliest stages of Alzheimer's dementia (see Section 1.7).

In summary, there are a number of alterations that can occur in RSC as a result of disconnection from the anterior thalamic nuclei but also the hippocampus. There is particularly consistent evidence of diaschisis in superficial layers of area 29 following lesions of the anterior thalamus. This suggests that, in rodents at least, not only is the RSC densely interconnected with the anterior thalamus, but normal RSC function is reliant upon its integrity. It is also worth noting that these striking changes in RSC were evident when only considering a small number of different markers, and there are likely to be numerous other effects of deafferentation which are as yet undetected. These disconnection studies provide a valuable insight into the potential functions of RSC. However, by their very nature, lesions produce a damaged brain which may not provide entirely accurate representations of normal brain activity. More naturalistic processes can be investigated using imaging to record rather than alter responses in RSC.

1.9 Rodent imaging

Several studies have used IEG expression imaging to study RSC function in rodents. When rats navigate in the light, there is increased IEG expression in area 30, but not after navigating in the dark (Pothuizen et al., 2009). Area 29, on the other hand, has increased expression after navigating in both light and darkness. This adds weight to the notion that area 30 is selectively involved in navigation using distal visual cues, whereas area 29 is more generally involved for navigation using both internal and external cues (Vann and Aggleton, 2005; Hindley et al., 2014a), perhaps reflecting area 30's greater connectivity with visual brain regions (van Groen and Wyss, 1992). A study in mice found greater increases in RSC IEG expression when testing remote (30 days old) rather than recently (1 day) acquired spatial memories (Maviel et al., 2004). During similar spatial learning in a Morris water maze, mouse RSC IEG expression is greater after navigating to an unmarked platform using distal visual cues rather than a clearly marked platform (Czajkowski et al.,

2014). The same study also demonstrated that retention of newly acquired spatial information can be improved by increasing levels of cAMP response-element binding protein in RSC, a technique which enhances memory consolidation in other brain regions (Han et al., 2008). Temporarily inactivating RSC on the other hand disrupts the amount of information which can be retained.

Again, this evidence from rodents seems to indicate that RSC is involved in using spatial information, particularly derived from distal visual cues, to help navigate an environment. But of course, as outlined in Section 1.2, given the anatomical differences between rodent and human RSC, the question remains as to how generalizable the findings from non-humans are to humans. I will now consider experiments which have recorded and imaged responses in human RSC.

1.10 Human neuroimaging

1.10.1 RSC electrophysiological dynamics

As mentioned previously, the anatomical location of RSC in humans (and other primates) makes it difficult to study using certain methodologies. Its position deep and medial within the brain makes it relatively inaccessible for transcranial magnetic stimulation and the amount of other brain tissue between RSC and the scalp is problematic for localising reliable signal with magnetoencephalography or electroencephalography. This inaccessibility has also made electrode implantation very challenging, but there are a few studies which have investigated human RSC electrophysiology using intracranial recordings that were made as part of patients' evaluation for the source of their epilepsy.

Human RSC displays theta band oscillations (3-5 Hz) at rest (Foster and Parvizi, 2012). There is a suppression of activity when people make simple arithmetic calculations (e.g. "46 + 3 = 49" True/False), but when people review autobiographical statements (e.g. "I took a shower this morning" True/False), there is significantly higher gamma band activity (70-180 Hz) in their RSC (Dastjerdi et al., 2011; Foster et al., 2012). Before this increase in high frequency band power during autobiographical retrieval, there is also theta band phase locking (3-4 Hz) between the RSC and parts of the medial temporal lobes (Figure 7; Foster et al., 2013). There is no similar phase coupling with any other parts of the brain,

when performing different tasks (e.g. arithmetic calculations or at rest) or at other frequency ranges. Thus, the electrophysiological coupling between the RSC and medial temporal lobes seems quite specific to autobiographical retrieval.

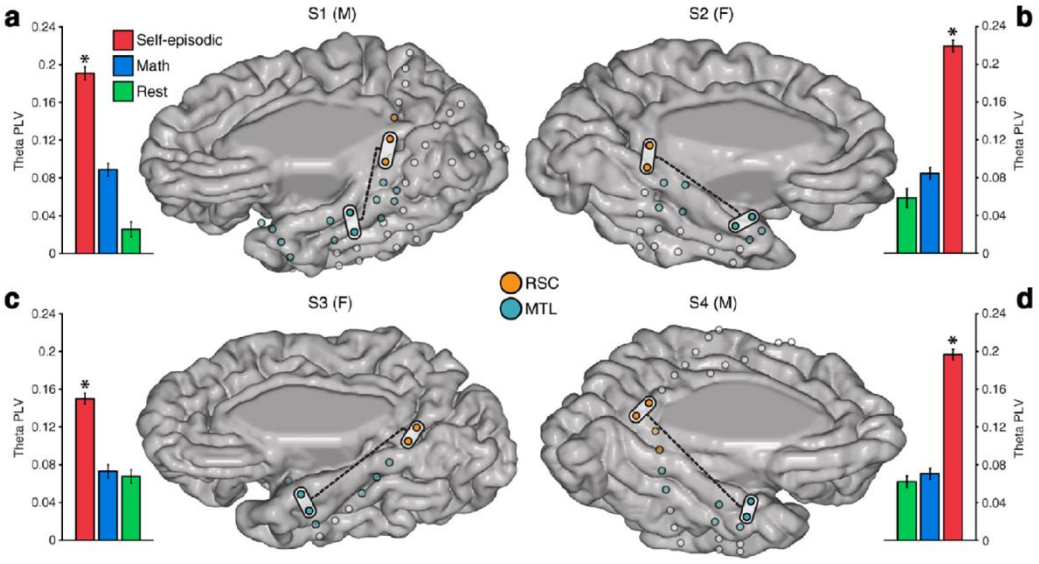

Figure 7 RSC electrode locations and theta phase locking values (PLV). The locations of electrodes in the RSC (orange) and medial temporal lobe (MTL, turquoise) of four subjects which show theta band phase locking during autobiographical memory retrieval (red bars). * Denotes significant theta band phase locking ($p < 0.05$ when compared to surrogate data). Only one set of RSC-MTL pairs was significant in each subject and these are highlighted by the dashed lines. (From Foster et al., 2013).

Recordings from electrodes implanted in this way provide valuable insights into the neural dynamics of human RSC, but their highly invasive nature preclude them from widespread use. Instead, the vast majority of imaging studies done in humans use fMRI as a non-invasive alternative, which also affords the ability to examine the healthy brain in vivo.

1.10.2 RSC network interactions

Consistent with the findings of other strands of RSC research, two neuroimaging meta-analyses indicate that RSC is a key part of a 'core' network of regions underpinning episodic autobiographical memory (of personally experienced events) and navigation (Svoboda et al., 2006; Spreng et al., 2009). This core network of which the RSC is part closely corresponds to the areas RSC is structurally connected to, namely parts of the medial temporal lobes, posterior cingulate cortex and the prefrontal cortex. However, there are some differences. The parts of prefrontal cortex which commonly coactivate with RSC tend to be more ventral and medial than the dorsolateral areas linked to RSC in

macaque anatomical tracer studies. The temporoparietal junction is also associated with the functionally defined network, despite sharing little, if any, anatomical connectivity with RSC. Conversely, anterior parts of the thalamus which are structurally connected to RSC are not usually apparent in neuroimaging experiments of autobiographical memory recall or navigation.

The two meta-analyses also suggest this core functional network is additionally important for imagining future events (prospection) and theory of mind (being able to infer the mental states of other people), although it should be noted that theory of mind tasks tend to activate a more superior posterior region than RSC proper (Buckner and Carroll, 2007). A similar set of regions has also been termed the 'default mode' (Raichle et al., 2001; Buckner et al., 2008) or 'task-negative' (Fox et al., 2005) network. These areas appear to be more active while the brain is at wakeful rest and not engaged in a specific task. In other words, they undergo a task-induced decrease in activation. However, rather than being 'task-negative' *per se*, this more likely reflects the mode of cognition when people are not actively engaged in a specific task, and instead their thoughts are directed internally rather than upon external stimuli. This 'mind-wandering' is most likely what explains the greater activity in these regions at rest (Mason et al., 2007), when people recall past experiences and perform mental simulations based upon these events (Buckner et al., 2008). The interactions between RSC and other parts of the default mode network have been linked to levels of overall consciousness in non-communicative brain damaged patients (Vanhaudenhuyse et al., 2010).

One study conducted a more formal comparison of regions sharing functional and structural connectivity with RSC (Greicius et al., 2009). This experiment combined diffusion tensor imaging (DTI) tractography and resting-state fMRI to see how these two modalities might be related (Figure 8). Resting-state fMRI measures temporal correlations in the spontaneous activity in different brain regions when a person is not performing a specific task while at rest. This technique has previously revealed a set of regions closely resembling the default mode network to be functionally linked (Kahn et al., 2008). Greicius and colleagues defined specific 'nodes' within the default mode network based upon their resting-state functional connectivity: medial prefrontal cortex, combined posterior cingulate and retrosplenial cortices and bilateral clusters in the medial temporal lobes. They then used these as 'seed' regions in a DTI analysis to look for evidence of

white matter tracts connecting them. This produced remarkably consistent results across individual subjects which also bore close relation to non-human primate anatomical tracer studies (see Section 1.3). Both medial temporal lobes were connected with RSC and slightly superior to this, another tract connected with medial prefrontal cortex (orange and blue tracts in Figure 6 respectively). The RSC-medial temporal lobe tracts presumably corresponded to the descending cingulum or "tapetum" (Wakana et al., 2004), whereas more superior parts of the cingulum bundle connected with prefrontal cortex (Concha et al., 2005a, 2005b).

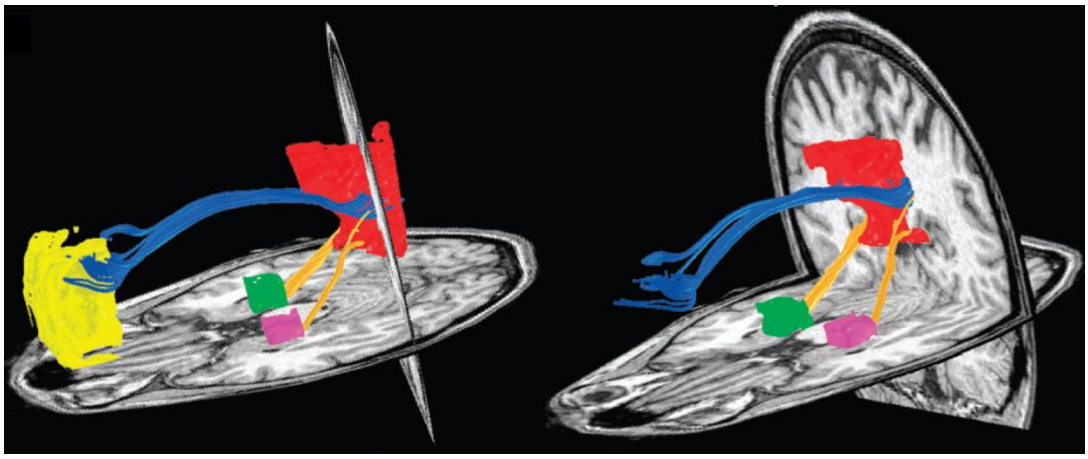

Figure 8 RSC functional and structural connectivity. Parts of the 'default mode' network share functional connectivity in a resting-state fMRI analysis, including: RSC and more extensive parts of posterior cingulate cortex (red), medial prefrontal cortex (yellow) and left (pink) and right (green) medial temporal lobes. DTI analysis revealed that these functionally connected regions also share structural connectivity (orange and blue). No tracts directly connected medial prefrontal cortex with the medial temporal lobes. (From Greicius et al., 2009 with permission from Oxford University Press).

The RSC appears to be involved in default mode processing at the earliest stages of its development, in two-week old neonates (Gao et al., 2009), suggesting it constitutes a fundamental part of the network. Structural connections and functional interactions between the different regions continue to undergo significant changes through to adulthood (Gao et al., 2009; Supekar et al., 2010). A more comprehensive structural connectivity analysis of the adult brain provides further evidence that RSC and the adjacent parts of posterior cingulate cortex form a key 'hub', linking numerous different parts of the brain for information processing (Hagmann et al., 2008).

One of the core network areas with which the RSC seems to have a close functional link is the posterior parahippocampal cortex (PHC), and this is particularly the case in relation to scene processing.

1.10.3 Scene processing

RSC and PHC are often both engaged during fMRI by tasks which in some way require the processing of scenes. Indeed they are even commonly referred to as being "scene-selective" (Park et al., 2007; Ward et al., 2010; Golomb et al., 2011; Nasr et al., 2011, 2013; Troiani et al., 2012; Rebola and Castelo-Branco, 2014). However, this label can cause some confusion when it comes to studying RSC function. Many experiments aiming to examine responses in RSC use a 'functional localiser' to define their region of interest. This commonly involves presenting subjects with a number of different images each showing either a full scene, an individual object or a face. A "RSC" region is then defined according to which areas were more active for scene than object or face stimuli. However, in addition to RSC proper (Brodmann areas 29 and 30), these functional localisers often also include much wider parts of posterior cingulate cortex and the parietal occipital sulcus (Figure 9). As such, studies often, but not always, give the functionally defined region a different title: the retrosplenial "complex". The similarity between the "cortex" and "complex" labels has the potential to cause confusion. This problem is compounded by the fact that the two variations use the same "RSC" abbreviation, with the "complex" or "cortex" distinction being only very briefly mentioned. There are also numerous instances in which the "cortex" name is inappropriately given when using a functionally defined region of interest (Epstein and Higgins, 2007; Epstein et al., 2007a; Park and Chun, 2009). This is now rarer following work which has explicitly drawn attention to the issue (Vann et al., 2009), but some studies still refer to retrosplenial "cortex" when describing wider, functionally defined areas (e.g. Nasr et al., 2011, 2013; Rebola and Castelo-Branco, 2014).

It is important to be clear what is being referred to given the significant differences in the anatomy, connectivity and functions of RSC proper and the adjacent posterior cingulate regions previously referred to in Sections 1.2-1.5. I will therefore abbreviate the functionally defined retrosplenial complex as "RSComp" and reserve "RSC" for referring to the anatomical areas 29/30.

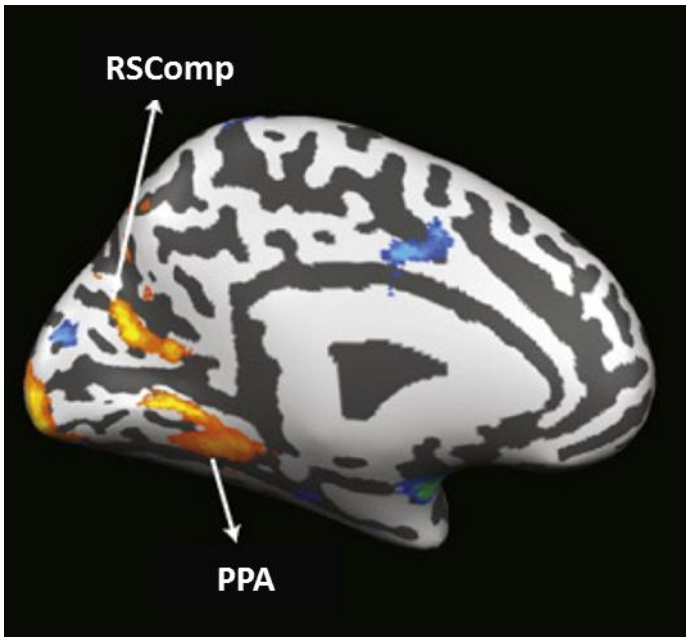

Figure 9 Example of retrosplenial complex (RSComp). The region indicated by the white arrow labelled 'RSComp' is an example of functionally defined RSComp. The region was identified using a 'scenes vs objects' functional localiser and is displayed on an 'inflated' image of the cortex. Gyri are shown in light grey and sulci are in dark grey. Compared to anatomical RSC (BA 29/30, see Figures 1 and 3A), RSComp usually extends into more posterior and superior cortical regions (although it varies between individuals). RSComp is usually displayed on inflated brains, which can add to difficulty in identifying the precise anatomical location being referred to. (From Schinazi and Epstein, 2010, with permission from Elsevier).

The representation of a scene which is stored in RSComp appears to be wider than just what is simply in view. RSComp representations of a scene extrapolate beyond the boundaries of what is being perceived at any moment in time (Park et al., 2007) and it also appears to contain information about the type of scene being viewed (e.g. beach vs forest; Walther et al., 2009). RSComp also treats mirror image reversals of a scene or object as different from the original image (Dilks et al., 2011). These results all indicate that RSComp does not merely process simple, low-level visual characteristics of a scene (which would be identical in mirror image reversals) but instead seems to contain a higher level representation of places (Fairhall et al., 2014). This representation seems to be particularly related to the spatial properties of a scene rather than the identity of its contents (Kravitz et al., 2011b; Harel et al., 2012; Troiani et al., 2012; Park et al., 2014).

RSC proper also appears to play a role in processing specifically spatial information about a scene. It is more active for images showing a full room than close-ups of single objects shown independently of the wider setting in which they are embedded (Henderson et al., 2008). There is similarly greater activation of RSC by scenes containing a clear three-dimensional structure (e.g. city streets, rooms) than more open landscapes or cityscapes

(Henderson et al., 2011). This role in processing spatial information is not just limited to visual tasks. RSC is also activated when exploring a 'scene' haptically (by feel) compared to information-matched objects which don't contain the same spatial structure (Wolbers et al., 2011). Thus, RSC and the wider RSComp appear to play a particular role in processing spatial characteristics of scenes.

In line with this suggestion, RSComp codes for the location that photographs are taken within an environment, irrespective of the viewpoint at that location (Vass and Epstein, 2013). It also treats different overlapping viewpoints from a single panoramic scene as the same (Park and Chun, 2009; Park et al., 2010). This provides further evidence that RSComp contains a wider representation of a whole scene, rather than just the current specific viewpoint. This RSComp viewpoint invariance is greater for scenes with which a person is more familiar (Epstein et al., 2007a) and the region is more active while viewing familiar than unfamiliar places (Epstein and Higgins, 2007; Epstein et al., 2007a). The strictly defined RSC is also more active for images of personally familiar places and objects (Sugiura et al., 2005) or even familiar voices and faces (Shah et al., 2001). This all points to RSComp/RSC potentially playing a role in integrating information into a broader cognitive representation based upon more detailed knowledge about a place. However, it should be noted that all evidence of RSComp integrating different viewpoints is lost if panoramic views are not presented in a continuous sequence (Park and Chun, 2009) or if people are performing a slightly different task while viewing an image of a scene (Golomb et al., 2011).

1.10.4 Spatial judgements

Further evidence of the importance of task demands upon RSComp responses comes from an experiment in which people were shown images of outdoor scenes and asked different questions about them (Epstein et al., 2007b). Consistent with other work (Epstein and Higgins, 2007; Epstein et al., 2007a), RSComp was more engaged when people viewed a familiar place than unfamiliar scenes, but there was a graded level of activation depending upon the task. RSComp was most active when subjects had to work out where the scene was located relative to a well-known landmark (e.g. "West or East of 36th Street"). The second highest level of activity was produced when indicating which direction the image faced (e.g. "Facing West of East"), with the lowest activation for familiar scenes arising

when people were simply asked whether or not they recognised it. RSC too is most active while people make proximity or distance judgements about familiar landmarks (Rosenbaum et al., 2004).

The engagement of RSC is not dependent upon using long-term spatial memories, however. It is equally involved in making purely perceptual spatial comparisons. When people make simple proximity judgements about items in an image (e.g. which object is closer to item A), RSC is more active if the judgement is being made relative to a building than a small ball (Committeri et al., 2004). This landmark-centred referencing produces even greater activity in RSC if the building is not actually in view when the comparison is made (Galati et al., 2010). This is consistent with the idea that RSC contains a wider representation of space which extends beyond the boundaries of what is simply visible (see Section 1.10.3). RSC could therefore be important for mentally simulating certain spatial information when it is not immediately available to the senses.

Further support for this idea comes from an experiment which showed greater activity in RSComp when people encoded the locations of items relative to a room's walls rather than less stable objects within it (e.g. a potted plant) or your own viewpoint at given time (Sulpizio et al., 2013). Furthermore, when people are shown a different view of a room to one they have previously seen and are asked to detect changes in the positions of objects within it, RSComp activity is modulated by the extent of that viewpoint change (from 0 to 135 degrees). Larger viewpoint changes will have presumably required a greater mental simulation effort. In a similar study, RSC was found to be more active when people imagine a rotation of their own viewpoint of a room rather than a rotation of a table-top full of items on it (Lambrey et al., 2012). RSComp involvement in making spatial comparisons does not even require three-dimensional manipulations. For spatial judgements about the relative locations of dots in 2-D on a screen, RSComp activity is correlated with the difficulty of the spatial comparisons (Nasr et al., 2013).

Taken together, these studies indicate that RSC and the wider RSComp are particularly engaged when making more difficult, detailed spatial judgements, both in purely perceptual tasks (Committeri et al., 2004; Galati et al., 2010; Nasr et al., 2013; Sulpizio et al., 2013) and those requiring recall of long-term spatial knowledge (Rosenbaum et al., 2004, 2007; Epstein et al., 2007b). Given the RSC's apparent role in manipulating spatial

information about a scene, it is important to consider how it might be engaged during navigation, especially in light of evidence of navigation deficits arising from RSC lesions in both humans and rodents.

1.10.5 Navigation

There are numerous instances in which RSC has been shown to be one of the most active brain areas when a person is engaged in navigation rather than simply following a given route (Maguire, 2001a; Hartley et al., 2003; Epstein, 2008; Spreng et al., 2009; Vann et al., 2009; Howard et al., 2014). Few studies, however, have attempted to establish what precise contribution RSC might make to this highly complex cognitive task. The most extensive investigation of the neural dynamics at play during navigation comes from a study in which experienced London taxi drivers drove around a highly realistic virtual reality simulation of the city while undergoing fMRI scanning (Spiers and Maguire, 2006, 2007a). This revealed that RSC is not engaged at all times during navigation, only with specific task demands, namely: when planning a new route; during sustained inspection of the environment and when expectations are either confirmed or violated (Spiers and Maguire, 2006). This points to RSC being important for manipulating, updating and integrating new spatial information into topographical representations of an environment. There have also been links drawn between how well a person knows the layout of a newly learned virtual environment and fMRI responses in RSC (Wolbers et al., 2004; Iaria et al., 2007) and RSComp (Wolbers and Buchel, 2005). RSC and more posterior parts of the parietal occipital sulcus also seem particularly engaged when people navigate a vehicle through a virtual reality environment from a first person perspective rather than an overhead view (Sherrill et al., 2013), both when people are planning and executing the journey. Navigation from a first-person perspective produces greater RSC activation if the target location has to be calculated relative an external cue rather than being clearly signposted by its location adjacent to a visible cue (Rodriguez, 2010), much like in rodents (Czajkowski et al., 2014).

The navigational relevance of individual environmental cues can also impact upon responses. RSComp is more active while people view buildings which are located at important “decision points” on a real-world route (Schinazi and Epstein, 2010). This is especially the case for landmarks in an area which people have only recently learned to

navigate and when the order that buildings are presented corresponds with how they were encountered while learning the route. It is interesting to note that the same is not true for small table-top objects (e.g. toys) placed at similar decision points along a route through a virtual reality 'museum' (Janzen and van Turennout, 2004; Janzen and Weststeijn, 2007; Wegman and Janzen, 2011). Thus, the nature of the landmark seems to be important for how RSComp responds.

It seems then that the involvement of RSC in navigation perhaps reflects processing of previously learned topographical information. RSC is active both when using this information to perform tasks but also while updating environmental representations. The precise nature of cues in the surrounding environment also appears to impact upon whether RSC encodes navigationally relevant information.

1.10.6 Episodic memory

The important role that RSC plays in supporting navigation is often closely linked with its involvement in more general memory processes (Spreng et al., 2009). In particular, there is one intriguing link between the two processes relating to a navigation-based mnemonic strategy, known as the 'method of loci', which vastly improves peoples' learning and retention of new information.

People with the ability to perform outstanding feats of memory (top performers at the World Memory Championships) display greater RSC activity than matched control subjects when recalling memorised information (Maguire et al., 2003). However, this was not due to innate RSC hyperactivity; it instead reflected the use of the method of loci memory mnemonic. This is a spatial learning strategy which dates back to ancient Roman and Greek times. The technique involves building a 'memory palace' where items are visualised in specific salient places along a route. During recall, this route is mentally retraced improving the ability to remember items encountered along the way. As well as navigation, RSC has been linked to processing particularly vivid and emotionally salient memories or scenes (Maddock, 1999). Thus, both of these results (mental navigation along a route and recalling particularly salient topographical information along the way) strongly engage RSC and this can greatly facilitate more general memory processes. Therefore, while lesions to RSC produce dense amnesia and specific navigational deficits

(see Section 1.6), by contrast, spatial strategies which engage RSC can give rise to superior memory retention.

The method of loci strategy in effect serves to turn semantic, factual information into more episodic-like memories and it is particularly for episodic memory recall which RSC is thought to be important (Maguire, 2001b; Gardini et al., 2006; Steinvorth et al., 2006; Svoboda et al., 2006; Cabeza and St Jacques, 2007; Spreng et al., 2009). Several studies have considered the specific types of memory which RSC may be involved in and the general view seems to be that RSC is more active when recalling recent than remote memories (Piefke et al., 2003; Gilboa et al., 2004; Steinvorth et al., 2006; Woodard et al., 2007; Oddo et al., 2010). This is broadly consistent with the effects of human RSC lesions, which tend to particularly affect recall of recently acquired information (see Section 1.6).

RSC is not only involved in the recall of past experiences. Indeed RSC is more active when imagining any form of personal event, both in the past or future (Addis et al., 2007; Szpunar et al., 2007; Botzung et al., 2008), or even fictitious scenarios (Figure 10; Hassabis et al., 2007). RSC seems particularly important for picturing events (both real or imagined) which involve the self, rather than things which are not personally experienced like incidents from movies or news stories (Summerfield et al., 2009). RSC is also linked to more general self-referential processing, with greater activity produced in the region when people make judgements about their own personality traits than those of others (Moran et al., 2006; Van Buuren et al., 2010).

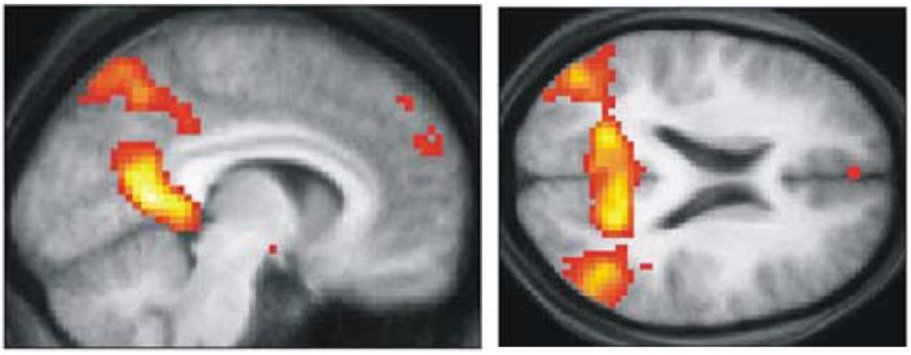

Figure 10 RSC is engaged when recalling the past or imagining future and fictitious experiences. A conjunction analysis demonstrating that RSC is part of a network of brain regions (also including bilateral hippocampi, parahippocampal, posterior parietal, middle temporal and medial prefrontal cortices) which is commonly involved in (re)imagining past, future and fictitious experiences. Displayed at threshold of $p < 0.001$ uncorrected. (Adapted from Hassabis et al., 2007).

The studies mentioned so far have all examined responses in RSC while a person is actively engaged in recalling some sort of memory, scene or behaviour. Intriguingly, however, RSC activity during "offline" periods appears to have an impact upon how well information is later remembered. After learning new object-scene associations, spontaneous 'reactivation' of these memory representations while people perform an unrelated task is linked to how accurately the pairings are subsequently recalled (Staresina et al., 2013). A similar process also seems to be at play during periods of sleep. After people learn new information in the presence of a specific odour, re-exposure to that odour during slow wave sleep both activates RSC and improves subsequent recall of the information (Rasch and Born, 2007; Rasch et al., 2007).

RSC therefore appears to be most engaged while people actively recall events from their recent past or imagine future and fictitious personal experiences. Reactivation of these representations during "offline" periods could also play an important role in ensuring effective memory consolidation. In addition to RSC, most of the studies described in this section also documented engagement of other brain regions, most notably the hippocampus, to be important in the same memory processes. It is important then to consider what the *specific* contribution of RSC might be to these complex cognitive tasks. I will now outline some of the most prominent current theories about RSC function.

1.11 Theories of RSC function

Several theories have been proposed to account for the RSC's involvement in navigation, more general scene processing and imagining past, fictitious and future events.

RSComp has been suggested to be primarily involved in determining precisely where you are located and how you are oriented within a broader environment. This representation is proposed to be quite sparse and centred around only the most prominent and well-travelled locations (Epstein and Vass, 2014). This would account for some of the tasks which engage RSComp during fMRI (Epstein and Higgins, 2007; Epstein et al., 2007b; Vass and Epstein, 2013) and provides a gross explanation of why it might be generally active during memory recall. However, it does not address the region's wider role in tasks requiring the manipulation of other topographical information (Committeri et al., 2004;

Spiers and Maguire, 2006) and is still imprecise about the exact nature of RSC/RSComp processing.

Another proposal suggests that RSC, together with PHC, may integrate information from external and internal cues to form coherent models of any given situation (Ranganath and Ritchey, 2012). This kind of integrative role could also extend beyond the purely spatial domain (Hindley et al., 2014b; Nelson et al., 2014), but is vague about what specific information RSC may handle. Alternatively, a theory building mostly upon work in rodents proposes that RSC plays a minor role (secondary to the postsubiculum) in using visual landmarks to control spatial signals (Yoder et al., 2011). However, there is little explanation of how this may relate to the wider range of cognitive tasks RSC is important for in humans (e.g. recall of past, future and fictitious experiences).

One theory suggests RSC involvement in episodic memory and processing place-related information, reflects contextual analysis of items (Bar, 2004; Aminoff et al., 2013). This is primarily based upon the finding that images of items which are strongly associated with a specific context, both spatial (e.g. office furniture) and non-spatial (e.g. birthday gift), elicit strong activation in RSC (Bar and Aminoff, 2003). However, subsequent work found these context effects were potentially confounded by the sense of space evoked by the stimuli (Mullally and Maguire, 2011, see also Henderson et al., 2008).

Another line of research places RSC within a network of regions involved in the process of "scene construction" (Hassabis and Maguire, 2007, 2009; Mullally and Maguire, 2013). This proposes that RSC, as well as areas such as the hippocampus and ventromedial prefrontal cortex, are involved in the construction, maintenance and visualisation of spatially coherent scene representations. This potentially explains the RSC's engagement by the wide range of tasks with which it has been associated. However, like other theories, scene construction leaves much about the RSC's precise contribution to the process open to interpretation.

The most specific proposal about the function of RSC comes from a computational model of spatial memory and imagery (Burgess et al., 2001a; Byrne et al., 2007; Vann et al., 2009). Our experience of environments comes solely from information derived from the body's various sense organs (e.g. visual from the eyes, proprioceptive from muscle stretch

receptors). Despite this 'egocentric' input, most spatial representations appear to be 'stored' allocentrically (centred around external cues in the environment), as evidenced by hippocampal place cells (O'Keefe and Nadel, 1978) and grid cells in the entorhinal cortex (Hafting et al., 2005). This model suggests that RSC might mediate or buffer the 'translation' of information between these egocentric and allocentric frames of reference. It suggests that head direction information in the anterior thalamus and retrosplenial cortex, as well as other regions (e.g. mammillary bodies), is used to directionally tune allocentric representations of space. RSC is suggested to be the key region coordinating this transformation, linking egocentric imagery in the parietal cortex with hippocampal allocentric information. The RSC would be well positioned to carry out such a transformation - its anatomical location sits between the medial temporal and parietal lobes; electrophysiological recordings indicate it contains representations of head direction, and lesions to RSC and connected regions produce direction-related deficits in both humans and rodents. This core function in processing scenes and 'stored' spatial information could also explain why RSC is so commonly engaged by navigation, memory recall and other imagery. However, the model is predominantly theoretical and there is very limited direct empirical evidence to suggest RSC does indeed use head direction information to transform between coordinate reference frames.

1.12 Summary and thesis objectives

From all this existing evidence, RSC appears to play a role in integrating different types of information to help produce coherent representations of the environment during navigation, recollection of past and imagining future or fictitious events. However, specific theories about its precise contribution to this complex process are either vague or based on limited empirical evidence. Perhaps one of the reasons why it has been difficult to establish the exact role of RSC is that it works in coordination with numerous other brain regions. This has made it hard to tease apart the function of RSC independently from related areas. Through the course of my PhD, therefore, a primary aim was to gain experimental control over the activation of RSC. I intended to primarily use fMRI to try and ascertain what information RSC alone may process; but where to start?

The work of a colleague hinted at a possible feature of everyday indoor items which RSC may be particularly involved in processing (Figure 11; unpublished data from Mullally and

Maguire, 2011; reported in Auger et al., 2012). It seemed that RSC may be more responsive to items which are permanent and do not usually change location from day to day. Reviewing the literature with this in mind, I believed this could potentially account for much of the region's behaviour in other tasks. After all, coherent representations of space need to be centred on permanent, stable environmental cues. I decided this was a reasonable starting point for the first of my experiments.

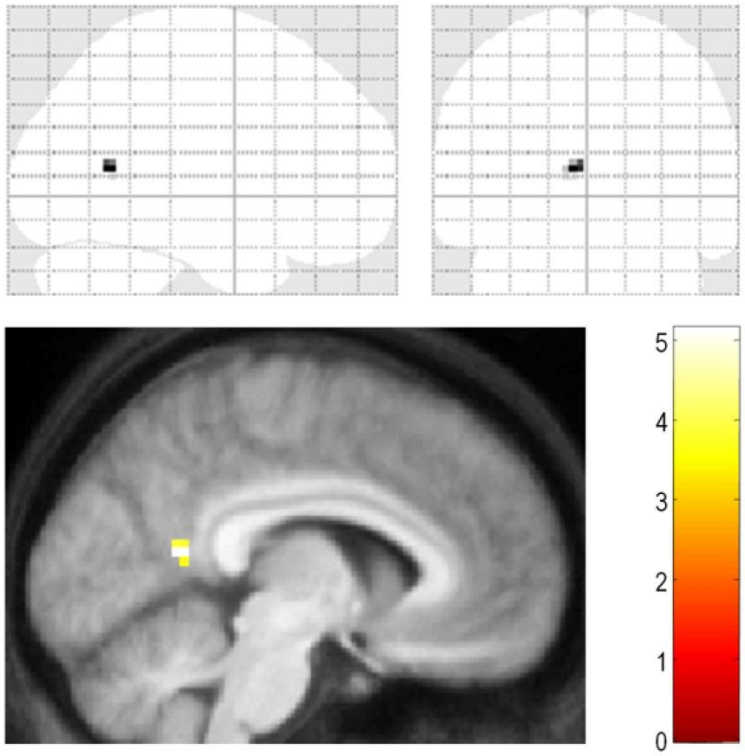

Figure 11 Indication of RSC responsivity to permanent items. Unpublished data from Mullally and Maguire (2011), indicated that RSC may be particularly engaged by items are more permanent and stable within an environment.

In Experiment 1 (Chapter 3) I investigated which, if any, feature of individual everyday outdoor items RSC and other brain regions responded to (such as their permanence, size, visual salience). I also considered how a person's navigational ability may relate to how well they recognised these landmark properties and their neural responses to them.

In Experiment 2 (Chapter 4), I built upon the findings of the first experiment to investigate how RSC processes the permanence of multiple landmarks presented simultaneously. I also considered how navigation ability may be related to these representations.

Experiment 3 (Chapter 5) I used a virtual reality environment which I created in collaboration with my colleague Peter Zeidman. 'Fogworld' (the name we gave the environment) contained numerous alien landmarks which either remained fixed in a single permanent location or constantly changed place. I used fMRI to scan people while they learned the permanence of these landmarks, enabling me to track the development of new neural representations of landmark permanence. I was also able to examine the learning of all participants, and compare people based upon their ability to learn the layout of the environment.

In Experiment 4 (Chapter 6), I explored whether or not RSC permanence representations might also develop for items learned in a smaller scale, two-dimensional setting. I also examined how the way in which landmarks are recalled might impact upon their neural representation. First, I wished to establish whether imagining an item (rather than viewing images of them as had been the case in my previous experiments) might elicit different permanence-related responses. Using this imagination paradigm, I was also able to compare responses to landmarks recalled in either large- or small-scale space.

In Experiment 5 (Chapter 7), I considered whether some other factor may be accounting for the RSC's apparent responsivity to landmark permanence. Specifically, I dissociated the permanence of landmarks from their usefulness for orienting and assessed which feature engaged RSC the most. I also compared representations of these two properties in good and poor learners of the information about the landmarks.

In Experiment 6 (Chapter 8), I investigated how generalisable RSC permanence representations might be. All my previous experiments had only considered the permanence of items in spatial terms. Here I sought to determine whether descriptions of behaviours or even abstract concepts which were permanent and reliable might also engage RSC.

In Chapter 2 I describe the methods used in these six experiments. Finally, in Chapter 9 I discuss the results produced from this set of experiments and draw them together to propose a specific role for the RSC in the wide range of cognitive functions with which it is associated. I also outline the current limitations of this theory and suggest ways in which

this theory could be explored in future work in order to gain an even better understanding of RSC function.

1.13 Publications

The following publications have arisen from work described in this thesis:

Auger, S.D., Mullally, S.L., Maguire, E.A. (2012). Retrosplenial cortex codes for permanent landmarks. *PLoS ONE*, 7(8):e43620.

Auger, S.D., Maguire, E.A. (2013). Assessing the mechanism of response in the retrosplenial cortex of good and poor navigators. *Cortex*, 49(10):2904-2913.

Chapter 2: Methods

2.1 Overview

In this chapter I introduce and explain the basic principles of the methods I used throughout my experiments. I first describe how I collected data, focussing mainly on the background and theory relating to MRI scanning. I then discuss how the raw imaging data are preprocessed and prepared for analysis. Finally, I outline the various forms of analysis which were common across my experiments. These include techniques which examine the magnitude and patterns of activation in RSC and other parts of the brain, as well as connectivity analyses to investigate how RSC interacts with other brain regions.

2.2 Participants

Participants were all healthy, right handed, had normal or corrected to normal vision and spoke excellent English. They were recruited through the UCL Psychology Department subject pool and the Institute of Cognitive Neuroscience's subject database. All experiments were carried out in accordance with the approval of the UCL Ethics Committee and subjects all gave written informed consent. Further details about the specific participants tested in each experiment are outline in the experimental chapters.

2.3 Experimental tasks

All experiments took place at the Wellcome Trust Centre for Neuroimaging at 12 Queen Square, London. Before starting, each participant was given an information sheet to read which outlined the nature of the experiment, data protection and ethics information. After being given the opportunity to ask questions, subjects then gave written informed consent. Behavioural testing, including pilot testing, as well as training or learning before scanning and post-scan debriefing typically involved tasks performed on a desktop PC in a quiet testing room. Stimuli were presented to subjects using the software package Cogent (Laboratory of Neurobiology, UCL).

All participants who underwent MRI scanning were thoroughly checked to ensure it was safe to scan them. They were provided with ear protection and lay in a supine position on the scanner table. Subjects were each given an alarm ball which they could activate by squeezing if they wished for the scan to be stopped at any point. A pulse oximeter was attached to the index finger of their left hand and they were given an MRI-compatible keypad for making responses in their right hand. All of my fMRI experiments were 'event-related' designs. This means that neural activity was investigated on a trial-by-trial basis (not across longer blocks of time). More detailed explanations of the precise tasks used in each experiment are outlined in the relevant chapters.

2.4 Acquisition of brain imaging data

2.4.1 Principles of Magnetic Resonance Imaging (MRI)

An MRI scanner has three key elements: a powerful electromagnet, a pair of radiofrequency (RF) coils and three gradient coils.

The main electromagnet creates a strong static primary magnetic field which is termed B_0. The strength of this magnetic field is measured in Tesla. All the experiments described in this thesis used 3 Tesla (3T) scanners.

About 77% of the brain's mass consists of water molecules (McIlwain and Bachelard, 1985) and each water molecule contains two hydrogen atoms. There are therefore a large number of hydrogen atoms in the brain. In normal circumstances, the protons in the nuclei of these hydrogen atoms spin with a random orientation. However, in the presence of an MRI scanner's strong magnetic field they become aligned in parallel with B_0. The protons do not spin perfectly about B_0, however, instead they 'precess' (or wobble, like a spinning top) around the main static magnetic field (Figure 12). The rate of this precession, or the 'Larmor frequency', is determined by the strength of the magnetic field; the stronger the magnetic field, the higher the Larmor frequency at which the protons precess.

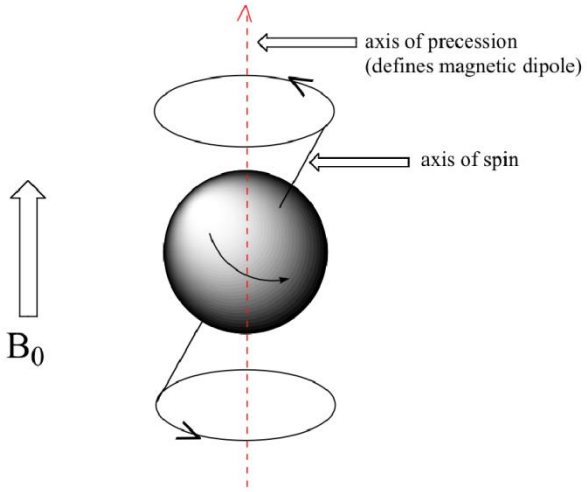

Figure 12 Proton precession. In the presence of an MRI scanner's static magnetic field (B_0), protons align with the field. However, the spin axis is not perfectly parallel with B_0. Instead, protons precess around the axis parallel to B_0 (the axis of precession). The frequency of this precession, the so called 'Larmor frequency' is determined by the strength of the magnetic field. From chemwiki.ucdavis.edu by Tim Soderberg, licensed under CC BT-NC-SA 3.0 US.

A scanner also has two RF coils, a 'transmit' and a 'receive' coil. These RF coils transmit additional electromagnetic fields and receive signal from them. The transmit coil emits RF pulses which are perpendicular to B_0 and tuned to the specific Larmor frequency at which the Hydrogen protons precess (depending on the strength of the magnetic field). This matching of the RF pulse and Larmor frequencies is known as 'resonance' (hence the 'R' in MRI). The resonant RF pulse has two effects upon Hydrogen protons (Figure 13): it 'excites' them, causing them to flip 180° into a higher energy state (anti-parallel to B_0); it also draws them into phase with one another (making them spin in synchrony)[1]. After the RF pulse has ended, protons fall back or 'relax' into their original alignment (parallel to B_0) and come out of phase with one another. The RF receive coil measures the time taken for protons to return to this equilibrium. The rate at which excited photons return to their original alignment (parallel to B_0) is known as the T1 relaxation time (represented in the vertical plane of Figure 13). The time for protons to come out of phase with one another is known as the T2 relaxation time (represented in Figure 13's horizontal plane). Both the T1 and T2 relaxation times vary in different tissue types and this contrast forms the basis of imaging body tissues. There is also a variant of the T2 relaxation time, T2*, which additionally depends upon inhomogeneity in the external magnetic field (this is especially

[1] A helpful analogy is to think of clocks: Two clocks which have the same frequency (e.g. they both tick one time per second) will not necessarily tick at the same time. If they tick in precise synchrony then they have the same frequency and are in phase with one another.

important for fMRI scanning, as will be explained in Section 2.4.2). RF signals therefore allow the properties of different tissues to be identified.

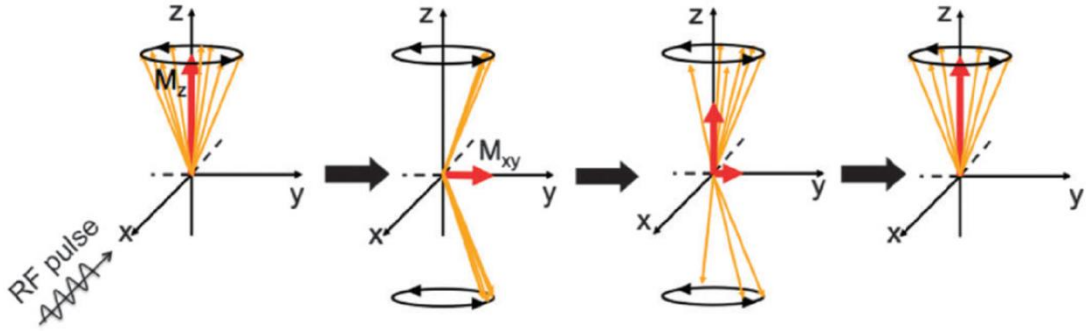

Figure 13 Effects of RF pulse upon protons. 'Z' denotes the axis parallel to an MRI scanner's static magnetic field (B_0). Leftmost panel: Before the onset of an RF pulse protons precess (orange lines) about an axis parallel to B_0 (red arrow). Second from left panel: An RF pulse, perpendicular to B_0, excites some protons causing them to 'flip' 180° (in the vertical place of this diagram) so that they now precess anti-parallel to B_0. At the same time, the spin of protons is also brought into phase (represented by the grouping of orange lines in the horizontal plane).Next panel: After the RF pulse, protons begin to 'relax' back to their original orientation (red arrow and orange lines in the vertical plane) and start to come out of phase with one another (red arrow and orange lines in the horizontal plane). Right panel: Protons eventually return to their original equilibrium. (From Figure 2, Lee and Hyeon, 2012, with permission from the Royal Society of Chemistry).

In order to produce spatially coherent images of the different tissues in the brain, RF signals need to be precisely localised. This is made possible by an MRI scanner's three gradient coils. One is aligned with the B_0 field and the other two are perpendicular to both B_0 and each other. These gradient coils are used to produce deliberate variations in the primary B_0 magnetic field. At the same time that RF pulses are emitted, the gradient coils set up a linear gradient in the magnet's bore so that one end or side has a greater strength and the other a lesser strength than the main static field. As I described earlier, the Larmor frequency of protons is dependent upon the strength of the magnetic field, so this also creates a linear gradient in the frequency of protons precession. This means that an RF pulse at a specific frequency will be able to "pick out" and only excite select sections of tissue which have the appropriate corresponding Larmor frequency. An MRI signal will therefore only be generated in that specific slice/section of the tissue. The thickness of this slice can be varied by altering the steepness of the magnetic field's gradient or the range of an RF pulse's bandwidth. This process is known as 'slice selection' (Figure 14).

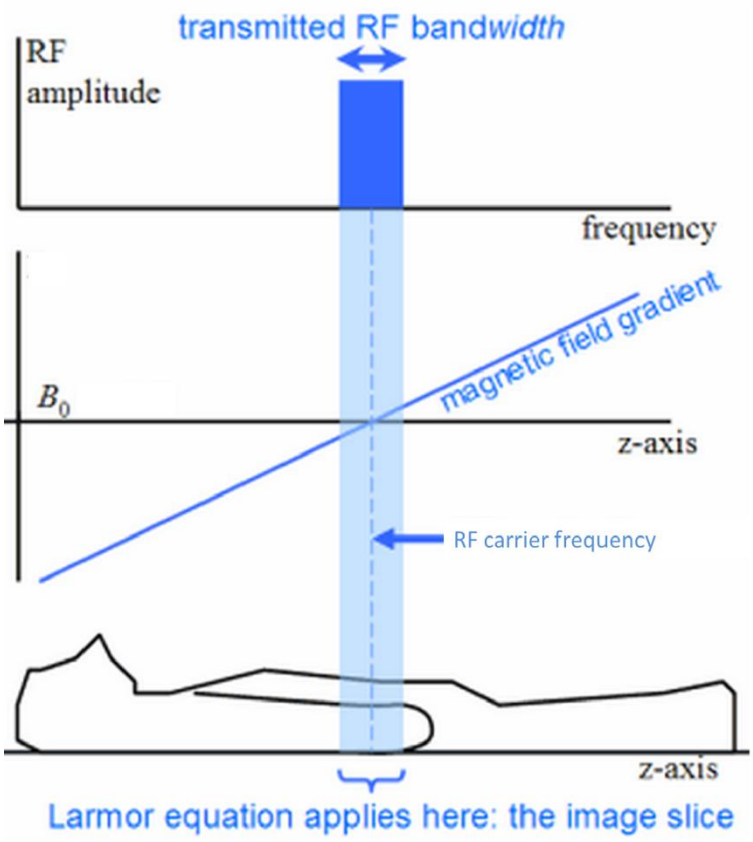

Figure 14 Slice selection. An MRI scanner's gradient coils set up a linear gradient in the static magnetic field (B_0) at the same time an RF pulse is emitted. This means that protons in different parts of the body will be precessing at different frequencies (as the Larmor frequency is determined by the strength of a magnetic field). The RF pulse will therefore "pick out" and excite only specific slices where the RF bandwidth matches (is resonant with) local Larmor frequencies (blue shaded area). (From www.revisemri.com by D M Higgins, licensed under CC BY-NC 2.5.)

Slice selection makes it possible to localise one dimension of the MRI signal. In order to produce a three dimensional image, the strength of the magnetic field is also varied *within* each of these slices. There are additional so called 'phase encoding' and 'frequency encoding' gradients perpendicular to the one used for slice selection. The frequency encoding gradient works on a similar principal to the slice selection gradient, whereby the Larmor frequency is made to vary depending on location within a slice. However, rather than only measuring locations which correspond with a specific frequency (as is the case with slice selection), all data from each slice are analysed using a Fourier transform. This breaks the MRI signal into frequency components and so reveals how much signal is coming out at specific frequencies. These frequencies relate to locations (according to the frequency encoding gradient) so this gives a picture of the signal coming out from tissues in specific locations within a slice (Figure 15).

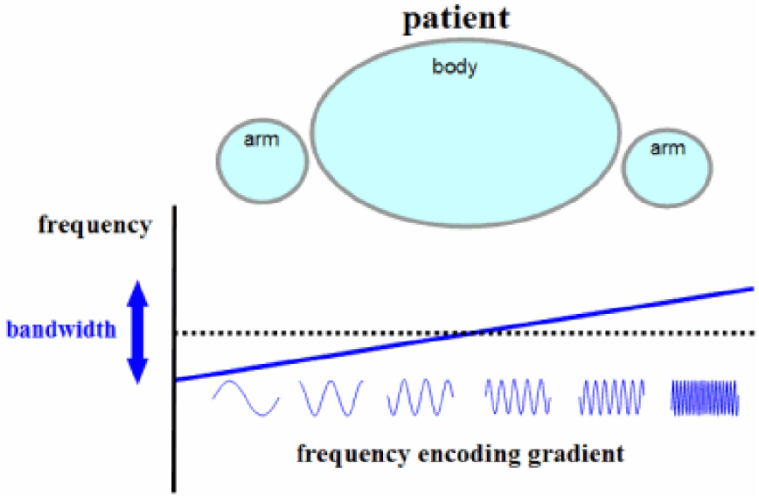

Figure 15 Frequency encoding gradient. Another gradient in the magnetic field is set up perpendicular to the one used for slice selection. This creates a range of Larmor frequencies in parts of the body in the same direction (the frequency encoding gradient). A Fourier transform can then separate these frequencies out to enable measurement of the MRI signal in different parts of a slice image. (From www.revisemri.com by DM Higgins, licensed under CC BY-NC 2.5)

A similar phase encoding gradient is only applied briefly and is switched off at the time the RF signal is recorded. This alters the phase of spins in a third dimension (perpendicular to the slice selection and frequency encoding gradients). So the phase of the MRI signal is now related to the location of protons in that third dimension. A Fourier transform can also break the RF signal into phase components, revealing how much signal is coming out at specific phases.

The combined frequency and phase components of the Fourier transformed signal measured from each slice can then be linked to specific locations within a slice. This process is repeated for all the slices in a whole brain 'volume'. All of these data are then combined and the signal separated into specific three dimensional units called 'voxels'. Each voxel represents a small cube of data collected from a specific location within the brain.

This is how MRI scanners generate and record signal from different types of brain tissue. However, in order to measure brain function and not just structure, the signal recorded needs to be sensitive to some other measure which is related to levels of neural activity. Multiple slice images also need to be taken rapidly in order to track changes in activity over time. This is what is done with fMRI.

2.4.2 Functional MRI

Active neurons consume both glucose and oxygen but have no internal stores of either substance. When activity within a brain region increases, it therefore receives an increase in blood supply to match the demand for these important substrates (Figure 16a). This 'neurovascular coupling' is tightly regulated in space and time. When neurons in a specific part of the brain become more active, there is a local increase in the delivery of oxygenated blood. Importantly, the magnetic state of the blood varies with its level of oxygenation.

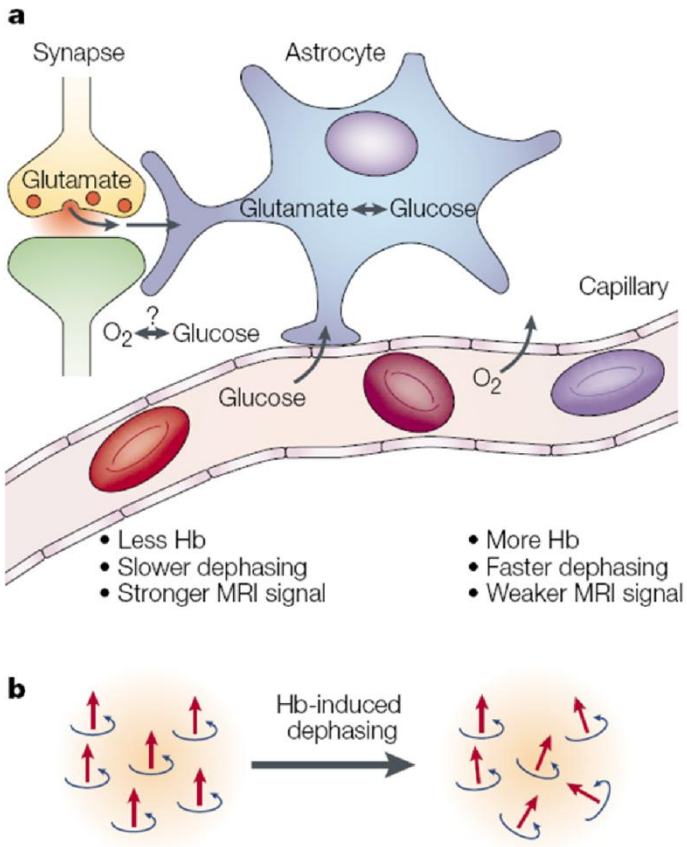

Figure 16 Neurovascular coupling and the fMRI BOLD signal. (a) Increased neural activity leads to a tightly controlled local increase in blood flow for the delivery of metabolic substrates (oxygen and glucose). (b) The blood oxygen level dependent (BOLD) signal is derived from the fact that haemoglobin (Hb), when not bound to oxygen (deoxyhaemoglobin), induces dephasing in nearby protons. (Adapted from Heeger and Ress, 2002, with permission from Nature Publishing Group).

Oxygenated and deoxygenated haemoglobin in the blood have different magnetic properties. When not bound to an oxygen molecule, the heme iron in haemoglobin contains four unpaired electrons, this makes deoxyhaemoglobin 'paramagnetic' (Pauling and Coryell, 1936). This means that deoxyhaemoglobin is attracted to magnetic fields and

distorts them (causing local dephasing of protons; Figure 16b). The same is not true for oxygenated haemoglobin. The ratio of oxyhaemoglobin to deoxyhaemoglobin in the blood therefore creates different levels of inhomogeneity in an MRI scanner's magnetic fields.

As I mentioned in Section 2.4.1, the T2* MRI signal depends upon inhomogeneity in the external magnetic field. This makes the T2* signal sensitive to the level of oxygenation in the blood (more oxygenated blood produces a greater T2* signal), meaning it provides an indirect marker of neural activity. FMRI measures this haemodynamic response accompanying neural activity in the brain, the so called Blood Oxygen Level Dependent (BOLD) signal (Ogawa et al., 1990, 1992).

2.4.3 Scanning parameters

Each of the experiments in this thesis used both structural and functional MRI. The experimental chapters describe the specific scanning parameters used for each study. Here I will outline briefly the nature of these key parameters.

The 'repetition time' (TR) is the time separating RF pulses emitted from the transmit coil. In this time, a whole brain volume is acquired. Setting a short TR makes tissue contrast particularly dependent upon T1 relaxation times. The 'echo time' (TE) refers to the time between the RF pulse being emitted from the transmit coil and the peak of the response (or the echo) it induces in the receive coil. Setting a long TE makes tissue contrast particularly dependent upon T2 relaxation times.

In each of my experiments, I acquired two main types of scan: structural and functional. Structural scans were "T1-weighted" meaning they had a short TR and a short TE, making them sensitive to T1 relaxation time. All the structural scans I acquired were at the same resolution with a voxel size of 1x1x1mm. Functional scans used sequences with a longer TR and a long TE to measure the T2* signal produced by BOLD responses. The functional images need to be acquired quickly in order to maximise the temporal resolution with which to detect changes in the BOLD signal. I therefore used sequences which utilise echo-planar imaging (EPI) to allow the rapid acquisition of MR images (Mansfield, 1977). The sequences used in all experiments had a 'flip angle' of 90°. This means that the RF pulse

was emitted at a 90° angle to the main magnetic field. All the functional scans in every experiment were at the same resolution, with a voxel size of 3x3x3mm.

Experiments 1, 4, 5 and 6 used 3T whole body MRI scanners (Magnetom TIM Trio, Siemens Healthcare). These experiments used a standard RF transmit body coil. However, whereas Experiment 1 used a 12 channel head receive coil, Experiments 4, 5 and 6 used a 32 channel head receive coil. This is relevant for the pre-processing which needed to be carried out (see Section 2.5.2). The scanning data for Experiments 2 and 3 were collected using a 3T Magnetom Allegra head-only scanner (Siemens Healthcare) with a standard transmit-receive head coil.

2.5 Preprocessing of brain imaging data

Before performing analyses upon fMRI data, it is necessary to carry out various preprocessing steps on the images acquired in the scanner. Preprocessing aims to transform the data into spatial alignment with one another and optimise the signal to noise ratio in preparation for analysis. All preprocessing steps and subsequent analyses were carried out using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/).

2.5.1 Discarding 'dummy' volumes

First of all, the first six volumes of every scanning session were discarded. This allows for T1-equilibration effects.

2.5.2 Bias correction

As I mentioned in Section 2.4.3, three of the studies (Experiments 4, 5 and 6) used a 32 channel head receive coil, which increases the amount and quality of measures that can be taken. However, there can be strong intensity inhomogeneities in the fMRI data acquired from 32 channel head coils. Bias correction aims to model these intensity variations (the 'bias field') and then correct for them and 'flatten' any differences between brain regions.

2.5.3 Realignment

Before entering the scanner, all participants were instructed to keep their head as still as possible throughout the experiment, and padding around the head when placed in the scanner assisted in this regard. However, there will inevitably still have been some head movement. Realignment aims to adjust for any movement that occurs between the acquisition of each image and remove movement-related artefact from the fMRI time-series. Each image is compared to the first one of the session and realigned to this common reference point. Six movement parameters are estimated which account for any translations and rotations in each of three dimensions (Figure 17). Even after realignment, there is still likely to be some residual error, so this process also produces six vectors for the estimated motion. These 'motion regressors' can then be included as regressors of no interest in subsequent analyses.

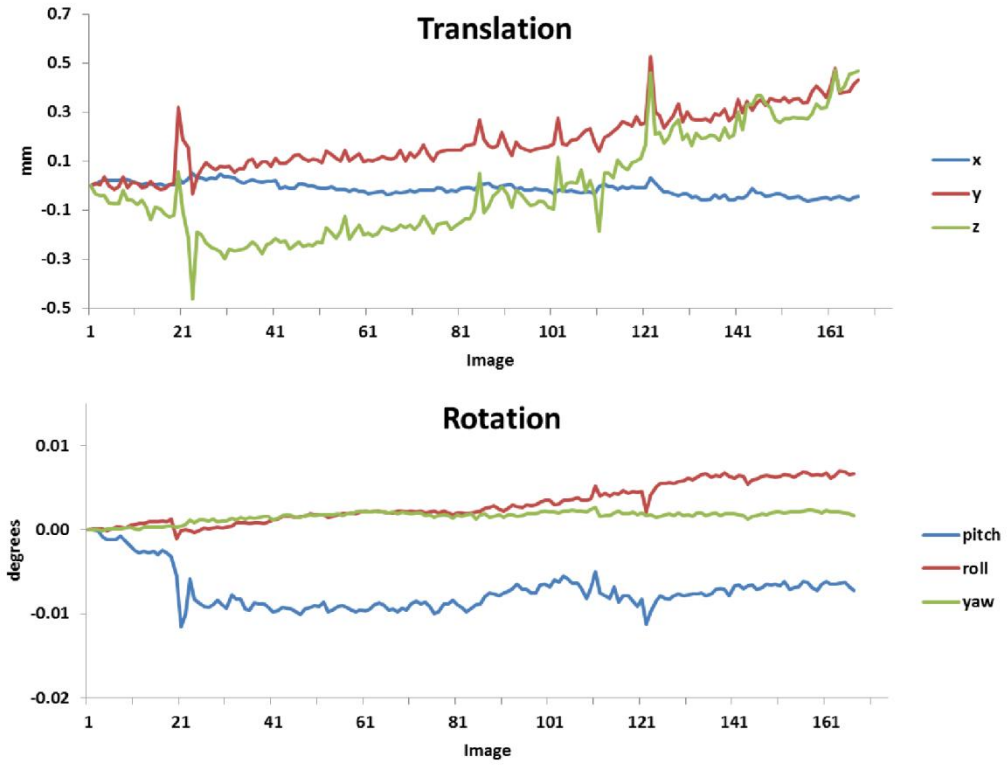

Figure 17 Example realignment movement parameters. The movement parameters estimated for one subject in Experiment 5 (Chapter 7) during the realignment preprocessing step. Lines show the estimated translation (top) and rotation (bottom) of the subject's head in three dimensions during the scan.

2.5.4 Unwarping

There can be some inhomogeneities in the strength of an MRI scanner's magnetic field. This is particularly evident at the interface between substances of different magnetic susceptibility (e.g. tissue-bone or tissue-air interfaces). As I discussed in Section 2.4.1, variations in the magnetic field alter the specific Larmor frequencies of protons and these are used to locate the origin of MRI signal. The field strength inhomogeneities can therefore cause some signal from the MRI images to be 'deflected' from their real location. To adjust for this I collected 'fieldmaps' in all my experiments. These map the magnitude and direction of any of field deformations. The fieldmaps were then used to model and "unwarp" artefacts brought about by interactions between these field inhomogeneities and movement of the participants.

2.5.5 Co-registration

In all my experiments I collected several different images for each participant (both structural and functional). It is useful for all these images to be under the same register when analysing them. Co-registration estimates a set of parameters which best matches a spatial transformation to overlay the structural and functional images. This makes it possible to overlay functional activations on a subject's anatomy.

The process is similar in principal to realignment (i.e. matching images together, see Section 2.5.3), but instead of matching functional scans together, it links low resolution T2* functional scans to a higher resolution T1 anatomical scan of the same individual. Structural and functional scans have different signal intensities in corresponding brain areas and the shapes of images also vary. Co-registration accounts for these differences and attempts to provide an optimised measure of the shared information in the two types of image.

2.5.6 Spatial segmentation and normalisation

In order to compare the location of functional activations in different participants, it is necessary to transform all their images into a standard stereotactic space. The T1-weighted structural scan is used to guide this transformation. The structural image is

segmented into white matter, grey matter and cerebrospinal fluid. This segmentation is based upon the standard Montreal Neurological Institute (MNI) template. SPM first calculates how to best transform images to match standard MNI space before segmenting them. These calculations are then used to warp functional images to fit (or 'normalise') them to a standard MNI template brain. This ensures that all the images from different participants are in a comparable coordinate system so that all their functional activations can be averaged. Averaging activations makes it possible to make more generalised inferences about the wider population and also to compare differences and similarities between various groups of people (e.g. good versus poor navigators).

2.5.7 Smoothing

The final preprocessing step I used in my standard SPM analyses was to apply a Gaussian smoothing kernel with full-width at half-width maximum (FWHM) of 8mm to each voxel's functional data. Despite all the other spatial preprocessing steps described above, there will still be some spatial differences between participants' scans. When comparing subjects, smoothing helps to suppress noise due to these residual differences in anatomy. Smoothing also serves a second purpose. For standard SPM analyses, comparisons made at the group-level (so called 'second-level' analyses) depend upon Gaussian random field theory which requires that data are smoothed for inferences to be valid.

In some experiments I used multi-voxel pattern analysis (MVPA; see Section 2.7) in addition to standard SPM analysis. MVPA examines specific patterns of activity across voxels within individual subjects rather than averaging across them. Smoothing is therefore unnecessary and may even remove important, fine-grained information which is present in the precise activity of voxels. I therefore used unsmoothed images for any MVPA analyses. All other analyses used smoothed data and in each experimental chapter I clearly outline whether or not smoothing was included in the preprocessing for each analysis.

After preprocessing the imaging data, I used a range of different analysis techniques in each of the experiments. Next, I will describe the principles upon which each method of analysis is based. These include standard mass-univariate analysis, MVPA and two types of

connectivity analysis - psychophysiological interactions (PPI) and dynamic causal modelling (DCM).

2.6 Mass-univariate analysis

Standard mass-univariate analyses consider the time series of every individual voxel separately using a general linear model (GLM). At each voxel, the GLM is used to test the hypothesis that the observed data *Y* (the fMRI time series) can be explained by a linear combination of explanatory variables with some residual error. This can be summarised with the following equation:

$$Y = X\beta + \varepsilon$$

Y is the observed data (a single voxel's BOLD signal at various time points, or 'time series'). *X* represents the components which might be influencing that voxel's observed time series and β defines the contribution that each of those components (in *X*) might be making to the observed data (*Y*). ε is the residual error between the observed data (*Y*) and that predicted by the model (*X*β).

In the analysis of fMRI data, a design matrix is constructed which corresponds to the *X* term in the formula above. This includes multiple regressors relating to components which may be impacting upon the fMRI time series (Y). These can be both regressors of interest (e.g. specific experimental conditions) and no interest (e.g. relating to subject movement or other potential confounds). Each row in the design matrix corresponds to a single scan or time point and each column specifies the onset and duration of each experimental condition (e.g. the time a certain type of image was on screen) or explanatory variable.

FMRI analyses work on the principle that each experimental manipulation brings about a change in neural activity which is detected by changes in the BOLD or haemodynamic response. The effects of experimental conditions therefore need to be considered in terms of the haemodynamic response they would be expected to elicit. For this reason, the design matrix's regressors of interest are convolved with the so called canonical haemodynamic response function (HRF) to model the haemodynamic effect that stimuli elicit (Figure 18). The HRF takes into account the time-delay between neural activity

occurring and the associated increase in supply of oxygenated blood. The peak in the BOLD signal occurs about six seconds after the onset of neural activity and reflects the time taken for an increased metabolic demand to be detected and bring about dilation of local vasculature.

It is only necessary for regressors which are thought to alter neural activity to be convolved with the HRF; other regressors (e.g. movement parameters) are included in the model without HRF convolution. The use of the canonical HRF assumes the haemodynamic response will be identical in different parts of the brain, whereas in reality this is not the case. Additional 'temporal derivative' regressors can be included in the GLM to account for this variation across voxels; I did not include them as they appear to provide little or no advantage over the canonical HRF for experimental designs similar to the ones I used (Sladky et al., 2011).

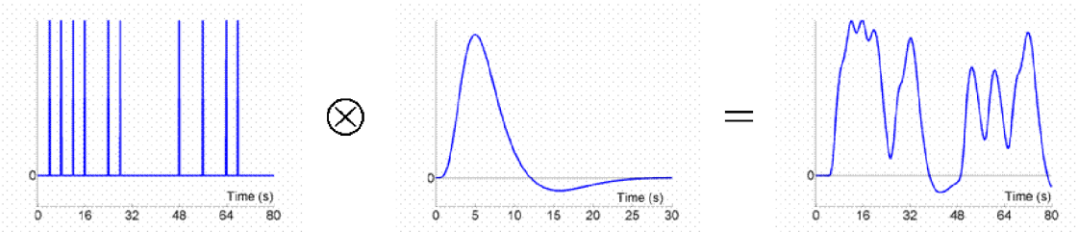

Figure 18 HRF convolution. Regressors which specify the onset and duration of specific events or trial types during the scan (left panel) are convolved with the canonical haemodynamic response function (HRF; middle panel), to produce a model of the haemodynamic response to stimuli (right panel). (From Friston, 2006 with permission from Elsevier).

After constructing a design matrix and convolving the relevant regressors with the HRF, the optimal parameters for β are estimated for every voxel in order to minimise the error (ε). In other words, the best fitting model ($X\beta$) of the observed fMRI responses (Y) is calculated. This 'model estimation' process uses a classical restricted maximum likelihood (ReML) algorithm to minimise the sum of the squared difference between the predicted and observed data. The output of this analysis is a set of parameter estimates (β) for each regressor at every voxel. The β values correspond to how big an influence each explanatory variable has upon the BOLD response in every voxel. These β parameters for each regressor can then interrogated using classical statistics.

In all my experiments, β images for different experimental conditions were directly compared with one another. This is achieved by defining specific contrasts. For example, if

you have three experimental conditions, each with its own column in the original design matrix, the hypothesis that the second condition's parameter is greater than the third's could be tested with the contrast: c = [0 1 -1]. A t-statistic can then be calculated by dividing this β contrast by the standard error of that contrast. The errors are calculated from the variance of the residuals (ε) from the model estimation process. This procedure produces an 'image' of statistics in each voxel which can be displayed with a statistical parametric map (SPM).

Comparisons for different experimental conditions can be made within individual subjects, but also between them. These are commonly referred to as first and second-level analyses respectively. Individual comparisons made at the first-level can be summarised in a single contrast image for each subject. I used these participant-specific contrast images to perform two types of second-level (between subject) analyses in my experiments: one looking for significant differences across all subjects and another comparing different groups of subjects.

The first type used one sample t-tests and tested the null hypothesis that there were no differences between contrasts across all subjects. I wanted to be able to make inferences about the wider population, not just the specific subjects who took part in the experiments, and so used random effects analyses. Random effects analyses consider the variance between subjects as well as within-subject variability in order to estimate the variance of the wider population from which a sample is drawn.

The second type of second level analysis I used directly compared responses of different groups of subjects (e.g. good versus poor navigators) with two sample t-tests. These comparisons tested the null hypothesis that there were no differences in the fMRI responses of the two subject groups.

2.6.1 Statistical thresholds

As mass-univariate fMRI analyses treat each voxel independently, it is essentially a series of t-tests. This makes is important to consider the appropriate thresholds to apply for the statistical maps.

In all my experiments, I was performing t-tests upon tens of thousands of voxels at a time. Using a standard statistical threshold of $p < 0.05$ in these circumstances would produce a large number of false positive results. By way of an example, if I performed t-tests upon 20,000 different voxels for a contrast which had no real effect upon any voxel's time course, a conventional $p < 0.05$ threshold would lead to about 1,000 false positives i.e. 1,000 voxels would wrongly be labelled as significant. It is therefore important for fMRI analyses to correct for the fact that multiple comparisons are being made.

One conservative method to correct for multiple comparisons is called 'Bonferroni correction'. For an analysis performing *n* independent t-tests, Bonferroni correction simply sets the threshold for statistical significance at *n* times smaller than usual e.g. 20,000 comparisons would use a threshold of $p < 0.05/20{,}000$ rather than $p < 0.05$. For fMRI analyses this is inappropriate as the high number of comparisons being made makes Bonferroni correction liable to setting unfeasibly high statistical thresholds. Bonferroni correction also assumes that the multiple comparisons being made are completely independent of one another. This is not necessarily the case for voxels in fMRI experiments. The parameter estimates (β) of voxels which are adjacent to one another will often be highly correlated as activity related to certain cognitive tasks will often cluster in anatomical locations. The spatial smoothing applied during preprocessing adds to this similarity between nearby voxels.

SPM fMRI analyses therefore use an alternative approach to correct for multiple comparisons by applying Random Field Theory to calculate the family-wise error (FWE) rate. This approach takes into account the level of smoothing and bases statistical thresholds upon the number of spatial clusters rather than setting them across *all* voxels (as would be the case with Bonferroni correction) or *individual* voxels (if there was no correction at all).

For most of my experiments, I report activations at a whole brain FWE corrected threshold of $p < 0.05$. However, in some circumstances this might still be too conservative a threshold (e.g. when comparing subtly different factors). In these instances I report results as the slightly less conservative threshold of $p < 0.001$ uncorrected, but only where there were clear *a priori* hypotheses about specific brain regions. I believe this approach provided a suitable balance for minimising the overall number of Type I (false positive)

and Type II (false negative) errors. In the methods section of each experimental chapter, I clearly outline which statistical thresholds were employed.

2.7 Multi-voxel pattern analysis (MVPA)

The mass-univariate analyses described above consider voxels in isolation, looking for those which show a linear increase in activation in response to certain experimental conditions. More subtle differences in neural representations related to the *patterns* of activity across *multiple* voxels can be examined using MVPA (Haynes and Rees, 2006; Norman et al., 2006; Chadwick et al., 2012). In my experiments, I used MVPA to try and identify whether the patterns of activation in certain brain regions might contain information about specific features of stimuli.

The principles of an MVPA analysis are illustrated in Figure 19, which I will refer to in the description which follows. This example considers whether or not it is possible to determine which memory a person is recalling, Memory A (blue) or Memory B (green), based upon the pattern of activation elicited in their hippocampus while recollecting. Participants recall memories A and B multiple times while undergoing fMRI scanning. Each time they recalled a memory, the associated hippocampal response is recorded (the Voxel Input).

A machine learning algorithm is then presented with this information and trained to distinguish which memory (A or B) a person is recalling based upon the associated hippocampal activity. In other words, it is trained to identify response patterns in the hippocampus which are consistently produced when recalling a certain type of memory. It uses this information to determine an optimal 'decision boundary' (the red dashed line) that best separates the two memories within a high-dimensional 'Feature Space' of the voxel patterns.

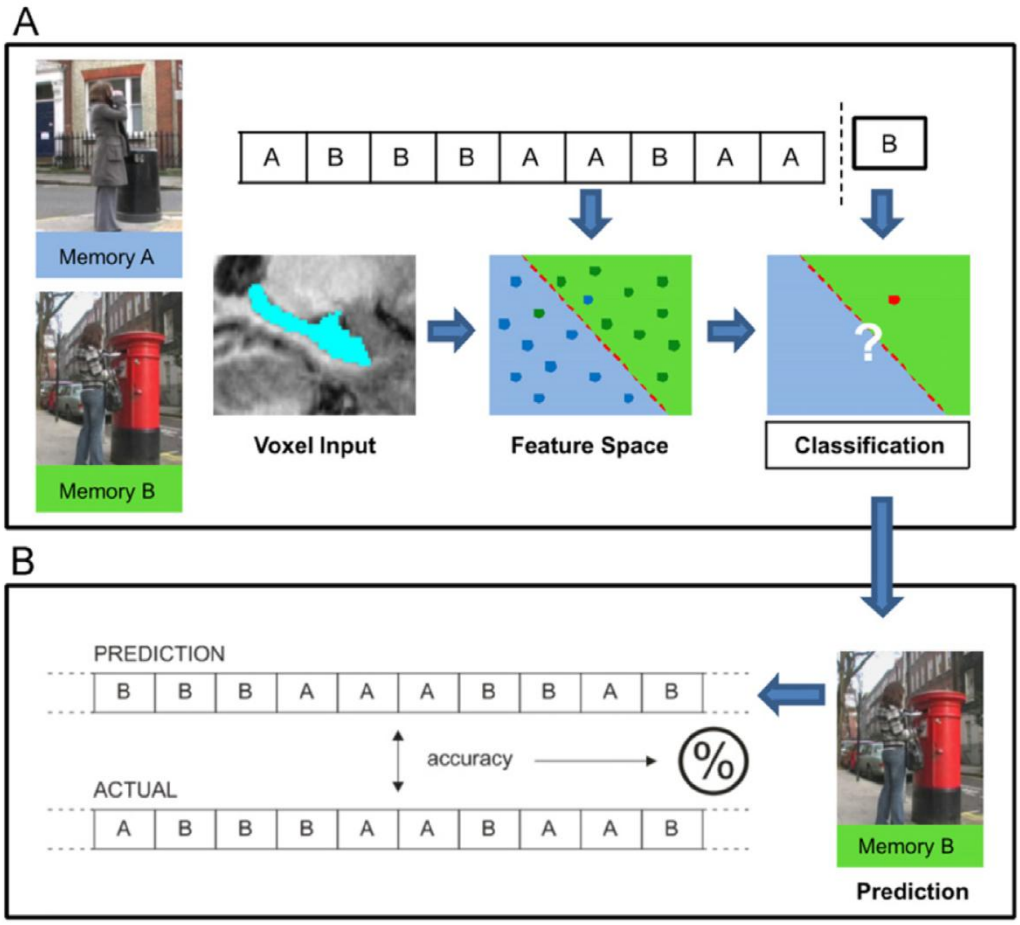

Figure 19 MVPA procedure. In this example, MVPA is used to try and classify whether a person is recalling Memory A or Memory B based upon the 'Voxel Input' from their hippocampus (A). The hippocampal pattern or activity when a person recalls memory A or B (letters at the top) is used to train a classifier to differentiate the hippocampal responses when recalling the two different memories (green or blue side of the red-dashed line, based upon information in a high-dimensional 'feature space'). The learning algorithm then makes a 'Classification' on an independent *test* trial's hippocampal activity (in this example B, the rightmost letter). It predicts which memory was being recalled at the time (B) and the accuracy of multiple classifications can then be assessed to produce an overall classification accuracy value for that brain region. (From Chadwick et al., 2012, licensed under CC BY-NC-ND 3.0).

After it has learned to distinguish the two memories in a *training* set of data, the algorithm then performs a 'Classification' based upon the hippocampal response pattern evoked on an independent *test* trial (red dot). The algorithm makes a 'Prediction' of which memory the person was recalling when that pattern of activation was produced (Figure 19B). This process is repeated multiple times changing which trial's data is excluded from the *training* set and used as the *test* trial. All the predictions are then compared with the actual memory which was being recalled on the corresponding trial. The accuracy with which the algorithm was able to distinguish between memories on test trials is then compared to chance. The classification accuracy value is used to infer the amount of information which is represented in the multi-voxel response patterns in that region. If

classification accuracy is significantly above chance, this indicates that the response patterns of the hippocampal neurons contain meaningful information about the memory a person is recalling.

However, not all voxels within a brain region are likely to carry meaningful information pertaining to the specific feature being classified in an MVPA analysis. It is therefore common practice to carry out 'feature selection' before performing a final classification to determine a region's classification accuracy. Feature selection aims to identify the most informative voxels within a brain region and then exclude uninformative voxels from the subsequent final classification. This in effect increases the signal-to-noise ratio. Whenever I used feature selection, I used a searchlight method (Kriegeskorte et al., 2006). A series of MVPA analysis were run, each centred around a different voxel within a brain region until all voxels had been examined. The voxels which were most likely to carry the relevant information (i.e. those which produced the greatest classification accuracy values) were then selected to use in the final classification.

To carry out an MVPA analysis, a first level SPM analysis is first run to obtain a summary β parameter for each trial in the experiment. Each trial is then 'labelled' so that these summary activations in every voxel can be linked to what type of trial was being performed at the time. This information provides the input to the learning algorithm for the training and testing of a classifier described above. After repeating this in each region of interest for every participant, classification accuracies can then be formally compared using classical statistical tests.

Various types of learning algorithm can be used for MVPA analyses; in all my experiments I used a linear Support Vector Machine (SVM) using the LIBSVM implementation (Chang and Lin, 2011). There are also many other ways in which the MVPA procedure can vary, such as how the training and testing datasets are defined, or which trials are used for feature selection. Whichever method is chosen, it is crucial that the data used for training and testing are kept independent (i.e. no *test* trials are ever included in the *training* set) and similarly that there is absolutely no cross-over in the trials used for feature selection and the final classification. This helps avoid any form of circular analysis or 'double dipping' (Kriegeskorte et al., 2009).

MVPA provides a sensitive means to examine subject-specific patterns of activity and how they may relate to specific experimental conditions. This contrasts with mass-univariate analyses which reveal information about the variability and mean levels of activity across numerous participants. Both these techniques are useful for investigating how responses *within* RSC relate to the demands of different tasks. However, given its widespread functional and structural associations with other brain regions (see Sections 1.3, 1.5, 1.8 and 1.10), I was also interested in examining the RSC's interactions with other regions. I therefore also used various types of connectivity analyses.

2.8 Connectivity analyses

In my first two experiments (chapters 3 and 4), I focussed primarily on establishing what information RSC itself processed and how this differed from other related brain regions (e.g. posterior parahippocampal cortex). Having primarily considered the function of RSC in isolation, I then began to additionally consider how information processing in RSC may impact upon its interactions with other brain regions. From the third experiment onwards, I therefore used two main types of connectivity analysis: psychophysiological interactions (PPI) and dynamic causal modelling (DCM).

The general approach I took was to first use whole brain mass-univariate and MVPA analyses to establish which brain regions might be involved in processing certain information. I then used PPI analysis to examine with which other brain areas these identified regions shared functional coupling during particular tasks. Finally, having established regions which were likely to be interacting with one another, where possible, I used DCM to investigate the nature of this effective connectivity (e.g. to infer the directionality of how the regions were interacting).

2.8.1 Psychophysiological interactions (PPI)

PPI is a measure of the functional connectivity between brain regions (Friston et al., 1997). It compares how psychological variables (e.g. components of an experimental task) relate to the physiological coupling between a 'seed' region and the rest of the brain. In my experiments, I selected specific seed regions from corresponding whole-brain univariate contrasts for the particular feature of interest. I then explored whether activity in any

other parts of the brain had a stronger correlation with the seed region in one experimental condition relative to another. In other words, I established a brain area which was responsive to certain information and then explored whether activity in any other brain areas could be explained by the interaction between the seed region's activity (physiological variable) and the experimental feature to which it was responsive (psychological variable).

To perform a PPI analysis, a summary of the fMRI time series (the eigenvariate) is first extracted from the seed region for use in a GLM analysis. In addition to the seed region's time series, regressors for task conditions (i.e. the time points when specific conditions were being performed) are included together in a design matrix. An additional PPI regressor is also included which models the interaction between the seed region's activity and the task regressor. As with regular mass-univariate SPM analyses (see Section 2.6), regressors of no interest (e.g. for head movement) are also included in the design matrix. The significance of the PPI regressor is then tested for each voxel in the brain to establish which, if any, brain areas show significant PPI connectivity with the seed region. Like standard univariate SPM analyses, this can be used to produce a group (second-level) summary.

I used a specific form of PPI analysis known as Generalized Psychophysiological Interactions (gPPI) analysis (McLaren et al., 2012). Normally, numerous PPI analyses need to be run for different individual contrasts. With gPPI, one model containing numerous PPI regressors for all experimental conditions is created. This is not only beneficial from a practical point of view, but has also been shown to improve model fit and sensitivity compared to standard PPI analysis (McLaren et al., 2012).

2.8.2 Dynamic causal modelling (DCM)

PPI provides a measure of task-dependent connectivity between brain regions. In order to better understand the nature of interactions identified by PPI analyses and to elaborate a mechanistic model, I then used a technique called DCM (Friston et al., 2003; Daunizeau et al., 2012). In DCM analyses, numerous plausible models of task-dependent connectivity between brain regions are compared. The 'winning model' then provides an indication about the potential nature of causal interactions between the pre-specified brain regions.

I will now outline some of the key principles underlying DCM analysis and the stages involved in carrying it out.

The first step in a DCM analysis is to create a set of neural models to compare. These are generic models of the information flow between a set of brain regions. In my experiments, I motivated which set of regions to consider by using only those which were responsive to the experimental condition of interest (in mass-univariate analyses) and/or interacting with one another (in PPI analyses).

The neural models are constructed based upon the following expression, which is known as the 'bilinear state equation':

$$\dot{x} = \left(A + \sum_k u_k B^{(k)} \right) x + Cu$$

This equation essentially assumes that the activity in a region (x) changes over time ($\dot{x}$) based upon interactions with other brain regions (the term inside the large brackets) and external driving inputs (C). The strength of the influence of other brain regions (inside the large brackets) is determined by both the strength of their endogenous connections (A) and the extent to which these connections are up- or down-regulated by task-related modulations (B).

Each model has three main user-specified components: intrinsic connectivity between the regions (the 'A matrix'), modulatory effects on these connections due to experimental conditions (the 'B matrix') and external driving inputs to the network (the 'C matrix').

DCM can be used to examine highly complex models involving numerous different brain regions and a range of experimental modulations. However, I aimed to keep my models as simple as possible, only ever considering two regions (one of which was always the RSC) and the impact of just one experimental condition. In all my DCM analyses, I assumed the two regions were connected bidirectionally (in the A matrix) and then compared all plausible combinations of modulation upon these connections (B matrix) and driving input (C matrix). I also used a variant of DCM called stochastic DCM, which additionally models endogenous fluctuations in neural activity (Daunizeau et al., 2012). This was particularly

appropriate for the endogenous, high-level cognitive representations I investigated. Stochastic DCM uses a similar state equation, but the main difference is an additional term ($\omega^{(x)}$) to account for endogenous fluctuations within each region:

$$\dot{x} = \left(A + \sum_k U_k B^{(k)}\right) x + Cv + \omega^{(x)}$$

These neural models are then combined with a haemodynamic model in order to help predict the BOLD responses they would bring about. The models are each fitted to the actual fMRI data (time series extracted from the regions being considered). This involves the estimation of a set of parameters (e.g. connection strengths between regions) to best match the model's predicted fMRI responses to the actual observed data.

The estimated models are then compared with one another to establish which has the greatest evidence and most closely matches the observed data. This comparison of models was done using Bayesian Model Selection (Stephan et al., 2009). Specifically, I used Random Effects Bayesian Model Selection in order to be able to make more general inferences about the wider population from which my sample of subjects were drawn. The model comparison procedure takes into account both the accuracy and complexity of each model. Increasingly complex models contain a greater number of free parameters and are therefore inherently more likely to provide a better fit of the data (a phenomenon known as over-fitting). More complex models are therefore penalised and the winning model is the one which provides the best balance between accuracy and complexity. That said, the models I compared were highly similar in terms of their complexity given that I kept them as simple as possible.

I only ever used DCM to identify which of a set of plausible models represented the most likely scenario in reality. It is possible to perform a more in depth examination of the estimated parameters within each model to try and infer more specific details about the precise network dynamics. For the purposes of my experiments I did not consider this to be necessary and was cautious to not over-interpret the results. I only used DCM to address clear, specific questions about how regions were most likely interacting with one another. Even so, when interpreting these results it is important to bear in mind that they are only based upon comparisons of very specific models of neural activity. There are a

wide range of other factors which the models would not have taken into account. Thus at best they provide a simplified indication about how regions may be interacting that is by no means definitive.

In all experiments where I found brain regions to share functional coupling according to a PPI analysis, I also performed DCM analyses. As will become apparent in subsequent chapters (specifically Experiments 3 and 5), DCM analyses did not always give rise to reliable results, most likely because of an insufficient number of trials/amount of data to enable DCM to operate optimally. In the experimental chapters, therefore, I only report DCM findings that were reliable and robust.

In the next six chapters I describe the experiments I carried out during the course of my PhD using the methods described in this chapter.

Chapter 3: Experiment 1

Retrosplenial cortex codes for permanent landmarks

3.1 Introduction

The ability to navigate is critical for survival. As such, there has been decades of research exploring how environments are represented internally, the key components of these representations, and the brain regions that support them. From the outset of systematic studies of navigation, prominent features in an environment, known as landmarks, have been posited to play a role (Tolman, 1948; Lynch, 1960; Golledge, 1991). In some theoretical formulations, landmarks are cast as the very building blocks of environmental representations (Lynch, 1960; Siegel and White, 1975; Downs and Stea, 1977). In others, such as the cognitive map theory, spatial relations between landmarks are regarded as the basis for a critical form of flexible navigation (O'Keefe and Nadel, 1978; Manns and Eichenbaum, 2009), while even accounts that emphasise navigation via path integration (i.e. estimating current location based on the movements made since the last known location), acknowledge the role of landmarks in maintaining accuracy (Gallistel, 1990; Yoder et al., 2011).

Given their importance for navigation (Lew, 2011), what is it about landmarks that makes them so useful? This seems like an obvious question, however, the majority of experiments involving landmarks have focused on their use or presence during active navigation or other spatial tasks. By contrast, the properties of the landmarks themselves have received much less attention, yet understanding this may provide important clues about how environmental representations are formed and how navigation is supported. There is a relative dearth of information about landmark features because it has proved difficult to develop an agreed method for assessing landmark properties (Caduff and Timpf, 2008). Characterisation of landmarks is a somewhat subjective process, and individual differences may contribute to the difficulty in deriving standardised landmark classifications. Several properties of landmarks have been highlighted as potentially important (Burnett et al., 2001), including the permanence or stability of the landmark

(i.e. the likelihood of the landmark being present), its usefulness for navigation (e.g. proximity to a decision point), and its visual features (e.g. size, salience, visibility).

With such difficulty establishing the key properties of landmarks, it is not surprising that the neural correlates of landmarks are not easily determined either. While there is a wealth of evidence from neurophysiological and lesion studies in animals, and neuroimaging and neuropsychological studies in humans for the brain areas involved in supporting navigation (Burgess et al., 2002; Spiers and Maguire, 2006, 2007a; Burgess, 2008; Spreng et al., 2009), scene processing (Epstein, 2008, 2011; Park et al., 2011), and representations of topographical features (Aguirre et al., 1998; Epstein and Kanwisher, 1998; Epstein and Morgan, 2011), findings have rarely been linked to specific landmark properties. There are a few exceptions; as noted above, the position of landmarks within an environment has been emphasised (Blades and Medlicott, 1992; Burnett et al., 2001; Miller and Carlson, 2011). In animal studies, whether landmarks are positioned proximally or distally is thought to influence navigation and the control of place fields, with distal landmarks being particularly significant, perhaps because they do not appear to change too much when the animal moves (O'Keefe and Nadel, 1978; see Lew, 2011; and Yoder et al., 2011 for recent reviews). Currently there is not agreement about the neural substrates of proximal and distal landmark control (Yoder et al., 2011). In human fMRI studies, posterior parahippocampal cortex (PHC) has been shown to be particularly responsive to items (in this case toys) encountered at navigationally relevant decision points in a virtual reality museum (Janzen and van Turennout, 2004; Janzen et al., 2008; Wegman and Janzen, 2011). Similar PHC activation has also been found for landmarks on real-world routes (Schinazi and Epstein, 2010), although this latter study utilised permanent landmarks (buildings) at decision points and observed additional activity in retrosplenial cortex (RSC) and along the parietal-occipital sulcus.

As previously noted, an item's size and permanence within the environment may also be important properties (Burnett et al., 2001). Interestingly, the combination of these two features was found to evoke a strong sense of space surrounding single acontextual objects (rendering them 'space-defining' - SD) even when imagined or viewed in isolation (Mullally and Maguire, 2011). Outdoor SD landmarks as well as indoor SD objects were associated with increased activity in PHC. Moreover, further interrogation of these data revealed a selective response in RSC that was specifically linked to item permanence over

and above that which was captured by the SD response alone (see Figure 11). These observations, combined with the greater sense of stability offered by distal landmarks (O'Keefe and Nadel, 1978), and the utility of permanent landmarks at decisions points (Schinazi and Epstein, 2010), underscore the potential importance of the stability or permanence of landmarks.

This not only makes intuitive sense – in order to build an environmental representation, stable features are clearly desirable – but landmark permanence has long been held to be a prerequisite for constructing effective cognitive maps (O'Keefe and Nadel, 1978). Control of hippocampal place cells during cognitive map formation is known to be stronger when landmarks are stable (Biegler and Morris, 1993, 1996; Knierim et al., 1995). Landmark permanence is not thought to be coded by the hippocampus directly, but rather hippocampal place cells may be guided by stability signals coming from elsewhere. The responsivity noted above of PHC and RSC during fMRI to attributes related to item permanence (Schinazi and Epstein, 2010; Mullally and Maguire, 2011) may make them candidate regions for coding landmark permanence. Further indirect evidence for this comes from Committeri et al. (2004; see also Galati et al., 2010), who observed PHC and RSC engagement when proximity judgements were made relative to enduring landmarks in a virtual environment. RSC is particularly interesting in this regard, as patients with RSC lesions, while still able to recognise landmarks, are unable to derive navigational information from them and so become disoriented (see Section 1.6). The presence of head direction cells in RSC (see Section 1.4) may provide a mechanism for registering permanent landmarks, and anchoring neural responses to them for use in environmental representations. This might also be true of other regions known, at least in animals, to contain head direction cells such as anterodorsal thalamus and the postsubiculum (Yoder et al., 2011), although evidence for the role of the latter two in human navigation is scarce.

In summary, while landmarks have been at the heart of empirical research and theoretical and computational models of navigation for decades, there is a surprising lack of direct information about the key attributes of landmarks and their neural substrates. I therefore set out to consider landmarks in a systematic manner, focussing specifically on landmark characteristics and the brain regions they engage. Based on the extant literature, the following features of landmarks were examined: their visual salience, their size, whether

they were space-defining (Mullally and Maguire, 2011), their navigational utility, the permanence of landmarks, and their portability.

There were three aspects to this study; first, in a set of behavioural experiments a large set of outdoor items were characterised for these attributes. This was followed by an fMRI study which utilised an optimised sub-set of these stimuli that covered a range of values for each landmark property, while also minimising any correlations between. Importantly, the participants in the fMRI study were naïve to my interest in landmarks and their properties, and during scanning merely viewed each image one at time and performed a vigilance task – pressing a button if a blue dot appeared on an item. The naivety of the fMRI participants, the incidental task, and the absence of manipulations related to navigation meant that I could conduct an unbiased and specific assessment of implicit and automatic neural responses to the landmark characteristics of interest. I hypothesised that PHC would be engaged by a range of the landmark features, given previous observations of its responsivity to landmarks at decision points, space-defining landmarks, large and more permanent landmarks (Committeri et al., 2004; Janzen and van Turennout, 2004; Galati et al., 2010; Schinazi and Epstein, 2010; Mullally and Maguire, 2011). By contrast I predicted that RSC (specifically BA 29/30, and possibly the anterodorsal thalamus/subicular region) might be particularly engaged by landmark permanence (Committeri et al., 2004; Galati et al., 2010; Schinazi and Epstein, 2010).

The third and final aspect of the study concerned individual differences. As alluded to, individuals can vary in their assessment of landmarks, and I wondered whether navigation ability could have an influence, and if so, whether this would be manifested in the brain regions engaged, thus providing further insights into the potential influence of landmarks in forming effective environmental representations.

3.2 Methods

3.2.1 Participants

Forty-eight healthy, right-handed participants (24 female, mean age 23 years, SD 2.90) took part in the three behavioural studies (16 participants - 8 females - in each study).

A new set of 32, healthy, right-handed participants with normal or corrected to normal vision (16 female, mean age 23.5 years, SD 3.05), none of whom had taken part in any of the behavioural studies, participated in the fMRI study.

All participants in both the behavioural and fMRI studies gave written, informed consent in line with local ethics committee guidance.

3.2.2 Stimuli

In order to investigate landmark features, I first compiled a set of 683 images. Each image depicted a single, everyday, outdoor item devoid of additional context and each was shown on a white background (see Figures 20 and 21 for examples). These images were used in the behavioural and fMRI experiments and were all the same resolution and occupied a similar portion of the screen.

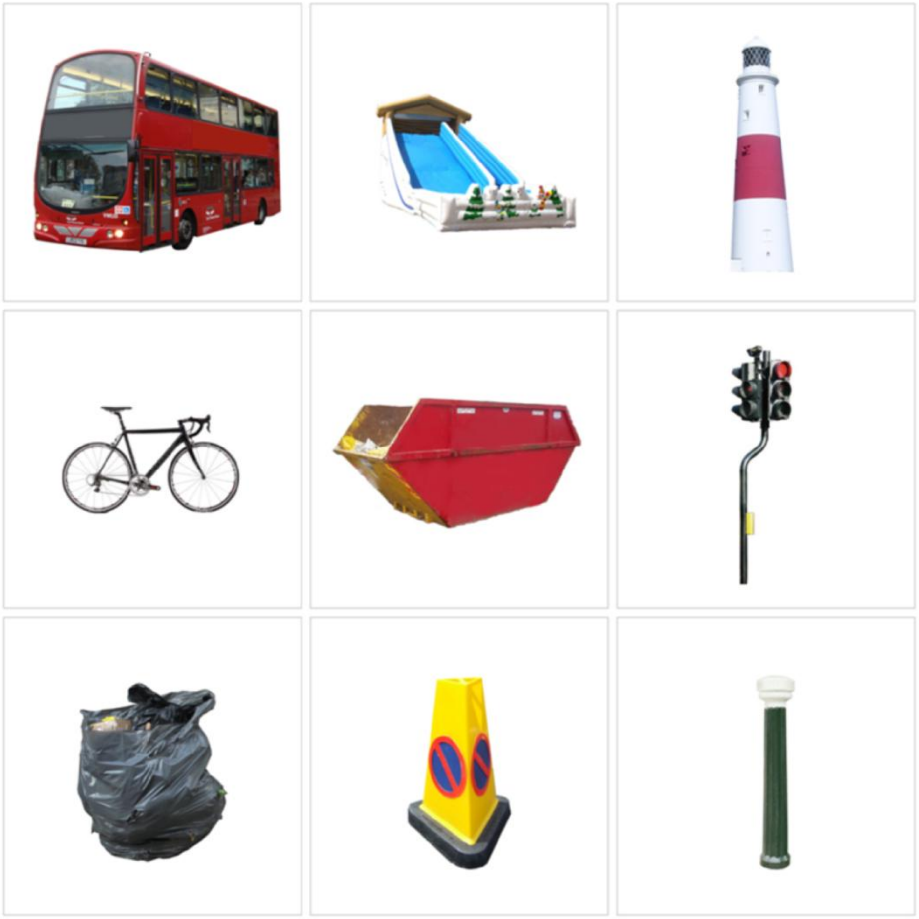

Figure 20 Example stimuli. Example items are shown from the 280 stimuli used in the fMRI study. For further examples, see Figure 21.

3.2.3 Behavioural studies: Characterising landmark properties

Across the three behavioural studies (each lasting approximately two hours per participant), six different features of each item were rated:

1. *Navigational utility*: Would you use this if you were trying to find your way?
(1) No (2) yes.

2. *Size:* What size do you expect the item in this picture would be in real life?
(1) Very small (2) small (3) medium (4) large (5) very large.

3. *Visual salience*: To what extent do you think this would grab your attention?
(1) Not at all … (5) very much.

4. *Space-defining or space-ambiguous (SD/SA):* Does this item rapidly evoke a sense of surrounding space? (1) Not space-evoking (2) space-evoking.

5. *Permanence*: How often would you expect the position of this item to change in everyday life? (1) Very often (2) often (3) occasionally (4) rarely (5) never. It was made clear to participants that this related to the overall landmark, and not to any (moving) parts of the landmark.

6. *Portability*: How easily do you think you could move this item? (1) Easily on my own (2) on my own with difficulty (3) with help from one other person (4) with help from multiple people (5) it's not moveable.

Two different features were rated in each of the three behavioural studies. In the first study participants rated the permanence and then the portability of each item. In the second study participants rated each item's navigational utility, and then its visual salience. In the third study participants evaluated the SD/SA nature of the items, and then gave ratings of their size. At the end of each study, participants completed the Santa Barbara Sense of Direction (SBSOD) questionnaire. This is a self-report questionnaire that has been shown to correlate strongly with actual navigation ability, and is increasingly

used as a reliable proxy for real-world wayfinding performance (Hegarty et al., 2002; Epstein et al., 2005; Janzen et al., 2008; Wegman and Janzen, 2011).

Using these item ratings, I selected an optimised set of 280 stimuli for use in the fMRI experiment (this number was the most that could be viewed within a reasonable time in the scanner). Selection was based upon consistency of responses for the features across at least 60% of participants, whilst ensuring a broad range of values for each attribute, given that I was interested in parametric responses. Most importantly, I also ensured that the final set of stimuli minimised the correlations between the item attributes. For example, items that were rated as permanent had a broad range of sizes, including many small and medium-sized permanent items as well as large permanent items.

3.2.4 fMRI study

A new set of participants took part in the fMRI experiment and they were completely naïve to the purpose of the experiment. Before entering the scanner, participants were informed they were being tested for vigilance and attention. They would be shown images of everyday outdoor items. They were instructed that a blue dot could appear anywhere on an image at any time and that they should respond with a button press as soon as they saw one. They were told to look closely at each image to ensure that they would not miss any of these dots. It was also stressed that participants should focus on the items and should not think about other objects, contexts or personal memories. Participants then practised the task using stimuli not included in the experiment proper.

During scanning, the 322 images (280 plus 42 catch trial stimuli) were shown centrally on a screen, one at a time for 3 seconds each, with a randomly jittered interval of between 2 and 5 seconds separating trials, during which a black central fixation cross was displayed on a white background. The catch trials, during which a small blue dot appeared somewhere on a landmark image for 1 second, occurred randomly during the scanning sessions (of which there were three). No stimuli were repeated. The order of trials was pseudo-randomised with the proviso that landmarks with different values for the numerous features were distributed across the scanning sessions and that there were no systematic patterns in the presentation order.

Immediately after scanning in a debriefing session, participants saw each stimulus again and rated them along two permanence-related parameters:

7. *Permanence (post-scan)*: How often would you expect the position of this item to change in everyday life? (1) Very often (2) often (3) occasionally (4) rarely (5) never. As in the behavioural studies, it was made clear to participants that this related to the overall landmark, and not to any (moving) parts of the landmark.

8. *Distance moves*: How far would you expect this item to move in a normal day?
(1) Over 10 miles (2) about 1 mile (3) about 100 metres (4) metres (5) centimetres.
This was only asked if the participant indicated in the previous question that the item could change position. This mix of imperial and metric ratings was found to be the most intuitive for participants.

In this post-scan debriefing session, participants also completed some neuropsychological tests (described in detail in Section 3.3.3) and the SBSOD questionnaire.

3.2.5 Scanning parameters and preprocessing

T2*-weighted EPI with blood oxygen level-dependent (BOLD) contrast was used for fMRI scanning on a 3T whole body MRI scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) operated with the standard RF transmit body coil and 12-channel head receive coil. Scanning parameters were selected to achieve whole brain coverage and optimised for the hippocampus and surrounding tissue: 48 oblique axial slices angled at -45^{o} from the axial to coronal plane (as defined in Weiskopf et al., 2006), 2.5mm thickness (with inter-slice distance factor 20%), repetition time TR = 3.36s (slice TR = 70ms), excitation flip angle = 90^{o}, echo time TE = 30ms, in-plane resolution 3mm x 3mm, field of view FoV = 192mm x 192mm, 64x64 matrix, phase encoding (PE) in the anterior-posterior direction, 13% oversampling in the PE direction, echo spacing 500µs. For reduction of signal loss in the hippocampal region, slices were angulated and a z-shim gradient moment of +0.6 mT/m*ms was applied (Weiskopf et al., 2006). The first 6 'dummy' volumes from each session were discarded to allow for T1 equilibration effects. Field maps were acquired with a standard manufacturer's double echo gradient echo field map sequence (short TE = 10ms, long TE = 12.46ms; 64 axial slices with 2 mm thickness

and 1 mm gap yielding whole brain coverage; in-plane resolution 3mm x 3mm). A 3D MDEFT T1-weighted structural scan (Deichmann et al., 2004) was acquired for each participant with 1mm isotropic resolution. FMRI data were analysed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images were realigned and unwarped (using the field maps), normalised to a standard EPI template in MNI space with a resampled voxel size of 3x3x3mm and smoothed using an 8mm FWHM Gaussian kernel.

3.2.6 Behavioural ratings analysis

It was first important to check whether it was appropriate to use the landmark characterisations made by the behavioural study participants for the fMRI analysis. I therefore first sought to test whether the two cohorts of subjects (in the behavioural and fMRI studies) gave similar ratings for the landmarks. I first compared the permanence ratings made by the behavioural and fMRI participants (listed above as numbers 5 and 7 respectively) for the 280 scan stimuli, to check whether or not they correlated with one another.

I next examined potential relationships between the 8 separate ratings that had been collected for the 280 scan stimuli. I did this by submitting the mean rating for each of the 8 features of all 280 scanning stimuli to a principal components factor analysis. For the principal components analysis, I used a varimax rotation and Kaiser normalization. For each stimulus, I then calculated orthogonal factor score coefficients for principal components which were identified by in factor analysis. This was done using the Anderson-Rubin method.

3.2.7 Scanning data analysis

I first examined whole brain fMRI responses to the various features of landmarks. It was important to consider any underlying components for the landmark features (as identified by the factor analysis). I therefore created parametric regressors from the principal components analysis' factor score estimates and entered these into a whole brain GLM analysis. This would enable me to examine activity that was linearly modulated by factor 1, and activity linearly modulated by factor 2.

A separate regressor was created for catch trials, and was treated as a covariate of no interest, as were individual movement parameters. Each trial was modelled from the time of onset of the stimulus for 1.5 seconds. This time period was selected as I was most interested in rapid and automatic responses to the stimuli. Regressors were convolved with the haemodynamic response function. Subject-specific parameter estimates pertaining to each regressor of interest (β) were calculated for each voxel. Second level random effects analyses were then run using one-sample t-tests on these parameter estimates (collapsed across sessions). For all whole brain fMRI analyses, I report any activations that survived a whole brain uncorrected threshold of $p < 0.001$ (minimum cluster size of 5 voxels) for PHC and RSC, given my *apriori* interest in these brain areas, and $p < 0.05$ (FWE corrected) for the rest of the brain.

I had a particular interest in how responses in RSC and PHC would relate to landmark features; I therefore also performed additional regions of interest (ROI) analyses in these specific brain areas. Anatomical masks for the PHC and RSC (defined as BA 29/30) were delineated by an experienced researcher not involved in the project on an averaged structural MRI brain scan from different set of n=30 participants, and guided by Duvernoy (Duvernoy, 1999) and Vann et al. (2009). For both of these ROIs, I extracted the fMRI BOLD response profiles relating to the principal components identified in the factor analysis. I plotted responses by grouping stimuli into 5 bins according to the values of their factor score estimates. Five bins were chosen as this approximately corresponded to the five options subjects had when rating most of the landmark features in the original behavioural studies. Subject-specific parameter estimates pertaining to regressors for each of these bins were calculated for each voxel. For each bin, contrast values in active voxels (i.e. those with a value greater than 0) were averaged in the PHC and RSC regions, collapsing across left and right (given that responses in the two hemispheres were very similar) using the MarsBaR toolbox and then plotted. This would allow me to examine how the two regions' responses varied in relation to the key landmark features.

3.2.8 Comparing good and poor navigators

I was also interested in investigating how a person's navigational ability may relate to their responses (both behavioural and fMRI) to landmarks. At the end of the post-scan debriefing session, each of the fMRI study participants completed the SBSOD

questionnaire to gauge their navigation ability (Hegarty et al., 2002). I defined two groups, good and poor navigators, by taking a median split of SBSOD scores.

In order to examine whether navigation ability had an effect on the processing of landmark attributes, I examined the ratings participants gave for the landmarks, taking their navigation ability into account. I first looked at how much overall agreement there was among good and poor navigators in the first set of behavioural studies when scoring the different features of the original 683 landmarks. For any specific landmark features for which there were differences, I then explored those ratings in greater detail, to determine what might be driving the effect (see Section 3.3.3 for specific details). I also compared how fMRI responses might differ according to associated differences in behaviour (again, more specific details are provided in Section 3.3.3)

I also conducted a voxel-based morphometry (VBM; Ashburner and Friston, 2000, 2005) analysis to investigate whether any structural brain differences were apparent between the good and poor navigators. Structural MRI scans were analysed using VBM implemented in SPM8, employing a smoothing kernel of 8mm full width at half maximum. Good and poor navigator groups were directly compared using a two-sample t-test, and a whole brain uncorrected threshold of $p<0.001$ for the PHC and RSC, and $p<0.05$ (FWE corrected) for the rest of the brain.

For all the analyses described above (behavioural, VBM, and fMRI) I also compared males and females to determine whether sex differences were apparent for any of these measures.

3.3 Results

3.3.1 Analysis of behavioural ratings

Given that permanence ratings were made by the behavioural participants (rating number 5 above) and post-scan by the fMRI participants (rating number 7 above), I examined the correspondence between these two sets of ratings for the 280 scan stimuli. The ratings were highly correlated ($r = 0.95$, $p<0.001$); in addition, there was no significant difference in the mean scores ($t_{46} = 0.810$; $p = 0.42$). This confirmed that the ratings made by the

behavioural and scan participants were comparable, and that the landmark characterisations made by the behavioural study participants were appropriate to use in the fMRI analyses.

Because I had 8 separate measures of features for the 280 scan stimuli, I reasoned that some of these variables may potentially load onto common underlying components. I submitted all the scores to a principal components factor analysis and two factors accounted for 81.94% of variance in the data (Table 1): navigational utility, size, visual salience, and SD/SA loaded strongly onto one factor, while the permanence-related features of permanence, permanence (post-scan) and distance moves - loaded together on the second factor. Portability loaded similarly on both factors reflecting its relationship to size on the one hand and permanence on the other. Thus the factor analysis confirmed the presence of two key components in the landmark features that I assessed, and in particular highlighted permanence of landmarks as a distinct factor.

Landmark Feature	Principal Components Analysis Loadings	
	Factor 1	Factor 2
Navigational utility	**0.787**	0.352
Size	**0.924**	0.043
Visual salience	**0.722**	-0.144
SD/SA	**0.908**	0.105
Portability	**0.665**	**0.599**
Permanence	0.235	**0.908**
Permanence (post-scan)	0.124	**0.978**
Distance moves	0.174	**-0.946**

Table 1 Results of the factor analysis. The ratings of permanence (both in the behavioural study and post-scan) and distance moves, loaded together on Factor 2. Navigational utility, size, visual salience and SD/SA loaded together on Factor 1. Portability loaded similarly onto both factors.

For each stimulus I calculated orthogonal factor score coefficients for the factor analysis' two principal components. Looking at the example stimuli in Figure 20, they are actually ordered in terms of these principal components analysis factor score estimates. From left to right, the items are more associated with greater values for Factor 2 (i.e. landmarks on the right are more permanent) and from bottom to top they have increasing values for Factor 1 (other features). Figure 21 shows a larger number of the stimuli, grouped according to how much they are associated with the two factors.

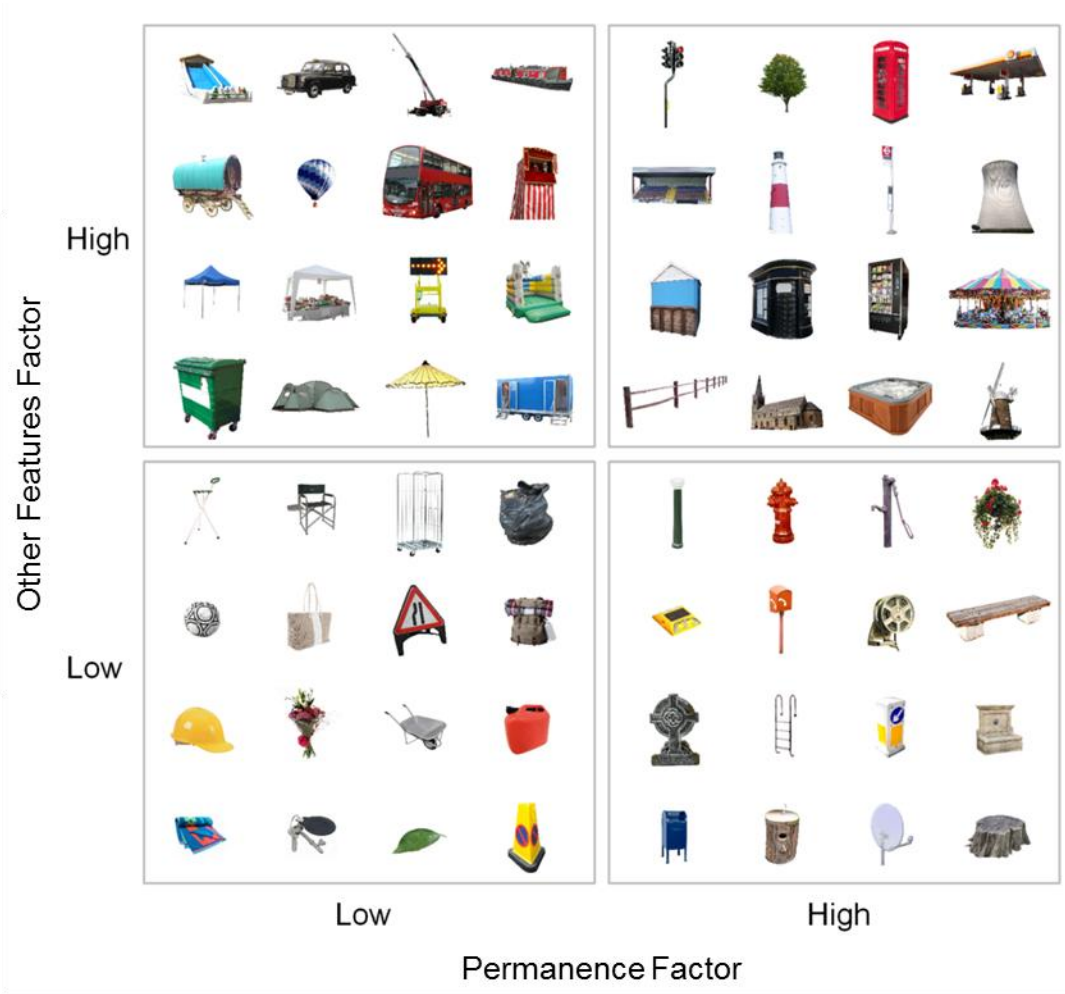

Figure 21 More example stimuli. The principal components analysis identified two key factors. Permanence-related features loaded together onto a 'Permanence Factor' (Factor 2 in Table 1). Other features not related to landmark permanence loaded onto another 'Other Features Factor' (Factor 1 in Table 1). Here, stimuli are grouped according to how they scored on the two factors. Items with low permanence (i.e. often change their location) are on the left, with permanent items on the right. Similarly, items which scored highly on the other factor are shown in the top half of the figure and those that had low scores on this factor are shown in the lower part.

3.3.2 Neural substrates of landmark properties

The fMRI participants, who were naïve to my interest in landmarks, engaged in a vigilance task. They performed with a high level of accuracy (mean 93.7%; SD 8.75), showing they focussed on the dot-detection task and maintained attention during the experiment. The catch trials were removed from the fMRI analysis.

My interest was in understanding the neural substrates of the landmark features, specifically, how the fMRI BOLD response reacted to changes in landmark attributes. In order to do this, I needed to take account of the fact that the landmark attributes shared some underlying components. I therefore created parametric regressors from the principal components analysis factor score estimates in order to examine activity that was linearly modulated by factor 1, and activity linearly modulated by factor 2.

For increasing values of the first factor (which had high loadings for navigational utility, size, visual salience, and SD/SA) increased activity was present in right PHC (30, -46, -8; Z = >8) and left PHC (-27, -61, -8; Z = 7.74) extending posteriorly into right and left occipital cortex (15, -94, 4; Z = >8; -18, -85, -8; Z = >8). There were additional peaks in left cerebellum (-15, -49, -41; Z = 5.44) and left superior parietal cortex (-21, -64, 55; Z = 4.95) (Figure 22A). Decreasing values of this factor were not associated with any changes in activity. Increasing scores for the second factor (which had high loadings for permanence, permanence (post-scan) and distance moves) were associated with increased activity in right PHC (30, -40, -5; Z = 6.44) and left PHC (-30, -43, -5; Z = 6.00), as well as in right RSC (9, -46, 10; Z = 4.79; 9, -52, 22, Z = 4.81) and left RSC (-9, 46, 7; Z = 4.82) (Figure 22B). Decreasing values of this factor were associated with changes in activity in left and right occipital cortex (-18, -91, 1; Z = 5.93; 24, -88, -2; Z = 5.88). In summary, all of the landmark attributes (i.e. both factors) significantly engaged PHC. However, permanence related-features induced further strong activation in RSC (specifically BA 29/30).

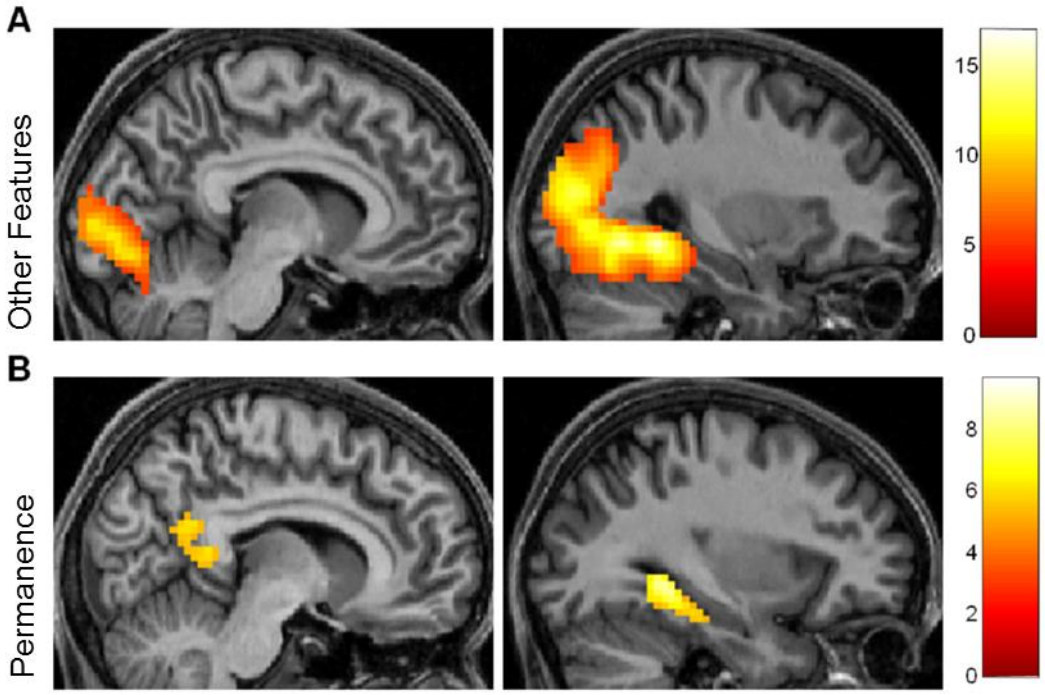

Figure 22 Brain regions engaged by the permanence and other features factors. Activations are displayed on sagittal views of the structural MRI brain scan of one participant chosen at random. The colour bars indicate the z-scores associated with each voxel. (A) The PHC and posterior visual areas were activated by increasing values of the other features factor. (B) RSC, along with PHC, was activated by the permanence factor.

I then conducted a second analysis focussed on anatomically-defined ROIs in PHC and RSC. The fMRI BOLD response profiles for PHC and RSC for the two factors were extracted and plotted. The PHC clearly responded to both factors, showing a linear increase in responsivity as the values for the factors increased (Figure 23A). This was not the case for RSC, where activity did not change as a function of increasing value of the features loading onto factor 1 (the "other features"). Furthermore, for the permanence-related landmark attributes (those which loaded onto factor 2), the profile of response in RSC was not linear. Instead, what is quite apparent from Figure 23B is that there was a large increase in RSC response specifically to the landmarks that were the most permanent. Indeed, comparing directly the landmarks rated as most permanent with those rated as least permanent (post-scan permanent ratings of 5 versus 1 or 2) in a whole brain fMRI analysis confirmed the engagement of the RSC (-6, -46, 4; Z = 4.22; and PHC: -30, -43, -5, Z = 5.28; 33, -37, -8; Z = 4.84) for the most permanent landmarks (Figure 23C).

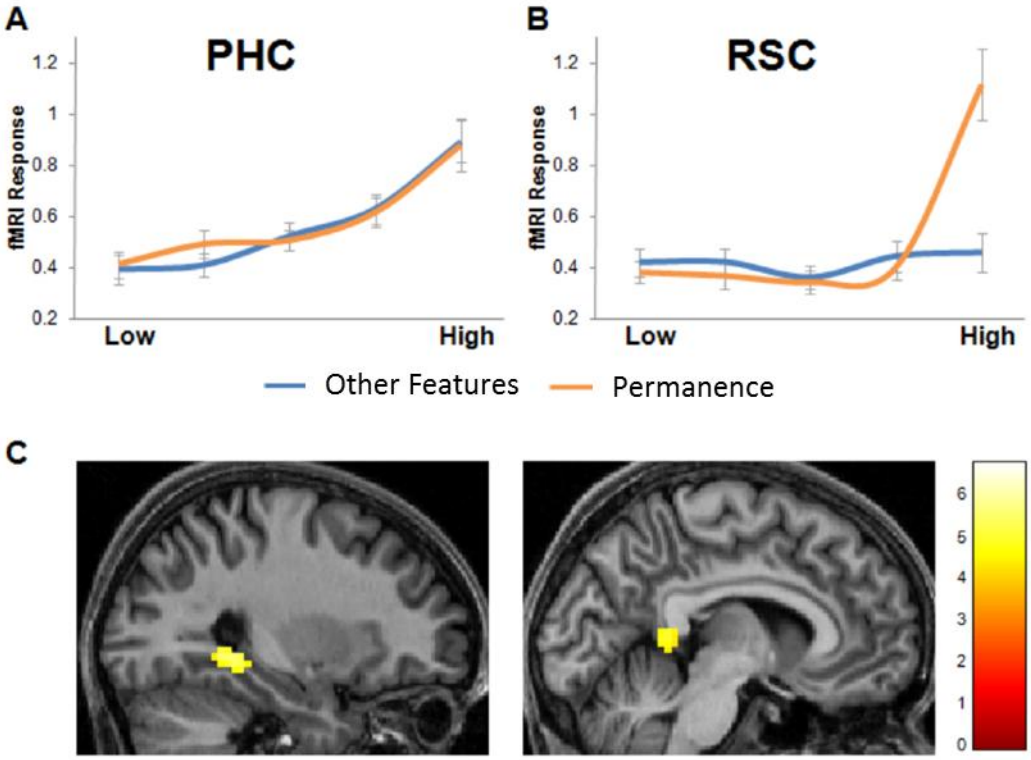

Figure 23 Response profiles of the PHC and RSC. The fMRI BOLD response to the other features (blue) and permanence (orange) factors are shown for the PHC (A) and the RSC (B). Mean scores are plotted +/- 1 SEM. Landmarks were grouped into 5 bins according to the values of their factor score estimates, and these were approximately equivalent to the five rating values, e.g. for the permanence factor 'low' means landmarks that were not at all permanent, ranging to 'high' meaning permanent landmarks. (C) Brain areas more active for landmarks rated as high compared to low in permanence. Activations are displayed on sagittal views of the structural MRI brain scan of one participant chosen at random. The colour bars indicate the Z-scores associated with each voxel.

I also examined the spatial frequency of the stimuli, to verify that this low level visual property was not driving the effects I observed (as has been suggested eleswhere, Rajimehr et al., 2011). I performed an additional analysis where I included this in the factor analysis. Spatial frequency did not load strongly on either the other features or permanence factors, confirming that it did not influence my findings.

In summary, the ROI analysis concurred with and extended the whole-brain results, showing that activity in PHC was influenced by parametric changes in a wide range of landmark properties, whereas RSC was sensitive specifically to the most permanent landmarks.

3.3.3 The effect of navigation ability

In this study I also explored whether navigation ability affected the characterisation of landmark properties, and how this might relate to fMRI responses. The good and poor navigator groups (from the fMRI study: n = 16 in each group; mean SBSOD score for the good group 5.5, SD 0.56; the poor group 3.9, SD 0.62; maximum score = 7) were matched for age (mean age good navigators 23.5 years, SD 2.78; poor 23.6 years, SD 3.39; t_{30} = -0.057; p = 0.96), sex (8 female in each group), the proportion (good 92.6%, SD 9.83; poor 94.8%, SD 7.69; t_{30} = -0.713; p = 0.48) and speed (good 416ms, SD 80.1; poor 456ms, SD 81.5; t_{30} = -1.383; p = 0.18) of catch trial dot detection during scanning, their visual memory as measured by the delayed recall of the Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944) (good 20.9, SD 6.90; poor 19.4, SD 6.78; t_{30} = 0.63; p = 0.53; maximum score = 36), and their visual information processing ability and abstract reasoning skills as measured by the Matrix Reasoning sub-test of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) (mean scaled score good 12.2, SD 1.38; poor 11.6, SD 1.82; t_{30} = 1.09; p=0.28; maximum score = 19). There were also no differences in grey or white matter volume anywhere in the brain according to the VBM analysis, including in PHC and RSC. Thus, the only evident difference between the good and poor navigators was in their declared navigation ability.

I first examined how much overall agreement there was among good and poor navigators in the first set of behavioural studies in scoring the different features of the original 683 landmarks. Examining the number of landmarks where at least 75% of participants within each group gave the same rating, there were no clear differences between good and poor navigators in the number of high consensus items for navigational utility, size, visual salience, or SD/SA. However, for ratings of permanence-related features, there was a large discrepancy between the amount of agreement within the groups (Figure 24A), with much greater consensus about the permanence and portability of landmarks among the good than the poor navigators.

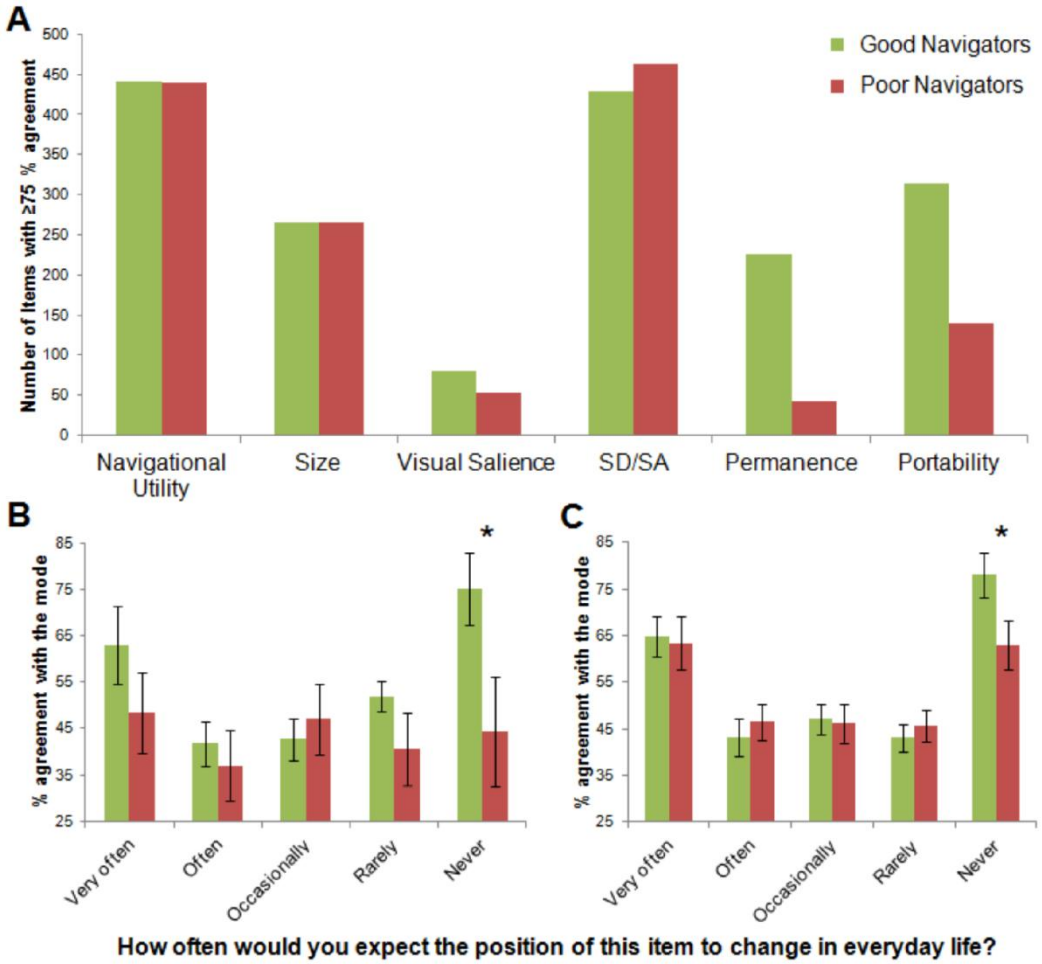

Figure 24 Landmark feature ratings segregated according to navigation ability. Good navigators are shown in green and poor navigators in red. (A) The number of landmarks where at least 75% of participants within each group gave the same rating. It is clear that the only difference between good and poor navigators was for permanence and portability. (B) Focussing on the permanence ratings, I examined how often each participant gave a rating which was different to the most common rating for each item (i.e. the mode). Good and poor navigators did not differ in rating items which were most commonly scored 1 to 4 for permanence, however, there was a significant difference between the groups for rating number 5, landmarks that were the most permanent and never moved. (C) This difference for the most permanent landmarks was replicated in the independent group of fMRI participants. * P < 0.05; graphs show the means +/- 1 SEM.

I then examined the permanence ratings in more detail; as a reminder, the permanence question that participants answered was: How often would you expect the position of this item to change in everyday life? (1) Very often (2) often (3) occasionally (4) rarely (5) never. I looked at how often each participant gave a rating which was different to the most common rating for each item (i.e. the mode). I found that good and poor navigators did not differ in rating items which were most commonly scored 1 to 4 for permanence, however, there was a significant difference between the groups for rating number 5, landmarks that were the most permanent and never moved (t_{14} = 2.183; p = 0.047; Figure

24B). To assess the robustness of this finding, I also examined the post-scan permanence ratings for the 280 scan stimuli provided by the independent group of 32 participants who took part in the fMRI component of the study. Here too, the only difference between good and poor navigators was for the most permanent landmarks (t_{30} = 2.082; p = 0.046; Figure 24C). Interestingly, there were no differences between the groups for any of the 'distance moves' ratings, including for landmarks that were rated to move by only centimetres (t_{30} = -0.412; p = 0.68), further underlining the specificity of the good-poor navigator difference only for items which truly never move. Examples of landmarks where good, but not poor, navigators had at least 75% agreement about their 'never moves' permanence rating, are shown in Figure 25.

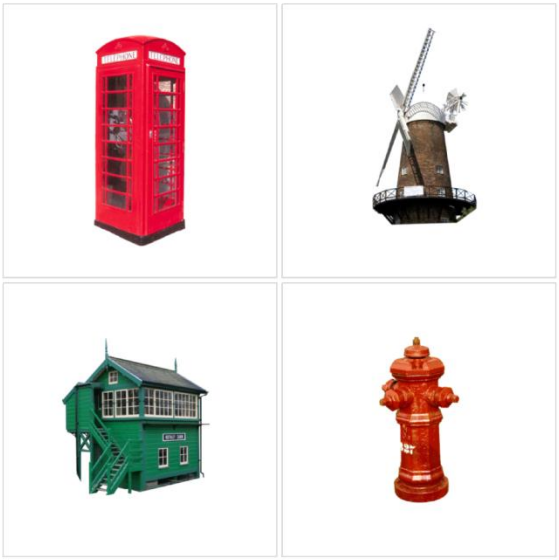

Figure 25 Examples of landmarks rated differently by good and poor navigators. Landmarks where good but not poor navigators had at least 75% agreement about their 'never moves' permanence rating.

As the behavioural difference between good and poor navigators was driven by the most permanent landmarks, in a whole brain fMRI analysis I directly contrasted good and poor navigators focussing specifically on the landmarks that never moved. This comprised a two sample t-test with FWE correction ($p < 0.05$) using an RSC anatomical mask ROI (the same one used in the ROI analyses), $p < 0.001$ whole brain uncorrected threshold for other navigation-relevant brain areas (see Sections 1.4, 1.5 and 1.10.5), and $p < 0.05$ (FWE corrected) for the rest of the brain.

There was significantly greater activity in RSC (-3, -49, 13, Z = 2.83) when good navigators viewed the most permanent, never moving landmarks than when poor navigators viewed

them (Figure 26). There was also significantly greater activity in good navigators in the anterodorsal thalamus (0, -4, 13; Z = 3.87). The graph in Figure 26 shows the mean response of active voxels in RSC for good and poor navigators for the most permanent items, with a significantly higher response in the good navigators. There were no differences in any other brain regions, including the PHC, and no brain areas were more active for poor navigators. I also compared the good and poor navigators for the other permanence ratings and found no differences between the groups for the ratings 1-4 either separately or combined.

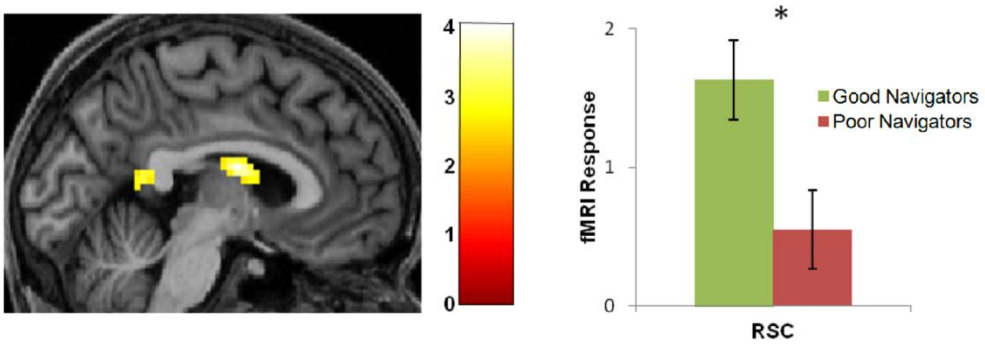

Figure 26 Brain regions more active in good than poor navigators when viewing the most permanent landmarks. Good navigators had greater activity in RSC and anterodorsal thalamus than poor navigators when viewing the most permanent items but not the less permanent ones. Activations are displayed on sagittal views of the structural MRI brain scan of one participant chosen at random. The colour bars indicate the Z-scores associated with each voxel.

I also analysed all of the behavioural, VBM, and fMRI data to compare males and females directly, and did not find any significant differences between the sexes. Thus, the between-group differences appear to be specific to navigation ability.

In summary, good and poor navigators, who were matched on a range of demographic, cognitive and structural brain measures, differed not only in their declared navigational ability, but in two other ways. Poor navigators had: (1) considerably less agreement when identifying the most permanent landmarks (but not any other features), a finding replicated across two independent samples of participants; and (2) significantly reduced activity in RSC and anterodorsal thalamus specifically in response to landmarks that were most permanent, even when performing an incidental vigilance that had no explicit spatial or navigational requirement.

3.4 Discussion

There were three key findings from this study. First, focusing on a range of landmark attributes, I ascertained that these features were underpinned by two components, which included the permanence of landmarks. Second, while I observed parametric responses in PHC to increasing values of both components, activity in RSC responded specifically to the most permanent landmarks. This is interesting because the role of the RSC is somewhat mysterious, as outlined in Chapter 1. Known to be involved in supporting scene processing (see Section 1.10.3), navigation (see Section 1.10.5) and autobiographical memory (see Section 1.10.6), there is little agreement about what its primary function might be (see Section 1.11). By revealing here its responsivity to landmark permanence, this could represent an intriguing new way of conceptualising its contribution. The third finding from my study provides further support for the relationship between the RSC and landmark permanence. I found that in two independent cohorts, poor navigators, relative to good navigators, made less reliable decisions about landmark permanence, specifically for the most stable landmarks. Moreover, this was accompanied by reduced RSC activity when poor navigators viewed the permanent landmarks. This offers a novel insight into a possible reason for poor navigation ability in some individuals. If a person cannot register effectively the most stable features in an environment, then the resultant internal representation of that environment may be less reliable and more likely to produce disorientation.

3.4.1 Processing of landmarks in RSC

Landmark properties have received surprisingly little direct attention in navigation neuroscience, despite being potentially informative about how environmental representations are formed and supported. Nevertheless, the permanence of landmarks has been noted to influence the control of hippocampal place fields in rats and the stability of resultant cognitive maps (O'Keefe and Nadel, 1978; Biegler and Morris, 1993, 1996; Knierim et al., 1995; Lew, 2011). The question of where landmark permanence is itself coded has not been addressed directly. My findings show that the human RSC responds specifically to the most stable landmarks. Given its strong connectivity with the hippocampal region (Section 1.3; van Groen and Wyss, 1990, 1992; Amaral and Witter, 1995; Vann et al., 2009; Sugar et al., 2011), information about the permanence of

landmarks that is coded in RSC may be shared with the medial temporal lobes, contributing to the formation of environmental representations. This view is compatible with the observation that temporary inactivation of the rat RSC transiently alters the spatial tuning of hippocampal place cells (Cooper and Mizumori, 2001). Moreover, several animal navigation studies have linked the RSC to processing behaviourally-significant and predictive environmental cues (Gabriel, 1993; Gabriel and Talk, 2001; Smith et al., 2002, 2011; Vann and Aggleton, 2005; Keene and Bucci, 2008c). Thus, the presence of stable landmarks/cues in any spatial experiment may engage or require the RSC.

Lesions to the RSC in rodents impair spatial navigation (Section 1.5; Vann et al., 2009). While the nature of the tasks varies, it is interesting to note that many of them involved fixed or more stable (distal) cues although, to my knowledge, the effect of RSC lesions on landmark/cue permanence per se has not been explicitly examined. In humans, too, landmark permanence has not been tested in the context of RSC damage. The consistent finding from such patients is, as with the animal data, one of disorientation (Section 1.6; Maguire, 2001a; Vann et al., 2009). Based on my findings I suggest that this disorientation could result from a failure to identify reliable stable landmarks from which to derive navigational information. If patients with RSC lesions are unable to identify the most permanent, stable cues in an environment, then their resulting representations will be disordered, adversely affecting navigation in both familiar and new environments. This may in part also explain the spatial disorientation experienced by those with Alzheimer's dementia, given that RSC hypometabolism has been observed in the earliest stages of the disease (Section 1.7; Vann et al., 2009; Pengas et al., 2010).

3.4.2 RSC and navigation ability

The poor navigators in this experiment may also, to some extent, have disordered representations of space as a result of ineffective processing of landmark permanence. They were matched to the good navigators on every measure – demographic, cognitive, and in terms of brain structure. There was also no significant difference between the two groups when making any of the ratings, including ratings of distance moves (even when items were rated to move by only centimetres). The two groups differed solely in the decisions they made about the most permanent landmarks, where the ratings of the poor navigators in particular showed much greater variance and consequently much less

consensus compared to the good navigators. Examining the examples provided in Figure 25, this seems quite surprising. For instance, how can a building be regarded as anything but permanent? Yet this result was replicated in two independent samples of participants, underlining the robustness of the finding. Alongside this misidentification of the most permanent landmarks, the poor navigators also had a reduction in RSC fMRI BOLD response specifically to the most permanent landmarks. This difference was only apparent for RSC and not for PHC. I believe this is further compelling evidence that the RSC codes for the most permanent landmarks, and this could be its fundamental contribution to spatial navigation. It is notable that good and poor navigators did not differ when rating the navigational utility of landmarks. It seems, therefore, that while participants, even poor navigators, had high agreement about what was likely to be navigationally useful, in practice, effective navigation may be more reliant on landmark features such as permanence.

3.4.3 RSC permanence processing in relation to other theories of its function

The retrosplenial region has been reported to be more engaged by familiar compared with unfamiliar landmarks, or with increasing familiarity of landmarks and spatial layout during learning (e.g. Wolbers and Buchel, 2005; Epstein et al., 2007b; Baumann and Mattingley, 2010), which seems difficult to reconcile with my permanence findings. However, those studies activated parts of RSComp located more posteriorly and superiorly in posterior cingulate cortex than RSC (BA 29/30). It has also been suggested that the role of the RSC is one of translation between egocentric and allocentric frameworks (Section 1.11 and reviewed in Vann et al., 2009), although direct evidence for this is lacking. That RSC might in fact be primarily concerned with coding the most permanent landmarks is not necessarily at odds with a translation account. The identification of permanent landmarks could be viewed as an intermediate between egocentric experience of the environment and then the use of landmark permanence information in allocentric spatial representations. In other frameworks, emphasis has actually shifted away from landmarks as the basis for environmental representations, with boundaries and other terrain features instead being regarded as key (Cheng, 1986; Gallistel, 1990; Wang and Spelke, 2002; Barry et al., 2006). In the real world, however, boundaries are often comprised of landmarks, e.g. large buildings, whereas this is not typically the case in rat enclosures. Indeed, the pre-eminence of boundaries in cognitive maps has been

questioned, with Lew (Lew, 2011) arguing that the apparent importance of boundaries may in fact relate to underlying properties such as their general stability during navigation, which resonates with my findings.

The mechanism for registering permanent landmarks may involve head direction cells, which are present in the RSC (Section 1.4; Chen et al., 1994b; Cho and Sharp, 2001), anchoring themselves to the most permanent landmarks. It is notable that, along with the RSC, the anterodorsal thalamus was also more active in the good compared to the poor navigators for the most permanent landmarks. The anterodorsal thalamus is heavily connected with the RSC (Section 1.3; Vann et al., 2009) and head direction cells are also present there (Taube, 1995). Damage to this region is known to cause spatial learning and memory impairments (Aggleton et al., 2010), and along with the RSC and hippocampus, the thalamus is thought to form a key circuit for spatial memory and recollection (Vann et al., 2009; Aggleton et al., 2010). Interestingly, I did not observe engagement of subicular regions or the hippocampus. My task did not involve active navigation; instead the participants during scanning merely performed a vigilance task while viewing single, isolated landmarks. Overall, this suggests that RSC and anterodorsal thalamus may be automatically and rapidly deployed at the earliest stages of processing items that have relevance for navigation. The output of this process may then be made available upstream to other medial temporal regions in the navigation system.

3.4.4 Other features of landmarks

The other clear component to emerge in my factor analysis comprised features such as landmark size, whether they were space-defining, their navigational utility, and their visual salience. Unlike the permanence factor, this component seems to reflect general visual properties of the items. Many fMRI studies report co-activation of PHC and RSC, and it has been a challenge to differentiate their individual contributions. Here, I observed the highly specific engagement of RSC for only the most permanent landmarks. By contrast, activity in the PHC parametrically increased for both the other features and permanence factors. This accords with the previous findings where PHC responded to space-defining landmarks which comprised large and permanent items (Mullally and Maguire, 2011), and objects at navigationally-useful decision points (Janzen and van Turennout, 2004; Janzen et al., 2008; Schinazi and Epstein, 2010; Wegman and Janzen,

2011). Interestingly, PHC activity did not differ between good and poor navigators, even for the most permanent landmarks, suggesting that PHC, unlike RSC, is not specifically concerned with the most stable landmarks. Instead, PHC appears to be involved in processing a broader range of generic object characteristics (e.g. object size and space-defining quality; Mullally and Maguire, 2011) indicative perhaps of a more general role in the construction and processing of spatial representations.

3.4.5 Summary and future directions

In conclusion, my results provide further evidence that despite being labelled as 'scene-selective' cortex (Epstein et al., 2007a; Henderson et al., 2007; Ward et al., 2010; Dilks et al., 2011; Golomb et al., 2011; Nasr et al., 2011), PHC and RSC do not in fact require scenes in order to be engaged, instead activating strongly in response to features of single isolated landmarks (see also Mullally and Maguire, 2011). By revealing the specific engagement of RSC in response to the most permanent landmarks, this may help to explain the ubiquity of RSC activations in fMRI studies not only involving scenes (Section 1.10.3) and navigation (Section 1.10.5), but also autobiographical memory (Section 1.10.6; Maguire, 2001b; Svoboda et al., 2006) and thinking about the future (Addis et al., 2007; Hassabis et al., 2007). Scenes, environments to be navigated, and real and imagined experiences all have a background context. Activation of the RSC in such instances may simply (but crucially) reflect the processing of permanent features in those scenes or events, thus helping to (re)construct a stable backdrop.

Overall, my results clearly motivate further studies in humans and non-humans that focus on landmarks. Moreover, they point to a need to establish precisely how the RSC comes to code for the most permanent landmarks, and the full extent of its influence on the ability to navigate successfully. The experimental chapters which follow describe my attempts to generate a greater understanding of landmark permanence representations in RSC, their relevance for spatial processing, and for cognition more generally.

Chapter 4: Experiment 2

Retrosplenial cortex response to multiple landmarks

4.1 Introduction

In the previous chapter I investigated which brain regions respond to various features of everyday outdoor items. There were three key findings. First, two main components underpinned the numerous landmark attributes I studied, one of which related to the permanence of landmarks. Second, the RSC was specifically responsive to only the most permanent, never moving landmarks. Finally, poor navigators were less consistent at identifying the most permanent landmarks and had reduced responses in their RSC (and anterodorsal thalamus) while viewing them. Thus, even when complex memories, navigation or scenes were not involved, a robust RSC response was evident at the level of single, permanent landmarks.

In the previous experiment it was important to consider landmarks in complete isolation and devoid of any background context in order to achieve strict experimental control over the stimuli. However, this does not accurately reflect how we usually encounter items in normal everyday life. In order to promote a proper understanding of the role of the RSC, it is necessary to test its reaction to multiple items, as this will inform whether its responsivity is item-specific or more general. This is especially relevant given the large amount of evidence that RSC is heavily involved in processing scenes (see Section 1.10.3).

Therefore, the question I addressed in my second experiment was whether RSC is simply engaged by the presence of permanence per se, irrespective of the number of permanent items being viewed, or whether is it mechanistically more nuanced, tracking the specific number of permanent items. Adjudicating between these two options is important, as going forward it could guide how I conceptualise the function of the RSC and probe the mechanisms that may operate therein. If RSC codes for just the presence of permanence, then its input into spatial and scene representations would be limited. However, if RSC represents each permanent item in a given view, then it could play a key role in detecting and mapping individual landmarks as we encounter them in our surroundings. This

operation could be crucial for successful navigation, as the very building blocks of any representation of an environment are the most stable items within it.

When first considering how to investigate RSC responses related to the permanence of multiple items, I initially thought it would be most appropriate to use naturalistic scene stimuli which varied in terms how many permanent items they contained. However, this would have made it difficult to closely regulate the precise features of all elements of a scene. An additional problem with using naturalistic scene stimuli would have been that all scenes have an inherent stable spatial structure. It might therefore have been difficult to separate out responses to the global permanence inherent within a scene from the permanence of the items within the scene.

Instead of using images of full scenes, I therefore decided to make use of the stimulus set I had already created for the previous experiment. These items were already characterised in detail for a number of different features. However, instead of presenting the items one at a time, in this experiment I created stimuli which each contained four individual items. By presenting multiple items simultaneously, devoid of any background context or overt scene-like structure, I would be able to maintain optimal experimental control whilst being able to assess the RSC response to multiple items.

The stimuli differed in terms of how many of their four items were permanent, i.e. with a fixed location in the environment - they contained either no, 1, 2, 3, or 4 permanent items (see Figure 27 for examples). I used multi-voxel pattern analysis (MVPA) to assess whether information about the number of permanent items in view could be decoded from activity in RSC. Following on from the previous experiment's findings, I also examined whether such effects differed between good and poor navigators. The stimulus quads were carefully designed such that variations in landmark size and visual salience could be assessed by the same method, allowing me to determine whether any patterns of response observed in RSC were specific to item permanence.

Presenting quads containing a mixture of permanent and non-permanent also allowed me to investigate whether there are any differences in how we attend to landmarks based upon their permanence. Could it be for example, that we pay greater attention to items which are reliable, permanent spatial cues? Another consideration would be whether a

person's navigation ability is reflected in the attention they pay to different types of everyday items. For this reason, I also measured the eye movements of participants while they viewed the stimulus quads.

4.1.1 Pilot experiments

Before proceeding with the fMRI scanning experiment, I first conducted two pilot experiments to optimise aspects of the experimental design. As outlined above, a key feature of the experiment was that the stimuli were not 'scenes' which might be considered to have an inherent stable spatial structure. I therefore needed to ensure that participants did not link together the four items in each stimulus and picture them as a cohesive scene. For this reason I enclosed each stimulus' four items within separate boxes and positioned them in distinct quarters of the screen. I also explicitly instructed participants to simply view each item individually and expressly instructed them to not link the items together into any sort of scene.

In the first pilot experiment, I sought to verify that people were indeed able to view the four items as separate entities and did not see them as a unified scene. A second goal was to determine an appropriate amount of time to present the stimuli during the fMRI experiment so that participants had enough time to view all four items, but not so much that they became distracted toward the end of trials. I presented all the stimuli I intended to use in the full experiment to a group of ten participants (5 females, mean age 25.0 years, SD 4.8) and instructed them to simply view each of the items and press a button to indicate when they had viewed all four. In the vast majority of trials, subjects had viewed all four items within six seconds, so this is the trial length I chose for the scanning experiment. The participants also confirmed that they did not link the items together into a scene.

In a second pilot experiment, I rehearsed the precise task to be used in the full experiment with five participants (2 females, mean age 24.0 years, SD 3.8); the only difference being that it did not take place inside an MRI scanner (see Section 4.2.2 for details). This not only confirmed that the task design was suitable, but also allowed me to combine the task with use of an eye-tracker. By doing this, I was also able to confirm that there were no overt

biases in where participants looked while all the items were on the screen (e.g. people did not spend more time looking at one particular location on the screen).

4.2 Methods

4.2.1 Participants

Thirty-two, right-handed, healthy participants (16 females, mean age 23.5 years, SD 2.5) took part in the experiment. All had normal or corrected to normal vision, were highly proficient in English and gave written informed consent in accordance with the local research ethics committee. None of the participants had taken part in any of my previous studies of item permanence.

4.2.2 Stimuli and procedure

Each stimulus comprised four different everyday outdoor items, with each item enclosed by a grey outline on a white background, and laid out in a grid (Figure 27). The stimuli differed in terms of how many of their four items were permanent - they contained either no, 1, 2, 3, or 4 permanent items (giving 5 category types). Permanent items were defined as those consistently rated as 'never moving' by an independent set of participants from the behavioural experiments described in the previous chapter (see Section 3.2.3). There were 20 stimuli for each of the 5 category types, giving 100 stimuli in total. I ensured that across the trials of each condition, the non-permanent elements were sampled from the full range of permanence ratings (excluding those that 'never moved'). The stimuli not only varied according to the number of permanent items they contained; their items also varied in terms of real-world size and visual salience. The size and visual salience of items was also determined by an independent set of participants from the previous behavioural experiments (Section 3.2.3). In designing the stimuli I ensured a full range of values of these two other landmark features, from the very smallest to largest, and from least to most salient items. This allowed me to also group the 100 stimuli into 5 categories for size and 5 for visual salience. In addition, the stimuli were designed to ensure that a range of size and visual salience values were represented within each permanence category. Overall, therefore, the experimental design allowed me to test the specific effects of item permanence independent of these two other item features. The location of the

permanent items within the grid was pseudorandomised to ensure they appeared equally in the 4 possible screen locations. In addition to the 100 stimuli depicting 4 items, there were a further 20 baseline stimuli. These consisted of 4 grey outlines which each contained a black centrally located fixation cross rather than an outdoor item.

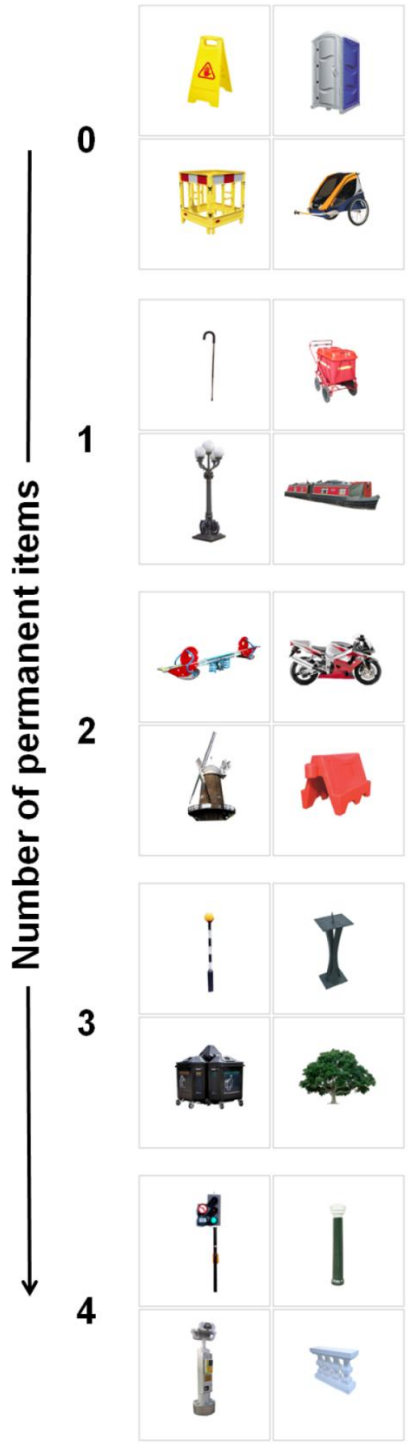

Figure 27 Example stimuli. Categories varied according to the number of permanent, 'never moving', items they contained. One example stimulus from each of the five permanence categories is shown here, ranging from no permanent items in the top stimulus, to all four items being permanent in the bottom stimulus.

Participants were naïve to my interest in item features and believed they were being tested for vigilance and attention. Before entering the scanner, participants were instructed to look closely at all 4 items (or fixation crosses) in each image and to respond with a button press whenever a small blue dot appeared on one of the items (or when a fixation cross turned blue). It was stressed that they should look at all 4 items equally so as to maximise their chances of detecting the blue dots. They were also instructed to focus on the items individually, and not think about any other objects, contexts or personal memories, nor should they link the 4 items together into a scene. Participants then practised the task with stimuli not included in the scanning experiment.

A typical trial in the scanner consisted of a stimulus being displayed for 6 seconds separated by a randomly jittered interval of between 2 and 5 seconds during which participants looked at a centrally located black fixation cross on a white background. There were 19 catch trials in addition to the 120 normal trials. During catch trials a small blue dot appeared somewhere on one of the 4 items for 3 seconds. Participants were instructed to respond with a button press if they saw a blue dot (or if a fixation cross turned blue in the baseline trials). The order of trials was pseudorandomised ensuring that all stimulus types were distributed across the scanning sessions, of which there were three. No stimuli were repeated.

Immediately after scanning, participants rated how difficult they found the task, and how difficult it was to keep the 4 items separate. Participants also completed several neuropsychological tests: the Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944), and the Matrix Reasoning sub-test of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Similar to the previous experiment, at the very end of the study participants filled out the Santa Barbara Sense of Direction Scale (SBSOD; see Section 3.2.3).

4.2.3 Eye-tracking

To assess whether participants attended to all 4 items in the stimuli equally, I recorded their eye movements during fMRI scanning with an MRI-compatible ASL-500 series eye-tracking system (http://www.asleyetracking.com) sampling at 50Hz.

4.2.4 Scanning details

MRI data were acquired on a 3T Magnetom Allegra head-only MRI scanner (Siemens Healthcare, Erlangen, Germany) operated with the standard transmit-receive head coil. Functional MRI data were acquired in three sessions with a blood oxygenation level-dependent (BOLD) sensitive T2*-weighted single-shot echo-planar imaging sequence which was optimized to minimize signal dropout in the medial temporal lobe (Weiskopf et al., 2006). The sequence used a descending slice acquisition order with a slice thickness of 2mm, an interslice gap of 1mm, and an in-plane resolution of 3 x 3mm. Forty eight slices were collected covering the entire brain, resulting in a repetition time of 2.88s. The echo time was 30ms and the flip angle 90°. All data were acquired at a -45° angle to the anterior-posterior axis. In addition, field maps were collected for subsequent distortion correction (Weiskopf et al., 2006). These were acquired with a double-echo gradient echo field map sequence (TE=10 and 12.46ms, TR = 1020ms, matrix size 64 x 64, with 64 slices, voxel size = $3mm^3$) covering the whole head. After these functional scans, a 3D MDEFT T1-weighted structural scan was acquired for each participant with 1mm isotropic resolution (Deichmann et al., 2004).

FMRI data were pre-processed using SPM8 (www.fil.ion.ucl.ac.uk/spm). The first 6 'dummy' volumes from each of the three sessions were discarded to allow for T1 equilibration effects. Images were realigned and unwarped (using the field maps) and normalised to a standard EPI template in MNI space with a resampled voxel size of 3×3×3mm. Functional data were left unsmoothed for the decoding analyses to facilitate the detection of information present across patterns of voxels. Each trial was modelled as a separate regressor for the 6sec stimulus duration and convolved with the canonical haemodynamic response function. Catch trials were combined into a single regressor and, along with participant-specific movement regressors, were included as covariates of no interest. Participant-specific parameter estimates pertaining to each regressor (β) were calculated for each voxel.

4.2.5 Regions of interest

Motivated by the findings of my previous experiment, my main ROI was the RSC. In the previous study of item features, I found that the PHC responded to permanence as well as

to a range of other features (see Section 3.3.2). Interestingly, however, and unlike RSC, the PHC was not sensitive to differences between good and poor navigators. I therefore included PHC as a second ROI in my analysis. As in the previous experiment, ROIs were defined using anatomical masks for RSC (BA 29/30) and PHC that had been delineated by an experienced researcher not involved in the project on an averaged structural MRI brain scan from a different set of n=30 participants, and guided by Duvernoy (1999), Insausti et al. (1998) and Vann et al. (2009). In a control analysis, I also examined a region not previously implicated in processing specific item features, the motor cortex.

4.2.6 Data analysis

The intention at the outset of this experiment was to use MVPA decoding as the main analysis method. However, in the first instance, I sought to ascertain if my ROIs were more engaged by permanent than non-permanent items, now that multiple rather than single items were being viewed. If so, this would accord with results from my previous experiment. I used the MarsBaR toolbox (http://marsbar.sourceforge.net/) to extract the principal eigenvariate of the fMRI BOLD responses within the anatomically defined ROI masks for each subject. In line with my previous findings, responses within the RSC and PHC were significantly greater for stimuli containing 4 permanent items than for those containing none (collapsed across hemispheres, BOLD response in arbitrary units, mean difference in RSC 0.45, SD 1.05; $t_{31} = 2.42$, $p < 0.02$; mean difference in PHC 0.55, SD 0.77; $t_{31} = 4.02$, $p < 0.0001$). However, using this mass-univariate approach, there were no significant correlations between responses in either of the regions and the number of permanent items in view (RSC: mean r = 0.13, SD 0.47; not significantly different from 0: $t_{31} = 1.577$, $p = 0.1$; PHC mean r = 0.17, SD 0.51; not significantly different from 0: $t_{31} = 1.937$, $p = 0.06$).

I then progressed to my main analyses using MVPA which has been found to be more sensitive in some circumstances to stimulus representations (Section 2.7; Norman et al., 2006; Haynes and Rees, 2006; Chadwick et al., 2012). I used this to assess whether patterns of activity in RSC and PHC contained sufficient information to decode the number of permanent items present for any given trial (for all 32 participants), with five possible options: 0, 1, 2, 3 or 4 permanent (i.e. never moving) items in view. As in previous studies (Chadwick et al., 2011, 2012; Bonnici et al., 2012), I first performed feature selection, to

reduce the set of features (in this case, voxels) in the dataset to those most likely to carry relevant information (see Section 2.7 for details). Having identified participant-specific voxels within the ROIs which provided the greatest amount of permanence information, the final classification used only these most informative voxels. For the overall classification procedure, data from 2 sessions were used for feature selection, with the remaining independent third session's data being used only for the final classification in order to avoid so-called "double dipping" (Kriegeskorte et al., 2009). The same process was repeated changing which sessions were used for feature selection and the final classification each time; these results were then averaged to provide an overall three-fold cross-validation.

During both the feature selection and final classification I used a standard cross-validation technique (Hsu and Lin, 2002; Duda et al., 2001). Data from a single trial was assigned as the *test* trial, with all remaining trials allocated as *training* trials. A linear SVM using the LIBSVM implementation (Chang and Lin, 2011) with fixed regularization hyperparameter C=1, was first trained using the *training* data and subsequently tested upon the *test* trial. This process was repeated in turn so that each trial was used as the designated *test* trial once. Classification accuracy was taken as the proportion of correct 'guesses' made by the SVM across all the trials.

Overall, this procedure produced an accuracy value for each region of interest based on the percentage of trials that were correctly classified. The set of accuracy values across the group of participants was then tested against chance level of 20% (as there were five possible options) using a one-tailed t-test. Other comparisons (e.g. between item features) were made using ANOVAs, the results of which were further interrogated using two-tailed t-tests. All statistical tests were performed using SPSS version 20. In order to test the specificity of any permanence representation in these regions, I conducted new analyses using the exact same procedure (including new rounds of feature selection) to analyse the size and visual salience of items depicted in stimuli.

4.2.7 Good versus poor navigators

Given my previous findings, I also divided participants into 16 good and 16 poor navigators by taking a median split of participants' scores on the SBOSD questionnaire administered

in the post-scan debriefing session. When comparing good and poor navigators, feature selection was not appropriate because this results in different voxels for each participant being used for the final classification, which could be biased by participants' navigation ability. Therefore, in order to compare good and poor navigators in an unbiased fashion, it was necessary to define a set of voxels to be used for classification in all participants. I identified this set of voxels based upon data from a completely independent cohort of participants in my previous fMRI study; specifically, the voxels which showed increased activity for items with greater permanence (see Figure 22B) which fell within the anatomical ROIs for RSC and PHC.

Given that removing feature selection reduces overall classifier accuracy (Guyon and Elisseeff, 2003), I used a 2-way classification in this decoding analysis, asking whether a majority (3 or 4) or minority (0 or 1) of the items in view were permanent. The classifier accuracies across sessions were averaged to give a classification performance value for each participant's ROIs. When interrogating the data, one-tailed t-tests were used to compare good and poor navigators, given the previous finding of difference between these groups for item permanence (Section 3.3.3). Two-way classifications were also performed for the size and visual salience of items, and comparisons made between the good and poor navigators. These analyses (including in this instance two-tailed t-tests) were carried out on voxels contained within the RSC and PHC anatomical masks which showed increased activity related to size and visual salience of items (see Figure 22A). In order to test the specificity of any differences identified between the good and poor navigator groups, I also performed identical comparisons when the participants were divided into males and females.

4.3 Results

4.3.1 Behavioural data

During scanning, participants, who were naïve to my interest in item features, engaged in a vigilance task. They performed with a high level of accuracy (mean 88.4%; SD 15.7), showing they focussed on this dot-detection task and maintained attention during the experiment. Performance was similar across each permanence category. Similarly, there was no difference between good and poor navigators on this measure (mean good

88.19%, SD 13.6; poor 88.54%, SD 18; t_{30} = -0.62, p=0.95). Vigilance catch trials were removed from the fMRI analysis.

Ratings provided in the post-scan debriefing indicated that participants found the task overall to be easy (1-very easy to 5-very hard: mean 1.8, SD 0.7). They also found it easy to view the four items in each stimulus separately without linking them together into a scene (1-very easy to 5-very hard: mean 1.8, SD 0.9).

For some analyses, the 32 participants were split into good and poor navigator groups (n = 16 in each) by taking a median split of SBSOD (Hegarty et al., 2002) scores that were provided in the post-scan debriefing (good group mean 5.6, SD 0.48; poor group mean 3.9, SD 0.90; maximum score = 7). The two groups had similar numbers of males (9 good and 7 poor navigators) and females (7 good and 9 poor navigators) and were also similar in age (mean age good navigators 23.6 years, SD 2.03; poor 23.4 years, SD 2.96; t_{30} = 0.278; p = 0.78), how easy/difficult they found the task overall (mean difficulty rating out of 5: good 1.8, SD 0.91; poor 1.8, SD 0.54; t_{30} = 0.000; p = 1.0), how easy/difficult they found it not to link the items together into a scene (mean difficulty rating out of 5: good 2.0, SD 1.03; poor 1.7, SD 0.70; t_{30} = 1.000; p = 0.33), their visual memory as measured by the delayed recall of the Rey-Osterrieth Complex Figure (good 23.6, SD 5.84; poor 23.4, SD 4.50; t_{30} = 0.119; p = 0.91; maximum score = 36), and their visual information processing ability and abstract reasoning skills as measured by the Matrix Reasoning sub-test of the Wechsler Abbreviated Scale of Intelligence (mean scaled score good 13.0, SD 2.10; poor 12.5, SD 2.22; t_{30}= 0.655; p = 0.52; maximum score = 19). I also carried out a voxel-based morphometry analysis (VBM; Ashburner and Friston, 2000, 2005) and found no structural brain differences between the groups anywhere in the brain, including PHC and RSC.

4.3.2 Eye-tracking data

Robust eye-tracking data were collected from 30 of the 32 participants. I defined 4 areas of interest within the visual field which corresponded to the locations of the 4 grey boxes within which items appeared on each stimulus. I calculated the proportion of each 6 second trial which participants spent looking at each of these 4 areas. I found no biases in terms of where the participants looked (mean time per trial spent looking at each location: top left 1.32s, SD 0.43; top right 1.26s, SD 0.41; bottom left 1.27s, SD 0.43;

bottom right 1.31s, SD 0.39, other screen locations 0.89s, SD 0.42; $F_{3,27} = 0.290$, $p = 0.83$). There were also no significant differences between good and poor navigators in the time spent looking at items in the 4 locations ($F_{3, 26} = 0.215$, $p = 0.89$). I also considered whether there were any systematic differences in the type of item participants first looked at after stimuli appeared on screen to see if, for example, permanent items were more commonly viewed first. There were no differences in the proportion of permanent items looked at first, for all subjects (permanent 49.7%, not permanent 50.3%; tested against 50% chance: $t_{29} = -0.386$; $p = 0.70$) and when comparing good and poor navigators ($t_{28} = -0.891$; $p = 0.38$).

4.3.3 MVPA

I found no significant differences between classifier accuracies in the two hemispheres ($F_{2,30} = 0.990$, $p = 0.38$) and so I report results collapsed across hemispheres. I first examined whether patterns of activity across voxels in RSC could be used to decode the number of permanent items (0-4) in view for a given trial. I found that decoding was possible, significantly above chance (chance = 20%; mean classifier accuracy 41.4%, SD 2.41; $t_{31} = 50.3$, $p < 0.0001$; Figure 28 and Figure 29). By contrast, it was not possible to decode the size of the items in view from patterns of activity across voxels in RSC (mean classifier accuracy 19.0%, SD 2.45; $t_{31} = -2.4$, $p = 0.02$ - note that this is just below chance). Classification of the visual salience of items was significantly above chance (mean classifier accuracy 21.7%, SD 3.42; $t_{31} = 2.89$, $p = 0.007$; Figure 28). Notably, however, and as is apparent from Figure 28, classification accuracy within RSC was significantly greatest for permanence than for the other landmark features ($F_{2, 30} = 608$, $p < 0.0001$; permanence vs size $t_{31} = 34.5$, $p < 0.0001$; permanence vs visual salience $t_{31} = 26.0$, $p < 0.0001$).

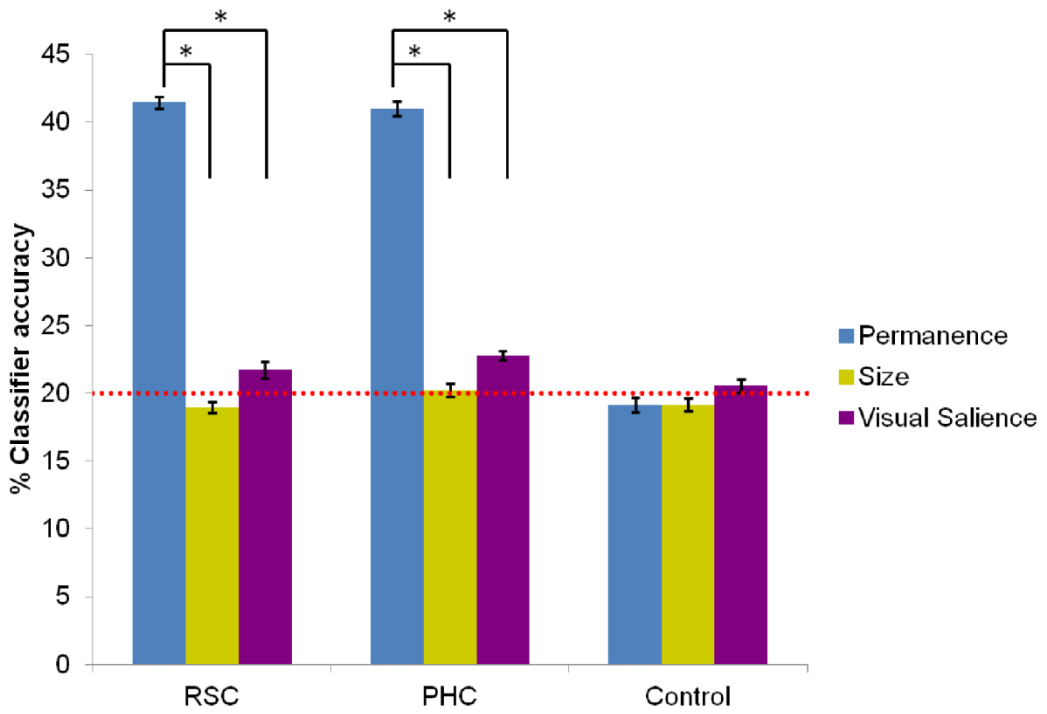

Figure 28 MVPA results. Mean classifier accuracy values for all 32 participants +/- 1 SEM, collapsed across hemispheres. Results for decoding of permanence (blue), size (yellow) and visual salience (purple) are shown for RSC, PHC and a control region (motor cortex). For RSC and PHC, five-way classification of the number of permanent items within each stimulus was not only significantly above chance (which was 20% - red dashed line) but also significantly greater than that for size and visual salience. * p <0.05.

I next considered my second ROI, the PHC, which in the previous study of landmark features showed increasing engagement the more permanent landmarks were (Section 3.3.2). Decoding of permanence category was possible from activity across voxels in the PHC (mean classifier accuracy 41.0%, SD 3.07; t_{31} = 38.7, p < 0.0001; Figure 28 and Figure 29). As with RSC, it was not possible to decode size (mean classifier accuracy 20.2%, SD 2.59; t_{31} = 0.5, p = 0.6), while classification of the visual salience of items was significantly above chance (mean classifier accuracy 22.8%, SD 1.98; t_{31} = 8, p = 0.001; Figure 28). As before (see Figure 28), classification accuracy within PHC was significantly greatest for permanence than for the other landmark features ($F_{2, 30}$ = 500, p < 0.0001; permanence vs size t_{31} = 30.3, p < 0.0001; permanence vs visual salience t_{31} = 27.8, p < 0.0001). Direct comparison of RSC and PHC showed no significant region by feature type interaction across all subjects ($F_{2, 30}$ = 1.89, p = 0.17) [or in good ($F_{2, 14}$ = 0.66, p = 0.53) or poor ($F_{2, 14}$ = 0.74, p = 0.49) navigators separately]. To summarise, I found that RSC and PHC tracked the number of permanent items in view, but not item size or visual salience.

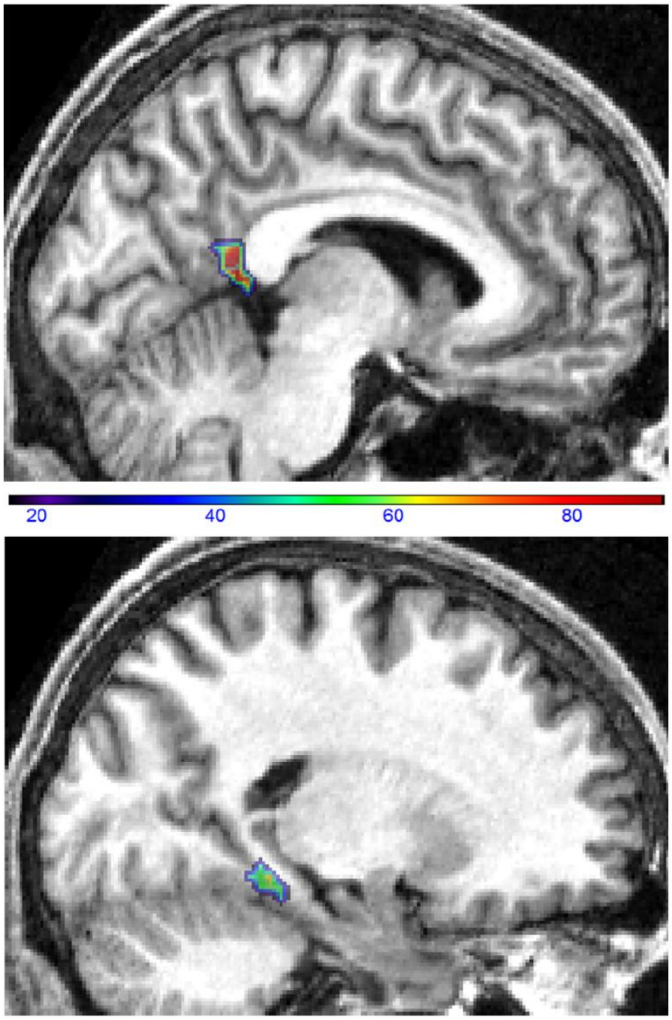

Figure 29 Voxels carrying the greatest amount of permanence information. In these heatmaps, shown on the structural MRI scan of one participant chosen at random, the colours represent the percentage of all 32 subjects in which each voxel was identified by feature selection to carry large amounts of permanence information; RSC top panel, PHC lower panel.

I also examined classifier accuracy values in control (i.e. not thought to be item feature-related) cortical regions in the left and right motor cortex. Classification accuracy was not above chance for permanence (collapsed across left and right hemisphere, mean classifier accuracy = 19.2%, SD = 3.2; t_{31} = -1.48, p = 0.15), size (mean classifier accuracy = 19.1%, SD = 2.7; t_{31} = -1.86, p = 0.07) or visual salience (mean classifier accuracy = 20.5%, SD = 2.8; t_{31} = 1.12, p = 0.27). This shows that my classification analysis was not biased towards invariably producing above-chance accuracies for permanence.

4.3.4 Good versus poor navigators

When comparing good and poor navigators, as in the analyses above, I found no significant differences between classifier accuracies in the two hemispheres ($F_{2,30}$ = 0.384, p = 0.68) and so I report results collapsed across hemispheres. I directly compared classifier accuracies between good and poor navigators to look for any differences in the amount of permanence information encoded in their neural responses in RSC. Significantly better classification of permanence was possible in the RSC of good (good mean 56.1% SD 3.3) compared to poor navigators (poor mean 53.1% SD 4.9; t_{30} = 2.056, p < 0.024; Figure 30). By contrast, there were no differences in classifier accuracies between good (good mean 53.7% SD 4.0) and poor navigators for PHC (poor mean 52.5% SD 3.1; t_{30} = 0.956, p = 0.17). This indicates that in RSC but not PHC there was significantly more permanence information in the patterns of neural responses of good navigators compared to poor navigators. Other analyses also showed that within good navigators there was significantly better decoding of permanence in RSC compared with PHC (t_{15} = 1.82, p = 0.04), while for poor navigators there was no such regional difference (t_{15} = 0.045, p = 0.33; Figure 30). I performed similar comparisons between good and poor navigators for size and visual salience. Mean classifier values: for size - RSC: good mean 49.3% SD 4.9; poor mean 49.8% SD 6.3; PHC: good mean 47.8% SD 3.4; poor mean 47.0% SD 2.6, and for visual salience - RSC: good mean 49.7% SD 4.5; poor mean 47.9% SD 4.5; PHC: good mean 48.7% SD 3.1; poor mean 47.7% SD 3.9. There were no differences between the two groups for either feature in RSC or PHC (all t</=1.14, p>0.26) or within each group (all t</=1.92; p>0.08). In a set of control analyses, I also compared males and females for permanence, size and visual salience, in both RSC and PHC, but found no significant differences based upon sex.

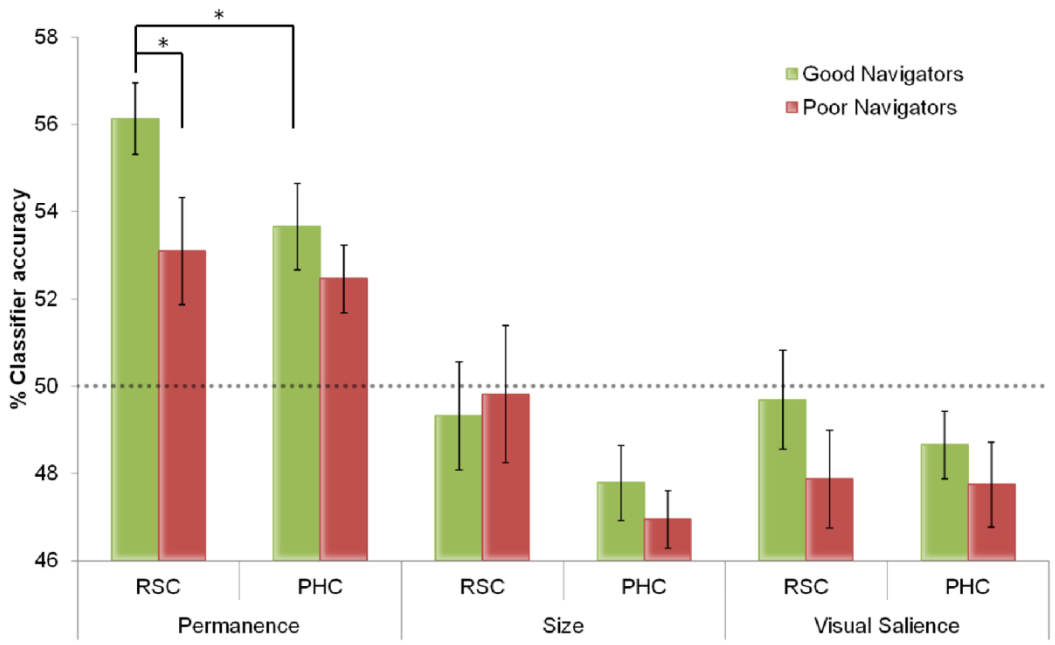

Figure 30 Results for good and poor navigators. Mean MVPA results +/- 1 SEM in good (green) and poor (red) navigators for each of the 3 item features in RSC and PHC. Permanence was the only feature that could be decoded significantly above chance (which was 50% - grey dashed line). Additionally, classification within the RSC of good navigators was significantly greater than that of poor navigators. RSC also contained significantly more permanence information than PHC within good navigators. * p <0.05.

To summarise, there were no demographic, cognitive or structural brain differences between the good and poor navigators. Neither were there any differences in decodable information in RSC and PHC about the size or visual salience of items in view. Furthermore, there was no difference in the ability to predict whether a majority or minority of viewed items were permanent based upon patterns of activity across voxels in PHC. The only difference between the two groups concerned the accuracy with which it was possible to predict whether stimuli containing a majority or minority of permanent items were in view, with good navigators having significantly more information about the number of permanent items in view in their RSC.

4.4 Discussion

In my previous fMRI study, I found that the RSC responded in a highly selective manner to only the most permanent items when stimuli were presented singly (see Figure 23A). Here I found that in a situation that was more akin to real life, with multiple items in view, the RSC coded for the specific number of permanent items contained in a visual array. Moreover, this effect was selective, and was not apparent for other item features such as

item size and visual salience. This detailed tracking of the amount of permanent items in view was echoed in the PHC, although the two brain structures diverged when participants were divided into good and poor navigators. There was no difference in the responsivity of the PHC between the two groups, while significantly better decoding of the number of permanent items in view was possible from patterns of activity in the RSC of good compared to poor navigators. Within good navigators, the RSC also facilitated significantly better prediction of landmark permanence than the PHC. Overall, these findings suggest that the RSC in particular could be concerned with precisely coding permanent stable items in the environment, and opens up the possibility that this might be a prerequisite for effective navigation.

4.4.1 RSC representation of permanent items

Following my previous findings (Chapter 3), the exact parameters within which the RSC operates when responding to item permanence were unclear. Specifically, I wondered whether the RSC response merely reflects the binary presence or absence of something permanent, or whether it contains information about every individual permanent item. The current results show that the RSC does not merely execute a general response to item permanence. Instead, it has a more nuanced representation of the exact number of permanent items that are in view, a fact which only became apparent when using the more sensitive method of MVPA. This throws new light on the mechanism at play within the RSC, and reveals a means by which the RSC could play a crucial role in laying the foundations of an allocentric spatial representation of an environment, which is dependent in the first instance on multiple stable landmarks (Siegel and White, 1975). It is also interesting to note that this response to item permanence was automatic. The participants were naïve to my interest in item features and instead performed an incidental vigilance task that involved searching the images for a blue dot which would occasionally appear on an item. Given the importance of being able to code for stable items in an environment, it is perhaps not surprising that such processing is implicit and automatic, as has been shown for the detection of other components such as animals or vehicles within scenes in the absence of direct attention (Fei Fei et al., 2002).

One might argue that my results could have been influenced by factors other than permanence, for example, item size (Konkle and Oliva, 2012); after all, big items tend to

move less and be more stable. However, not only did I ensure that a range of real-world size values were represented within each permanence category, but the stimuli were designed such that real-world size could be analysed across five categories in a similar manner to permanence. Yet classifiers operating on voxels in the RSC were unable to predict item size. In a similar vein, the decoding of visual salience of the items from activity in RSC was significantly worse than for permanence. The eye-tracking data confirmed that there were no biases in terms of where and for how long subjects looked within the visual arrays, and this included their viewing of permanent items. Contextual effects (Bar, 2004; but see Mullally and Maguire, 2011) are also an unlikely explanation of my findings because stimuli were presented without any explicit contexts - each item within a stimulus was displayed on a white background inside a grey outline (Figure 27). Even if subjects had somehow implicitly processed the typical context for each item, the disparate nature of the four items in an array would likely have given rise to conflicting contextual information, thus adversely affecting classifier performance. The permanent items were all perceptually and semantically different, not just in terms of their size and visual salience, but also more generally; they included disparate items such as buildings, trees, telephone boxes, small fixed garden ornaments. Given that the only unifying property between the permanent items was this high-level feature, it is perhaps surprising that the magnitude of classifier accuracy was so great, being very significantly above the level of chance. This reinforces the functional importance of the representation of permanence, and underscores the selective response of the RSC to this item feature.

Subjects were also instructed not to link the items that comprised an array together into a scene, and confirmed in post-scan ratings they had not done so, rather they had viewed them as separate entities. This, along with the finding of the RSC responding specifically to the number of permanent items, does not fit easily with the idea that RSC (and PHC) processes the three dimensional geometric structure of scenes (Epstein, 2008; Henderson et al., 2008, 2011; Epstein and Ward, 2010) or that RSC contains no information about objects (Harel et al., 2012). My results are more consistent with a proposal from MacEvoy and Epstein (2011) that a unified representation of whole scenes arises from parallel processing of individual objects within them. Here, I provide further evidence for the simultaneous processing of multiple items, but extend this by identifying a mechanism whereby the properties of local items within a space are key (Mullally and Maguire, 2011), with their permanence seeming to be particularly important. The increased activity in RSC

in response to scenes with an explicit three dimensional structure that have been reported frequently in the literature (see Section 1.10.3) could reflect the presence of multiple permanent items within them. This accords with my previous proposal (discussed in Section 3.4) that the RSC's contribution may be to provide input regarding permanent items upon which other brain areas (e.g. the hippocampus) can then build effective spatial and scene representations that are central to episodic memories, imagining the future and spatial navigation (Sections 1.10.6 and 1.11; Addis et al., 2007; Hassabis et al., 2007; Ranganath and Ritchey, 2012; Maguire and Mullally, 2013). The specific nature of RSC input was unclear. This experiment demonstrates that RSC represents every individual permanent item that is in view, indicating that the information it represents and makes available is detailed and precise.

4.4.2 Good versus poor navigators

It is particularly interesting that the information available in the multi-voxel activity patterns in RSC related significantly to the efficacy of participants' spatial navigation. I previously found poor navigators to be less reliable at characterising permanent, 'never moving', items compared to good navigators, and also to have reduced responses in RSC when viewing permanent items in isolation (Section 3.3.3). The present study extends these finding by showing that despite the two groups being closely matched on a range of demographic, cognitive and structural brain measures, poor navigators had less informative neural responses about the permanence of multiple items that were in view simultaneously. Furthermore, the difference in engagement between good and poor navigators was specific to RSC, and not apparent in PHC; while within good navigators, the RSC facilitated significantly better prediction of landmark permanence than the PHC. It seems, therefore, that while RSC and PHC play a role in processing permanent items, only responses in RSC seem to relate to behavioural performance.

This may also help to explain the spatial disorientation that is typically associated with bilateral lesions to the RSC (see Section 1.6; Maguire, 2001a; Vann et al., 2009) and in Alzheimer's disease where RSC hypometabolism is observed at the earliest stages (see Section 1.7). An inability to orientate oneself in space might arise from unreliable identification of the landmarks which are permanent from those which are not in RSC, analogous to that observed here in the poor navigator group. It is not just that poor

navigators have reduced overall activity in the RSC while viewing a permanent landmark (as reported in Section 3.3.3), but there is also reduced information to help identify the most permanent, reliable landmarks in our surroundings.

However, the eye tracking data indicated that there were no differences in the attention which good and poor navigators directed towards permanent items. This could have perhaps reflected the nature of the task used in this experiment. Subjects were performing an incidental vigilance task which specifically required them to attend to all four items in each image (and they were expressly instructed to do so). This could have masked any potential differences in attention related to item permanence which might normally exist. However, even with equal attention to the permanent and transient items, the RSC of good and poor navigators seemed to respond to them differently. This lack of an overt behavioural difference but with detectable changes in associated neural representations perhaps points toward the difference being at an automatic, fundamental level of processing.

4.4.3 Future directions

While I have drilled down into RSC function here and uncovered a potential concrete explanation for its engagement in a range of cognitive functions that involve spatial contexts and scenes, clearly much remains to be understood. Future work will need to examine this RSC-permanence hypothesis in relation to real-world scenes. The cellular mechanisms within RSC that support the coding of item permanence in complex visual arrays or scenes also need to be investigated. Studies in humans (Section 1.10.1) and non-humans (Section 1.4) have yet to explicitly examine the direct effects of permanence on neural responses. I speculate that the mechanism for registering permanent items may involve head direction cells, which are present in the RSC (Chen et al., 1994; Cho and Sharp, 2001), perhaps anchoring themselves to each permanent item.

However, perhaps the most pressing question raised by my two experiments so far is how does the RSC come to learn about item permanence in the first place? I address this key issue in the next chapter.

Chapter 5: Experiment 3

De novo learning about landmark permanence

5.1 Introduction

We continually encounter new and ever-changing environments. To interact with these surroundings effectively, we must be able to form dependable representations of them. However, it is unclear how such representations come about and how different brain regions contribute to this learning process. The hippocampus (HC) and other parts of the medial temporal lobe play well-established roles in representing space, particularly within familiar environments (O'Keefe and Nadel, 1978; Morris et al., 1982; Burgess et al., 2002). There is also a larger distributed network of regions, including RSC, which interact with the HC and with one another when using these representations during navigation (Maguire et al., 1998; Spiers and Maguire, 2006), recollection of episodic memories (Burgess et al., 2001b; Svoboda et al., 2006; Spreng et al., 2009) or when imagining future events (Addis et al., 2007; Hassabis et al., 2007). These representations could be centred upon an environment's boundaries/borders (O'Keefe and Burgess, 1996; Barry et al., 2006; Doeller et al., 2008; Savelli et al., 2008; Solstad et al., 2008; Lever et al., 2009; Bird et al., 2010), objects within it (Manns and Eichenbaum, 2009; Horne et al., 2010; MacEvoy and Epstein, 2011; Chan et al., 2012; Deshmukh and Knierim, 2012), or some other feature (McNaughton et al., 2006; Stankiewicz and Kalia, 2007; Moser et al., 2008; Rajimehr et al., 2011; Baumann and Mattingley, 2013). Either way, the most stable features of an environment appear to be of particular importance (Biegler and Morris, 1993; Committeri et al., 2004; Galati et al., 2010; Lew, 2011; Yoder et al., 2011). Indeed it makes intuitive sense that a crucial requirement for a lasting, reliable representation of an environment is that it is based upon the most stable items. As such, the identification and handling of the most permanent, non-moving, environmental cues is an essential brain function.

In my previous two experimental chapters (Chapters 3 and 4), I observed that the RSC plays a role processing landmarks which are permanent and non-moving. Representations of other landmark features, such as whether or not they are encountered at navigationally relevant 'decision points' in an environment (Janzen and van Turennout, 2004; Schinazi

and Epstein, 2010), whether an item evokes as sense of surrounding space (Mullally and Maguire, 2011) or whether it is large and visually salient (Section 3.3.2; Konkle and Oliva, 2012), have been found to engage other regions such as the PHC. This kind of processing appears to be automatic, with features being registered even when attention is not directly drawn to them. However, little is known about the mechanisms and scope of these kinds of representation, or how they react to the changes that occur in our surroundings during everyday life.

For perceptual features, like size and visual salience, neural processing might be expected to remain constant as more is learned about a landmark. For the more abstract, experience-dependent properties like a landmark's permanence, however, it is less clear how representations evolve as knowledge accumulates. For instance, it may be that such representations can only form after years of direct, real-world experience with an item; or alternatively it could be a more rapid, adaptable process, evident after just a few exposures to something previously unfamiliar.

There is also no indication as to how a brain region which is usually engaged by a particular characteristic might respond before that feature is apparent. Considering the case of a region that processes permanent items, if the permanence of landmarks is not known, it might be expected to respond to some other, immediately available feature like landmark size or salience, as a kind of proxy for permanence until the reality becomes clearer. Alternatively, responses might be far more selective, only engaging once that specific property of a landmark is known; remaining insensitive to other features beforehand. A better insight into these mechanisms is necessary to gain a fuller understanding of how the brain performs the fundamental computations involved in representing and adapting to changes in the surrounding world.

In order to investigate this, I designed and used a new virtual reality environment. Subjects learned the layout of this environment through numerous exposures to it while undergoing fMRI scanning. Previous fMRI experiments using virtual reality contained landmarks that were readily recognisable and nameable (e.g. Hartley et al., 2003; Committeri et al., 2004; Spiers and Maguire, 2006; Iaria et al., 2007; Galati et al., 2010; Wegman and Janzen, 2011; Sulpizio et al., 2013). This was not appropriate for the purposes of this experiment, however, as I specifically required that subjects had no prior

expectations or thoughts about how permanent landmarks would be. The world I devised was therefore completely alien to participants and contained 60 entirely novel, unique landmarks that participants would never have encountered before. The locations in which these landmarks appeared were manipulated, with half being permanent, remaining fixed in a single place, and the rest changing their location on every exposure. This made it possible to track the neuronal evolution of knowledge gained from direct experience of the new environment and more specifically the most stable items within it. The environment was carefully constructed so that it contained a sufficient number of landmarks to provide enough detail to reliably investigate these processes, whilst not being so complex that it could not be learned within the time constraints of scanning.

Scanning and testing people as they learned about this new alien world had two key benefits: first, subjects were completely unfamiliar with the landmarks populating the environment and so had no preconceived ideas about their usefulness for navigation or permanence. The 'stripped-back' nature of the environment thus allowed me to investigate at a more fundamental level how we learn about environments and to study the *de novo* acquisition of information which is crucial for orienting ourselves within our surroundings. Second, by using virtual reality and completely novel objects, I was able to tightly control numerous features of the items and exposure to them. Crucially, therefore, the single difference between the permanent and transient landmarks was purely whether or not they remained fixed in a single location. This ensured that any conclusions I drew about the processing of landmark permanence would not be confounded by other features of the items (Troiani et al., 2012) or familiarity with them (Sugiura et al., 2005), as is often a risk when using real world/recognisable stimuli; instead I would be experimenting with 'clean' representations of permanence.

Unlike my previous two experiments, this paradigm also provided a more naturalistic setting for studying landmark properties, as it involved subjects directly interacting with landmarks and their environment. Studying the freely-behaving brain often makes it difficult to maintain tight experimental control over stimuli (Maguire, 2012), but the present setup, I believe, provided a balance of the two.

In this chapter, I consider in depth the development of these new representations of landmark permanence across all the participants. However, as in my previous two

experiments, I also noted that there was a good deal of variance in the ability of people to learn the layout of the alien world and navigate around it. Later in the chapter, I therefore go on to investigate how and why these individual differences arise.

5.2 Methods

5.2.1 Participants

Ten subjects (5 female, mean age 28 years, SD 4.8) took part in a landmark ratings study (see Section 5.2.2). A different set of thirty-two subjects (16 female, mean age 23.7 years, SD 2.4) took part in the fMRI study. All were healthy, right-handed, highly proficient in English, had normal vision and gave informed written consent in accordance with the local research ethics committee.

5.2.2 Creating and characterising the novel landmarks

I first created 134 completely unique 3D, 'alien' figures to be used as the landmarks in the virtual reality environment (see Figure 31A for examples). The landmarks were made with the animation software Blender 2.61 (Blender Foundation, Amsterdam, Netherlands, http://www.blender.org/). I then conducted a landmark ratings study to characterise numerous features of this novel set of landmarks. The features I collected ratings for were as follows:

- Salience ("*To what extent does this item grab your attention?"*, 5 point scale: 1 = Not at all, 5 = Very much);
- Other associations ("*Does this remind you of anything?*", Yes/No);
- Likeableness ("*How do you feel about this item?*", Like/Dislike);
- Animateness ("*Does this item look like it could be alive or not?*", Alive/Not Alive);
- Memorableness ("*Have you already seen this item?*" Yes/No – answered having seen the items numerous times whilst rating the other features).

Using these ratings, I selected two groups of 30 landmarks (from the original set of 134) to be used as the permanent and transient landmarks within the virtual reality environment.

I carefully selected these object groups to ensure that they did not differ in terms of any of the features rated (t-tests of permanent versus transient groups: Salience: $t_{58} = 0.669$, $p = 0.51$; Other associations: $t_{58} = 0.000$, $p = 1.0$; Likeableness: $t_{58} = 0.312$, $p = 0.76$; Animateness: $t_{58} = -1.089$, $p = 0.28$; Memorableness: $t_{58} = 0.247$, $p = 0.81$) or in terms of the actual size ($t_{58} = 0.000$, $p = 1.0$) or other visual features like the mean spatial frequency ($t_{58} = -0.562$, $p = 0.58$) of the items. Having selected the two groups, one was randomly allocated as the permanent set, the other as the transient set.

5.2.3 Creating the virtual reality environment

I collaborated with a colleague, Peter Zeidman, to create the custom virtual reality environment which would be populated by these landmarks. This novel environment, which we called 'fogworld', was created using the jMonkeyEngine 3.0 beta game engine (http://jmonkeyengine.org) and Java JDK 1.6 (Sun Microsystems, Santa Clara, California). The world contained 5 different coloured intersecting straight paths (yellow, red, grey, blue and green; Figure 31C). Each path had 12 landmarks (6 permanent, 6 transient) evenly distributed alongside it (Figure 31B). A trial consisted of travelling along one of these paths. There were a total of 60 trials, with the 5 paths being travelled 12 times each. Permanent landmarks remained in the same location on each trial, whereas transient ones appeared in a different location, anywhere in the environment, on every exposure. The locations that all 60 landmarks appeared on each of the 60 trials were meticulously designed so that both permanent and transient landmarks were equally distributed either side and along the whole length of each path. This ensured that the permanent and transient landmarks, as well as being matched for their perceptual features (see Section 5.2.2), were placed in equivalent locations within the environment.

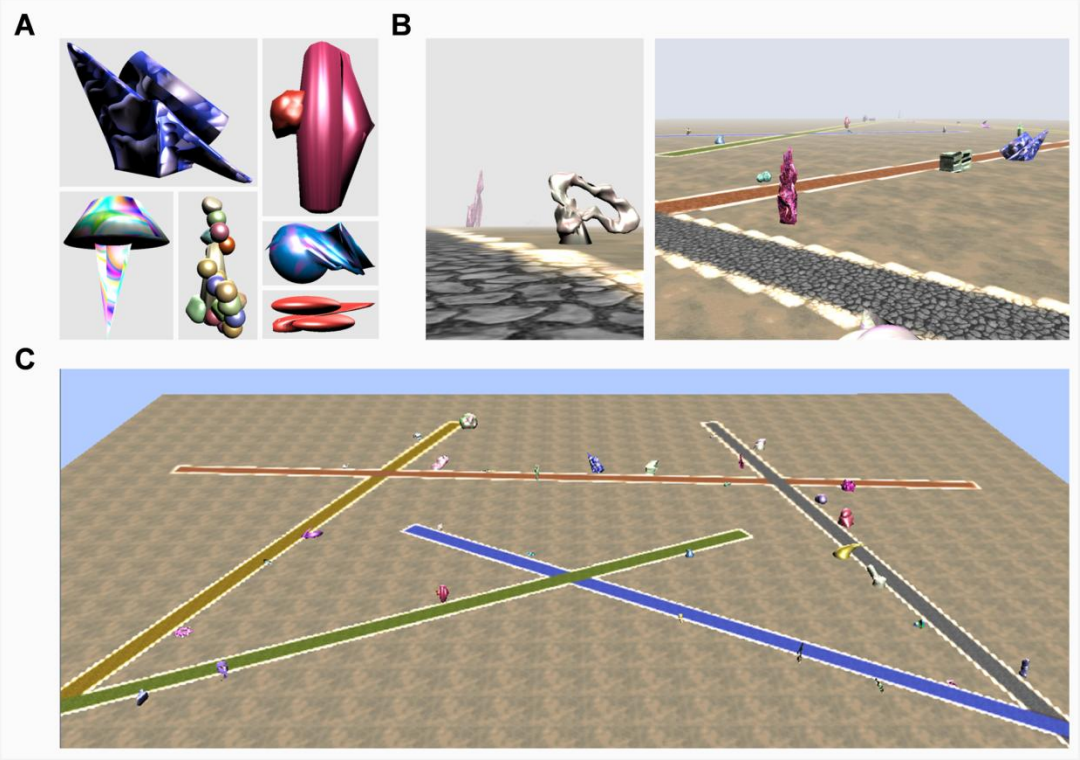

Figure 31 The virtual reality environment. Examples of some of the landmarks (A), landmarks positioned within the virtual world (B) and an overhead view of the environment showing all 5 different coloured, intersecting paths (C) - note this aerial perspective was never seen by participants during learning.

Having determined the identities and precise locations of permanent and transient landmarks within the virtual environment on all 60 trials, I created a video for each trial to be presented to subjects while they underwent fMRI scanning. Each video took a first person perspective travelling along one of the paths. In these videos, the environment was covered in a shroud of fog to restrict the field of view and ensure close control over the exposure subjects had to all the landmarks. This was especially important given the suggestion that RSC might be sensitive to the familiarity of stimuli (see Sections 1.10.3 and 1.10.4). On each trial, the camera travelled along a path in a straight line. When a landmark emerged out of the fog, the camera turned to bring the landmark into the centre of the screen, where it was positioned for 2 seconds, the camera then panned back to the middle of the path as it continued travelling forwards (see Figure 32A from top to bottom). The paths were always travelled in the same direction, with the same start and end point each time.

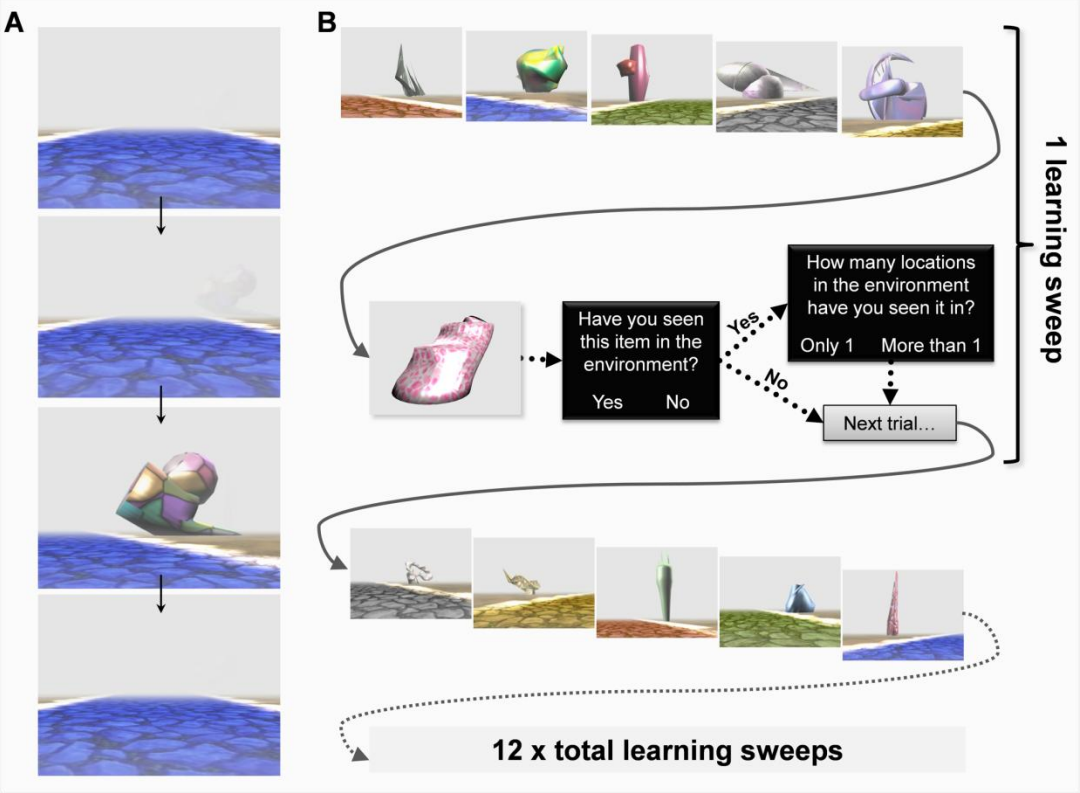

Figure 32 Experimental paradigm. While undergoing fMRI scanning, subjects were presented with videos travelling along the various paths. (A) Shows an example sequence of video frames with a landmark emerging through the fog, the camera turning towards it before returning back to the middle of the path. (B) After viewing videos of each of the five different paths once, subjects answered a series questions about individual landmarks to test their learning throughout the experiment. After being tested on 13 landmarks (5 permanent, 5 transient and 3 previously unseen), they were shown the next round of learning videos (with the paths in a different order). A learning "sweep" consisted of one round of videos of the five paths and the questioning period which followed. There were 12 of these learning sweeps.

In order to encourage subjects to learn an integrated representation of the whole environment, rather than just see them as 5 separate routes, the paths intersected with one another. Each path intersected with two others (see Figure 31C). The first intersection was located 3 landmarks after the start of the path and the second was 3 landmarks before the end, with 6 landmarks between the two intersections. When the videos came to one of these intersections, the camera turned either left or right and the fog cleared enough to reveal 3 landmarks on the adjoining path. After 3 seconds, the landmarks were obscured by the fog again with the camera returning to the centre while continuing along the route. There were an equal number of left and right turns at each intersection throughout the whole experiment and the ordering of the turns was pseudorandomised to ensure it was not predictable. The number of times each landmark was viewed during one of these intersection turns was also closely controlled so that overall exposure to all the landmarks remained identical. These 60 videos (used for the 60 trials) were each approximately 1 minute in length.

5.2.4 Task and procedure

Before scanning, subjects had the task fully explained to them. They were instructed to learn the layout of the environment as best they could and told that they would be tested in a variety of ways after scanning without the specific nature of those tasks being revealed. Subjects were informed that some of the landmarks would always remain in the same location whereas others would appear in a different place every time they saw it. They were shown an example trial (containing landmarks and a path which did not appear during the main experiment) to familiarise them with the format of the main scanner task.

While undergoing fMRI scanning, subjects learned the layout of the environment and its landmarks by viewing videos travelling along each of the 5 paths, one at a time. Each trial consisted of a single journey along one of the paths and at the end of a video, subjects were immediately shown the next learning trial on a different path.

Once all five paths had been travelled once, there came a questioning period to gauge how much information subjects had learned throughout the experiment (Figure 32B). In these questioning periods, participants were first shown an image of a single landmark displayed, in isolation, on a plain grey background for 2 seconds. They were then asked whether or not they remembered the landmark from the environment ("*Have you seen this item in the environment?*", Yes/No). If they remembered seeing it, they were then asked about its permanence ("*How many locations in the environment have you seen it in?*", Only 1/More than 1), before being questioned about another landmark. Within each questioning period, subjects were tested in this way on 13 landmarks: 5 permanent, 5 transient and 3 previously unseen.

The combination of a 13 trial questioning period and videos of the 5 different paths preceding it are referred to as a learning 'sweep'. The ordering of trials along the 5 different paths within each learning sweep was pseudorandomised so there were no biases in when the paths were travelled relative to each other. In the questioning period between learning sweeps, the ordering of the three types of landmark (permanent, transient or unseen) was also pseudorandomised for the same reasons. There were a total of 12 learning sweeps throughout the whole experiment (divided into 4 scanning runs of 3 sweeps each). Each 3 sweep scanning run lasted 15-20 minutes and subjects could take a

short break (while remaining in the scanner) between scanning runs if they felt it necessary.

Once out of the scanner after the learning experiment had concluded, subjects were shown images of individual landmarks (all 60 from the environment and 26 previously unseen ones) and rated whether or not they recognised them from the environment ("*Do you remember seeing this item in the environment?*", Yes/No). After that, questions were only asked about the landmarks from the environment. Participants first rated the permanence of the environment's landmarks ("*How many positions in the environment do you think this item was in?*", Only 1/Many); next they rated the salience of each landmark ("*To what extent does this item grab your attention?*", Not at all/A bit/ A lot) and finally the size that landmarks were in the environment ("*What size is this item?*", Small/Medium/Large). A different randomised order of landmarks was used for each of these questions.

After rating all three features of the landmarks, participants were then tested on their learning of the environment's overall layout with three different tasks: drawing a sketch map, followed by placing landmarks on an empty map on which the paths were shown, and finally an in situ volitional navigation task. The sketch map drawings gave an impression of how well subjects had learned the overall layout of the environment, the landmark placement task tested their knowledge of landmark locations, and the navigation task provided the most rigorous assessment of how much information people had learned about the environment as a whole.

For the sketch map test, subjects were handed a blank sheet of A3 paper and a black pen; they were then instructed to draw a map of the environment "in as much detail as possible". They were instructed to put down as much as they could remember about the environment's layout, all the paths and the positions of landmarks. The sketch map drawings were later marked according to how accurately the relationships between paths were drawn, which indicated how well subjects had learned the structure of the environment, independent of landmarks.

After finishing their sketch map, participants were handed a map (on A3 paper) showing the real layout of the environment from an aerial perspective and its five different

coloured paths (this was the first time an aerial perspective of the environment had ever been shown to them). However, this map contained no landmarks. They were then shown images of 25 landmarks (21 permanent and 4 transient), one at a time, on a computer screen. Each landmark image had a number next to it and participants were instructed to write that number on the map where they believed the landmark was located. They were told to be as accurate as possible in placing each landmark, being careful which path and which part/side of the path they located it. The map had an additional box in the corner of the page where they could indicate if they thought a landmark was transient. After locating each landmark on the map, subjects then rated how confident they were that the landmark was indeed located where they had indicated (5 point scale, not at all to very confident).

The final active navigation task provided a thorough examination of how well participants had learned the layout of the whole environment. This test was performed on a computer. Participants were first shown an image of a landmark and instructed that they would have to navigate to where they thought it was located in the environment by as direct a route as possible. On each trial, subjects were placed within a version of the environment in which there was no fog and the target landmark had been removed (Figure 33A). They moved their way to where they thought that landmark belonged (using the arrow keys on a keyboard) and then indicated their chosen location by pressing the space bar. There were a total of 12 of these trials (9 permanent and 3 transient landmarks). If they thought the target landmark was transient (and so could not be placed in a single location), subjects were instructed to press the space bar and indicate that they thought it was transient.

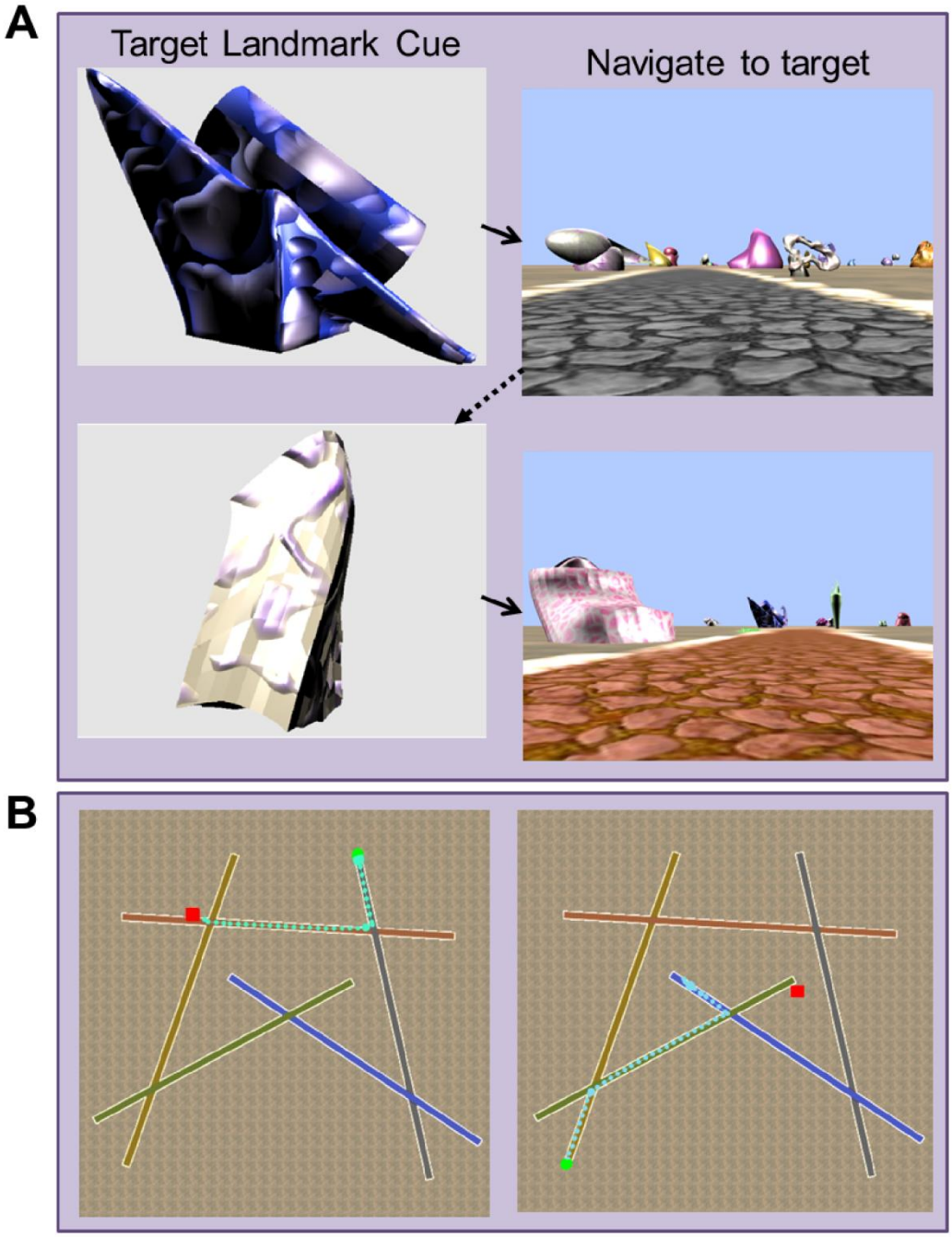

Figure 33 Post-scan navigation test. (A) For each trial in the post-scan navigation task, subjects were shown an image of a target landmark and then attempted to navigate to where they believed it belonged in the environment. (B) Examples of the path taken by subjects in the navigation task. The green circle indicates their starting position and the dotted line indicates the route they took from that start point. The left shows a trial in which a subject was able to navigate accurately and directly to the target location (red square). The right panel shows a trial on which a subject navigated to the correct part of a path (on the right hand side at the end of the path) but the wrong path colour (blue instead of green).

Finally, subjects filled out a debriefing questionnaire to ascertain other general information such as how difficult they had found the tasks.

5.2.5 Pilot experiments

The precise number of landmarks which were included in the environment and the amount of time/number of trials subjects were given to learn (as described in Sections 5.2.2-5.2.4) were finalised after I conducted two pilot experiments.

Originally, it was not my intention to just have permanent and transient landmarks. I had initially planned to include an additional third category of landmarks which sometimes, but not always, changed location. There would have been 20 of each of these three landmark types, giving the same total number of landmarks (60) as in the final design. However, after piloting the three-category design with four subjects (2 female, mean age 21.0 years, SD 1.8), it became clear that this was too complex for people to learn in a reasonable amount of time.

I therefore adapted the design to have only permanent and transient landmarks (30 each), with everything else as described above (e.g. number of trials). This final design was tested with two participants (1 female, mean age 22.0 years, SD 0.0) who both found the task difficult, but were able to learn an acceptable amount about which landmarks were permanent or transient.

5.2.6 Scanning parameters and preprocessing

T2*-weighted single-shot echo-planar images with blood oxygenation level-dependent (BOLD) contrast were acquired on a 3T Magnetom Allegra head-only MRI scanner (Siemens Healthcare, Erlangen, Germany) operated with the standard transmit-receive head coil. Functional MRI data were acquired across four sessions with a sequence which was optimized to minimize signal dropout in the medial temporal lobe and used a descending slice acquisition order with a slice thickness of 2mm, an interslice gap of 1mm, and an in-plane resolution of 3 x 3mm (Weiskopf et al., 2006). Forty eight slices angled at -45° to the anterior-posterior axis were collected covering the entire brain, with a repetition time of 2.88s, 30ms echo time and 90° flip angle. A 3D MDEFT T1-weighted structural scan was also acquired for each participant with 1mm isotropic resolution (Deichmann et al., 2004). The first 6 ‘dummy’ volumes from each of the four sessions were discarded to allow for T1 equilibration effects. FMRI data were analysed using SPM8

(www.fil.ion.ucl.ac.uk/spm). Images were realigned and unwarped using field maps which were acquired with a double-echo gradient field map sequence (TE=10 and 12.46ms, TR = 1020ms, matrix size 64 x 64, with 64 slices, voxel size = $3mm^3$) and then normalised to a standard EPI template in MNI space with a resampled voxel size of 3×3×3mm and smoothed using an 8mm FWHM Gaussian kernel.

5.2.7 Behavioural analyses

During scanning, two ratings were collected from subjects to gauge how well they recognised landmarks and knew their permanence. I assessed the rates at which subjects came to recognise permanent and transient landmarks. To do this, I performed separate linear regression analyses for permanent and transient landmarks to see how the accuracy with which subjects recognised them changed throughout the learning phase. I then compared the slopes of these linear estimates across all subjects in order to establish whether or not subjects had learned to recognise the two types of landmark equally.

After scanning, subjects rated numerous features of all the landmarks. First, whether or not they remembered the item (*Do you remember seeing this item in the environment?*, Yes/No). Similar to the comparison of recognition ratings made during scanning, I compared the accuracy with which people recognised the two types of landmark in the post-scan debrief to assess the overall learning of permanent and transient items. Subjects then indicated whether they thought an item was permanent or transient (*How many positions in the environment do you think this item was in?*, Only 1/Many). They then rated some of their visual properties, namely their salience (*To what extent does the item grab your attention?*, Not at all/A bit/ A lot) and size (*What size is this item?*, Small/Medium/Large). To assess the validity of these ratings and confirm whether or not subjects had successfully learned about the landmarks, I compared them with the corresponding actual permanence and size of landmarks and also the salience scores from the separate initial ratings study.

I had ratings of multiple features for each landmark. Similar to Experiment 1 (see Sections 3.2.6 and 3.3.1), I therefore submitted the ratings of these four features, as well as the landmarks' actual permanence, to a principal components analysis. This principal components factor analysis was conducted using the mean ratings for each feature of all

60 landmarks from every subject; it used a varimax rotation and Kaiser normalisation. I then generated orthogonal factor score estimates using the Anderson-Rubin method for use in a whole brain fMRI analysis (see Section 5.3.3). The factor analysis and all statistical tests were performed using SPSS version 20 (http://www.spss.com).

After rating the landmark features, subjects performed three further tests to ascertain how well they had been able to learn the layout of fogworld. They were required to draw a sketch map, place landmarks on a map of the environment and finally navigate within fogworld.

For the sketch map task, one mark was awarded for each correctly drawn intersection between two paths (e.g. included an intersection between red and yellow paths), a further mark was awarded if the parts of the paths involved in that intersection were accurate (e.g. start of the red path intersecting with the end of the yellow path). So a maximum of 2 marks were available for each of the environment's five path intersections, giving an overall maximum mark of 10. Any extra incorrectly drawn intersections (e.g. yellow path intersecting with grey path) were penalised 1 mark, with a minimum possible score of 0.

For the landmark placement task, there were 25 trials (21 permanent, 4 transient). Three marks were awarded for each trial: 1 mark for drawing it next to the correct path (e.g. next to blue path), 1 for drawing it on the correct part of that path (i.e. before 1st intersection, between the 2 intersections or after 2nd intersection) and a final mark for drawing a landmark on the correct side of the path (right or left). A correctly identified transient landmark was also awarded 3 marks. The maximum possible score was 75.

For the navigation task, each trial was marked out of 3, giving a maximum score of 36. One mark was awarded for locating a landmark on the correct path, 1 mark for the correct part and side of the path and a final mark was awarded if they had taken a direct route to the landmark. If they correctly identified that the target landmark was transient (and so could not be located in a single position), they were awarded a full 3 marks.

5.2.8 fMRI: permanent versus transient landmarks

Similar to my previous two experiments and other work (e.g. Wegman and Janzen, 2011), I compared fMRI responses while subjects viewed images of individual, isolated landmarks displayed during the questioning periods at the end of each sweep, unless otherwise stated. Using this time period, rather than when landmarks were viewed in the navigation videos, removed potential problems associated with visual confounds (e.g. path colour), and variable, and likely more unconstrained, neural responses that may have occurred during the one minute long learning video periods.

My primary interest was in seeing whether a neural representation of landmark stability could emerge for previously unseen items over the course of just a single scanning experiment. I therefore directly contrasted fMRI BOLD responses to permanent and transient landmarks in the whole brain, dividing the scanning experiment into quarters (which corresponded to the four scanning runs), each consisting of three learning sweeps.

The four scan runs were analysed individually in order to assess changes as subjects learned about the items. Potential problems associated with incidental changes in the BOLD signal over time were avoided by specifically comparing changes in the difference between permanent and transient landmarks. Permanent and transient landmark regressors were convolved with the haemodynamic response function. A separate regressor was created for the learning video time periods. This, along with participant-specific movement regressors were treated as covariates of no interest. I calculated subject-specific parameter estimates pertaining to each regressor of interest (β) for each voxel. Second level random effects analyses were then run using one-sample t-tests on these parameter estimates. I report all fMRI results at a whole brain threshold of $p < 0.05$ (FWE), unless otherwise stated.

5.2.9 fMRI: use of the factor analysis component scores

As described in Section 5.2.7, I also collected ratings of features of the landmarks and submitted these scores to a principal components analysis. I then examined fMRI responses in relation to these factors. Similar to the comparison of permanent and transient landmarks (Section 5.2.8), I analysed the four scan runs individually, creating

parametric regressors from the orthogonal factor score estimates for every landmark in relation to each of the principal components. These parametric regressors were each convolved with the haemodynamic response function. Separate regressors of no interest were included for head movement and learning video time periods. Subject-specific parameter estimates pertaining to each regressor of interest (β) were created for each voxel and second level random effect analyses were run in the same way as for the permanent versus transient landmark comparison (Section 5.2.8).

5.2.10 fMRI: accounting for subject-specific learning differences

In the previous analyses of fMRI data (Sections 5.2.8 and 5.2.9), I used the amount of time that people had been exposed to the environment to probe the development of neural representations of the various landmark features. However, even though subjects will have inevitably learned more about the landmarks with more exposure to them, using this measure does not account for differences in how much individuals had learned at different points throughout the experiment (see Section 5.3.1). To get a more direct characterisation of the dynamics of each subject's learning, I used the ratings they gave about the landmarks during each sweep's questioning period.

For each subject, I used their accuracy in answering these questions to construct a range of different models of their learning-state throughout the experiment. I compared the mean squared error (MSE, in arbitrary units) and percentage variance explained by 3 different methods of modelling the data: a "state-space" model estimated by maximum likelihood using an expectation maximisation algorithm (Smith et al., 2004); a "state-space" model estimated by a Bayesian approach (Smith et al., 2007) and a moving average of accuracy across each sweep and the sweeps immediately preceding and following it. The "state-space" learning models were created with the MATLAB- and WinBUGS-based software provided at http://www.neurostat.mit.edu.

The state-space model estimated by a Bayesian approach (Smith et al., 2007) provided the best fit of the data, and so I used this to create subject-specific parametric regressors of each subject's estimated learning state during each sweep of the scan for use in a whole brain GLM analysis. Separate regressors were created for permanent and transient

landmarks so that I could contrast responses to the two types of landmark in direct relation to how well people knew the permanence of landmarks.

As SPM automatically mean centres parametric regressors within each scanning block, I concatenated the four sessions into one and added extra regressors to model the mean signal for each session. Parametric regressors are additionally mean centred by SPM at the first-level, so in order to accurately reflect between-subject differences in the overall extent of learning across the whole experiment, I added their overall performance in the post-scan navigation task (the most rigorous measure of learning) as a second-level covariate of interest. Significant clusters are reported at a whole brain uncorrected threshold of $p < 0.001$ for the RSC (but see Section 5.4.4 for details of further analysis of significance) and $p < 0.05$ FWE corrected for the rest of the brain. I chose this statistical threshold for the RSC given the more subtle nature of this specific contrast (compared to the more simple comparison of all permanent with all transient landmarks) and my specific prior hypotheses about RSC processing landmark permanence.

5.2.11 Connectivity analyses

I then used gPPI (Section 2.8.1) to examine changes in the functional connectivity of regions associated with learning landmark permanence. The seed regions and contrasts used for these analyses were all based upon corresponding univariate whole-brain comparisons described in Sections 5.2.8 and 5.2.10.

First, for any regions responsive to landmark permanence (from the analysis described in Section 5.2.8 and reported in Section 5.3.2), I looked for brain areas with which they showed increased functional coupling for permanent compared to transient landmarks. Early and late parts of the scanning session were compared separately (learning sweeps 1-6 and 7-12 respectively). I analysed the two halves instead of four quarters (as was the case for analyses described in Sections 5.2.8, 5.2.9 and 5.2.12) in order to increase the number of trials and power with which to detect these potentially subtle effects.

For a second connectivity analysis, I used a seed region and contrast which additionally accounted for inter-individual differences in learning (described in Section 5.2.10 and reported in Section 5.3.4). Specifically, I used the same parametric regressors and second

level covariate of interest described in the previous section (5.2.10). The seed region(s) were any significant clusters from the corresponding mass-univariate analysis (see Section 5.3.4). I contrasted changes in the seed region(s)'s whole brain functional connectivity associated with viewing permanent versus transient landmarks in relation to how well subjects had learned landmark permanence.

5.2.12 Representations related to knowledge of permanent landmark locations

I next looked for evidence of more detailed landmark representations within any regions which displayed responsivity to landmark permanence (see Section 5.3.2). The post-scan navigation task provided a reliable measure of how well participants knew the *in situ* locations of permanent landmarks by the end of learning. I therefore used this information to look for neural representations related to this knowledge.

I wanted to use a sensitive multivariate analysis method to examine these representations within different brain regions. However, in this instance, I wished to assess the multi-voxel representations in relation to a continuous variable (i.e. how much individuals knew about permanent landmark locations). MVPA with a linear SVM can only be used to make categorical classifications (see Section 2.7) and so was not appropriate for this specific analysis. I therefore instead employed an alternative type of multivariate analysis method known as multivariate Bayes (MVB). This is a model-based decoding method (Friston et al., 2008; FitzGerald et al., 2012; Chadwick et al., 2014) which compares competing hypotheses about the mapping between multi-voxel response patterns to a psychological target variable using a hierarchical approach known as parametric empirical Bayes. Specifically, I used MVB to look for patterns of voxel activity within permanence responsive regions, which mapped onto knowledge of permanent landmark *locations* as assessed in the post-scan navigation test.

MVB analyses use the same design matrix as a standard univariate SPM analysis, with columns for experimental variables of interest as well as regressors of no interest. A contrast is then specified (in this instance from subjects' scores on the post-scan navigation task) and a 'target' variable is derived from this after accounting for potential confounds (e.g. head movement). The patterns of voxel activity within each ROI are then fitted to this target variable, producing a model evidence value. These model evidence

values are then compared to a null model to determine the log model evidence. Models are constrained at a second hierarchical layer based upon priors from the patterns of voxel weights (which map every voxel to the target variable) and their variance.

Log model evidence values therefore represent the mutual information shared by the psychological variable (in this case knowledge of permanent landmark locations) and the pattern of voxel responses within a brain region. I used the SPM software's default settings for the MVB analyses, with 9 greedy search steps and size of successive subdivisions set at 0.5 to test for evidence of sparse representations relating to knowledge of landmark location.

I reasoned that a representation relating to knowledge of permanent landmark locations would be strongest while subjects explicitly viewed them in that location. Unlike my other fMRI analyses, I therefore examined fMRI responses during the learning videos, rather than for the questioning period images in which landmarks were isolated and devoid of more complex spatial information. I looked for patterns of multi-voxel activity, while people viewed permanent landmarks *in situ*, which related to how well they were able to subsequently locate them in the post-scan navigation task.

I modelled the whole time period that permanent landmarks were in view during the learning videos. As with the analyses described in Sections 5.2.8 and 5.2.9, the four quarters of the scan were analysed individually to explore changes over time. In order to maximise the sensitivity of the analysis, I defined the regions of interest anatomically (with one exception – see below) where possible, as exploring responses within the whole bilateral anatomical regions rather than smaller functionally-defined clusters within them provided maximal multi-voxel information for the characterisation of representations.

Anatomically defined masks (see Section 5.3.6 for details of the brain regions) were delineated by an experienced researcher, not involved in this project, guided by Duvernoy (1999) and Vann et al. (2009) on an averaged structural brain scan from a different set of n = 30 participants. For permanence-responsive regions which did not relate to a clearly defined anatomical locus, I instead used the cluster of voxels which were activated by permanent landmarks (in the contrast described in Section 5.2.8 and reported in Section 5.3.2).

I report all analyses with a log model evidence value above three as significant, as is common practise (Kass and Raftery, 1995; Penny et al., 2004; Friston et al., 2008). I conducted further control analyses using the permutation function within MVB (with 100 samples) to check there was no bias towards the MVB procedure producing a positive result.

5.3 Results

5.3.1 Behavioural analyses

During scanning, there was no difference in the rate at which subjects learned to recognise permanent and transient landmarks (mean difference in rate = 0.0084, SD = 0.063; t_{31} = 0.763, p = 0.45). In the post-scan debriefing session too, there was no difference in how well subjects recognised permanent or transient landmarks (permanent mean accuracy = 82.9%, SD = 4.9; transient mean accuracy = 76.3%, SD = 4.4; t_{31} = 1.745, p = 0.09). Subjects were also accurate at identifying novel landmarks which they had not seen before (mean = 93.0%, SD 2.3).

As well as rating whether or not they remembered each item (*Do you remember seeing this item in the environment?*, Yes/No), after scanning, subjects rated numerous other features of all the landmarks. These included whether they thought an item was permanent or transient (*How many positions in the environment do you think this item was in?*, Only 1/Many), how salient they thought them to be (*To what extent does the item grab your attention?*, Not at all/A bit/ A lot) and finally the size that they were in fogworld (*What size is this item?*, Small/Medium/Large).

I compared the ratings subjects made in the post-scan debrief with the corresponding actual values of permanence and size, and the salience scores from the separate initial ratings study in order to test the validity of ratings and confirm whether or not subjects had successfully learned about the landmarks (Table 2).

Permanence ratings made in the fMRI study debrief were strongly correlated with the actual values (r = 0.793, p < 0.0001), indicating that subjects had successfully learned this information. Similarly, the size ratings in the debrief bore strong relation to the actual

values (r = 0.726, p < 0.0001). Comparing the salience ratings from the ratings study and the fMRI study was particularly interesting. Although the correlation between the two was significant (p = 0.02), the slope of the correlation was not particularly marked (r = 0.314). The landmarks in the initial ratings study were viewed singly one at a time. By contrast, there was a tendency for people in the post-scan debriefing session of the fMRI study to rate landmarks as more salient if they had been experienced in fogworld to be large (r = 0.428, p = 0.001) or permanent (r = 0.315, p = 0.01). In other words, the salience of landmarks (or how "attention grabbing" they were) was not just an inherent property; it was also influenced by how and where they had been experienced within the environment.

	Salience - ratings study	Size - actual	Permanence - actual	Permanence - debrief	Salience - debrief	Size - debrief
Salience - ratings study	1.000	0.088 0.5	0.087 0.5	-0.001 1.0	**0.314*** 0.02	0.129 0.3
Size - actual	0.088 0.5	1.000	0.000 1	0.068 0.6	**0.428**** 0.001	**0.726**** <0.0001
Permanence - actual	0.087 0.5	0.000 1.000	1.000	**0.793**** <0.0001	**0.315*** 0.01	0.117 0.4
Permanence - debrief	-0.001 1.0	0.068 0.6	**0.793**** <0.0001	1.000	**0.325*** 0.01	0.093 0.5
Salience - debrief	**0.314*** 0.02	**0.428**** 0.001	**0.315*** 0.01	**0.325*** 0.01	1.000	**0.749**** <0.0001
Size - debrief	0.129 0.3	**0.726**** <0.0001	0.117 0.4	0.093 0.5	**0.749**** <0.0001	1.000

Table 2 Correlations between features of the 60 landmarks. Correlations are shown between: mean salience scores from the initial ratings study; the actual size and permanence of landmarks in the virtual reality environment; and ratings of permanence, salience and size given in the fMRI study post-scan debrief. Each cell shows the Pearson correlation r value above the corresponding p value. Significant correlations are highlighted in bold text. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

In addition to rating the permanence, size and salience of landmarks, participants in the scanning experiment also indicated how memorable they were (see Section 5.2.4). I submitted their ratings of these four features (permanence, memorableness, salience and size), along with the actual permanence of landmarks to a principal components analysis. The features clearly separated onto 4 orthogonal factors, which accounted for a total of 96.4% of variance in the data. These 4 factors were strongly related to the permanence, memorableness, size and salience of the landmarks from 1 to 4 respectively (Table 3 and Figure 35).

Landmark Feature	Principal Components Analysis Loadings			
	1	2	3	4
Permanence (actual)	**.952**	.014	.037	.118
Permanence (rating)	**.896**	.256	.072	.172
Memorable	.156	**.969**	.104	.140
Size	.063	.101	**.980**	.160
Salience	.202	.147	.174	**.952**

Table 3 Principal components analysis loading values. The loading values of each landmark feature to the four principal component factors. Values above 0.5 are highlighted in bold. Factor 1 was strongly related to landmark permanence, factor 2 to their memorableness, factor 3 to their size and factor 4 to the visual salience of landmarks. See also Figure 35.

After rating the various features of individual landmarks, subjects were tested on how well they had learned the layout of the environment in a variety of ways. There was a good deal of variance in the subjects' scores on each of these tests: sketch map drawings (mean score out of 10 = 4.9, SD = 3.3), landmark placement (mean score out of 75 = 34.7, SD = 11.5) and navigation task (mean score out of 36 = 12.8, SD = 8.1). However, an individual's scores on each test were significantly correlated with one another (all $n = 32$ and $p < 0.01$ corrected for multiple comparisons; sketch maps versus landmark placement: $r = 0.59$; sketch maps versus navigation task: $r = 0.51$; landmark placement versus navigation task: $r = 0.79$). This shows that subjects varied in their ability to learn about the environment.

I also collected confidence ratings for the landmark placement test. However, subjects tended to rate every trial with similar confidence which made it difficult to interpret anything meaningful from their ratings.

5.3.2 fMRI: permanent versus transient landmarks

By the final quarter of learning (the last 3 learning sweeps) there were significantly greater responses to the permanent landmarks in right (6, -53, 5; $Z = 5.41$) and left (-6, -55, 10; $Z = 5.90$) RSC, as well as right superior posterior parieto-occipital sulcus (POS) (9, -73, 31; $Z = 5.01$) and posteriorly in the left occipital lobe (-6, -79, -8; $Z = 5.00$) (Figure 34). There were also activations in the HC (-21, -28, -11; $Z = 3.71$) and PHC (21, -37, -14; $Z = 4.12$) at a slightly reduced threshold ($p < 0.0001$ uncorrected; compared with the whole-brain FWE corrected $p < 0.05$ reported otherwise). These increased responses to permanent landmarks were even present as early as the third quarter of the scan (sweeps 7-9 of 12)

in similar regions (right RSC: 12, -51, 3; Z = 5.31; left RSC: -12, -55, 6; Z = 5.72; left POS: -6, -76, 40; Z = 4.93; left occipital: -15, -76, -11; Z = 5.53), but not the HC or PHC. There were no differences in either of the first two quarters of learning. Thus, not only did a strong representation of permanence develop for the previously unfamiliar landmarks, but this was present within 40 minutes of seeing them for the very first time (with fewer than 10 exposures). Furthermore, in being centred upon bilateral RSC, these responses were entirely consistent with my previous experiments with real-world stimuli. No regions were more active for transient than permanent landmarks.

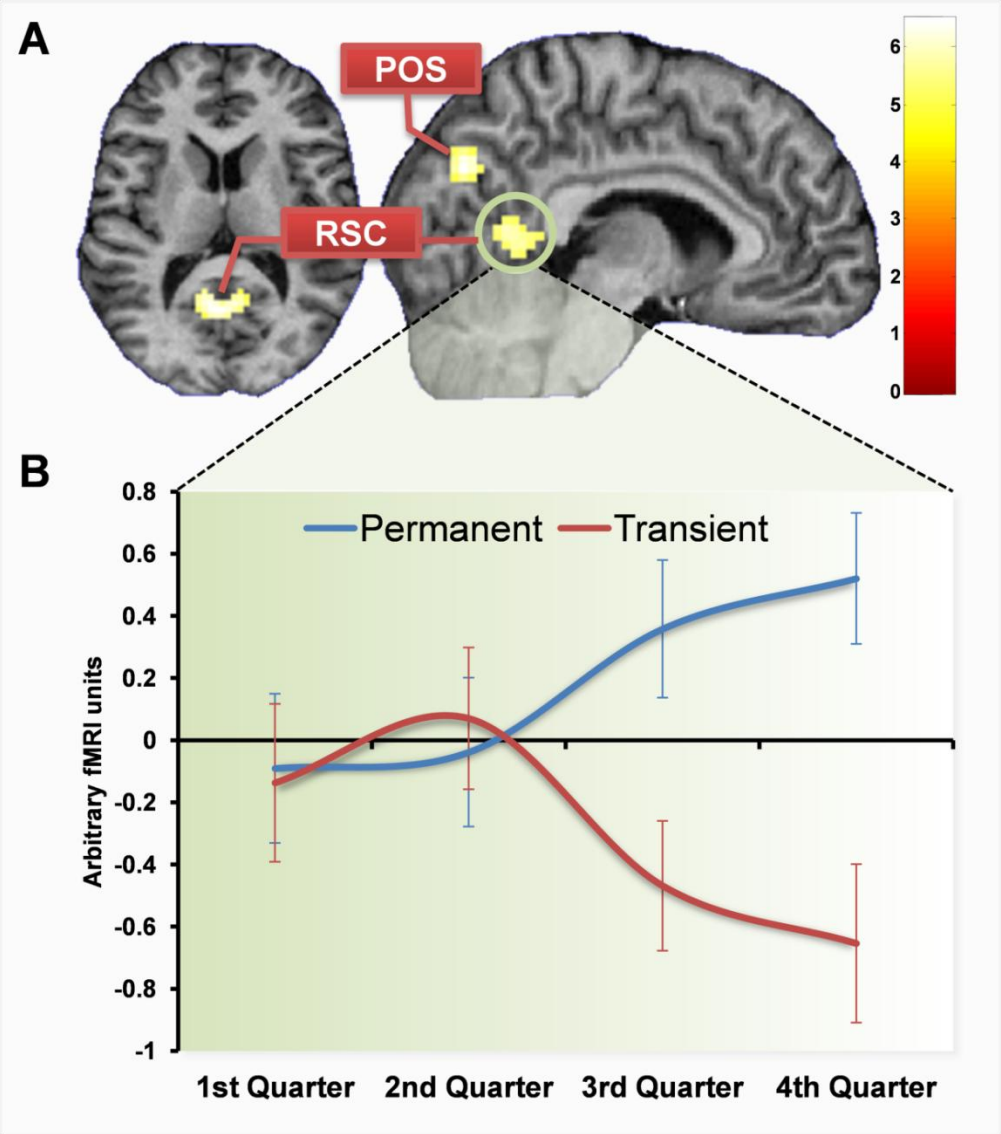

Figure 34 Brain regions more engaged by permanent than transient landmarks by the end of learning. (A) Shows activations in both RSC and POS. Activations are shown on an MRI brain scan of a single, representative subject. The colour bar indicates Z-scores associated with each voxel. (B) Shows a plot of BOLD responses within the RSC cluster (circled in green). In the first two quarters of the scan, responses to permanent (blue) and transient (red) landmarks did not differ, but as subjects learned landmark permanence, BOLD responses increased for permanent landmarks with a corresponding decrease for transient landmarks.

5.3.3 fMRI: comparisons using the factor analysis component scores

I then sought to explore how fMRI BOLD signals may relate to each of the principal components from the factor analysis of landmark features; first of all to see whether or not they had any identifiable neuronal correlates, and second, to explore how they might evolve over the course of learning. To do this, I created factor score estimates for every landmark corresponding to each of the 4 orthogonal principal components and then used these values to generate parametric regressors for a whole brain fMRI analysis.

Increasing values of the permanence-related factor (factor 1) were associated with significant activations in bilateral RSC (left: -12, -55, 7; Z = 5.60; right: 9, -52, 4; Z = 5.12), as well as POS (left: -9, -91, 25; Z = 5.59; right: 9, -73, 31; Z = 5.54) in the final quarter of learning, but only right RSC in the 3rd quarter (12, -48, 1; Z = 5.03) and no regions in either of the first 2 quarters (top of Figure 35, in blue). Once again there were also increased responses in the left HC (-18, -28, -11; Z = 3.99) and right PHC (24, -37, -14; Z = 4.24) at a slightly reduced threshold ($p < 0.0001$, the same as reported for the HC and PHC in Section 5.3.2) in the last quarter of scanning.

The more easily remembered landmarks (those with greater values for factor 2) did not produce any significant activation in the final quarter of learning. However, right at the start of learning (in the first quarter), there was a greater response in POS to landmarks which people went on to later remember better in both the right (15, -70, 31; Z = 5.35) and left (-9, -76, 28; Z = 5.30) hemispheres (second from top of Figure 35, in red). There were also similar significant activations in the middle two quarters of learning (2nd quarter, left: -3, -76, 40; Z = 4.94; right: 9, -67, 31; Z = 4.98; 3rd quarter, left: -6, -64, 31; Z = 4.88; right: 3, -64, 37; Z = 4.76). Intriguingly, these bilateral regions both overlapped with those which later went on to respond to more permanent items in the final quarter.

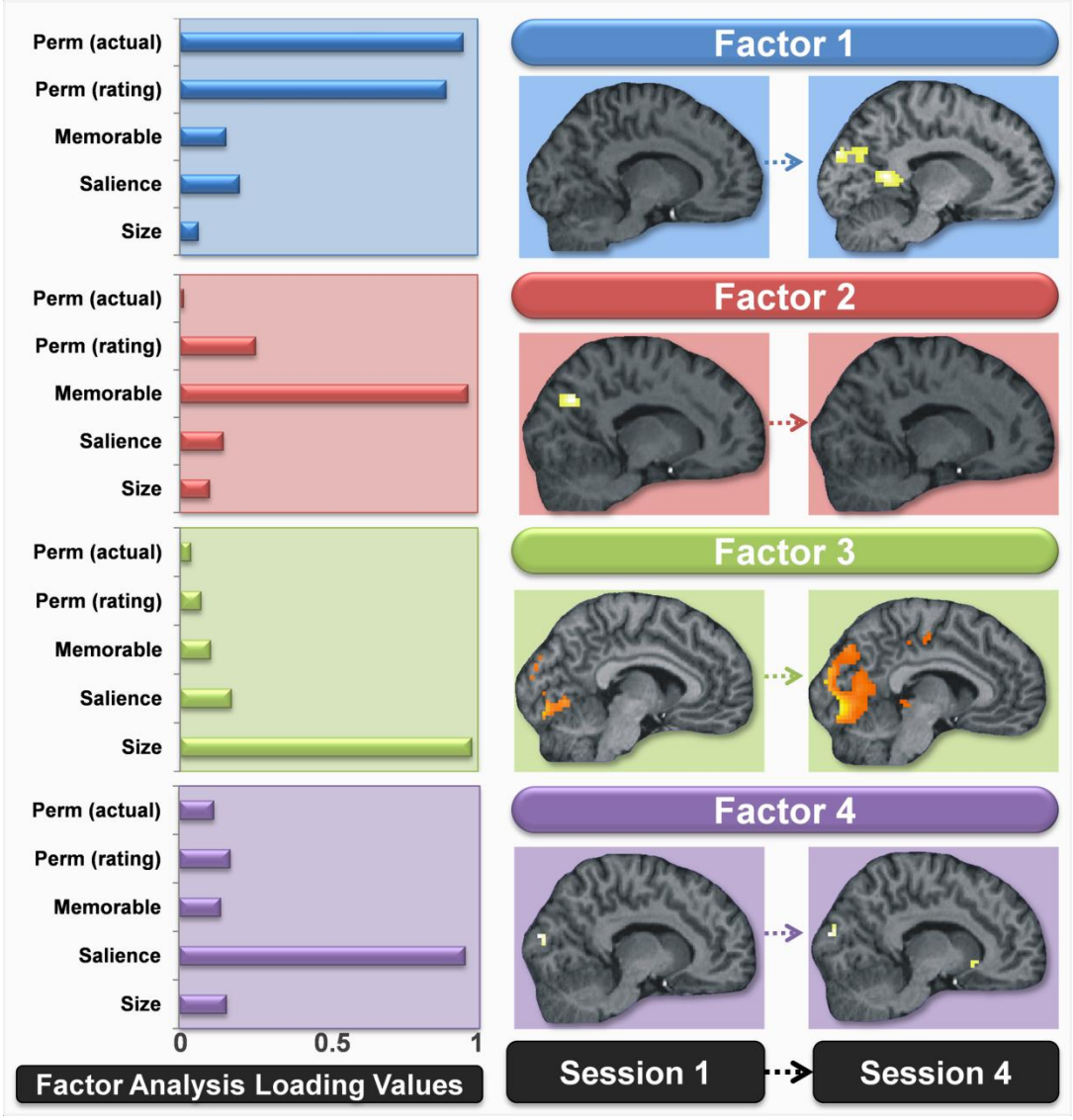

Figure 35 Changes in the brain regions engaged by different landmark features over the course of learning. The bar graphs to the left show how strongly each of the four factors from the principal components analysis were related to the various features rated by subjects in the post-scan debrief (see also Table 3; blue = factor 1, red = factor 2, green = factor 3, purple = factor 4). The associated brain regions responding to these four factors in the first and last quarters of learning are also shown. The more permanent landmarks (blue) produced responses in RSC and POS by the end of scanning having not done so before. Landmarks with greater values for factor 2 engaged POS at the start but not the end of learning. Activations for factors 3 (green) and 4 (purple) in more posterior visual areas remained constant throughout. All activations are shown on an MRI brain scan of the same single subject. Each factor's activations are shown on the same sagittal slice and all are shown at a whole brain uncorrected threshold of $p < 0.00001$ for display purposes (note that this threshold was chosen as it provides the clearest summary of how activations for all four factors changed over the course of scanning).

Thus, there were parts of the POS which initially responded to more memorable landmarks but then switched their response to more permanent ones (Figure 36A). Given this overlap, I plotted the response profiles of voxels in this overlapping region for the two factors. I extracted contrast estimates of the principal eigenvariate of responses within the overlapping voxels for factor 1 (permanence) and 2 (memorableness) in each of the four

scanning runs using the MarsBaR toolbox and averaged across all subjects. Figure 36B shows the clear switch in responses within this region; with large activations initially present for the most memorable items (factor 2), but as subjects learned about the landmarks it instead (in the middle of the third quarter) became increasingly engaged by those which were more permanent (factor 1).

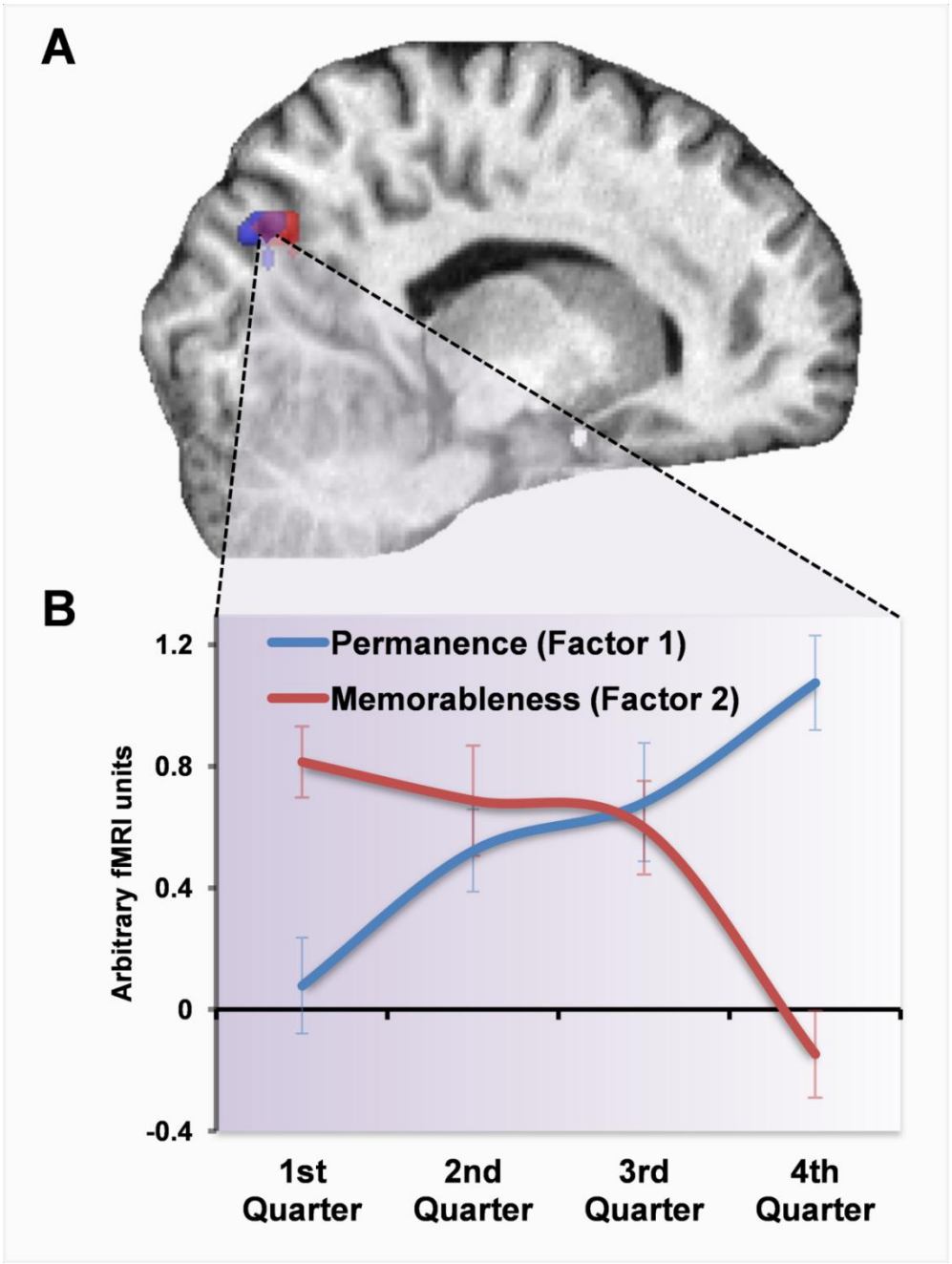

Figure 36 Response profile in the POS. (A) Overlapping parts of POS (purple) responded to more memorable landmarks (those with higher factor 2 values) in the first quarter of learning (red) and more permanent ones (with higher values for factor 1) in the final quarter (blue). (B) The response profile of the overlapping (purple) voxels for the two factors throughout whole scan. Responses were initially greater for memorable landmarks but then switched over the course of learning to eventually become responsive to permanence. Activations are shown at the default threshold of $p < 0.05$ (FWE).

Responses to the size and salience related factors (factors 3 & 4 respectively) remained constant throughout learning, with the greatest activations consistently occurring in posterior, visual areas of the brain (Figure 35 in green and purple respectively). For example, average responses across learning were greatest for larger landmarks in a cluster located in superioposterior parts of the occipital lobes (18, -88, 22; Z = 7.71), whereas a smaller cluster in just the right hemisphere was most active for more salient landmarks (21, -91, 16; Z = 5.54).

In summary, as subjects learned the permanence of landmarks, a representation of this emerged within the RSC. POS also developed responses to more permanent landmarks, but this region was also initially activated by landmarks which were subsequently remembered better. The HC and PHC were eventually more engaged by the most stable items, but later on and less strongly than the two primary regions. More perceptual features of the landmarks, like their visual salience and size, were associated with tonic responses in posterior visual areas.

5.3.4 fMRI: accounting for subject-specific learning differences

I compared three methods of modelling the learning state of subjects throughout the scanning period, based upon the responses they made during the questioning period within each sweep. The Bayesian implementation of a "state-space" model provided a better fit by both accuracy measures (MSE = 204, SD = 88; r^2 = 64) than the "state-space" model estimated by maximum likelihood (MSE = 226, SD = 85; r^2 = 44) and the moving averages model (MSE = 221, SD = 86; r^2 = 36). I generated learning curves for each subject from this winning model; examples of three such learning curves are shown in Figure 37. I then used the learning curves to directly look for regions, anywhere in the brain, where responses matched how well a subject knew about the permanence of landmarks.

Comparing the difference in responses to permanent and transient landmarks according to how well subjects knew their permanence, the greatest activation was in the RSC (9, -58, 22; Z = 4.38), a second peak was also present in the body of the caudate nucleus (18, -10, 25; Z = 4.03). The RSC activation was also significant after applying small volume correction within the whole of bilateral RSC ($p_{FWE\text{-}corr}$ = 0.01; using the same anatomical RSC mask described in Section 5.2.12). Therefore as subjects learned to distinguish

permanent from transient landmarks, responses within their RSC directly reflected their knowledge of this difference.

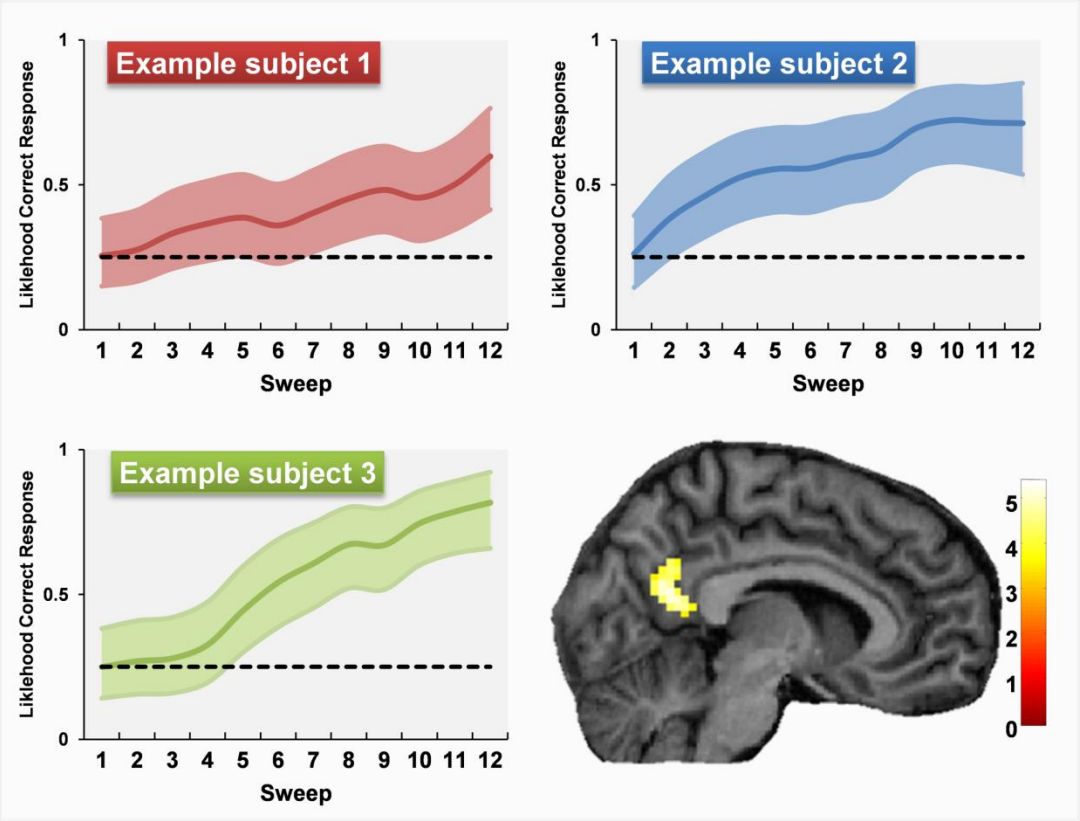

Figure 37 Example permanence learning curves and brain regions with a response profile directly related to this learning. Examples from three subjects are shown. Learning curves were used to create subject-specific parametric regressors corresponding to the amount of permanence knowledge gained throughout the scan. A whole brain comparison of fMRI responses to permanent versus transient landmarks according to how well subjects knew their permanence revealed responses in RSC directly related to these curves (displayed at $p < 0.001$ whole brain uncorrected).

5.3.5 Connectivity analyses

I then examined changes in the functional connectivity of regions associated with learning landmark permanence. A gPPI analysis revealed that in the second half of the learning period, the parts of RSC and POS which responded to landmark permanence (see Figure 34) also both showed increased functional coupling with the HC when viewing permanent compared to transient landmarks (Figure 38A). In both RSC and POS, this greater functional connectivity was with anterior parts of the HC bilaterally; for the RSC, this was with more medial parts of HC (right: 21 -16 -23; Z = 4.23; left: -30 -10 -26; Z = 3.42), whereas POS interacted with more lateral anterior HC (right: 30 -7 20; Z = 3.70; left: -30 -13 -20; Z = 3.89). Neither RSC nor POS showed any differences in connectivity related to

permanence during the first half of learning; these only emerged as subjects learned the stability of landmarks.

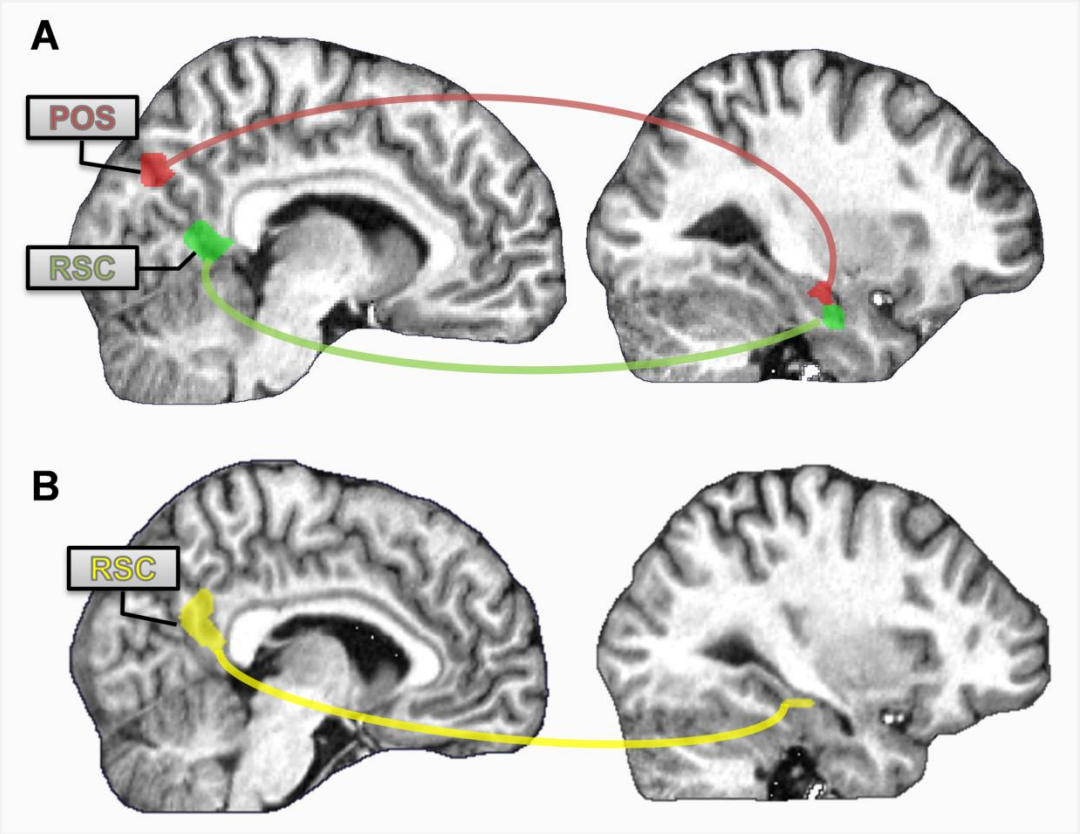

Figure 38 PPI analysis showing areas with increased functional connectivity to permanence responsive regions. (A) shows parts of the HC where activity correlated with RSC (green) and POS (red) more strongly when viewing permanent than transient landmarks by the end of learning. (B) The HC also showed increased functional connectivity with RSC while viewing permanent landmarks which was directly related to how much individual subjects had learned landmark permanence throughout the scan.

To directly assess changes in connectivity associated with learning of permanence, I performed a further gPPI analysis using the subject-specific permanence learning models. For the same parts of RSC where greater responses emerged as subjects learned the permanence of landmarks (displayed in Figure 37), the greatest increase in functional coupling developed with left lateral HC (-30, -28, -14; Z = 3.99) (Figure 38B). Thus, as subjects learned the permanence of landmarks, their RSC not only developed greater responses to the permanent landmarks but also increased its functional connectivity with the HC. In other words, the more subjects learned landmark permanence, the more their RSC-hippocampal functional coupling increased when viewing permanent landmarks.

5.3.6 Representations related to knowledge of permanent landmark locations

Given that RSC, POS, HC and PHC had all been engaged specifically by permanent items, I examined anatomically defined RSC, PHC and HC and functionally defined POS regions (see Section 5.2.12) to look for evidence of representations related to how much people knew about where permanent landmarks were situated in the environment (determined by their performance in the post-scan navigation task).

RSC, POS or PHC did not have any activity related to knowledge of permanent landmark location at any point throughout the scanning session (Figure 39). There were similarly no significant results in the HC during the first three quarters of learning. However, in the final quarter of the learning period, hippocampal responses had emerged which were significantly related to knowledge of the permanent landmark locations (log model evidence = 12.8; posterior probability = 1.0). Using the permutation function within MVB, with 100 samples, the hippocampal result in the final quarter of scanning gave a significant randomisation p value (p = 0.0396,), whereas all others were non-significant.

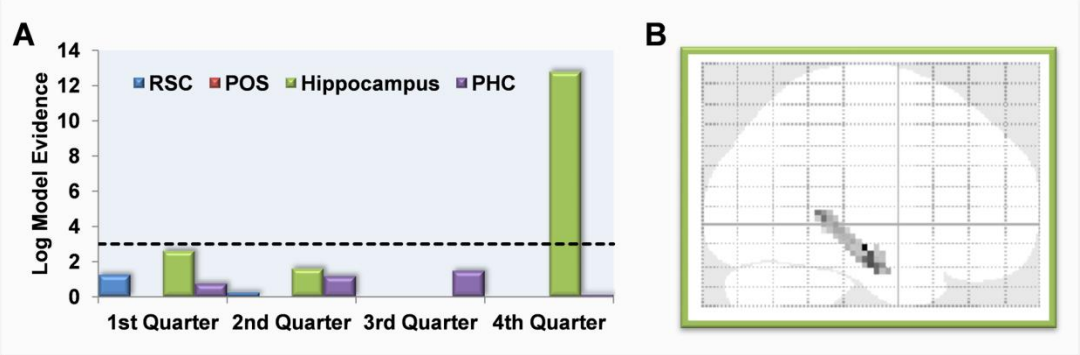

Figure 39 MVB analysis of regions with responses which map onto knowledge of permanent landmark locations. The log model evidence values for response patterns within the RSC (blue), POS (red), HC (green) and PHC (purple) relating to knowledge of permanent landmark locations are shown in each of the four scanning runs (A). By the final quarter of learning, the pattern of activity in the HC mapped onto the amount subjects knew about where permanent landmarks were located in the environment. The dashed black line indicates the threshold at which log model evidence values are considered to be reasonably strong (3; Kass and Raftery, 1995; Penny et al., 2004; Friston et al., 2008)**. (B) Shows the conditional estimates for the voxel-weights as a maximum intensity projection.**

5.3.7 Comparing good and poor navigators

In section 5.3.1, I highlighted how there was marked variation between individuals in the amount they had been able to learn about the fogworld environment. For this reason and given the results of my previous two experiments, I then directly compared the

behavioural and fMRI responses of two groups - good and poor learners - to investigate what might account for these differences.

I used the post-scan navigation task (see Section 5.2.4 and Figure 33) to define good and poor navigators groups, as this provided the most rigorous test of how well subjects had been able to learn about fogworld. Each subject's score on this task was totalled and a median split taken to determine the good and poor navigator groups. The groups were defined based upon performance in the navigation task, but as previously mentioned in Section 5.3.1, scores on this, the sketch map and landmark placement tests bore close relation to one another. There were therefore significant differences between the good and poor navigator group mean scores for both of these other tasks (Table 4; sketch map score mean difference = 3.25, t_{30} = 3.129, p = 0.004; landmark placement score mean difference = 15.4, t_{30} = 5.113, p < 0.0001). Representative examples of good and poor navigators' sketch maps are shown in Figure 40.

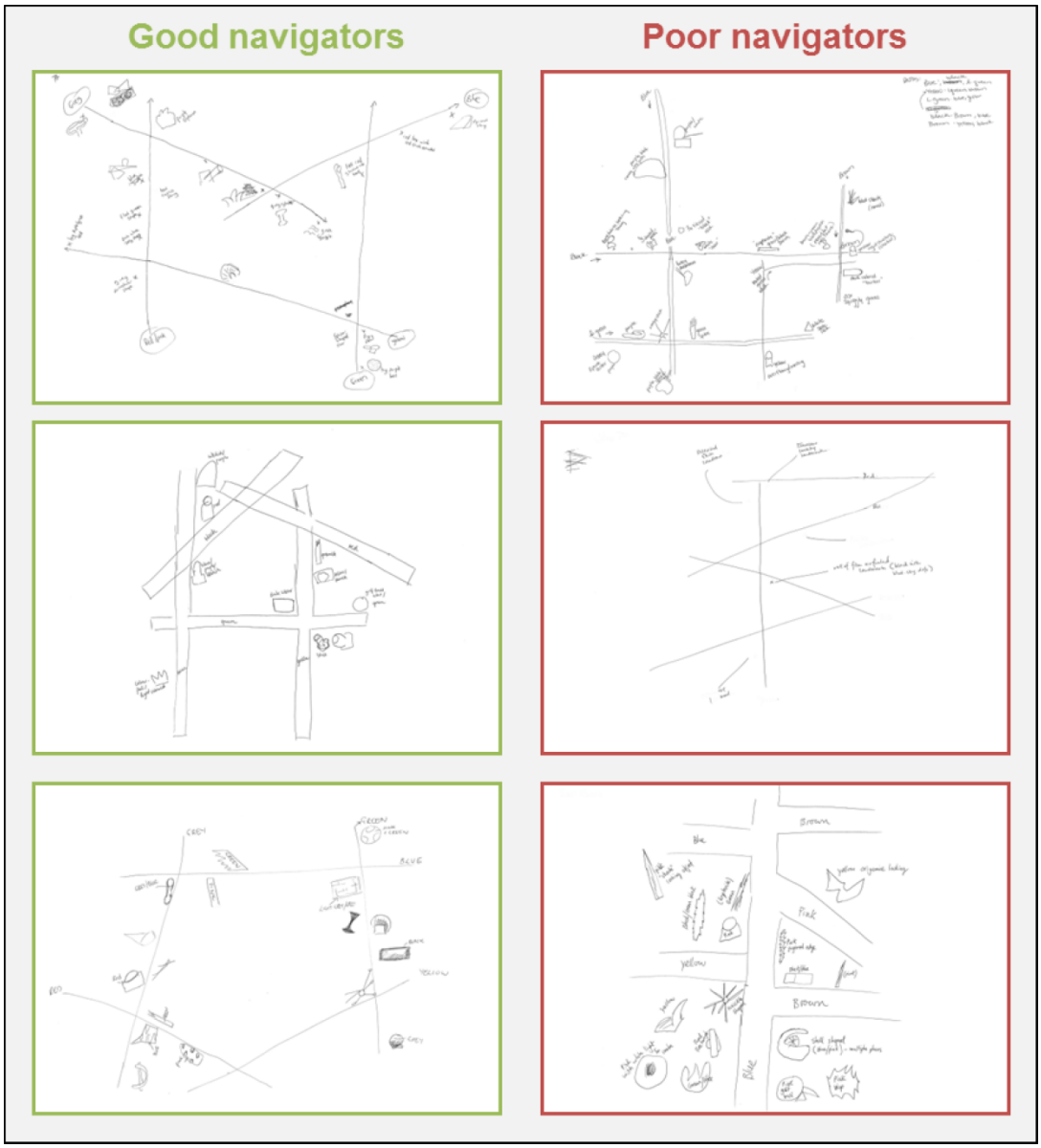

Figure 40 Sketch maps of good and poor navigators. Three representative examples of sketch maps drawn by good (green, left) and poor (red, right) navigators. Good navigators' sketch maps on average contained a greater amount of accurate detail about the layout and relationships between fogworld's five paths.

Before the start of the experiment, subjects also filled out the SBSOD questionnaire. Interestingly, the good and poor navigators according to the post-scan navigation task did not differ in terms of their SBSOD scores (mean difference = 0.4, t_{30} = 0.968, p = 0.3). This suggests that the SBSOD scale is measuring a different spatial ability to that which the post-scan navigation task requires. This is discussed in depth in the general discussion Chapter 9 (specifically Section 9.2.2).

In the post-scan debrief, all subjects rated whether or not they recognised landmarks from fogworld, as well as their permanence, size and visual salience. I compared the responses

of good and poor navigators to these questions. The two groups were equally able to recognise landmarks from the environment (% correctly recognised: good mean = 95.0%, SD 4.8; poor mean = 91.1% SD = 11.4; t_{30} = 1.245, p = 0.2) indicating that the poor navigators had not simply been paying less attention during the learning phase. The two groups also rated the landmarks as being similar in terms of their size (size ratings 1/small – 3/large; good mean = 2.1, SD 0.14; poor mean = 2.1, SD 0.17; t_{30} = 0.113, p = 0.9) and visual salience (salience ratings 1/not at all – 3/a lot; good mean = 2.1, SD 0.20; poor mean = 2.0, SD 0.21; t_{30} = 0.404, p = 0.7), so there did not appear to be any differences in how they regarded the landmarks. The good and poor navigators were also very similar according to numerous other measures (see Table 4). However, the two groups demonstrated a specific difference in their ability to learn the permanence of landmarks, with the good navigators being significantly better post-scan at identifying whether landmarks were fixed or not (% correct permanence rating: good mean = 73.5%, SD 10.9; poor mean = 57.5%, SD 10.6; t_{30} = 4.235, p = 0.0002) (Figure 41A).

Measure	Good navigators (SD)	Poor navigators (SD)	Mean Difference (95% CI)	p value
Baseline Characteristics				
n	16	16	n/a	n/a
Sex	8 females	8 females	n/a	n/a
Age	23.8	23.6	0.13 (-1.6 - 1.9)	0.9
SBSOD score	5.11 (0.9)	4.74 (1.2)	0.37 (-0.4 – 1.2)	0.3
Visual memory[1]	24.2 (4.9)	23.6 (5.0)	0.63 (-2.9 - 4.2)	0.7
Abstract reasoning ability[2]	13.8 (1.2)	12.8 (1.9)	1.1 (-0.08 - 2.2)	0.07
Debrief Measures				
Landmarks recognised (% correct)	95.0 (4.8)	91.1 (11.4)	3.8 (-2.4 - 10.1)	0.2
Landmark Permanence (% correct)	73.5 (10.9)	57.5 (10.6)	16.0 (8.3 - 23.4)	0.0002
Landmark Size (1/small - 3/large)	2.1 (0.1)	2.1 (0.2)	0.006 (-0.11 - 0.12)	0.9
Landmark Salience (1/not at all - 3/a lot)	2.1 (0.2)	2.0 (0.2)	0.03 (-0.12 - 0.18)	0.7
Sketch map (max = 10, median = 5)	6.5 (3.1)	3.25 (2.8)	3.25 (1.12 - 5.37)	0.004
Landmark placement task (max = 75, median = 33.5)	42.4 (10.6)	27.0 (5.9)	15.4 (9.27 – 21.60)	< 0.0001
Navigation task (max = 36, median = 11.5)	19.2 (6.0)	6.3 (3.4)	12.9 (9.4 - 16.4)	< 0.0001
Debrief Questionnaire				
How difficult they found the overall task (1/very easy - 5/very hard)	4.2 (0.5)	4.4 (0.6)	-0.3 (-0.7-0.2)	0.2
How difficult they found learning the environment (1/very easy - 5/very hard)	4.2 (0.7)	4.4 (0.7)	-0.2 (-0.7 - 0.3)	0.4
How frequently other thoughts came to mind/mind wandered (1/not at all - 5/often)	3.6 (1.4)	3.8 (1.0)	-0.2 (-1.1 - 0.7)	0.6
Whether they thought there was enough time to learn the environment (1/too much - 5/too little)	3.5 (0.7)	3.4 (0.8)	0.06 (-0.5 - 0.6)	0.8
Previous video game experience (1/none - 5/very experienced)	2.4 (0.9)	2.8 (1.3	-0.4 (-1.2 - 0.4)	0.7

Table 4 Characteristics of the good and poor navigator groups. Group means and between group comparisons are shown. Brackets next to the individual group mean scores denote standard deviation, whereas brackets next to the mean difference values show the 95% confidence interval. [1]Visual memory was measured using the delayed recall of the Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944). [2]Abstract reasoning ability was measured using the Matrix Reasoning sub-test of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

Throughout the learning phase during scanning there were additional mini-test periods, to gauge how subjects' learning evolved over time. I examined subjects' responses during these mini-tests to see *when* the differences apparent in the comprehensive post-scan

testing session detailed above may have arisen. As with the post-scan testing session, there were no differences in how well subjects recognised the landmarks at the start, middle or end of the learning process (Figure 41B). However, once again the poor navigators were significantly worse at identifying the permanence of landmarks not only by the final third of the learning phase (good mean % correct = 56.7, SD 13.8; poor mean = 44.7, SD 13.3; t_{30} = 2.509, p = 0.02), but as early as the middle third (after seeing them as few as 10 times; good mean = 47.5, SD 12.0; poor mean = 39.1, SD 10.1; t_{30} = 2.153, p = 0.04).

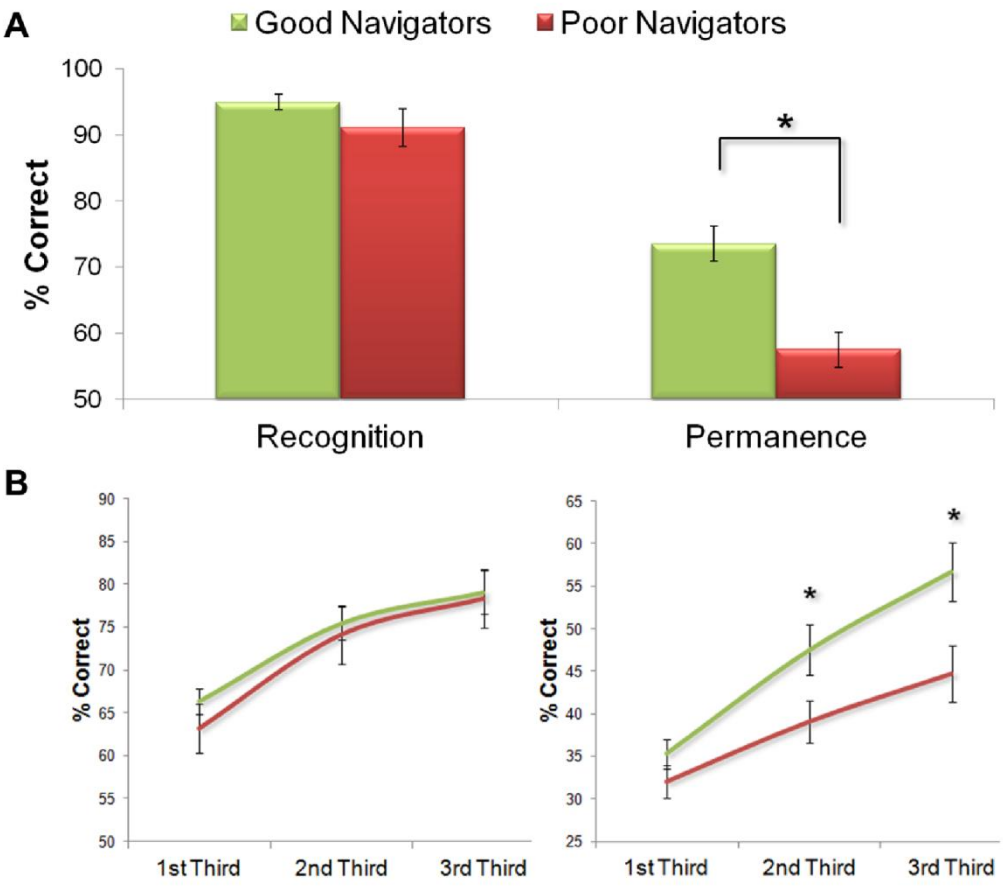

Figure 41 Differences between what good and poor navigators learned. Good and poor navigator mean (and SEM) percentage correct responses during the post-scan testing phase (A) and learning phase mini-tests during scanning (B) for the recognition and permanence questions. Graphs on the left show how well subjects were able to recognise whether or not landmarks were from the environment, while on the right they indicate how well they had learned landmark permanence. Both (A) and (B) show how good and poor navigators did not differ in their ability to recognise landmarks, but poor navigators were significantly worse at learning their permanence; with the deficit emerging in the second and final thirds of the learning phase.

The only difference, therefore, between the good and poor navigators was their ability to learn the permanence of landmarks.

Given this specific difference in the ability of good and poor navigators to identify whether landmarks were permanent or transient, I looked for associated differences in their neural responses. I compared the fMRI responses of good and poor navigators, focussing specifically on three brain areas in particular based upon their previously demonstrated roles in processing features of real-world stimuli, RSC and PHC (see Chapters 3 and 4) and relation to navigation expertise, the HC (Maguire et al., 2000; Ohnishi et al., 2006; Janzen et al., 2008; Woollett and Maguire, 2011). I defined the regions anatomically using the masks described in Section 5.2.12.

Similar to the majority of the other imaging analyses (see Sections 5.2.8, 5.2.9 and 5.2.10), the comparisons of good and poor navigator fMRI responses were made for the time period while subjects viewed images of single, isolated landmarks during the in-scan questioning periods.

I specifically compared responses for permanent and transient landmarks in the three ROIs for good and poor navigators. Separate subject-specific regressors were created for the time permanent and transient landmark images were in view to be directly contrasted. These regressors of interest were convolved with the canonical HRF. Additional regressors were created to account for the remaining time during the scanning session and subject-specific head movement, all of which were treated as covariates of no interest. The first and second half of the learning phase (scanning runs 1-2 and 3-4 respectively) were analysed separately in order to examine changes occurring over the course of learning. For each voxel, subject-specific parameter estimates pertaining to each regressor of interest (β) were calculated. The primary contrast of interest was a direct comparison of the permanent and transient landmark regressors and contrast estimates of the principal eigenvariate of this contrast's responses within the three ROIs were extracted using the MarsBaR toolbox. Figure 42 shows the averaged responses of good and poor navigators in both the first and second half of learning.

I first performed ANOVAs to assess whether there were any differences in how RSC, HC or PHC responses changed over the course of learning depending upon a person's navigation ability. Only in RSC was there a significant interaction indicating a difference in how good and poor navigator responses to permanent and transient landmarks changed over the course of learning (interaction - RSC: $F_{1,30} = 4.412$, $p = 0.04$; HC: $F_{1,30} = 0.685$, $p = 0.4$; PHC:

$F_{1,30}$ = 0.489, p = 0.5). I then interrogated these results further using t-tests. As expected, early on in learning phase (in the first half), the responses of good and poor navigators did not differ in their permanence discrimination in any of the three regions (light shaded bars in Figure 42). However, RSC of good navigators then went on to develop significantly greater discriminatory responses between the permanent and transient landmarks by the end of scanning (mean increase = 0.87, SD 1.4; t_{15} = 2.507, p = 0.02). The same did not happen in the RSC of poor navigators (mean difference = 0.14, SD 1.1; t_{15} = 0.525, p = 0.6) or the HC or PHC of either good (HC mean difference = 0.68 SD 1.4; t_{15} = 1.946, p = 0.07; PHC mean difference = 0.71 SD 1.7; t_{15} = 1.677, p = 0.1) or poor (HC mean difference = 0.46 SD 1.4; t_{15} = 1.319, p = 0.2; PHC mean difference = 0.65 SD 1.3; t_{15} = 1.916, p = 0.08) navigators. This meant that by the end of learning, good navigator RSC responses discriminated the permanence of landmarks significantly more than that of poor navigators (mean difference = 0.74, Std Error Difference 0.35 ; t_{30} = 2.112, p = 0.04), but there were no such differences in either of the other two regions (HC: mean difference = 0.35, Std Error Difference 0.39; t_{30} = 0.908, p = 0.4; PHC: mean difference = 0.18, Std Error Difference 0.39; t_{30} = 0.473, p = 0.6). Therefore, the less effective learning of landmark permanence by poor navigators was associated with a less developed discrimination between permanent and transient landmarks specifically within their RSC.

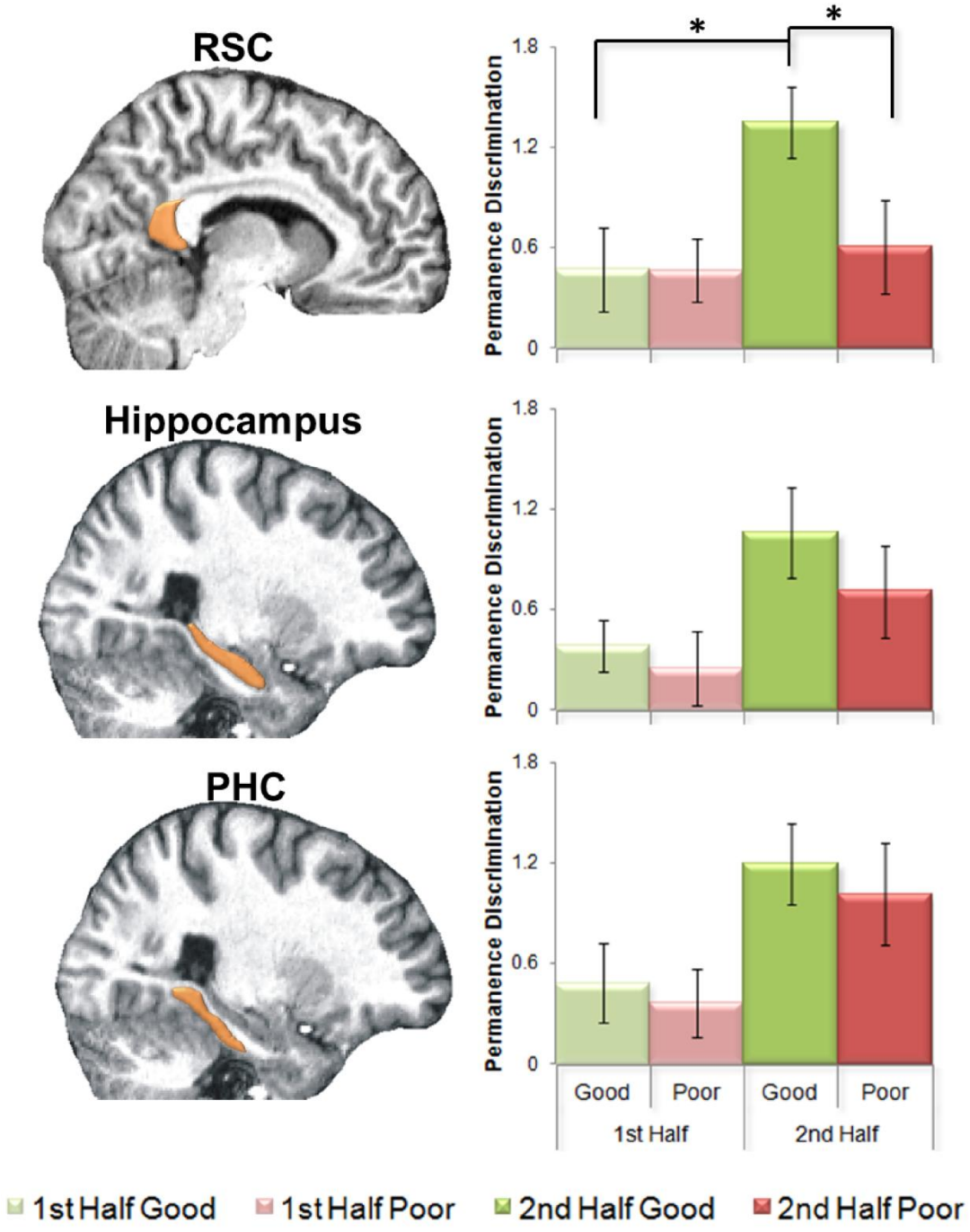

Figure 42 Permanence discrimination difference between good and poor navigators in RSC. Graphs show the difference in fMRI BOLD response (in arbitrary units) for permanent and transient landmarks in the RSC (top), hippocampus (middle) and PHC (bottom) of good (green) and poor (red) navigators in the first (light shading) and second (dark shading) halves of the learning phase. The locations of the three brain regions are indicated on a sagittal slice of a single, representative subject's structural MRI scan. In the RSC, but no other region, good navigators had a significantly greater difference in response between permanent and transient landmarks than poor navigators.

5.4 Discussion

Having subjects learn a virtual reality environment while undergoing whole brain fMRI scanning allowed me to track the neuronal evolution of representations of landmark permanence and other features.

I demonstrated that as the permanence of 'alien' objects was learned, RSC became selectively engaged by non-moving, fixed landmarks and not those which constantly changed their location. Furthermore, modelling how much subjects knew about the permanence of landmarks throughout the course of learning revealed that this was directly related to activity solely in RSC. The POS initially responded to the most memorable landmarks, but as more was learned about them, it switched to instead become engaged by the permanent items. The HC, despite not previously being implicated in processing item permanence, was eventually activated by the stable landmarks at the end of the scan experiment. At the same time as this hippocampal response to the fixed items emerged, it also showed increased functional coupling with the RSC, and activity patterns within the HC mapped onto how much subjects knew about where the permanent landmarks were located in the environment.

This experiment provided two further novel findings: First, poor navigators demonstrated significantly less learning of the permanence of landmarks. Second, this was associated with significantly less discrimination between permanent and transient landmarks in their neural responses within RSC but not PHC or HC. It seems, therefore, that poor navigation ability could result from defective processing of the most stable environmental cues in the RSC, which could in turn hinder the reliability of spatial representations based upon them.

5.4.1 Representation of landmark permanence in RSC

Given the short timescale over which subjects learned the permanence of the completely novel landmarks within an abstract virtual world, it is notable just how strong the RSC permanence representations were. It did not even take the whole scanning session for RSC to develop clear sensitivity to the stability of landmarks; RSC was considerably more active when viewing permanent items within just 10 exposures. This demonstrates the

remarkable adaptability of the process and hints at it being fundamental for learning about and orientating within our surroundings.

My previous two experiments used everyday, outdoor items. These familiar, real-world stimuli will have inevitably come with semantic and associative 'baggage' making it difficult to achieve precise experimental control over numerous different features of the items which are often correlated with one another (Troiani et al., 2012) and could potentially confound any conclusions drawn (Sugiura et al., 2005). Here however, virtual reality allowed me to investigate completely pure representations of landmark permanence as this new information was freshly acquired.

An additional advantage of using the virtual reality world was that it provided a more ecologically relevant means with which to test the representation of landmark properties; it ensured subjects were actively engaged with the landmarks as they learned the layout of the environment. However, one potential drawback of such a naturalistic, freely-behaving task is that it could introduce noise and variability to subjects' neural responses. This limitation was avoided by measuring neural responses to the landmarks while they were being viewed in complete isolation, as images presented between the learning videos. This not only ensured that subjects were focused on the specific relevant individual landmark at the necessary time, but also removed potential visual confounds which would have been present during the videos (e.g. path colour).

Taken together with my previous two experiments, this study highlights the highly flexible nature of RSC permanence representations. They can exist for items which are both: real-life and virtual; highly familiar or newly encountered; viewed passively or actively interacted with and when attention is explicitly drawn or not to their permanence.

By scanning subjects as they learned the permanence of items, I was also able to uncover new information about how representations of landmark properties develop before they have become fully established. At the start of the learning process, RSC was not responsive to any feature of the items. Indeed, it was only by the third quarter of scanning that RSC became engaged at all, specifically by the permanent landmarks. The same was not true, however, for the POS region. The POS became strongly responsive to permanent landmarks at a similar time to RSC, but unlike RSC was engaged by another feature of the

items (their memorableness) before their permanence became apparent. This is an important distinction as it indicates that the representation that develops in RSC is not only very sensitive to permanence but it is also highly specific. In the absence of reliable information regarding the permanence of landmarks, RSC did not inappropriately respond to some other feature.

Modelling the learning-state of each individual subject throughout the experiment provided further insight into the nature of how RSC processes landmark permanence. Activity in the RSC was directly related to how well people knew the permanence of items. This reveals that the permanence representation that emerges is not just a simple binary response which indicates whether or not an item is known to be particularly stable. Instead it appears to be more informative, relating to the precision with which the permanence of landmarks is known. In addition, therefore, to identifying the most stable environmental cues, the RSC could also indicate how reliable subsequent representations based upon them might be.

As well as RSC, part of the body of the caudate was also more active for permanent landmarks in relation to the amount people had learned landmark permanence (Section 5.3.4). However, this same region was not more active for any of the contrasts comparing responses to permanent and transient landmarks in Sections 5.3.2 and 5.3.3. Activity in the caudate nucleus has previously been linked to poor navigation ability (Wegman and Janzen, 2011), but more specifically the use of non-spatial (Iaria et al., 2003) and stimulus-response (Bohbot et al., 2011) based navigation strategies. So it is not clear precisely what the caudate activation in this experiment might have reflected, but it could perhaps be related to simple stimulus-response type representations developing for permanent landmarks as people came to recognise them. For example, if a permanent landmark is consistently encountered before one of the intersections on a path, the caudate nucleus may come to register this information. Associating landmarks with certain subsequent (or preceding) spatial features is not strictly a response *per se*, but the two may share some common form of neural representation.

Overall, these results point towards a sophisticated, selective and specific processing of landmarks within RSC based exclusively upon their permanence. It will be interesting for further work to explore if higher order representations like this exist for other experience-

dependent features in other brain regions or whether RSC permanence processing is a special case.

5.4.2 Role of the POS

Bilateral parts of the POS demonstrated an intriguing profile of responses; first activated by the items which were subsequently remembered better by subjects, then only later becoming engaged by the fixed landmarks once their permanence was known. This region was not implicated in processing permanent landmarks in either of my previous experiments. So what is it about the memorable landmarks at the start and permanent landmarks by the end of learning in this study which engaged POS, and which was not a feature of my first two experiments?

These combined results are consistent with POS playing a role in relating landmarks with a specific location. This would be in keeping with previous interpretations of processing within RSComp (Vass and Epstein, 2013), which often extends into more posterior parts of the POS. In such an interpretation, at the start of the learning process, encounters with the most memorable landmarks (and the location they were experienced in) will have been most apparent and so elicited the largest early responses. The level of activity for memorable landmarks would then diminish as ones which are not fixed are repeatedly encountered in conflicting places. The region would, at the same time, become increasingly engaged by the permanent landmarks with repeated experience of them in the same place. The large responses at the start of the scan to the most memorable landmarks would also explain why, unlike RSC, activity in POS was not directly related to the permanence learning-state. This interpretation would also explain why POS has not previously been found to process permanent landmarks in my two previous experiments, as those everyday items were never associated with any specific locations.

So whereas the RSC appears more specialised in processing the permanence of landmarks, the response profile of POS is more consistent with it playing some role in relating landmarks with the specific locations where they have been encountered.

5.4.3 Role of the HC

Another region which responded to permanent landmarks in the present study, having not previously been found to do so, was the HC. Like the POS, this could again be explained by the fact that the present study, unlike my previous ones, examined items which were connected with specific locations within a large-scale environment. However, in contrast to POS, the HC was not engaged by any landmarks early on, only later once the permanent ones became apparent. Furthermore, unlike RSC, activity in the HC was not directly related to how well subjects had learned the permanence of items. Whereas RSC appeared to track the general permanence of landmarks, the HC was only engaged by landmarks which were both known to be permanent *and* associated with a specific place.

The MVB analysis indicated that once the hippocampal representation had emerged, it contained more spatial detail related to how much subjects knew about where the permanent landmarks were located. It seems then that the RSC may universally code for the stability of features within an environment, potentially providing this as an input to the HC, which could in turn utilise the information to build detailed spatial representations based upon the most reliable cues. This would be consistent with the dense anatomical connectivity that exists between the two regions (see Section 1.3 and van Groen and Wyss, 1990, 1992; Amaral and Witter, 1995; Vann et al., 2009; Sugar et al., 2011), the fact that inactivation of RSC is associated with disruption of hippocampal place fields (Cooper and Mizumori, 2001) and previous accounts of hippocampal involvement in retrieving spatial information about objects (Save et al., 1992; Manns and Eichenbaum, 2009; Baumann et al., 2010; Ekstrom et al., 2011).

I did not find responses relating to the landmarks in any other brain regions, but object-centred firing has also been observed in rodent lateral entorhinal (Deshmukh and Knierim, 2012) and anterior cingulate cortex (Weible et al., 2012), even for locations formerly (but no longer) occupied by objects (Tsao et al., 2013). It will be interesting for future work to explore whether similar representations may also exist in humans and how they may relate to the current findings.

5.4.4 Uses of the RSC permanence representation

The present study provides an alternative interpretation of previous work which found that RSC is engaged when making judgements about locations relative to stable items (Committeri et al., 2004; Sulpizio et al., 2013; see also Section 1.10.4). These previous studies concluded that activity within the RSC reflected coding of space relative to stable landmarks. However, my findings suggest it could in fact indicate a more simple, fundamental representation of the landmark itself, specifically that of its inherent stability. This suggests that the elementary discrimination between stable and moving landmarks demonstrated here within RSC, is then used to anchor representations of surrounding space. Sulpizio et al. (2013) also found RSC to be sensitive to viewpoint direction within a room but not relative to unstable objects. This could be linked to the presence of head direction cells within the RSC (see Section 1.4), perhaps suggesting that head direction cell firing is centred upon permanent landmarks and this information is integrated within RSC.

It would therefore appear that the discrimination between stable and changeable landmarks in RSC could play a crucial role in a number of fundamental computations when processing space. This would go some way in helping explain its strong, ubiquitous engagement during scene processing, while navigating (Section 1.10.5), recalling episodic memories and imagining future events (Section 1.10.6). It also makes the insights into potential mechanistic details of the RSC permanence representation presented here particularly significant. As discussed earlier (in Section 5.4.1), the RSC response to stable items is both highly sensitive and specific as well as potentially containing more informative detail about the precision of permanence representations. These would all be crucial attributes for the fundamental role I propose RSC is performing; if representations of space are based upon permanence information from RSC, it needs to be dependable. If this were not the case, one could imagine a situation similar to what is seen in people with impaired RSC function due to lesions (see Section 1.6) or Alzheimer's disease/Mild Cognitive Impairment (see Section 1.7) – i.e. that of disorientation and amnesia - as the fundamental basis of spatial representations is compromised. A similar interpretation could also be applied to the differences I found between good and poor navigators in this experiment, as I will now discuss.

5.4.5 RSC permanence processing and navigation ability

Differences have previously been found in the brains of good and poor navigators, related to both navigation (Maguire et al., 2000; Hartley et al., 2003; Ohnishi et al., 2006; Woollett and Maguire, 2011) and processing space more generally (Epstein et al., 2005; Janzen et al., 2008; Baumann et al., 2010; Wegman and Janzen, 2011). My first experiment revealed that poor navigators were also specifically less reliable at identifying everyday, outdoor items which are permanent and this was associated with reduced responses in their RSC while viewing them (see Chapter 3). My second experiment took this further, indicating that the RSC of good navigators contained more information about the permanence of multiple landmarks viewed simultaneously (see Chapter 4). It was not clear, however, whether inherent differences in neural responses as people *learn* about new environments may impact upon wayfinding ability. Previous descriptions of changes in the brain associated with navigation ability have tended to be centred upon the HC and are only evident over longer time scales, either days (Janzen et al., 2008) or years (Woollett and Maguire, 2011). Here, I was able to directly address these issues.

Section 5.3.1 highlights that over the course of learning this alien virtual reality environment, there was large variation in people's ability to acquire important orienting information. Section 5.3.7 goes on to demonstrate that these differences between good and poor navigators emerge very rapidly. Having seen the landmarks fewer than 10 times, poor navigators were significantly worse at identifying which were the most stable and reliable environmental cues. This demonstrates that poor navigators do not merely differ in utilising permanence information which has been learned over extended periods of time (Sections 3.3.3 and 4.3.4), but that they show poorer learning about which landmarks are fixed and which are not. Furthermore, the changes are only evident for how good and poor navigators process the *permanence* of landmarks, not any other feature. This is borne out in both people's behavioural responses (Figure 41) and those of their RSC (Figure 42).

This specific link between wayfinding ability and learning of landmark permanence opens up exciting new avenues to better understand what impacts upon our ability to orientate and navigate within an environment. It also presents a novel way in which to try and improve people's ability to navigate. If poor navigation ability is at least partly explained

by a failure to form reliable representations of environments by basing them upon inappropriate, non-permanent landmarks, it might be possible to 'train' poor navigators to directly focus on and learn to use the most permanent environmental cues. This kind of intervention could perhaps even be beneficial in the earliest stages of Alzheimer's dementia to improve not only navigation performance but also more general spatial orientation at least in the early phase of the disease.

One interesting final point of note is that the good and poor navigators, as defined by performance in the post-scan navigation task, did not differ in terms of their scores on the SBSOD questionnaire. This suggests that the SBSOD scale might not always be the most appropriate measure of ability at certain spatial tasks, such as this experiment's explicit learning of specific new information about alien landmarks. I discuss this issue in greater depth in Section 9.2.1, but it is something which I also take into account in my subsequent experiments. Rather than solely relying on the SBSOD to compare groups of people who self-report as good or poor navigators in everyday life, where possible I seek to use more direct, objective measures related to an experiment's specific task demands.

5.4.6 Conclusions

In summary, in this experiment I demonstrated the ability of different brain regions to develop selective responses to the most stable items in an environment. These neural representations emerge rapidly for completely novel, alien landmarks situated in an abstract virtual environment. RSC develops specific and reliable responses to only the fixed landmarks and activity in this region is directly related to how well their permanence is known. Parts of POS initially responded to landmarks which subjects subsequently went on to remember better, but over the course of learning switched to become engaged by the most permanent landmarks. The HC, not previously implicated in processing permanent landmarks, developed responses to fixed items later on than the other two regions whilst also displaying increased functional coupling with both RSC and POS. Hippocampal activity was also related to subjects' knowledge about permanent landmark locations. These results are consistent with the RSC coding for the permanence and reliability of environmental cues which could in turn act as a fundamental input for other regions, such as the HC, to build more detailed spatial representations centred upon the most stable environmental features. I also went on to demonstrate that RSC processing of

stable environmental cues is closely linked to the corresponding ability to identify these permanent landmarks behaviourally. Poorer performance on this very specific task (learning whether or not a landmark is permanent), was in turn directly linked to a person's more general ability to orientate and navigate in an environment.

Chapter 6: Experiment 4

Does scale matter?

6.1 Introduction

My first three experiments provide evidence that the RSC, along with a set of related brain regions, processes items which maintain a permanent location in space. These representations of landmark permanence in RSC are also linked with a person's ability to navigate, both in the real world (Experiments 1 and 2) and in a newly-learned virtual environment (Experiment 3). This relationship between the ability to orientate oneself in space and RSC permanence processing provides an intriguing new, specific target for understanding the more general memory and orienting deficits brought about by extensive damage to RSC by lesions (Section 1.6) and in the earliest stages of Alzheimer's dementia (Section 1.7).

All my previous experiments, however, only examined permanence-related responses for landmarks which are associated with large-scale, three-dimensional environments. Tasks in these complex settings often require a high cognitive load, making them unsuitable for use with patient populations or indeed with non-human species. In the experiment described in this chapter, I aimed to establish whether a simplified desktop computer task could be used to establish neural representations of landmark stability. If this were possible, it could provide a more straightforward means with which to assess how people (and other species) process permanence. It could even perhaps be adapted more generally to create a method for helping 'train' more efficient and effective permanence representations.

The first goal of this experiment was therefore to assess whether permanence representations can emerge for landmarks learned solely in small scale space (on a two dimensional computer display) and then subsequently recalled by people while undergoing fMRI scanning. Specifically, I tested the hypothesis that permanence-responsive regions, RSC in particular, would become more engaged when people recall permanent rather than transient items.

Another aspect I set out to study in this experiment was the RSC's potential involvement in scene construction. In the general introduction (Chapter 1), I outlined how the RSC's importance for a broad range of tasks requiring the manipulation of spatial information during navigation (Section 1.10.5), making spatial judgements (Section 1.10.4) or more general processing of scenes (Section 1.10.3) and autobiographical memories (Section 1.10.6) could be subsumed under the common underlying processes of scene construction (Section 1.11). However, despite being an integral part of the scene construction network, the precise contribution RSC might make remains untested; previous research has instead tended to focus more on other regions such as the hippocampus (Maguire and Mullally, 2013; Mullally and Maguire, 2013). Given RSC's responsivity to permanent landmarks, its involvement in scene construction could be a consequence of the process' prevailing use of stable spatial cues. However, permanence-related responses have never been demonstrated for constructive, endogenous processes, only with externally presented visual images. In this experiment I therefore also sought to establish whether it is possible for permanence representations to be elicited by purely internally generated mechanisms, with people simply imagining a landmark. If RSC involvement in scene construction does in fact reflect processing of permanent environmental features, it would be expected to favourably process permanent rather than transient imagined landmarks. Having people imagine landmarks in this way might also be expected to engage other more established nodes in the scene construction network, such as the hippocampus, so I also aimed to determine if and how RSC may interact with these regions.

Using an imagination-based paradigm also presented the opportunity for me to investigate whether the setting in which landmarks are recalled (i.e. in large or small scale space) might impact upon their neural representation.

In this experiment, I therefore had three main aims: first, to establish whether permanence representations can emerge for items learned in a simple two-dimensional desktop array; second, to test whether permanent landmarks only engage RSC and related regions when viewed as an external visual stimulus or whether internally-driven constructive representations produce similar activity; third, to assess whether the spatial scale in which a landmark is recalled has any influence upon the nature of the neural responses it elicits.

6.2 Methods

6.2.1 Participants

Thirty two participants (16 female, mean age 22.3 years, SD 2.6) took part in the experiment. All were healthy, right handed, spoke excellent English, had normal vision and hearing and provided written informed consent in line with the local research ethics committee. None of these subjects had taken part in the previous fogworld study.

The experiment had three main phases: a pre-scan learning session, this was immediately followed by a testing session inside an MRI scanner and then there was a final post-scan debriefing session.

6.2.2 Pre-scan learning phase

In the pre-scan learning session, participants were presented with numerous images, one after the other, on a computer screen. These images showed novel, previously unfamiliar, items located in one of 56 possible locations on the screen (laid out in an 8x7 grid). The unique items were drawn from the same set of stimuli created for Experiment 3 (see Section 5.2.2) using Blender 2.61 (Blender Foundation, Amsterdam, Netherlands, http://www.blender.org/). However, whereas previously the items were presented to subjects within a large scale, three dimensional virtual reality environment, here, they were only ever shown as part of a two-dimensional array.

The novel items were each displayed multiple times during the learning phase and would either always appear in the exact same position on the screen (permanent items) or in a different location every time (transient items). The permanent and transient items were matched for their salience, any associations with real-life items, likeableness, animateness and memorableness, as indicated by a separate group of subjects in Experiment 3's ratings study (Section 5.2.1 and 5.2.2). The locations which permanent and transient items appeared were also matched, so that the frequency that the two types appeared in the four quarters of the screen was equal. There were a total of 50 items and on each learning trial they were presented in pairs to optimise the efficiency of learning, in as short a time as possible before commencing fMRI scanning. These pairs were fixed, so that each item

was always presented along with its specific partner. The 25 pairs were matched so that permanent and transient landmarks were equally likely to be paired with a permanent or transient landmark. A pair of two permanent landmarks would both always be shown in the same location on the screen; pairs which were both transient would each appear in a different place on every exposure; for a pair containing a permanent and a transient landmark, one would always be in the same screen location and the other would be in a different place every time subjects saw it.

Subjects were informed that they would be shown a number of different items, some of which would always appear in the same location and others which would be in a different place every time they saw it. They were instructed that they had to learn to recognise whether or not an item was always in the same place and for those that were, be able to identify what that location was. The learning session consisted of 15 learning "sweeps". In every sweep, each of the 25 item pairs was presented one at a time in a randomised order for 4.5 seconds with a 0.5 second interval between images. These timings and numbers of stimuli were found to be optimal in pilot studies (see Section 6.2.5); ensuring people would be able to learn the necessary information sufficiently without being too fatigued going into the testing phase.

After sweeps 1, 3, 7, 9 and 13, there were a series of mini-tests in order to keep participants engaged and motivated throughout the learning phase. Each of these 5 mini-tests had 2 trials, in which an image of a single item was presented in the centre of the screen for 3 seconds. Participants then had to indicate whether or not they recognised it (Have you seen this item before? Yes/No), whether it was permanent or transient (How many different locations? Only 1/Different every time) and whether they could identify its paired item from a set of four options (Which is its partner? choice from 4 items, 3 of which had not previously been seen). The 10 items used for these mini-tests were subsequently excluded from the set used for the testing phase inside the scanner.

After the end of the 15th learning sweep, the testing phase task that would occur in the scanner was explained to participants (see Section 6.2.3). They then practised the task to ensure it was fully understood before commencing scanning. Just before entering into the MRI scanner, participants were shown one final 16th learning sweep to ensure the information was fresh in their mind at the start of the testing phase.

6.2.3 Testing phase during fMRI

While undergoing fMRI scanning, participants imagined viewing the items they had just learned in one of two ways: in either small- or large-scale space. In both conditions, participants were instructed to imagine the item in isolation, in a single location where they thought it belonged. For small-scale recall trials, participants were instructed to imagine viewing it as if it were on a screen in front of them. For large-scale recall trials, they were instructed to imagine being positioned at a single specific location within a large scale "world" (which corresponded to the bottom centre of the screen in the learning phase), looking at the landmark from a ground-level perspective.

Before starting this task inside the scanner, participants were given thorough training to ensure they fully understood what was required of them. It was emphasised that items should be imagined as vividly as possible "in their mind's eye", only in a single location and completely on their own (i.e. not think of the item it was paired with during learning). They were shown example images of how they should try to picture items in both small- or large-scale and also practised imagining items in both scales while describing out loud what it was they were picturing to ensure they were performing the task correctly. No participants reported any difficulty with doing any of the tasks.

On each trial inside the scanner (Figure 1), a cue image showing a single item was displayed in the centre of the screen for 4 seconds. Beneath the item was a single word indicating whether the item should be imagine in large scale ("world") or small scale ("screen"). An image was then presented instructing participants to "Close eyes and imagine….". After 6 seconds of imagining, a chime sounded indicating that participants should open their eyes. A question was then presented asking where they had just been imagining the item. Participants could select from one of four options for both large (far left, far right, near left, near right) and small (top left, top right, bottom left, bottom right) scale trials. A fixation cross was then presented in the centre of the screen for a randomly jittered time between 2 and 4 seconds before the next trial commenced.

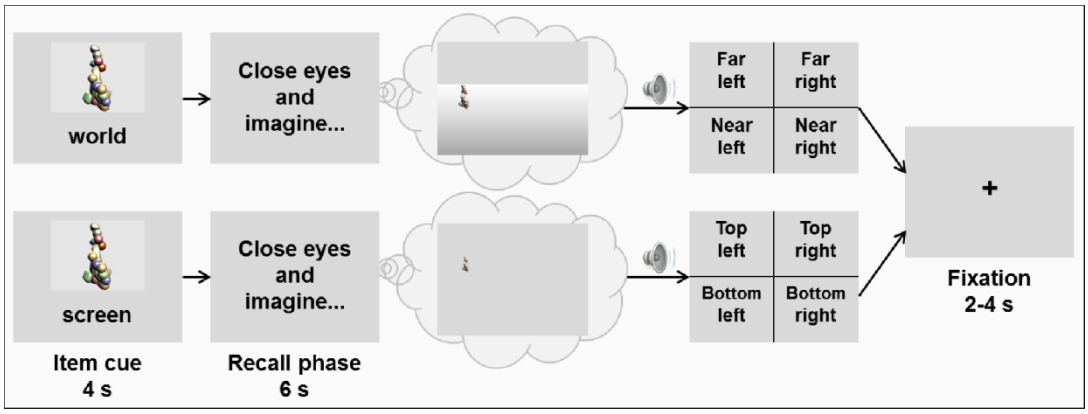

Figure 43 Example testing phase trials. For each trial in the testing phase, while undergoing fMRI scanning, participants were first presented with an item cue for 4 seconds. This showed the item to be recalled as well as instructing the participant whether to imagine it in large- or small-scale space. Participants then closed their eyes and imagined viewing the landmark as cued. After 6 seconds recalling the landmark, a chime would sound, prompting participants to open their eyes and indicate where they had imagined the landmark in large- (far left, far right, near left, near right) or small- (top left, top right, bottom left, bottom right) scale space. A fixation period of between 2 and 4 seconds separated each trial.

From the original set of 50 items, the 10 used in the learning phase mini-tests were excluded from the scanning set. Each of the remaining 40 items were recalled four times in total, twice in large- and small-scale space, giving a total of 160 trials. These were spread across 4 scanning runs, each lasting approximately 10-11 minutes. In each run, every item was recalled once, in a randomised order. In the first 2 runs, each item was recalled in both large- and small-scale space (i.e. if an item was recalled in large scale space in run 1, it would be imagined in small scale space in run 2 or vice versa). This was then repeated in runs 3 and 4, so that every item was again imagined in both large- and small-scale space, but in a completely different, randomised order.

6.2.4 Post-scan debriefing

Immediately after scanning, participants performed a series of tests in a debriefing session to ascertain how well they had learned information about the items. They were first tested on how well they recognised the items. Images of all 50 items from the pre-scan learning phase as well as 25 extra foils, which they had previously never seen, were shown one at a time in a randomised order. For each one, participants indicated whether they recognised them (Have you seen this item before? Yes/No) and then rated the permanence of just the 50 learned items (How many different locations? Only 1/Different every time). Next, they indicated which location they thought each item was located on the screen during the learning phase (which quarter of the screen), or alternatively if they

knew it didn't appear in a single location. Finally, participants were handed a grid containing all 50 items, they were then shown images of single landmarks on a computer screen and had to indicate which item from the grid was its pair during the learning phase. This last test was performed for 16 of the items in the interest of participant fatigue. Finally, subjects filled out a debriefing questionnaire in which they indicated the vividness and difficulty with which they felt they were able to imagine landmarks in large and small scale space.

6.2.5 Pilot studies

The precise details of the paradigm described in Sections 6.2.2-6.2.4 were informed by the results of two pilot studies.

Initially, I had intended to have people learn the permanence of a set of 90 landmarks (instead of the 50 eventually used in the pre-scan learning session). Ten of these 90 would have been used for the learning phase mini-tests and discarded from the scanning set. The remaining 80 for the testing phase would then each be recalled once in both large and small scale space. However, testing this with a group of four people (3 female, mean age 23.0 years, SD 3.3), it proved too difficult to learn the permanence of landmarks sufficiently within a reasonable amount of time. I decided that the learning session should not take any longer than an hour in total; otherwise participants would be too fatigued before commencing the main task inside the MRI scanner.

I therefore adapted the paradigm so that fewer (50) items would be learned in the pre-scan session. I also modified the in-scan testing phase so that each of the 40 stimuli (after discarding the 10 used in the learning phase mini-tests) were recalled twice in both large and small scale space each. This meant that although there was less overall information for subjects to learn, the number of trials in the testing phase was not compromised and retained the same power for analysing fMRI responses as the original design. This modified design was tested with six subjects (3 female, mean age 22.2 years, SD 3.1) and performance was much improved compared with the original design. I therefore proceeded to the main experiment using this optimised paradigm.

6.2.6 Scanning parameters and preprocessing

T2*-weighted echo planar images (EPI) with blood oxygen level-dependent (BOLD) contrast were acquired on a 3T whole body MRI scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) using the standard RF transmit body coil and 32-channel head receive coil. Scanning parameters were selected to achieve whole brain coverage and optimised for the hippocampus and surrounding tissue: 48 oblique axial slices angled at −45° from the axial to coronal plane (as defined in Weiskopf et al., 2006), 2.5 mm thickness (with inter-slice distance factor 20%), repetition time TR = 3.36s (slice TR = 70 ms), excitation flip angle = 90°, echo time TE = 30 ms, in-plane resolution 3 mm×3 mm, field of view FoV = 192 mm×192 mm, 64×64 matrix, phase encoding (PE) in the anterior-posterior direction, 13% oversampling in the PE direction, echo spacing 500 μs. To reduce signal loss in the hippocampal region, slices were angulated and a z-shim gradient moment of +0.6 mT/m*ms was applied (Weiskopf et al., 2006). Field maps were acquired with a standard manufacturer's double echo gradient echo field map sequence (short TE = 10 ms, long TE = 12.46 ms; 64 axial slices with 2 mm thickness and 1 mm gap yielding whole brain coverage; in-plane resolution 3 mm×3 mm). A 3D MDEFT T1-weighted structural scan with 1 mm isotropic resolution (Deichmann et al., 2004) was acquired for each participant. FMRI data were analysed using SPM8 (www.fil.ion.ucl.ac.uk/spm). The first 6 'dummy' volumes from each scanning run were discarded to allow for T1 equilibration effects. The remaining images were realigned, unwarped (using the field maps) and normalised to a standard EPI template in MNI space with a resampled voxel size of 3×3×3 mm. For the whole brain univariate contrast of permanence vs transient landmarks (see below), images were then smoothed using an 8 mm FWHM Gaussian kernel. For the MVPA analyses, images were left unsmoothed to facilitate the detection of information present across patterns of voxels.

6.2.7 Behavioural analyses

After scanning was completed, subjects were tested in a variety of ways to determine how well they had learned about the landmarks (see Section 6.2.4). I first compared how well subjects were able to recognise, permanent and transient landmarks to determine whether they had paid equal attention to both during the pre-scan learning session and

the testing phase inside the MRI scanner. Next, I assessed whether there were any differences in how well subjects knew the permanence of the two types of landmark.

In the third debrief test, participants indicated where they thought landmarks were located (which quarter of the screen), just as they had during the scanning session. I therefore compared performance of participants on these two tasks to ascertain whether their in-scan performance matched post-scan responses.

A fourth test in the post-scan debrief required subjects to identify landmarks' paired items from the full set of 50. This test was not of primary importance for the central aims of this experiment, but I assessed the participants' accuracy on this extra task to gauge how well they had been able to learn this additional information. I finally considered the responses subjects made on the debrief questionnaire to determine whether there were any differences in the vividness and difficulty with which they felt they were able to imagine landmarks in large and small scale space.

6.2.8 Permanent versus non-permanent landmarks - whole brain univariate fMRI analysis

In the first instance, I wanted to establish which, if any, brain regions might be more active when imagining permanent items. I was especially interested to determine whether similar regions would be engaged as when viewing visual images of landmarks learned in larger scale real-life (Experiments 1 and 2) and virtual reality (Experiment 3) environments.

The 6 second imagination period was modelled for each trial and separate regressors were created for trials in which the item being imagined was known to be permanent by the participant (i.e. a permanent landmark which the participant correctly identified as being so during the post-scan debriefing session) and for those which were not (transient and incorrectly rated permanence landmarks). These regressors were convolved with the haemodynamic response function. Additional regressors of no-interest were created from participant specific movement parameters and parts of the time-course when subjects were not imagining landmarks.

Subject-specific parameter estimates pertaining to each regressor of interest (β) were calculated for each voxel. Second level random effects analyses were then run using one-sample t-tests on these parameter estimates (collapsed across all 4 sessions). I report all of the fMRI activations that survived a whole brain family-wise error corrected threshold of $p<0.05$. I carried out a whole brain univariate analysis to look for regions which responded to the interaction between landmark type (permanent or transient) and the scale it is recalled in (large or small scale space). I also carried out a whole brain analysis collapsing across all large and small scale imagination trials. I then performed separate contrasts on large and then small scale trials individually, to assess whether either condition produced particularly strong permanence responses.

6.2.9 Connectivity analyses

I then assessed the functional connectivity between regions which showed increased activation while people imagined a permanent landmark. This was done using two different techniques: firstly a gPPI analysis (Section 2.8.1) to identify regions displaying functional coupling, and then DCM (Section 2.8.2) to investigate the nature of information flow between them.

For the gPPI analyses, the brain regions which were previously identified as being more engaged when people imagined permanent compared to transient landmarks (see Sections 6.2.7 and 6.3.2) were used as seed regions. For each seed region, I compared whole brain functional connectivity while participants were imagining permanent versus transient landmarks (collapsing across all large and small scale recall trials). All significantly activated clusters at a family-wise error corrected threshold of $p<0.05$ are reported.

For any regions displaying increased functional coupling while people imagined a permanent landmark, I then used DCM to interrogate the nature of the interaction. Specifically, I was interested in establishing which brain region would be driving any modulations in connectivity when an imagined landmark is permanent. I constructed multiple plausible models of task-dependent effective connectivity between regions already shown to be interacting with one another. For the DCM analyses, I created a design matrix containing two main regressors of interest: the first modelling all imagination trials and the second just those in which the landmark recalled was

permanent. The first regressor (all imagination trials) was used as the input for each model (C matrix) and the second was used to model modulation of connections by landmark permanence (B matrix). Each model assumed reciprocal connections between the regions (A matrix) and then all possible plausible permutations of input region (C matrix) and modulatory connections (B matrix) were constructed (see Figure 46A). I used stochastic DCM in DCM10 (Daunizeau et al., 2012), which also models stochastic fluctuations in the state equations to account for neural noise, which is of particular relevance when modelling endogenously driven processes such as the imagination paradigm used here. Each model was then fitted to the fMRI data and a random effects bayesian model comparison method was used to determine which was the winning model (Stephan et al., 2009).

6.2.10 MVPA analyses

I then sought to explore more subtle effects, namely whether the manner in which a landmark is recalled impacts upon their neural representations in permanence-responsive brain regions. To do this I used the more sensitive measure of MVPA to analyse the fMRI data (Section 2.7).

Several MVPA analyses were carried out. Each one modelled the 6 second period that participants imagined an item as a separate regressor. These regressors were convolved with the canonical haemodynamic response function and participant-specific movement regressors were added as covariates of no interest. Participant-specific parameter estimates pertaining to each regressor (β) were then calculated for each voxel.

Motivated by the findings of previous work (Experiments 1, 2 and 3), my main ROIs were the RSC, PHC, HC as well as the part of the permanence responsive POS region from Experiment 3. These ROIs were used for all decoding analyses. Where possible, ROIs were defined anatomically. Bilateral RSC (BA 29/30), PHC and HC masks were delineated by an experienced researcher not involved in the project on an averaged structural MRI brain scan from a different set of $n = 30$ participants, and guided by Duvernoy (1999), Insausti et al. (1998), and Vann et al. (2009). The POS ROI was not based upon a distinct anatomical locus and was instead defined as the region shown to be responsive to permanent landmarks in Experiment 3 (see 5.4.1 and Figure 34A).

In the first two scanning runs, each item was recalled once in both large and small scale space; the same was then repeated in the final two runs, giving two separate sets of trials to be used for feature selection and a completely independent final classification. In each instance, I then repeated the same process changing which runs were used for feature selection and the final classification; these results were then averaged to provide an overall two-fold cross-validation.

All decoding analyses used a linear SVM employing the LIBSVM implementation (Chang and Lin, 2011) with fixed regularization hyperparameter $C = 1$. For both feature selection and the final classifications, I used a standard leave-one-out cross-validation technique (Duda et al., 2001; Hsu and Lin, 2002), as described in Experiment 2 (Section 4.2.6). The classification accuracy values across all participants were then tested against chance (which in this instance was 50% given that all classifications were two-way) using a one-tailed *t*-test. All statistical tests were performed using SPSS version 20.

This MVPA procedure was used to assess the ROIs' response patterns in relation to 3 different features of what participants imagined: the permanence of a landmark; whether a landmark was being recalled in large or small scale space and where a landmark was being imagined.

I first wanted to assess whether the way in which a landmark is recalled would impact upon the permanence representation in each ROI. To do this, I performed separate classifications of landmark permanence for large and small scale recall trials. In other words, when a participant imagined a landmark in large-scale space, I tested the ability to classify whether it was permanent or transient. I then repeated this using just small-scale recall trials. I used the Bonferroni method to correct for the multiple permanence classifications being made for large and small scale trials separately. I then performed an equivalent analysis to identify which ROIs may contain information pertaining to how a landmark is imagined. So instead of large and small scale trials being separately tested for their permanence information, permanent and transient trials were tested for their recall-related information. I also applied Bonferroni correction for the multiple comparisons being made separately upon permanent and transient landmarks.

Finally, a series of two-way classifications were performed to determine whether responses in any ROI might contain information relating to *where* a landmark was being imagined. During the scan, immediately after recalling a landmark, participants indicated where they had imagined it. For small-scale recall trials they selected a quarter of the screen (top left, top right, bottom left, bottom right) and for large-scale trials they selected from the corresponding four areas (far left, far right, near left, near right). I performed four two-way classifications based upon these responses to look for neural representations relating to whether a landmark is imagined: on the left versus right; near versus far in large-scale space and left versus right; bottom versus top in small-scale space.

6.3 Results

6.3.1 Behavioural results

In the post-scan debriefing session, subjects performed a series of tests to assess how much they had learned about the landmarks in the initial pre-scan learning phase. When asked whether or not they recognised landmarks, subjects were highly accurate for both permanent (mean accuracy = 97.8%, SD 3.2) and transient (mean accuracy = 98.4%, SD 3.0) landmarks and there was no difference in their ability to recognise the two types (t_{31} = 1.054, p = 0.3). Subjects were also highly accurate at identifying that they had not previously seen novel foils (mean accuracy = 98.0%, SD 4.5). Subjects then rated the permanence of landmarks and again there was no difference in their accuracy for either type of item (permanent mean accuracy = 90.7% SD 13.9; transient mean accuracy = 89.5% SD 12.6; t_{31} = 0.592, p = 0.6). Mean accuracy on the post-scan landmark location task was 75.6% (SD 16.9) which was significantly greater than the same task during scanning (mean accuracy for questions during scan = 65.5%, SD 8.2; t_{31} = 5.344, p < 0.001). However, individuals' scores during and after scanning were strongly correlated (r = 0.753, p < 0.0001), so it appears that performance after scanning was improved collectively across all subjects, perhaps owing to the more comfortable setting. For the pair identification test in the post-scan debrief, subjects were correctly able to identify a landmarks' paired item from a choice of 50 with 64.3% (SD 27.6) accuracy.

In their answers to the debriefing questionnaire, there was no difference in the subjects' self-reported vividness of large or small scale recall (post-scan debrief vividness rating: 5

point scale, not at all – very vivid; small scale mean = 3.50 SD 0.62, large scale mean = 3.28 SD 0.96; t_{31} = 1.422, p = 0.17). However, subjects did report imagining in small scale to be marginally easier than large scale (difficulty rating: 5 point scale, not at all – very difficult; small scale mean = 2.50 SD 1.11, large scale mean = 3.06 SD 1.08; t_{31} = -2.414, p = 0.02).

6.3.2 Brain areas more engaged when imagining permanent landmarks

I examined whole brain fMRI responses to determine which, if any, regions were responsive to the interaction between landmark permanence and the scale at which a landmark is recalled. No brain region was responsive to this interaction. Next, to determine which brain regions produced greater responses during recall of permanent landmarks, I compared whole brain BOLD activity associated with imagining landmarks which were known to be permanent with those which were not (collapsed across spatial scale). There were significant bilateral activations in both RSC (left: -9, -46, 13; Z = 5.78; right: 9, -49, 16; Z = 5.33) and posterior HC (left: -30, -34, -8; Z = 7.25; right: 24, -34, -2; Z = 5.50) as well as a smaller cluster in left inferolateral temporal cortex (-39, -58, -5; Z = 6.28) (Figure 44). This confirmed that similar regions are involved in processing permanent landmarks which have only been learned in small-scale space as compared with those purely experienced in large-scale virtual (Experiment 3) or real-world environments (Experiments 1 and 2).

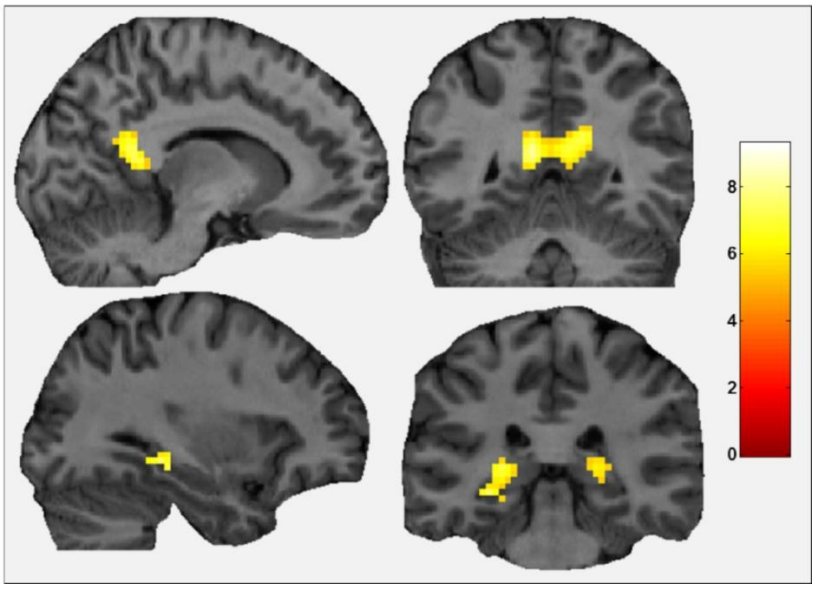

Figure 44 Regions showing increased activity when imagining a landmark learned to be permanent. Both RSC (top) and the HC (bottom) showed increased engagement when imagining an item learned to be permanent. Activations are displayed on sagittal and coronal views of a single representative participant's structural MRI brain scan. The colour bar indicates the Z-scores associated with each voxel.

I also performed similar separate whole brain analyses on just large- and small- scale imagination trials. No significant activations were present in just large- or small- scale trials alone; only when the two conditions were combined. Finally, I compared whole brain responses to transient versus permanent landmarks and found no brain region which was more engaged when recalling transient items.

6.3.3 RSC-HC connectivity

Given that both RSC and posterior HC were more engaged when people imagined a permanent landmark, I looked for evidence of functional connectivity between these two regions during permanent recall trials. I used the bilateral parts of HC and RSC identified in the whole brain univariate analysis (Section 6.3.2) as seed regions for a gPPI analysis. This indicated that the HC has increased functional coupling with RSC (-6, -43, 10; Z = 4.40; cluster $p_{FWE\text{-}corr}$ = 0.029), but no other brain region, when an imagined landmark is permanent compared with transient (Figure 45). The RSC region identified by this whole brain PPI analysis was strikingly similar to that which had already been shown to be more engaged when imagining a permanent landmark in the whole brain univariate fMRI contrast (see Figure 44).

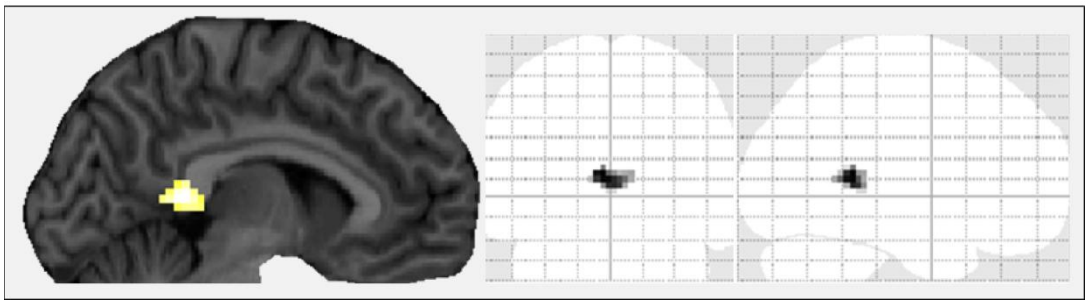

Figure 45 Brain regions which interact more with HC when imagining permanent landmarks. The whole brain gPPI analysis revealed that RSC was the only region which shared increased functional coupling with the permanence-responsive parts of the HC on permanent recall trials. Activations are displayed on a sagittal view of a single representative participant's structural MRI brain scan, displayed at a threshold of p < 0.001(unc).

I then used DCM to assess the neural dynamics of the two regions' interaction. I compared four simple, plausible models of connectivity between the bilateral parts of HC and RSC which were more engaged when imagining a permanent than a transient landmark (Figure 46A). Model 1 had RSC as the input region, with RSC then driving permanence responses in HC and vice versa for Model 2 (input to HC with HC then driving RSC responses). Models

3 and 4 assumed bidirectional modulation by permanent landmark recall, but with input to the RSC or HC respectively. The winning model was Model 1, in which RSC activity drives HC permanence responses (see Figure 46B) and this model accounted for an average of 93.6% of variance in the fMRI data for all subjects (SD = 2.83).

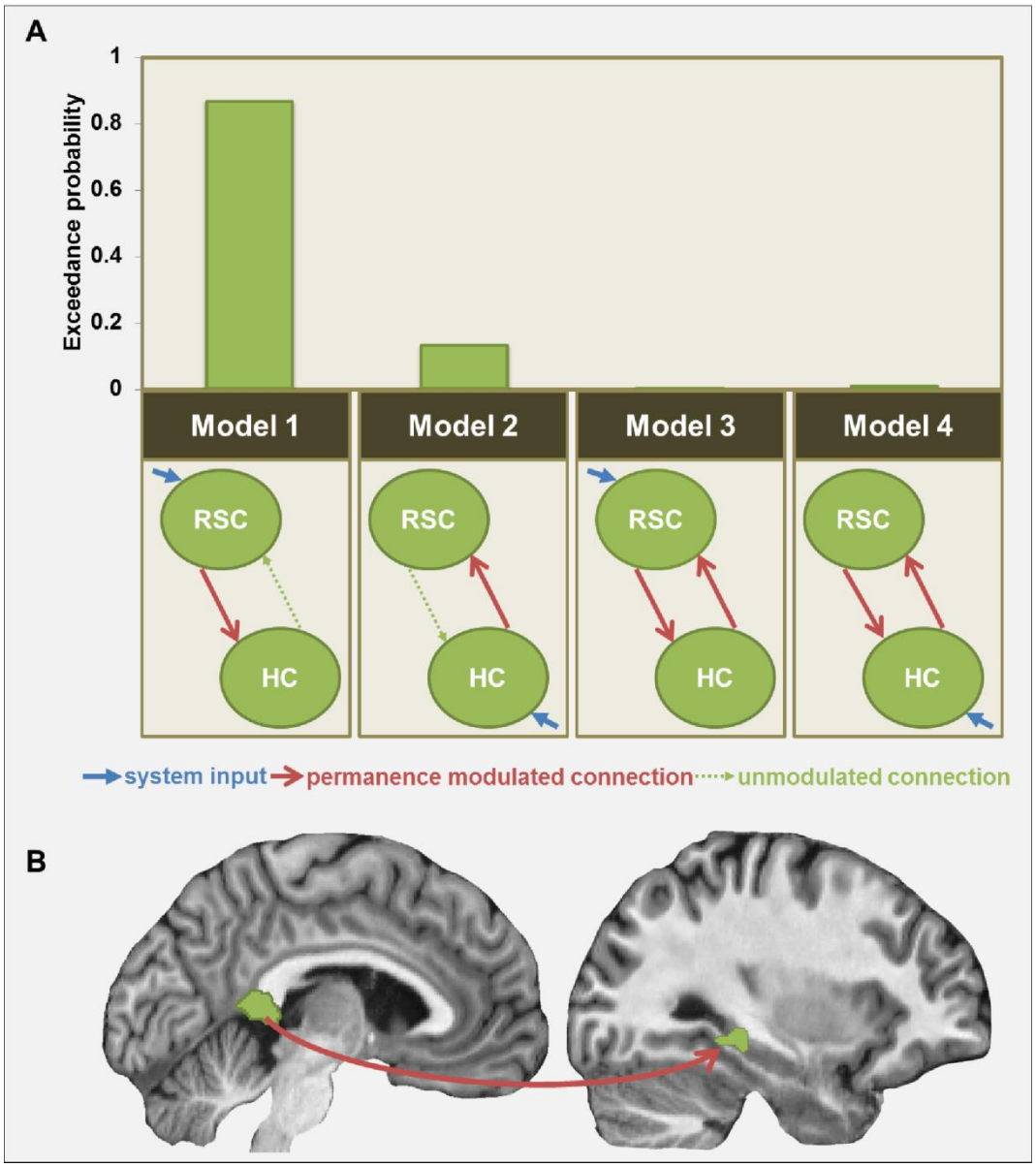

Figure 46 Connectivity between permanence responsive brain regions. (A) Shows the four models of RSC-HC interaction which were compared in the DCM analysis. The posterior exceedance probabilities from the Bayesian model selection are displayed above each corresponding model. Model 1, with RSC driving permanence responses in HC, provided the best fit of the 32 subjects' fMRI data (B).

I also performed further DCM analyses on large and small scale imagination trials independently. In both cases, RSC was shown to be driving permanence related activity in the HC. These results indicate that RSC modulates activity in the HC when people imagine

a permanent landmark and that this process is consistent and robust whether imagining in large or small scale space.

6.3.4 Patterns of activity associated with landmark permanence

Having established the involvement of and interactions between permanence-responsive regions, I then probed these representations in greater detail. Specifically, I was interested in whether the spatial scale within which subjects recalled a landmark would have any impact upon the resultant permanence representations. To investigate this, I used the more sensitive measure of MVPA. I considered large and small scale recall trials separately in order to remove any potential variation in the multi-voxel activity which may be brought about by the nature of how a landmark is imagined. Using these independent analyses, I assessed the ability to classify landmark permanence based upon the multi-voxel activity patterns in various brain regions previously implicated in processing landmark permanence (see Section 6.2.9).

When participants imagined a landmark in large scale space, it was possible to classify its permanence significantly above chance based upon patterns of activity in RSC (chance = 50%; mean classifier accuracy 53.8%, SD 7.9; $t_{31} = 2.732$, $p = 0.01$) and POS (mean classifier accuracy 55.3%, SD 8.8; $t_{31} = 3.403$, $p < 0.001$), but not PHC (mean classifier accuracy 51.0%, SD 12.1; $t_{31} = 0.456$, $p = 0.6$) or HC (mean classifier accuracy 49.8%, SD 7.0; $t_{31} = -0.196$, p = n/a – as one-tailed t-test cannot produce a p-value for below chance classification) (Figure 47A). The exact same analysis performed upon small scale recall trials produced no significant results (RSC: mean classifier accuracy 48.9%, SD 8.4; $t_{31} = -0.721$, p = n/a; POS: mean classifier accuracy 50.2%, SD 11.0; $t_{31} = 0.100$, $p = 0.5$; PHC: mean classifier accuracy 49.0%, SD 7.8; $t_{31} = -0.708$, p = n/a; HC: mean classifier accuracy 49.9%, SD 7.6; $t_{31} = -0.073$, p = n/a). Thus, despite the fact that landmark permanence had been learned only in small scale space, permanence-related responses were only evident in RSC and POS when recalling landmarks in large scale space. This is not explained by any differences in the self-reported vividness of large or small scale recall, nor was it that imagining in large scale was any easier, indeed if anything, participants found recall in large scale space marginally more difficult (see Section 6.3.1). So the difference in permanence-related responses appears to be driven by the nature of recall itself, perhaps

owing to large scale recall being more immersive and more closely mirroring how landmarks are usually encountered.

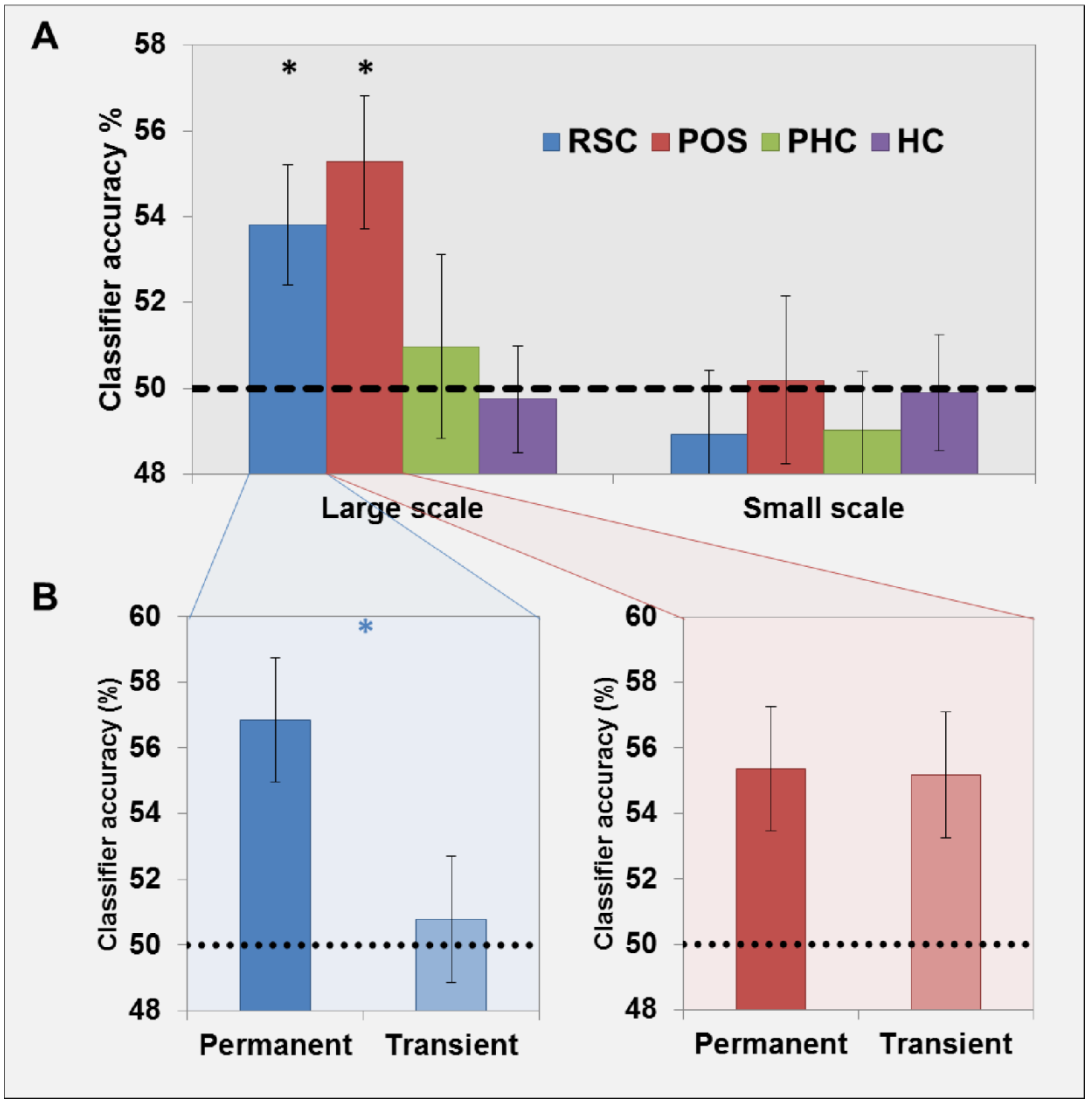

Figure 47 Decoding landmark permanence. Mean classifier accuracy values from MVPA analyses for all 32 participants. Error bars indicate the standard error of the mean. (A) Shows the accuracy of classifications in determining whether a landmark was permanent or transient when it was being recalled in large (left) or small (right) scale space based upon activity within RSC (blue), POS (red), PHC (green) and HC (purple). Only RSC and POS contained significant amounts of permanence information when landmarks were imagined in large scale space. (B) Shows the relative accuracy of using RSC (blue) or POS (red) activity to identify permanent (darker colours) and transient (lighter colours) landmarks. RSC activity was significantly more informative about permanent than transient landmarks and indeed identification of transient landmarks alone was at chance. There were no such differences in POS. * $p < 0.05$.

I then interrogated the accuracy of these RSC and POS permanence classifications on large scale recall trials in greater detail. Specifically, I considered the accuracy classifying permanent and transient landmarks separately, rather than the combined accuracy across both types of landmark (Figure 47B). In POS, there was no difference in the ability to

successfully identify landmarks which were permanent or transient (mean difference = 0.2%; SD 8.2; t_{31} = 0.134, p = 0.9). However, there was significantly more permanence information in RSC activity patters when recalling permanent than transient landmarks (mean difference = 6.1%; SD 14.7; t_{31} = 2.334, p < 0.03). Indeed, identification of the transient landmarks from RSC activity patterns was not even above chance (mean classifier accuracy 50.8%, SD 10.9; t_{31} = 0.407, p = 0.3). There were no other such differences in other brain regions (PHC and HC), or when recalling landmarks in small scale space. Thus, when landmarks are recalled in large scale space, whereas significant classification of both permanent and transient landmarks is possible in POS, voxels in RSC could only be used to identify when a landmark is permanent. So POS seems to play a more generalised role in processing landmark permanence, but RSC appears to possess a specific signature which identifies a permanent landmark encountered in large scale space.

For all the main analyses described above, I also compared classifier accuracies for good and poor navigators according to the SBSOD questionnaire and found no differences between the groups (large-scale permanence: RSC: good mean = 53.9%, poor mean = 53.7%; POS: good mean = 53.3%, poor mean = 57.2%; PHC: good mean = 52.5%, poor mean = 49.4%; HC: good mean = 52.1%, poor mean = 47.5%; small-scale permanence: RSC: good mean = 48.2%, poor mean = 49.6%; POS: good mean = 49.0%, poor mean = 51.4%; PHC: good mean = 52.3%, poor mean = 45.7%; HC: good mean = 48.5%, poor mean = 51.3%; t-tests directly comparing groups all p > 0.05). There were similarly no differences comparing males and females or the best and least successful permanence learners based upon responses during the pre-scan learning phase. However, I believe the study perhaps lacked sufficient power to reveal such differences, if any existed.

6.3.5 Patterns of activity associated with spatial scale of landmark recall

I then used MVPA to looks for patterns of activity which may relate to the spatial scale within which a landmark was recalled. I trained and tested classifiers on multi-voxel activity patterns in the same brain regions as previously (Section 6.3.4, see also 6.2.9), only this time used them to distinguish the spatial scale that landmarks were recalled in. I analysed recall of permanent and transient landmark separately to remove potential noise in the multi-voxel activity patterns related to the type of item being imagined. PHC was

the only region where above chance classification of the scale of recall (large versus small) was possible and this was only the case when recalling permanent (mean classifier accuracy 55.6%, SD 9.5; t_{31} = 3.338, p < 0.01) not transient (mean classifier accuracy 50.0%, SD 9.9; t_{31} = 0.028, p = 0.9) landmarks (Figure 48), with the difference between the two also being significant (mean difference = 5.6%; SD 13.8; t_{31} = 2.276, p = 0.03). For those permanent landmark trials, there was no difference in how well the classifier identified whether recall was for large or small scale (mean difference = 2.6%; SD 7.5; t_{31} = 1.980, p = 0.06). Therefore, only patterns of activity in PHC contained significant amounts of information pertaining to whether a permanent landmark was recalled in large or small scale space.

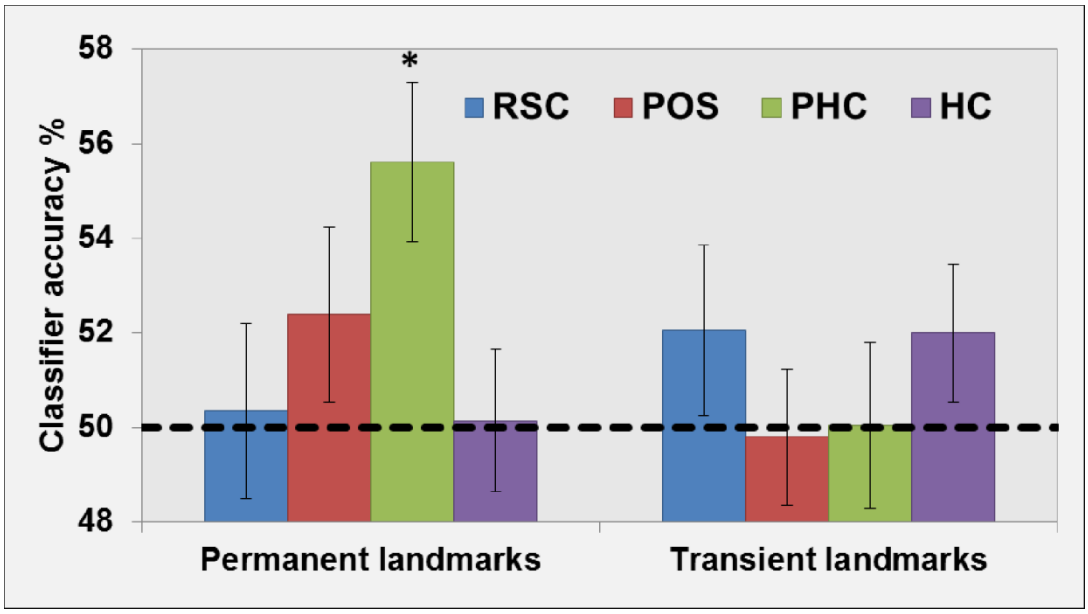

Figure 48 Decoding the spatial scale of landmark recall. Mean classifier accuracy values for all 32 participants for determining whether a permanent (left) or transient (right) landmark was recalled in large or small scale space. Above chance classification of recall scale was only possible for permanent landmarks from activity in PHC (green). RSC (blue), POS (red) and hippocampal (purple) activity could not be used to successfully determine the spatial scale of recall. Error bars indicate the standard error of the mean. * p < 0.05.

6.3.6 Patterns of activity associated with the location in which a landmark is imagined

Immediately after recalling a landmark on each trial inside the scanner, subjects indicated where they had just imagined it. This allowed me to look for neural representations relating to where a landmark was pictured, irrespective of the type of landmark. Using the same regions of interest as for the other MVPA analyses, I used several different 2-way

classifiers to independently look for patterns of activity which would identify whether subjects were recalling landmarks: on their left/right, or near/far when recalling in large-scale space or on the left/right or top/bottom of small-scale space. The only instance which produced above chance classification was for determining which side subjects recalled a landmark in large-scale space. Here, it was possible to classify whether subjects were recalling a landmark to their left or right based upon activity patterns in PHC (mean classifier accuracy 57.9%, SD 12.5; $t_{31} = 3.580$, $p < 0.001$) and HC (mean classifier accuracy 54.2%, SD 9.9; $t_{31} = 2.391$, $p = 0.01$), but not RSC (mean classifier accuracy 51.6%, SD 9.5; $t_{31} = 1.678$, $p = 0.2$) or POS (mean classifier accuracy 51.3%, SD 11.2; $t_{31} = 1.984$, $p = 0.3$) (Figure 49).

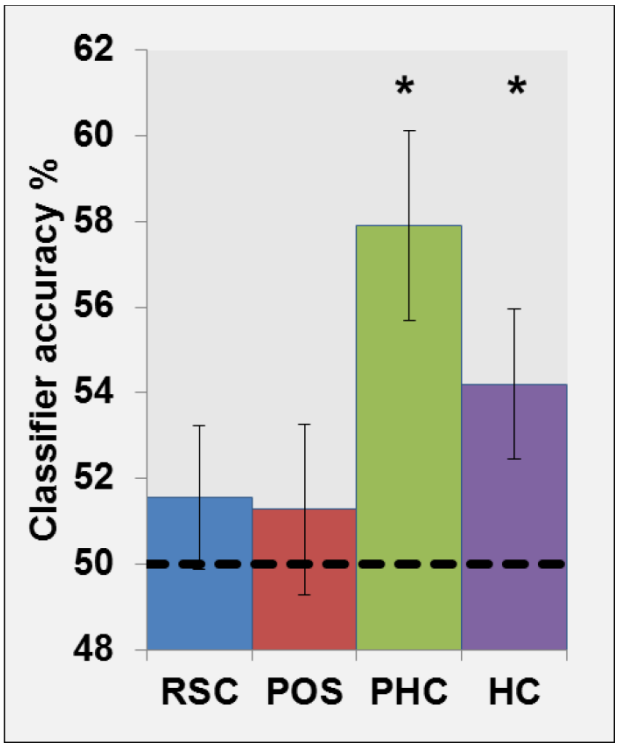

Figure 49 Decoding where a landmark was imagined. Mean classifier accuracy for where a landmark was recalled in large scale space. Activity within PHC (green) and HC (purple), but not RSC (blue) or POS (red), could be used to determine whether a landmark was being imagined to the left or to the right. Error bars indicate the standard error of the mean. * $p < 0.05$.

6.4 Discussion

Over the course of the 30-40 minute pre-scan learning phase, participants were successfully able to ascertain the permanence of completely unfamiliar, alien landmarks in small-scale space. Immediately after learning and during fMRI, responses were apparent

within two brain regions in particular, RSC and the HC, relating to whether or not a landmark was permanent (Section 6.3.2). These two regions directly interacted with one another when people imagined a permanent landmark, with RSC seeming to drive permanence related activity in HC (Section 6.3.3). The representation of landmark permanence was also evident in the multi-voxel patterns of activity in RSC as well as the POS region which was previously implicated in processing newly learned landmark permanence in Experiment 3 (Section 6.3.4, see also Sections 5.3.2 and 5.3.3). Thus, RSC permanence representations generalise beyond complex large-scale environments (Chapters 3, 4 and 5) to also reflect learning in small-scale, two dimensional space and for items which bear no apparent relevance for navigation or orientation.

This study also revealed that RSC permanence representations can be elicited by endogenously driven imagery, not just external visual stimuli. During the testing (scanning) phase, participants recalled landmarks by imagining them in either small- or large-scale space while undergoing fMRI scanning. This made it possible to investigate how the neural representations of landmarks are dependent not just upon the nature of the items themselves, but also the way in which they are recalled. Both RSC and POS were sensitive to the spatial scale a landmark was recalled in, indeed it was only possible to classify permanence based upon activity patterns brought about when subjects imagined them in large scale space.

This presents a potential problem for one of the main stated aims of this experiment, namely devising a task which could test permanence representation in non-human species. If RSC is only engaged by landmarks when they are imagined in large-scale space, this would not be amenable to use with other primates or rodents. However, the results of this experiment do not necessarily demonstrate that RSC and POS do not contain any representation of landmark permanence during small-scale recall. Indeed, the initial univariate whole brain contrast only revealed engagement of RSC when imagining known permanent landmarks in both small- and large-scale space, but not for either condition alone. The single condition univariate analyses were perhaps underpowered for revealing significant permanence-related activations, but the fact that strong responses were evident when combining the two, suggests that small-scale imagination trials contributed some sort of permanence-related activity. However, what the MVPA analyses do show is that imagining landmarks in more immersive, large-scale space yielded stronger, more

discriminative patterns of activity; this makes intuitive sense given that it more closely mirrors how landmarks are encountered in the real world. It remains to be seen whether small-scale recall could reliably engage permanence-responsive regions. Perhaps a task requiring people to use landmarks more actively for navigation and orientation could elicit such a response in small scale space. Given the importance of establishing whether RSC permanence representations can be elicited for landmarks both learned *and* recalled in small-scale space, this is something which I pursued in the next experiment (Chapter 7). There, I used a paradigm which had more power to detect representations which did not require participants to imagine a landmark in large-scale space. This is important for determining the feasibility of using tasks in small-scale space with non-human species.

6.4.1 Permanence processing in RSC, HC and POS

Responses in POS were equally informative about permanent and transient landmarks when imagining them in large-scale space. This was not the case in RSC, however, where activity could only be used to identify permanent landmarks. So whereas POS appears to contain a broader representation of landmark stability, RSC is much more specific in processing just permanent landmarks. It is also interesting to note that despite being more engaged when imagining a permanent landmark, HC neural responses contained insufficient information to classify landmark permanence. The lack of discriminative power in HC responses could reflect the fact that, as shown by the connectivity analyses, permanence responses here came downstream as a result of more fine-grained RSC processing. HC responses therefore perhaps contain extra noise (introduced by a range of other scene construction related processes) producing a coarser permanence representation.

These findings help clarify what the role of RSC within the scene construction network might be (Section 1.11; Hassabis and Maguire, 2009; Maguire and Mullally, 2013; Mullally and Maguire, 2013). Experiment 3 (Chapter 5) showed that connectivity between the RSC and HC increases directly in line with learning about how permanent landmarks are and this was also related to the emergence of hippocampal representations linked with more detailed knowledge of where permanent landmarks were located in the complex large-scale environment. In the current study, RSC and HC were once again found to interact with one another when a permanent landmark is imagined in a specific location. However,

the present study's DCM analysis provides additional information which suggests that RSC actually drives permanence-related responses in HC. So the specific processing of only the most permanent landmarks in RSC appears to act as an input to the HC when constructing an imagined scene. This information from RSC could serve two valuable purposes: identifying the most stable environmental features to anchor spatial representations to and for subsequently evaluating the reliability of constructed scenes.

RSC has also been proposed to help translate between allocentric and egocentric representations of space (Section 1.11; Byrne et al., 2007; Vann et al., 2009). The present study could be viewed as being consistent with such an account. The large-scale recall trials will have required the "translation" of information learned in an allocentric setting (i.e. landmark position on a two dimensional screen) to an egocentric point of view; whereas recall in small-scale space (where I found no informative fMRI response patterns) would not necessarily have to involve such a reference frame translation. However, even though the present study is potentially consistent with such an account of RSC function, it is not able to discern whether it is translation *per se* or simply the more immersive nature of recall in large-scale space which elicits more informative RSC permanence representations. Determining the relative importance of these two factors would require a comparison with landmarks learned in a large-scale, egocentric setting and subsequently recalled in allocentric terms. Either way, given the specificity of the RSC result to permanent not transient landmarks, this study indicates that if any translation between spatial reference frames does occur in RSC, then it is likely centred upon permanent landmarks. This would ensure the stability and reliability of interactions with the surrounding environment.

The wider RSComp is suggested to help in localising and orientating oneself in space (Section 1.11; Epstein and Vass, 2014) or computing distance and direction to a goal location (Wolbers and Buchel, 2005; Baumann and Mattingley, 2010; Sherrill et al., 2013). The landmarks in this study only differed in terms of their permanence and possessed no value for orienting or navigating. Furthermore, participants only ever pictured landmarks from a single imagined location and the distance/direction landmarks appeared relative to this viewpoint were closely matched between the two landmark groups. This would suggest that, in this instance at least, RSC does not necessarily process anything to do with location or orientation. Indeed the apparent involvement of RSC in these more complex

cognitive processes could again more simply reflect their use of permanent, stable environmental features. This is an issue I examine in the next experiment.

6.4.2 PHC

Various accounts posit that PHC is critical for the recognition of landmarks with particular value for navigation and/or orientation (Janzen and van Turennout, 2004; Epstein and Vass, 2014; see also Chapter 3) or with particular contextual associations (Bar and Aminoff, 2003). Here however, PHC did not appear to be involved in processing features intrinsic to landmarks themselves (i.e. their permanence) when they have been learned in small scale space. Instead, PHC activity was sensitive to *how* permanent landmarks were recalled. Responses in PHC contained information pertaining to whether a permanent landmark was recalled in either large- or small-scale space (Section 6.3.5). This could perhaps be accounted for by the difference in the sense of space evoked in these two conditions, which been shown to be a property represented in PHC (Kravitz et al., 2011a; Mullally and Maguire, 2011).

Neural responses in PHC, as well as HC, also contained information about whether a landmark was imagined to the left or right hand side of a viewpoint in large scale space (Section 6.3.6). These two regions both contain so called “spatial view cells” in non-human primates (Robertson et al., 1998) and this could be the first evidence of which I am aware for similar representations being present in humans (but see Dilks et al., 2011).

6.4.3 Lack of inter-individual differences

Unlike my previous experiments, I found no evidence of differences in permanence processing in relation to a person’s navigation or other spatial abilities. I believe several factors could account for this finding. In the current experiment, I required subjects to be well trained and know the permanence of landmarks very well before commencing the testing phase inside the MRI scanner. Unlike the previous experiment (Chapter 5), I was not examining the acquisition of new knowledge, as it was necessary for the permanence representations to be firmly established from the beginning of the fMRI study. In doing this I effectively ensured that there was much less individual variation in performance on the scanner task; subjects were performing much closer to ceiling levels. Inter-individual

variation was also reduced in comparison to the previous experiment as this was not nearly as demanding a task. There were fewer landmarks to learn (50 compared with the previous 60) and there were not the same complex spatial relationships between numerous landmarks to learn. In other words, by ensuring that I could examine permanence representations most reliably inside the scanner (by having well trained subjects perform a relatively simple task), inter-individual variation was inevitably reduced.

The present study also included more experimental conditions than has previously been the case in my three other experiments. Here, I was not only studying landmark permanence, but also how the way in which they were recalled impacted upon representations in RSC. This would have reduced the power with which I could detect potentially subtle differences between good and poor performers.

Finally, compared with Experiment 3, the paradigm used here did not provide as clear a marker for assessing the navigation ability of subjects. There was no form of explicit, objective navigation test. Subjects filled out the SBSOD which revealed differences in Experiments 1 (Section 3.3.3) and 2 (Section 4.3.4), but that is perhaps not as appropriate a measure for the simple two-dimensional desktop task in this experiment. Indeed the SBSOD has been shown to provide a more accurate estimation of a person's ability at difficult survey tasks than for more simple smaller scale tests (Weisberg et al., 2014). Differences in RSC responses related to the permanence of landmarks are perhaps only evident for more demanding 'real-world' and complex spatial situations.

6.4.4 Conclusions

This study demonstrated that RSC, POS and HC developed responses related to item permanence, even if they have only ever been experienced in small scale space. These representations were particularly notable when an item was subsequently imagined as part of a large-scale environment, from an egocentric perspective. However, whereas POS processed permanent and transient landmarks in equal measure, activity in RSC was much more selective in identifying only the most stable cues. Activity in RSC then drove permanence related responses in HC. Activity in PHC, on the other hand, appeared less

sensitive to what *type* of landmark is being recalled and instead to *how* or, in conjunction with HC, *where* they are imagined.

The fact that neural representations of permanence can emerge with a simple desktop task opens up the possibility of testing the process in non-human species as well as human patient populations. However, in order to determine whether tests related to this task could be used in non-human species, further work will be required to establish whether these findings can pertain to *retrieval* in small-scale space and when landmarks are viewed, not imagined. This could make it possible to explore the potential links between RSC permanence processing and more general navigation and orienting deficits (Maguire, 2001a; Vann et al., 2009; Pengas et al., 2012). The role of permanence and the RSC in orienting is an issue I take up in the next experiment. It also remains to be seen just how generalisable the representation of permanence in these brain regions is. Do they, for example, process more wide-ranging abstract concepts of permanence and reliability, or is it a purely spatial phenomenon? This is a question I will address in the final experiment (Chapter 8).

Chapter 7: Experiment 5

Dissociating landmark permanence from orienting value

7.1 Introduction

The RSC and wider RSComp appear to play an important role in using environmental landmarks to help orientate oneself in space (see Section 1.11; Epstein and Vass, 2014). People with lesions to the RSC are unable to orientate using familiar landmarks despite having no problems recognising them (Section 1.6; Maguire, 2001a; Vann et al., 2009) and this region is consistently engaged in neuroimaging studies involving related processes (Section 1.10; Spiers and Maguire, 2006; Iaria et al., 2007; Spreng et al., 2009). However, there is debate regarding what it is about orientating with landmarks that recruits RSC.

Various accounts suggest that RSC is involved in performing spatial operations upon landmarks to orientate and localise specific places (Sections 1.10.3 and 1.10.4; Nasr et al., 2013; Sherrill et al., 2013; Epstein and Vass, 2014; Hindley et al., 2014a). Alternatively, the RSC's association with this wide range of complex spatial computations could more simply reflect representations of the landmarks these spatial relationships are centred around. My previous four experiments (Chapters 3-6) have demonstrated that RSC codes for items which are permanent and remain fixed in a single location, irrespective of many other features. However, given that stable environmental cues are usually the most useful for orienting (Galati et al., 2010; Epstein and Vass, 2014), it has been difficult to determine which aspect the RSC processes – the landmarks themselves or the act of orienting with the landmarks.

In the experiment described in this chapter, I sought to dissociate these two variables and investigate whether RSC codes for landmarks which are permanent or those which can be used for localising targets. I adapted the paradigm used in my fourth experiment which demonstrated the possibility of establishing permanence representations for novel items in small-scale, two-dimensional space. In this instance, however, the landmarks would not only vary according to their permanence (i.e. whether or not they always appeared in the same location) but also in whether or not they could be used to localise a specific target,

indicated by a treasure chest. Using the same set of completely novel, 'alien' items I created for Experiment 3 and used again in Experiment 4, I had participants first learn the two key properties for a set of landmarks (permanence and relevance for orienting) and then examined these representations with fMRI scanning. Before learning, people had no prior conceptions about the landmarks' permanence or relevance for orienting, which allowed me to investigate uncontaminated, pure representations of these features.

The 'relevant' landmarks, which could be used to locate a target treasure chest, also provided another type of spatial representation for me to study. The HC has repeatedly been shown to process the distance between specific spatial locations (Spiers and Maguire, 2007b; Morgan et al., 2011; Baumann et al., 2012; Sherrill et al., 2013). RSC has also been implicated in computing distance to a goal location (Wolbers and Buchel, 2005; Baumann and Mattingley, 2010; Sherrill et al., 2013). These previous experiments have tended to examine representations of distance coding while people actively navigate within large scale, complex environments. Here, I could investigate whether the RSC and HC might process the distance between a relevant landmark and its associated target treasure location on a much smaller scale - a simple, desktop setting with people merely viewing landmarks in isolation.

Another consistent finding across my previous experiments is that RSC responses related to landmark permanence are also linked to a person's ability to navigate and acquire new spatial information (although see Section 6.4.3). In my first experiment (Chapter 3), another region which is heavily connected with RSC, the anterior thalamus ("AThal", Sections 1.3 and 3.3.3; Vann et al., 2009; Jankowski et al., 2013), was also shown to process permanent landmarks differently depending upon a person's spatial abilities. This is particularly interesting given that the two regions both contain head direction cells in rodents (Section 1.4), the firing of which are under a certain amount of control from environmental landmarks (Yoder et al., 2011). I therefore also sought to examine how differences in the amount people learned about the landmarks may relate to activity within their RSC and its interactions with other connected brain regions, especially within the head direction 'circuit', such as AThal and subiculum (Yoder et al., 2011).

The main focus, therefore, of this experiment was to dissociate the permanence of landmarks from their relevance for orienting and to investigate, when the two are placed

in opposition, which factor the RSC processes and how this may relate to spatial abilities. I also had subjects perform additional short tasks to investigate fMRI responses related to the accuracy of spatial information provided by landmarks.

7.2 Methods

7.2.1 Participants

Thirty two healthy, right handed participants took part in the experiment (16 female, mean age 21.5 years, SD 3.8). All had normal vision and gave written informed consent in accordance with local research ethics committee policy. None had taken part in my previous experiments involving these stimuli.

7.2.2 Stimuli

In a pre-scan learning session, participants were shown numerous images on a computer screen. Each image contained a single landmark and a treasure chest (see Figure 50 for examples). The landmarks came from the set of completely unique, 'alien' items which had been created for Experiment 3 (see Section 5.2.2) and the participants had no prior experience of them. The landmarks and treasure chests were viewed multiple times and could both appear in any one of 64 screen locations (in an 8x8 grid arrangement). Each landmark varied according to two key features:

1) Permanence – a landmark either always appeared in the exact same location on the screen ("permanent") or in a different place every time ("transient").
2) Relevance – a landmark was either "relevant" for locating treasure (and always appeared in the exact same location *relative to* a treasure chest) or "irrelevant" for orienting (landmark and treasure chest were in completely different relative locations every time).

This gave 4 different types of landmark (Figure 50): Permanent Relevant (landmark and treasure both always appeared in the exact same location on the screen), Transient Relevant (landmark and treasure always appeared in a different location on the screen, but their relative locations were fixed), Permanent Irrelevant (the landmark always

appeared in the same location, but the treasure was in a different place every time), Transient Irrelevant (both landmark and treasure appeared in constantly changing locations). There were 15 of each stimulus type giving a total of 60 landmarks.

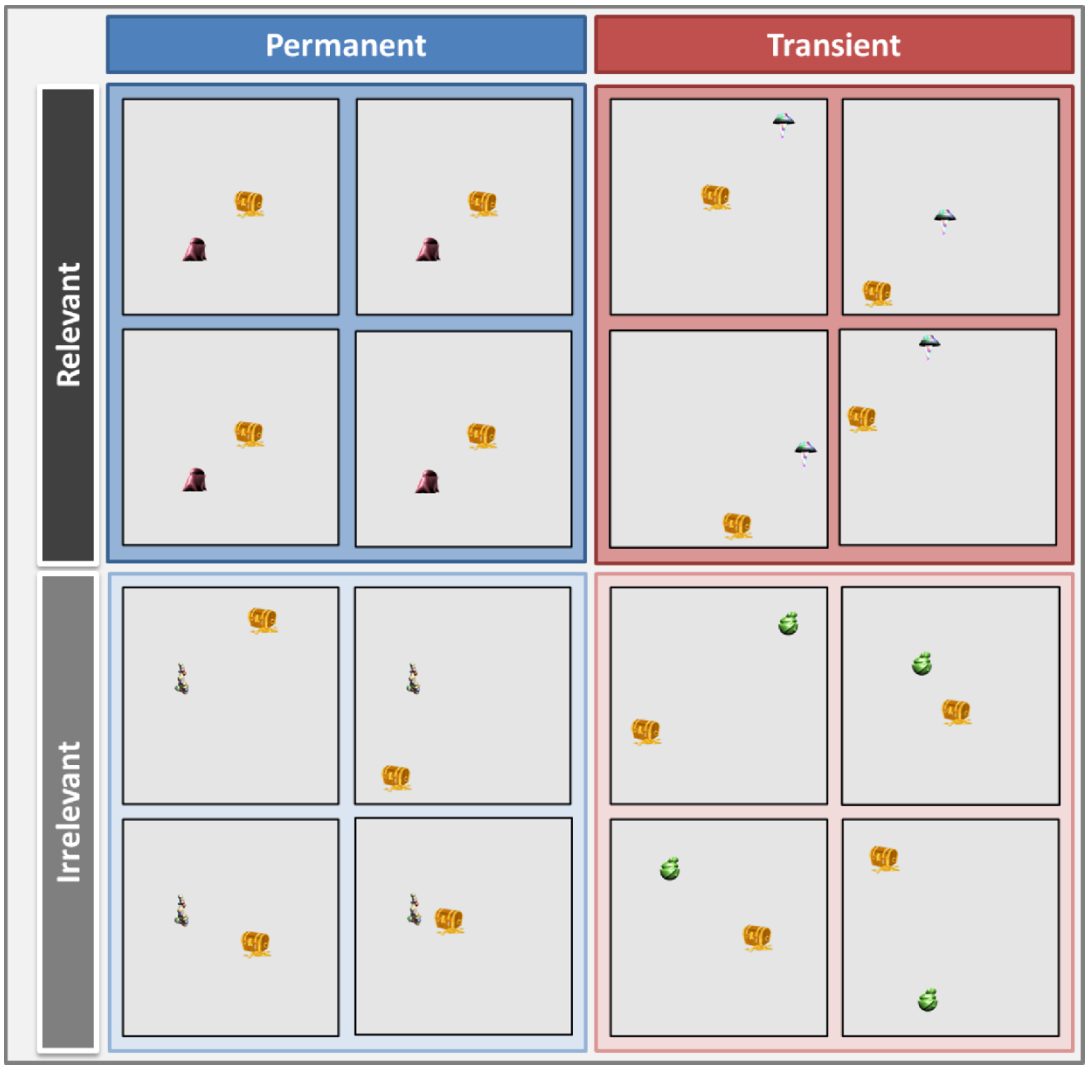

Figure 50 The four types of stimuli. Four examples of each stimulus type are shown here. Landmarks varied in terms of the permanence and orienting relevance. Permanent landmarks (left/blue) were always positioned in the exact same screen location, whereas transient landmarks (right/red) appeared in a different place every time. Relevant landmarks (top/darker) could always be used to locate where a treasure chest would be, whereas irrelevant landmarks (bottom/lighter) could not be used to orient with respect to a target location. There were a total of 60 landmarks (15 of each of the 4 different types). To facilitate this illustration, landmarks and treasure chests in these images are not shown to the same scale as was used in the experiment.

The four landmark groups were matched for a number of other perceptual features based upon ratings given in a separate study with a different set of participants (Section 5.2.2), these included: Salience (To what extent does this item grab your attention? *1/Not at all – 5/Very Much*) ($F_{3,56}$ = 0.350, p = 0.8), Associations with other items (Does this remind you

of anything? *Yes/No*) ($F_{3,56}$ = 0.502, p = 0.7), Strength of association with other items (How strongly does it remind you of this? *1/Only slightly – 5/Very Much*) ($F_{3,56}$ = 0.439, p = 0.7), Likeableness (How do you feel about this item? *Like/Dislike*) ($F_{3,56}$ = 0.886, p = 0.5), Animateness (Does this item look like it could be alive or not? *Alive/Not alive*) ($F_{3,56}$ = 0.414, p = 0.7), Memorableness (Memory of having seen items after answering all other questions about them *Yes/No*) ($F_{3,56}$ = 0.039, p = 1.0). The landmarks were all of the same size and the locations that they appeared on the screen were matched so that an equal number from each of the four groups appeared in all four quarters of the screen. The locations that treasure chests were positioned relative to landmarks was also matched, so that an equal number of treasure chests appeared above/below and left/right of the four different types of landmark.

The experiment comprised two main parts: a learning phase outside of an MRI scanner, followed by a testing phase while participants underwent fMRI scanning.

7.2.3 Pre-scan learning phase

The learning phase had a total of 15 learning "sweeps". In each sweep, all of the 60 landmarks were presented (with a treasure chest) once, in a different randomised order to all other sweeps. At the end of sweeps 2, 4, 6, 8, 10, 12, 14 and 15, there were "mini-test" periods. On each trial in these mini-tests an image of a single landmark was shown on a grey background, in the centre of the screen. Participants then rated the permanence (Is this landmark…. *Permanent/Transient*) and relevance (Could you use this landmark to find the treasure? *Yes/No*) of that landmark before moving to the next trial. Each mini-test consisted of eight trials except for the final mini-test, after sweep 15, which had four trials; in this way, each of the 60 landmarks was rated once in the mini-tests. This ensured that exposure to all the landmarks in the learning phase was identical.

The mini-tests served two main purposes - to ensure participants remained focussed on learning the two key features of each landmark, and to gauge the amount they had learned throughout the learning phase.

Before starting the learning phase, participants had the task clearly explained to them. They were instructed that they had to view the images of landmarks and treasure chests

and concentrate on learning the two key features for each landmark i.e. whether or not it was permanent (always appearing in the exact same place) and whether it could be used to find treasure. They were told that the task inside the MRI scanner would require them to use landmarks to help find treasure. No indication was given about precisely how their knowledge of the landmarks would be tested, just that they needed to focus on learning the two key properties for each landmark.

The number of landmarks, learning sweeps and mini-tests used were all optimised to ensure that people could learn and retain sufficient new information about the permanence and relevance of the landmarks without leaving them too fatigued going into the testing phase (see also Section 7.2.5).

7.2.4 Testing phase in the scanner

At the end of the learning phase, participants were prepared for scanning and had the tasks with which they would be tested explained to them. In this testing phase, while undergoing fMRI scanning, participants performed three different tasks, each requiring them to use the information they had acquired in the learning phase.

For the first task, participants were presented with images of a single landmark, one at a time, for 3 seconds each, in the centre of the screen on a grey background (Figure 51). Immediately after viewing this landmark image, they then rated the permanence and relevance of that landmark. The order that the participants were asked to rate the permanence and relevance of landmarks was randomised, to ensure they could not anticipate which feature they would need to answer first while the landmark image was on screen. The way in which the permanence and relevance questions were asked also varied in order to keep subjects attending carefully; there were three varieties for each feature:

Permanence –

1) Is this landmark always in the same location? *Yes/No*.
2) Is this landmark always in…. *Same place/Different place*.
3) Is this landmark's location…. *Fixed/Not fixed*.

Relevance –

1) Is this landmark relevant for finding treasure *Yes/No*.
2) For finding treasure, is this landmark… *Useful/No use*.
3) For finding treasure, is this landmark…. *Helpful/Not helpful*.

Participants rated the permanence and relevance of each landmark on three separate occasions, using each of the three question variations once, in a randomised order. This gave a total of 180 trials (60 landmarks each rated three times) which were split into three scanning runs of 60 trials. Within each scanning run, every landmark was viewed and then rated once, in a randomised order. Between trials, there was a 2-4 second jittered interval in which a small black cross was presented in the centre of a grey background. Participants were instructed to fixate on this cross during the inter-trial interval.

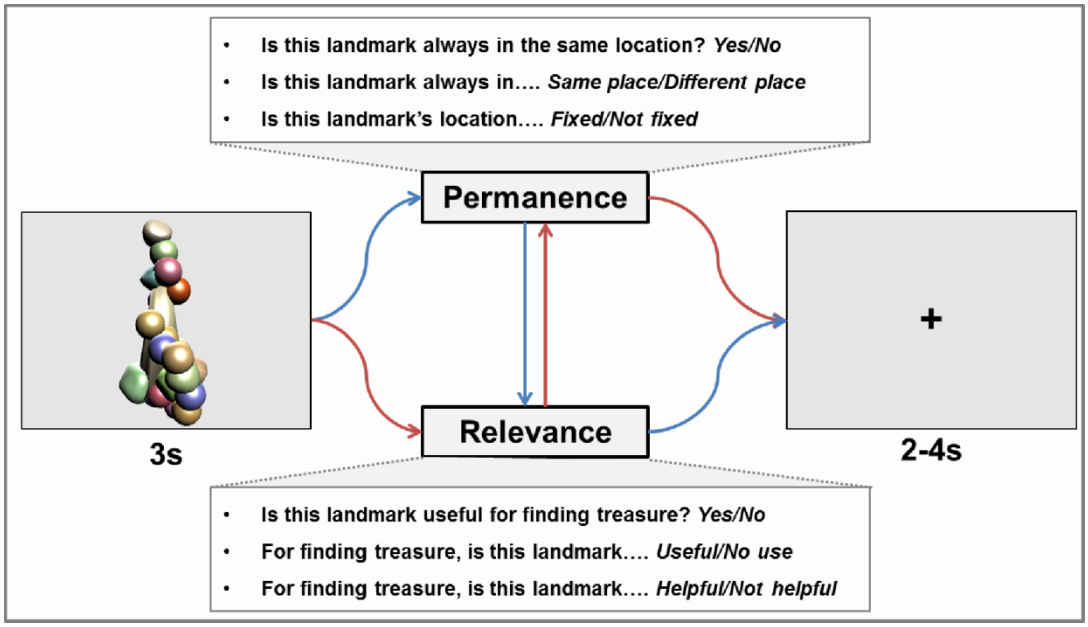

Figure 51 The first testing phase task.

This first testing phase task formed the main focus of this experiment. I included two additional short tasks in the testing phase in order to examine fMRI responses to landmarks (+/- treasure chests) in slightly different circumstances. The second and third tasks came after subjects had completed all three runs of the first task.

In the second testing phase task, subjects were again shown images of single landmarks one at a time, but instead of all being positioned centrally, the landmarks were in a

specific location on the screen. For permanent landmarks, this was either the correct location that it had always been shown in the learning phase, or a different incorrect location. Transient landmarks continued to appear in a different place on every exposure. Each landmark was used for two trials - permanent landmarks were shown once in a correct location and once incorrectly positioned; transient objects were in two different locations. Images of the individual landmarks in a specific screen location were presented for three seconds each and subjects then answered a question regarding the accuracy of the landmark's location: Is this landmark in the right place? *Yes/No/Not fixed*. Subjects were instructed to answer *Yes* or *No* for permanent landmarks which were in the correct or incorrect place or indicate if the landmark was in fact transient and '*Not fixed*'. There was then a 2-4 second jittered interval in which a small black cross was presented in the centre of a grey background. Participants were instructed to fixate on this cross during the inter-trial interval. There were a total of 120 trials of this second task (60 landmarks each presented twice) which were completed in a single scanning session of approximately 14 minutes. The ordering of the 120 trials was pseudorandomised to ensure an even distribution of landmark types across the whole task.

For a third and final testing phase task (Figure 52), subjects were shown an image of a landmark and a treasure chest for three seconds. Each of the 60 landmarks was used on two separate trials (giving a total of 120 trials). For relevant landmarks, these two trials consisted of one in which the treasure was in the correct location (relative to the landmark) and one with incorrectly positioned treasure. For irrelevant landmarks, the two trials simply had treasure in two different locations. On each trial, after viewing the landmark-treasure chest image, participants were shown a question screen ("Is this where the treasure would be?") and indicated whether they thought the treasure was positioned accurately (*Yes*), inaccurately (*No*) or whether the landmark was uninformative about treasure location (*Can't tell*). There was then a jittered 2-4 second intertrial interval in which a fixation cross was presented in the centre of the screen. The ordering of trials and instances of correctly/incorrectly positioned treasure chests were both randomised.

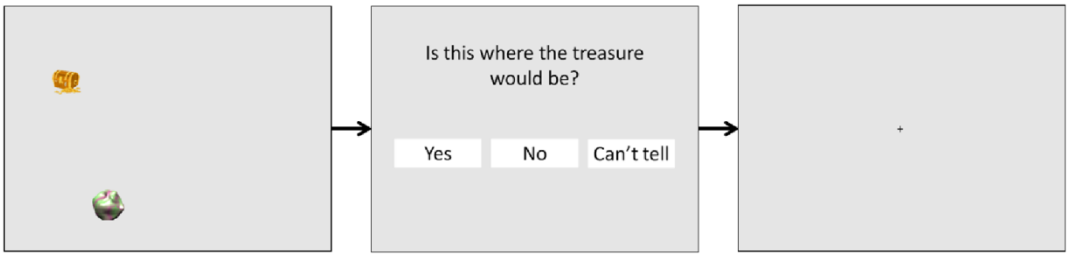

Figure 52 The third testing phase task.

After the testing phase inside the scanner was complete, participants were debriefed. I discussed with participants how difficult they had found the tasks, when during the learning phase they felt they began to know the landmark features, and what (if any) particular strategies they adopted to learn them.

7.2.5 Pilot experiment

All elements of the task design described in Sections 7.2.3 and 7.2.4 were tested in a pilot experiment. Four participants (3 female, mean age 23.5 years, SD 5.3) completed all aspects of the task, with the only difference between the pilot and full fMRI experiments being the use of an MRI scanner. All four participants were able to acquire a sufficient amount of information about both the permanence and orienting value of landmarks within the designated time. There were also no differences in peoples' ability to learn the permanence and orienting value of landmarks, and subjects performed the testing phase tasks with no significant problems. I therefore did not feel it necessary to make any adjustments to the paradigm.

7.2.6 Scanning parameters

T2*-weighted echo planar images with BOLD contrast were acquired on a 3T whole body MRI scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) operated with the standard RF transmit body coil and a 32-channel head receive coil. Scanning parameters were selected to achieve whole brain coverage but optimised for the hippocampus and surrounding tissue: 48 oblique axial slices angled at −45° from the axial to coronal plane (as defined in Weiskopf et al., 2006), 2.5 mm thickness (with inter-slice distance factor 20%), repetition time TR = 3.36s (slice TR = 70 ms), excitation flip angle = 90°, echo time TE = 30 ms, in-plane resolution 3 mm×3 mm, field of view FoV = 192

mm×192 mm, 64×64 matrix, phase encoding (PE) in the anterior-posterior direction, 13% oversampling in the PE direction, echo spacing 500 µs. For reduction of signal loss in the hippocampal region, slices were angulated and a z-shim gradient moment of +0.6 mT/m*ms was applied (Weiskopf et al., 2006). To allow for T1 equilibration effects, the first 6 'dummy' volumes from each scanning run were discarded. Field maps were acquired using a standard manufacturer's double echo gradient echo field map sequence (short TE = 10 ms, long TE = 12.46 ms; 64 axial slices with 2 mm thickness and 1 mm gap yielding whole brain coverage; in-plane resolution 3 mm×3 mm). A 3D MDEFT T1-weighted structural scan (Deichmann et al., 2004) was acquired for each participant with 1 mm isotropic resolution.

7.2.7 Preprocessing

FMRI data were analysed with SPM8 (www.fil.ion.ucl.ac.uk/spm). Images were bias corrected, realigned and unwarped (using the field maps) and normalised to a standard EPI template in MNI space with a resampled voxel size of 3×3×3 mm. For all the whole brain univariate and connectivity analyses, images where then smoothed using a Gaussian kernel with full width at half maximum of 8mm. MVPA used unsmoothed images (see Section 2.7). I analysed the data from the three different testing phase tasks separately.

7.2.8 Behavioural analyses

In the learning phase and all three testing phase tasks, subjects rated both the permanence and orienting relevance of landmarks. I therefore analysed all these sets of ratings to determine whether or not there were any differences in how well subjects had been able to learn the permanence and orienting relevance of landmarks.

In the first testing phase task, landmark permanence and orienting relevance was asked in three different ways (see Section 7.2.4 and Figure 51). The ordering of the permanence/relevance questions was also randomised. I therefore additionally analysed the first testing phase task responses using one-way ANOVAs to determine whether the way or order in which the permanence and relevance questions were asked had any impact upon the accuracy of responses.

Given the results of my previous experiments (see Chapters 3, 4 and 5), I also assessed whether there was a significant relationship between how well individual subjects were able to learn about the landmarks and their self-reported navigation ability according to the SBSOD questionnaire. For this analysis I used subject responses made in the first testing phase task as this contained the greatest number of trials, so provided the most rigorous characterisation of subjects' learning. I compared the accuracy of participants' answers to all questions in this part of the experiment with their SBSOD score. All statistical analyses were performed using SPSS version 20.

7.2.9 Whole brain univariate analyses

In the first testing phase task, participants viewed images of individual landmarks in isolation on a plain background in the centre of the screen. To assess fMRI responses in relation to the permanence and orienting value of landmarks, I first performed an interaction analysis. I then analysed the main effects of each condition (landmark permanence and relevance). Namely, I compared whole brain BOLD responses for: permanent versus transient; transient versus permanent; relevant versus irrelevant, and irrelevant versus relevant landmarks. For each contrast, I created regressors for each condition of interest and convolved them with the canonical HRF.

For all fMRI analyses, each testing phase trial was modelled from the time of onset of a landmark image for 1.5 seconds (the first half of the landmark image presentation time). Similar to my first experiment (Chapter 3), this time was selected to ensure responses corresponded to automatic and rapid processing of the landmarks and to minimise any fMRI responses which might have been associated with preparing to answer the upcoming questions. Separate participant-specific movement regressors were treated as covariates of no interest.

In each analysis, subject-specific parameter estimates pertaining to each regressor of interest (β) were calculated for each voxel. Second level random effects analyses were then run using one sample t-tests on the parameter estimates (collapsing across the three scanning runs of the first task). For all these contrasts I report any activation which survived a whole brain FWE corrected threshold of $p < 0.05$, unless otherwise stated.

There are multiple instances in which the HC has been shown to process the distance between specific spatial locations (see Section 7.1; Spiers and Maguire, 2007b; Morgan et al., 2011; Baumann et al., 2012; Sherrill et al., 2013) and so I also examined for BOLD responses during the first testing phase task which were related to the distance between a landmark and its associated treasure location. For every relevant landmark, I calculated the distance between it and its target treasure location. I used these values to create parametric regressors for a whole brain GLM fMRI analyses. Specifically, I looked for activity that was linearly modulated by a target location which was closer or further away from its associated landmark. I report any fMRI activations that survived a whole brain FWE corrected threshold of $p < 0.05$, except for the HC where, given my prior hypotheses regarding this specific region, I report activations at a whole brain uncorrected threshold of $p < 0.001$.

7.2.10 Connectivity analyses

I was also interested in how RSC interactions with other brain regions may relate to people's ability to learn spatial information about the landmarks (see Section 7.1). As such, for any landmark features to which RSC was responsive in the whole brain univariate analyses (a so called "feature-of-interest"), I also investigated how its interactions with other brain areas varied during the first testing phase task depending on how well participants had learned that feature. Specifically, I used a gPPI analysis (Section 2.8.1) to examine the functional coupling between RSC and the rest of the brain while people viewed landmarks possessing the particular feature-of-interest. I then added the participants' accuracy rating of that landmark feature during the testing phase as a second-level covariate of interest. I also performed additional gPPI analyses for any other regions shown to be responsive to landmark permanence or relevance from the whole brain univariate analysis.

As seed regions, I used clusters from the corresponding whole brain univariate fMRI contrasts with a specific focus on RSC (i.e. the clusters within RSC which were responsive to a particular feature-of-interest). For all the gPPI analyses, I report any significant activation which survived a whole brain FWE corrected threshold of $p < 0.05$.

For any functional connectivity identified by the gPPI analyses, I used DCM (Section 2.8.2) to investigate the nature of the information flow between the regions. The PPI analyses specifically indicated which regions were interacting more in connection with better learning of the feature-of-interest. I therefore compared how the nature of the interaction between the regions may differ between those who had been able to learn the information particularly well and those who had not. To do this, I split the participants into "good" and "poor" learners by taking a median split of their accuracy rating of the specific feature-of interest in the first task of the testing phase. I then performed separate DCM analyses in the two groups and compared the fit of their models to the fMRI data.

For each participant, I created a design matrix with two main regressors of interest: one modelling all landmarks, to be used as the input for each DCM model (C matrix) and another for just those with the specific feature-of-interest (e.g. permanent landmarks), to be used as the models' modulatory input (B matrix). Each model assumed the presence of endogenous self-connections and reciprocal connectivity between the two regions (A matrix). I then constructed models of all plausible combinations of input and modulatory connectivity, giving 4 models in total: two unidirectional models in which input comes into one region and this then drives responses in the other (changing which region drives and which is driven for the two variants) and two bidirectional models with both regions driving each other's responses but input coming from one or the other (see Figure 54B for the precise model architectures compared). I used DCM10, to fit each model to the fMRI data and also modelled stochastic fluctuations in the state equations to account for neural noise which is particularly relevant for these endogenously driven interactions (Daunizeau et al., 2012). Separate random effects bayesian model comparisons were used to determine the best fitting, winning model in the good and poor learners (Stephan et al., 2009). Each model's posterior probability for the two subject groups were then also compared using classical t-tests.

7.2.11 MVPA

To examine subject-specific neural representations of the key landmark features, I also used the more sensitive measure of MVPA to analyse the first testing phase task's fMRI data (Section 2.7). Separate regressors were created for each of the 180 trials and

convolved with the HRF. Participant-specific parameter estimates pertaining to each trial regressor were then calculated and used in the MVPA analyses.

I selected ROIs to use for the MVPA analyses from brain areas shown, in this and my previous studies, to process permanence and related landmark features, namely: RSC, HC and PHC, as well other related regions in the present study's whole brain univariate or PPI analyses (which included a region which was comparable to the POS in Experiments 3 and 4). ROIs were defined anatomically for RSC, HC and PHC using bilateral masks which were delineated by and experienced researcher, not involved in this project, on an averaged structural MRI brain scan from an independent group of participants (n = 30) and guided by Duvernoy (1999), Insausti et al. (1998) and Vann et al. (2009).

MVPA analyses were performed for every subject in order to ascertain whether or not it was possible to decode the type of landmark being viewed based upon patterns of activation in each of the ROIs. All MVPA analyses used a linear SVM implemented through LIBSVM (Chang and Lin, 2011) with fixed regularization hyperparameter $C = 1$. I used a similar feature selection and standard cross-validation procedure to those described in Sections 4.2.6, 5.6.3 and 6.2.9. The testing phase consisted of three scanning runs; I therefore used two runs for feature selection and the independent dataset from the remaining run for the final classification. This was repeated twice more, changing the scanning run which was used for the final classification on each occasion. The classifier accuracy values from these three repetitions were then averaged to provide an overall three-fold cross-validation. This produced a single participant-specific classification accuracy value for each ROI. I then performed t-tests upon these values to assess whether or not accuracy across all subjects was significantly above chance (i.e. t-tests were all one tailed).

I first used this MVPA procedure to assess the ROIs' response patterns for any representations of the features with a 4-way classification of landmark type (Permanent Relevant vs Transient Relevant vs Permanent Irrelevant vs Transient Irrelevant; chance = 25%). Similar to the PPI connectivity analysis, I then looked for any relationship between these results and people's ability to learn the information about the landmarks. Specifically, I assessed for correlations between the 4-way classifier accuracy values in

each ROI and participants' associated performance rating the landmark features (mean accuracy of landmark ratings in testing phase).

For ROIs implicated in coding for landmark features by the 4-way classification, I also performed separate 2-way classifications of permanence and relevance to assess representations of the two properties independently.

Finally, I investigated whether it was possible to classify the distance between a relevant landmark and its associated treasure location, in addition to the related univariate analysis (described at the end of Section 7.3.1). I took a median split of the relevant landmarks' distances from their related treasure location to define "close" and "far" groups. I then performed an MVPA analysis to determine whether the activation patterns elicited whilst viewing these landmarks might contain information about the proximity of their target location.

7.2.12 fMRI analyses for second and third testing phase tasks

In the second testing phase task, subjects saw pictures of individual landmarks in correct and incorrect locations. Similarly, in the third testing phase task, participants were presented with images of accurate and inaccurate landmark-treasure chest pairings. This allowed me to compare fMRI responses to landmarks according to the accuracy of the spatial information they provide.

I analysed data from the two sessions separately, but in both instances each trial was modelled for the full 3 seconds that an image of a landmark (with or without an additional treasure chest) was on screen. I made separate regressors for images which showed a landmark providing accurate information about its own location (in the case of the second task) or that of its paired treasure chest (for the third task) and those which did not (landmark in an inaccurate location and transient landmarks for task two; treasure in an inaccurate location and irrelevant landmarks for task three). These regressors of interest were convolved with the canonical HRF. Subject-specific movement regressors were also included as covariates of no interest. Subject-specific parameter estimates pertaining to each regressor of interest (β) were calculated for each voxel. Second-level random effects analyses were run using one-sample t-tests on those parameter estimates. For all fMRI

univariate contrasts, I report any activation which survived a whole brain FWE corrected threshold $p < 0.05$ (minimum cluster size 10 voxels).

I then performed gPPI analyses using significant clusters from the whole brain fMRI univariate analyses as seed regions to see which parts of the brain they interacted more with when landmarks provided information about treasure location (i.e. relevant versus irrelevant landmarks). I report results at the voxel-level threshold of $p < 0.001$ whole brain uncorrected for regions previously implicated in processing spatial features of landmarks (e.g. RSC, HC and PHC) and $p < 0.05$ whole brain FWE corrected for elsewhere.

7.3 Results

7.3.1 Behavioural data

The participants were successfully able to learn both the permanence and relevance of the landmarks and there were no differences in their accuracy rating the two features in the final pre-scan learning phase "mini-test" (mean permanence accuracy = 93.0%, SD = 15.9; mean relevance accuracy = 86.7%, SD = 16.8; $t_{31} = 1.761$, $p = 0.09$). There were also no differences in the rate at which they learned landmark permanence or relevance (mean accuracy in sweep 8/midway "mini-test": permanence = 73.0%, SD = 18.5; relevance = 71.1%, SD = 16.6; $t_{31} = 0.543$, $p = 0.6$).

Responses made by participants during the first testing phase task also indicated that there were no differences in how well subjects knew the permanence and orienting relevance of landmarks (mean permanence accuracy = 90.1%, SD = 10.7; mean relevance accuracy = 87.7%, SD = 12.5; $t_{31} = 0.426$, $p = 0.4$).

The three different ways in which the questions were asked for the first task inside the scanner also had no impact upon the accuracy of responses for permanence (question one mean accuracy = 90.6%, SD = 9.8; question two mean accuracy = 89.2%, SD = 12.2; question three mean accuracy = 90.4%, SD = 10.6; $F_{2,93} = 0.155$, $p = 0.9$) or relevance (question one mean accuracy = 87.6%, SD = 13.2; question two mean accuracy = 87.3%, SD = 13.0; question three mean accuracy = 88.3%, SD = 11.9; $F_{2,93} = 0.054$, $p = 0.9$).

The order of the questions also had no impact upon the accuracy of subject responses for either permanence (mean accuracy if first question = 89.7%, SD = 11.1; mean accuracy if second question = 90.5%, SD = 10.3; $t_{31} = 0.324$, $p = 0.8$) or relevance (mean accuracy if first question = 88.0%, SD = 13.4; mean accuracy if second question = 87.2%, SD = 12.0; $t_{31} = 0.132$, $p = 0.9$). Therefore, any differences in fMRI activation were not the result of variation in the extent that participants knew the landmark features or difficulty they had rating them.

Comparing the accuracy of responses for the second and third testing phase tasks once again demonstrated that there were no differences in how well subjects had learned the permanence and orienting relevance of landmarks (mean permanence/task two accuracy = 87.2%, SD = 11.3; mean relevance/task three accuracy = 82.3%, SD = 16.0; $t_{31} = 1.421$, $p = 0.2$).

The amount that subjects learned about the two features of the landmarks was not related to their self-reported navigation ability according to the SBSOD ($r = 0.073$, $p = 0.7$).

7.3.2 Brain areas responding to properties of the landmarks

I first performed whole brain univariate contrasts on the task one data to look for regions which were more engaged by permanent and/or relevant landmarks. An interaction analysis found no regions where activity was influenced by a combination of both landmark properties. I then performed separate analyses to assess the main effects each individual condition.

Comparing fMRI responses when participants viewed permanent and transient landmarks, there was increased activity for permanent items within right RSC (Figure 53A; 15, -52, 19, Z = 5.86), extending into more posterior parts of POS, as well as additional bilateral clusters in posterior occipital cortex (left: -18, -88, -8, Z = 6.34; right: 18, -91, -2, Z = 6.31). A similar contrast comparing relevant landmarks with those which were irrelevant for localising treasure produced no significant activation in RSC, but there were small bilateral clusters in posterolateral temporal cortex (Figure 53B; right: 39, -82, 25, Z = 7.26; left: -33, -82, 34, Z = 6.05). No brain areas were more responsive to transient than permanent or irrelevant than relevant landmarks.

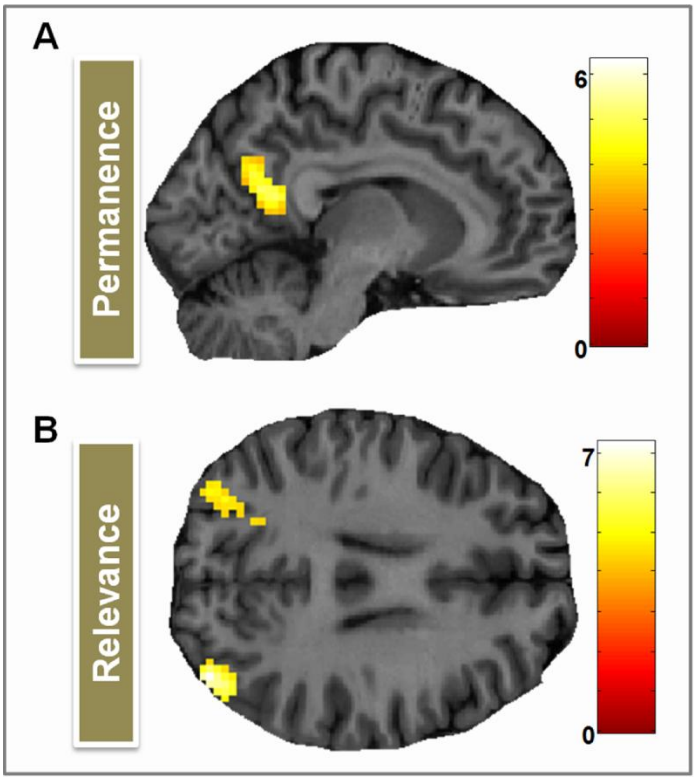

Figure 53 Brain areas responsive to landmark permanence and relevance. (A) The RSC and more posterior parts of POS were more engaged by permanent than transient landmarks. (B) Bilateral clusters in posterolateral temporal cortex were more active when people viewed a relevant than an irrelevant landmark. Activations are displayed on a sagittal (A) and axial (B) section of a single representative subject's structural MRI brain scan. The colour bars indicate each voxel's associated Z-score.

For relevant landmarks, I also looked for fMRI responses related to the distance between them and their associated treasure location. A larger distance between a landmark and its target location, was associated with a greater BOLD response in right HC (Figure 57A; 30, -28, -11, Z = 4.89). No region was more engaged by landmarks associated with closer treasure locations.

7.3.3 RSC interactions with other brain areas and knowledge about landmarks

I then looked for brain areas with which the permanence-responsive RSC was interacting and how this may be related to how well participants had learned landmark permanence. A gPPI analysis revealed that while participants viewed permanent landmarks, the better they had learned the landmark permanence the more their RSC displayed functional coupling with the anterior thalamus (Figure 54A; AThal: -12, -19, 7, Z = 5.80); there was also an additional significant cluster in the cerebellum (in the posterior part of the

quadrangular lobe: -9, -70, -11, Z = 6.59). At a slightly reduced threshold ($p < 0.001$ whole brain uncorrected), there was an additional significant activation in the left HC, including the subiculum (-21, -22, -8, Z = 4.34). This is particularly interesting given that the subiculum, RSC and AThal all contain head direction cells in rodents (Sharp et al., 2001). I also ran further comparable gPPI analyses using the other brain areas shown to be responsive to landmark permanence or relevance in the whole brain univariate analyses (i.e. all those mentioned in Section 7.4.2). No other region displayed any differences in functional connectivity relating to the amount of information learned about landmarks.

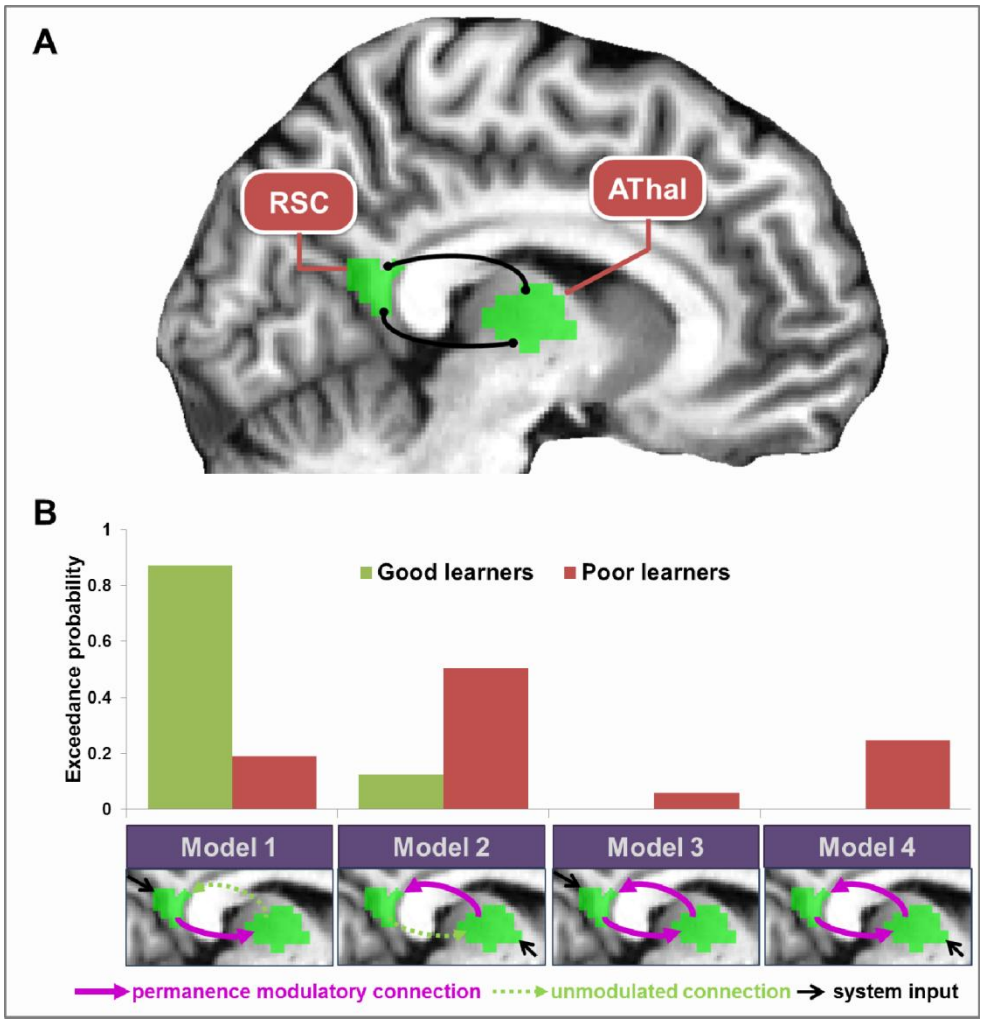

Figure 54 RSC connectivity associated with inter-individual differences in permanence learning. (A) A gPPI analysis revealed that when participants viewed an image of a permanent landmark, the better they had learned landmark permanence, the more their RSC interacted with anterior parts of the thalamus (AThal). (B) To examine the nature of this RSC-AThal interaction in good and poor learners, I performed a DCM analysis. In good learners, the winning model (Model 1) had RSC driving activity in AThal while a permanent landmark was in view. This was not the case in poor learners where a winning model was less apparent. Taken together, these results suggest that the better people were able to learn landmark permanence, the more their RSC drove activity in AThal for permanent landmarks.

I then investigated the nature of the RSC-AThal interaction using DCM. I compared four biologically plausible models of connectivity between the two regions (see bottom of Figure 54B): Model 1 - input coming via RSC with RSC then driving responses in AThal for permanent landmarks; Model 2 – input coming via AThal and this driving RSC, and finally two models in which the two regions mutually modulate one another's responses, with input coming through either RSC (Model 3) or AThal (Model 4). I was specifically interested in differences in the interaction between these regions based upon how well subjects had learned landmark permanence. I therefore performed separate DCM analyses in the best and worst permanence learners (based upon their landmark ratings in the first task of the testing phase). In the good learners, Model 1 was the clear winner (Figure 54B). In poor learners a winning model was not so apparent, but Model 2 provided the best fit. To formally compare the model fits in good and poor learners, I assessed the mean posterior probabilities for each of the four models. The only difference between the groups was for Model 1, which had a significantly greater posterior probability in good learners (Model 1: $t = 2.339$, $p = 0.03$; Model 2: $t = 0.344$, $p = 0.7$; Model 3: $t = 1.616$, $p = 0.1$; Model 4: $t = 1.671$, $p = 0.1$). There was also no significant difference in the posterior probabilities of the four models for poor learners ($F_{3,60} = 0.988$, $p < 0.4$), whereas this difference was significant for the good learners ($F_{3,60} = 8.772$, $p < 0.0001$). Thus, only Model 1 in the good learners provided a significantly better fit than all the others. This indicates that the increased interaction between RSC and AThal shown by the gPPI analysis likely reflected RSC driving responses in AThal more the better people knew the permanence of landmarks.

7.3.4 MVPA

To explore the representations of landmark features in greater detail, I used the more sensitive measure of MVPA. I first investigated whether it was possible to decode which of the four landmark types (Permanent Relevant, Transient Relevant, Permanent Irrelevant or Transient Irrelevant) a participant was viewing based upon the multi-voxel patterns of activity in RSC, HC and PHC (defined anatomically - see Section 7.3.3) as well as two other regions implicated in this study: POS (the parts of the cluster responding more to permanent than transient landmarks in the univariate analysis, see Figure 53A, excluding the parts in RSC) and AThal (from the PPI analysis – see Figure 54A). Figure 55A illustrates results of this 4-way MVPA analysis. Landmark type could be classified based upon

responses in RSC (mean accuracy = 26.3%, SD = 3.7; t_{31} = 1.924, p = 0.03) and HC (mean accuracy = 27.1%, SD = 3.5; t_{31} = 3.410, p < 0.001), but not PHC (mean accuracy = 25.3%, SD = 3.6; t_{31} = 0.512, p = 0.3), POS (mean accuracy = 25.4%, SD = 4.0; t_{31} = 0.618, p = 0.3) or AThal (mean accuracy = 25.7%, SD = 4.9; t_{31} = 0.808, p = 0.2).

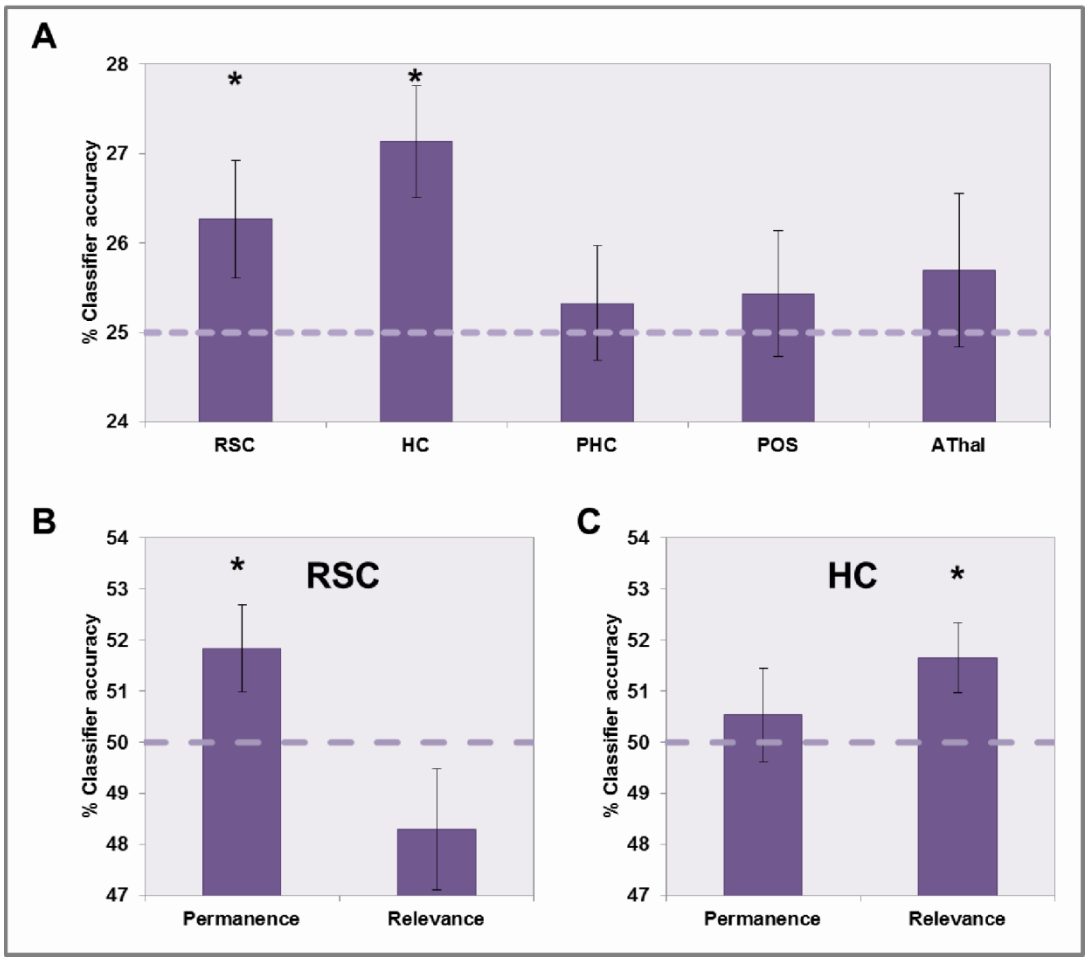

Figure 55 MVPA in relation to landmark permanence and relevance. (A) The classification accuracy for decoding between the four types of landmark in each of the ROIs. Above chance classification was only possible in RSC and HC. Separate 2-way classifications of landmark permanence and relevance were performed in RSC (B) and HC (C) to determine which feature each region was particularly sensitive to. RSC responses could be used to classify landmark permanence but not relevance, whereas HC activity contained information relating to the relevance but not permanence of landmarks. Dashed lines indicate each classification's chance level, error bars show the standard error of the mean and * denotes classifications which are significantly above chance (p < 0.05).

To establish whether the significant 4-way classification in RSC and HC was driven by representations of landmark permanence or relevance, I performed separate, independent 2-way classifications for each feature based upon responses in the two regions. In RSC (Figure 55B), response patterns could be used to classify the permanence (mean accuracy = 51.8%, SD = 4.8; t_{31} = 2.168, p = 0.02) but not relevance (mean accuracy

= 48.3%, SD = 6.7; t_{31} = -1.444, p = n/a – as one-tailed t-test cannot produce a p-value for below chance classification) of landmarks significantly above chance. The opposite was true of HC (Figure 55C), where relevance (mean accuracy = 51.6%, SD = 3.9; t_{31} = 2.398, p = 0.01) but not permanence (mean accuracy = 51.5%, SD = 5.7; t_{31} = 1.507, p = 0.07) could be decoded. Thus, there were subject-specific activation patterns related to whether or not a landmark was permanent in RSC or relevant in HC.

Given that the gPPI and DCM analyses revealed differences in neural activity relating to how well participants had learned about landmarks, I also compared each person's 4-way classifier accuracies from each region with their corresponding behavioural accuracy rating the landmark features. Only in RSC was there a significant relationship between the two (Figure 56), with better knowledge of the landmark features linked to better classifier accuracy (r = 0.473, p = 0.006), no such relationships existed for responses in HC (r = 0.191, p = 0.3), PHC (r = 0.063, p = 0.7), POS (r = 0.091, p = 0.6) or AThal (r = 0.238, p = 0.2).

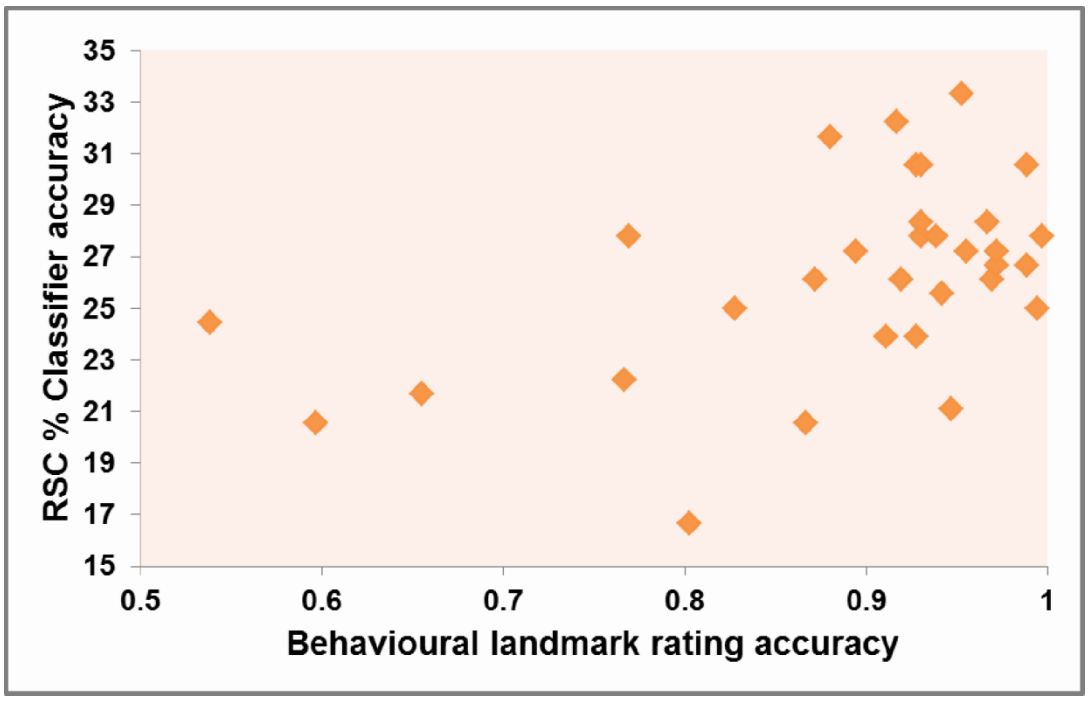

Figure 56 Associations between learning of landmark features and RSC classifier accuracy. The overall accuracy of each participant rating the landmarks' properties plotted against the accuracy classifying those features from their RSC response patterns. The two were significantly correlated (r = 0.473, p = 0.006), so the better a participant knew the landmark features, the better responses within their RSC could be used to distinguish them. This was not the case in any other brain region.

Similar to the univariate analysis of fMRI responses relating to the distance between a relevant landmark and its associated treasure location (see end of Section 7.4.2), I examined whether it was possible to decode this distance using MVPA. The multi-voxel response pattern elicited in HC while people viewed an image of a landmark could be used to classify whether or not it was relevant for finding treasure which was nearby or far away (Figure 57B; mean accuracy = 53.2%, SD = 9.8; t_{31} = 1.852, p = 0.04). This was not the case in any other of the ROIs (RSC mean accuracy = 49.6%, SD = 8.9; t_{31} = -0.264, p = n/a – as one-tailed t-test cannot produce a p-value for below chance classification; PHC mean accuracy = 51.0%, SD = 9.7; t_{31} = 0.605, p = 0.3; POS mean accuracy = 51.3%, SD = 11.3; t_{31} = 0.626, p = 0.3; AThal mean accuracy = 50.1%, SD = 8.2; t_{31} = 0.048, p = 0.5).

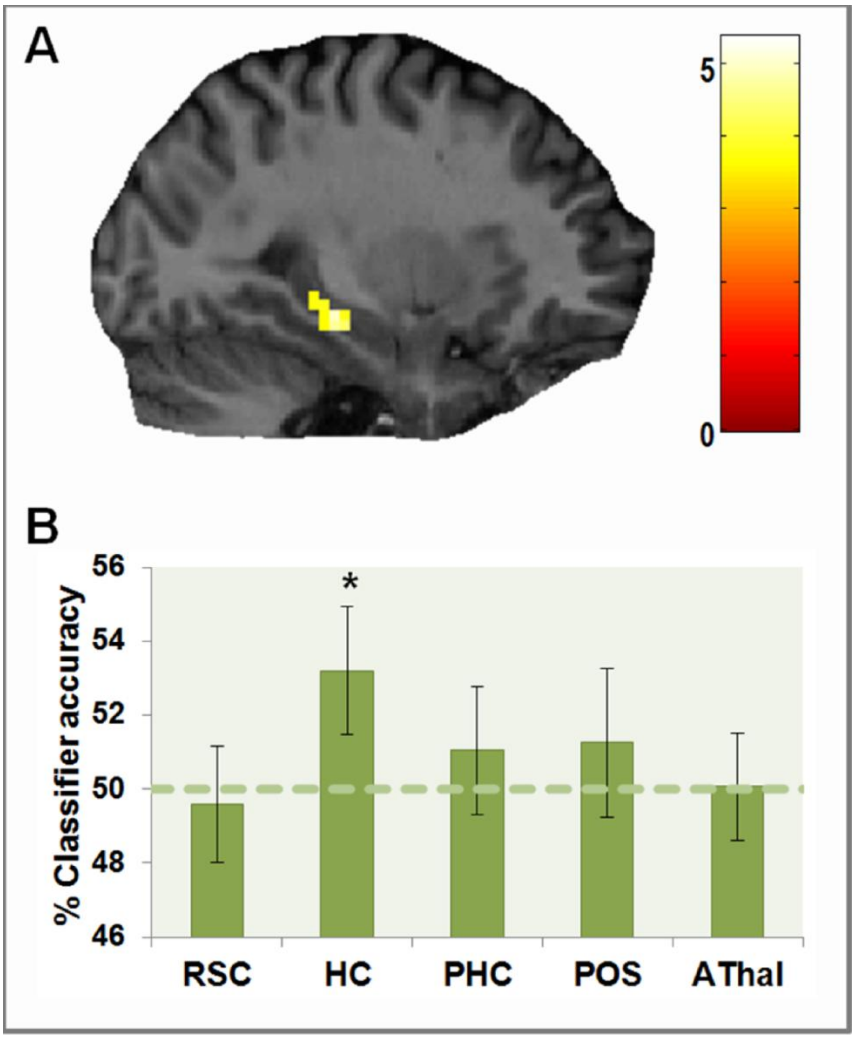

Figure 57 HC processing the distance between a relevant landmark and its target treasure location. (A) The HC was more engaged by landmarks which were associated with a more distant target treasure location. Activations are displayed on sagittal sections of a single representative subject's structural MRI brain scan. The colour bar indicates each voxel's Z-score. (B) Only HC had patterns of activation which could be used to decode whether a relevant landmark's associated treasure was nearby or further away. The green dashed line indicates the chance level (50%) for this two-way classification, error bars show the standard error of the mean and * denotes classifications which are significantly above chance (p < 0.05).

7.3.5 Whole brain univariate analyses for second and third testing phase tasks

I performed separate whole brain univariate analyses for the second and third testing phase tasks. For the second testing phase task, no region had greater fMRI activity for landmarks shown in a correct location than those which were not (permanent landmarks in incorrect location or transient items). Neither did any region have increased activation for the opposite contrast (landmarks not in a correct permanent location versus permanent landmarks in correct location).

For testing phase three data, I compared fMRI activity based upon whether or not landmarks provided accurate information about the location of treasure (Figure 58A). There was greater activity in the left HC (-21, -19, -14; Z = 7.95), right anterior cingulate (ACC: 6, 20, -8; Z = 8.59) and right mid-cingulate (9, -19, 46; Z = 7.86) cortices for landmarks which provided accurate, reliable information about treasure location compared to those which did not (relevant landmarks with incorrectly positioned treasure, and irrelevant landmarks). The opposite contrast (Figure 58B) found increased BOLD responses in bilateral inferior temporal cortex (ITC; right: 36, -58, -17; Z = 9.52; left: -27, -55, -14; Z = 9.04).

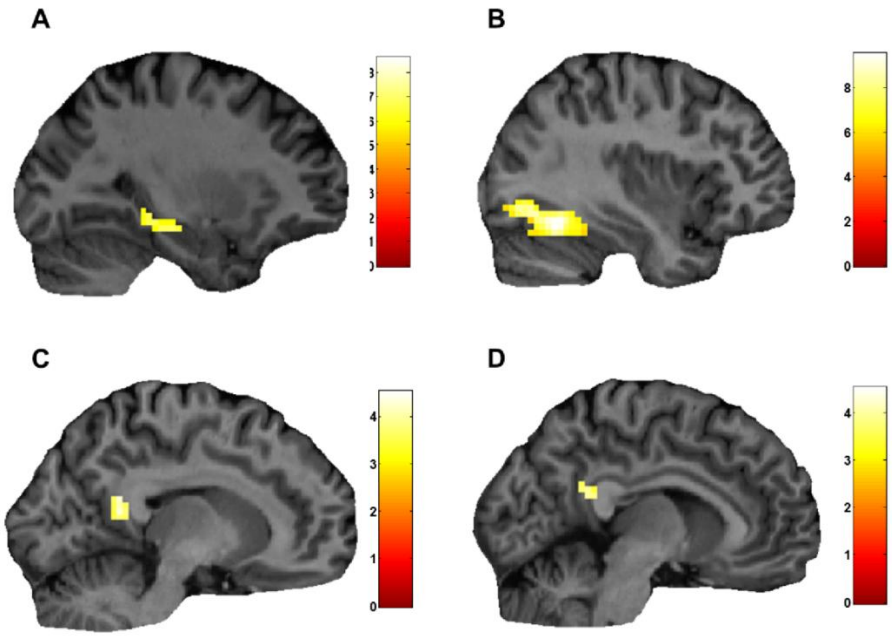

Figure 58 Results from the third testing phase task. Whole brain univariate contrasts showing regions more active for landmarks providing accurate information about treasure locations (A) and those which do not (B). PPI results showing regions with increased functional connectivity to the HC (C) and ITC (D) when a landmark is uninformative about treasure location. Activations are shown on sagittal sections of a single representative subject's structural MRI scan. Colour bars indicate each voxel's associated Z-score.

The HC, therefore, appeared to specifically process landmarks which provided correct spatial information, whereas ITC was engaged by landmarks which could not be used for locating treasure.

7.3.6 Connectivity analysis for task three

I then used gPPI analyses to establish how the regions identified in the whole brain univariate analysis for the third testing phase task interacted with other brain areas depending upon how relevant a landmark is for locating external cues.

The HC was not found to interact with any other regions, except when viewing uninformative landmarks, when it displayed increased functional coupling with right RSC (12, -49, 13; Z = 4.26) than for informative ones (Figure 58C). Similarly, ITC interacted more with right RSC (12, -46, 22; Z = 4.36) for uninformative compared to informative landmarks (Figure 58D).

Finally, I sought to investigate the nature of these interactions using DCM. However, no models were able to provide reliable fits of the fMRI data, probably owing to an insufficient number of trials in this task.

7.4 Discussion

My previous experiments have provided numerous examples of RSC coding for the permanence of landmarks (Chapters 3, 4, 5 and 6). However, it has not yet been possible to determine whether these are true representations of a landmark's permanence or if they rather reflect the fact that permanent landmarks tend to be the most reliable cues for orienting. This study dissociated these two important landmark properties in order to establish whether a primary function of RSC is to orientate using landmarks or more simply distinguish the most stable environmental cues upon which to centre these more complex processes.

When people viewed a permanent landmark, there was increased activity in RSC extending posteriorly into the POS. The same was not true, however, for landmarks which could be used to locate a target treasure chest. MVPA analyses also revealed that RSC

contains subject-specific patterns of activity associated with the permanence, but not relevance, of landmarks. This was not the case in any other brain region.

The HC contained multi-voxel response patterns relating to whether or not a landmark was relevant for locating a treasure target. HC also coded for the distance between a treasure chest and its associated landmark, both in terms of its average level of engagement across all participants and in subject-specific patterns of activity. Therefore, permanence seems to be the primary feature processed by RSC, with other brain regions, primarily the HC, coding for landmarks' other properties and spatial relationships.

7.4.1 Landmark processing in RSC

RSC is involved in a diverse range of complex cognitive functions including navigation (Section 1.10.5), scene processing (1.10.3), episodic memory and imagination of future and fictitious events (Section 1.10.6). However, there is limited evidence to indicate what specific role it might contribute to these processes. In my previous experimental chapters, I have proposed that a key function of the RSC is to identify permanent predictable landmarks which might then be used to build environmental representations. However, the permanent landmarks in these previous experiments were always inherently more relevant and reliable cues for orienting. Here, by dissociating these two properties, I was able to confirm that RSC does indeed appear to primarily process landmark permanence independent of any utility for making spatial judgements.

The dominance of permanence, rather than relevance, representations in RSC and POS is inconsistent with the suggestion that a key function of these regions lies in using landmarks to localise and orientate within space (Epstein and Vass, 2014). The role RSC plays in these more complex processes could merely reflect the fact that they are usually centred upon permanent environmental features. RSC has also been suggested to assist in translating between and integrating egocentric and allocentric spatial information (Section 1.11; Byrne et al., 2007; Vann et al., 2009; Sherrill et al., 2013; Sulpizio et al., 2013), I believe this could similarly reflect the reliance of these processes on manipulating mainly permanent cues.

RSC has also previously been implicated in processing information relating to the distance and direction to a goal location (Wolbers and Buchel, 2005; Baumann and Mattingley, 2010; Sherrill et al., 2013). However, this did not appear to be the case in the present study; only the HC showed any sensitivity to the distance between a landmark and its associated treasure location. Once again, RSC's apparent involvement in these processes may have previously reflected their reliance upon the use of permanent, stable environmental cues.

In my previous experiment, I found that RSC was particularly responsive to permanence when participants recalled landmarks in large-scale space. However, as I discussed in Section 6.4, there was evidence that landmarks in small-scale space might also be sensitive to permanence, just to a lesser extent than in more immersive three-dimensional circumstances. In this experiment, items were only ever experienced in small-scale, two-dimensional space and RSC was more active for permanent than transient landmarks. This experiment's greater number of trials assessing responses to landmarks in small-scale space was therefore able to confirm that permanence representations are indeed not exclusive to large-scale environmental representations.

7.4.2 Landmark processing in HC

Two of my previous experiments (Experiments 3 and 4) have found HC to be responsive to permanent landmarks. This might seem at odds with the results of this study where I found no evidence of HC activity relating to landmark permanence. However, this could be accounted for by the fact that the HC has only ever been shown to process permanent landmarks when they are associated with a precise location (Experiments 3 and 4) and not for those devoid of any specific spatial connections (Experiments 1 and 2). This points towards the HC perhaps playing more of a role in handling the spatial relationships between landmarks and other parts of their environment, rather than the permanence of landmarks themselves. This is consistent with the results of the present study, where a landmark's permanence was dissociated from other spatial relationships and consequently the HC was not engaged.

Further weight is added to this account of HC function by the fact that HC coded for whether landmarks could be used to locate treasure and if they could, the distance

between the two. There are several examples of the HC representing the distances between items in larger, three-dimensional environments (Spiers and Maguire, 2007b; Morgan et al., 2011; Baumann et al., 2012; Sherrill et al., 2013), but here I demonstrate that this also holds true for smaller scale, more basic spatial relationships.

Taken together, these findings suggest that the HC does not merely process simple features of landmarks themselves (like RSC permanence processing), but rather more detailed information about the spatial relationships between different components of an environment. This could be a crucial function for constructing and maintaining spatially coherent scene representations (Hassabis and Maguire, 2009; Maguire and Mullally, 2013).

7.4.3 RSC and inter-individual differences in learning about landmarks

Responses in RSC also related to how well people were able to learn about the landmarks, both in the region's patterns of activation and its interaction with AThal. Better learning about the key landmark features was associated with more instructive response patterns in RSC about this same information. Furthermore, the better participants had learned which landmarks were permanent, the more their RSC interacted with AThal while viewing them. This increased functional connectivity appeared to specifically reflect RSC driving permanence related activity in the AThal of good but not poor learners.

My previous experiments demonstrated activity in RSC related to a person's ability to acquire new spatial information and navigate (Chapters 3, 4 and 5). In each case, variation in these general spatial abilities was also found to be associated with more specific differences in processing landmark permanence, both behaviourally and in RSC's neural responses. The present study adds to this growing body of evidence that performance in spatial tasks is directly linked to RSC representations both of highly familiar everyday items (Experiments 1 and 2) as well as while learning new information about previously unfamiliar landmarks (Experiment 3).

RSC activity has also been linked to the ability to learn other forms of new information, not just that related to landmark permanence. RSC responses during a baseline period between learning and recall of paired associate stimuli can predict the accuracy with

which the newly acquired information is later remembered (Staresina et al., 2013). This implicates RSC in the maintenance, reactivation and consolidation of recently learned information, not just its acquisition and recall. It would be interesting to investigate how this "offline" RSC processing might differ for permanent or transient features and whether or not it is related to a person's more general spatial and navigation abilities.

In this experiment, as in those reported in Chapters 5 and 6, the ability of participants to learn about the specific landmark features was not related to their self-reported navigation ability according to the SBSOD. I discuss possible reasons for this in depth in Chapter 9 (Section 9.2.2).

7.4.4 RSC interaction with AThal

RSC does not act in isolation and is connected to a wide range of other cortical and subcortical brain regions (Sections 1.3 and 1.10.2; van Groen and Wyss, 1990, 1992; Van Groen and Wyss, 2003; Greicius et al., 2009; Vann et al., 2009; Sugar et al., 2011). This is particularly true of AThal, where RSC shares dense reciprocal connectivity with a number of different nuclei (Van Groen and Wyss, 2003; Wright et al., 2010). These connections are not just structural. The two regions influence one another's processing of space and together help support navigation (Clark et al., 2010; Jankowski et al., 2013), especially when it requires the use of environmental landmarks (Yoder et al., 2011). However, despite the large amount of evidence of mutual interaction between RSC and AThal in rodents, there are far fewer examples of similar communication in humans.

My first experiment provided a rare example of a link between processing in RSC and AThal (Chapter 3). In that study, RSC and anterodorsal parts of the thalamus were shown to be more active in good compared to poor navigators when viewing permanent landmarks (Section 3.3.3). The present experiment builds upon this finding using a more direct measure of people's understanding of landmark permanence. This revealed that rather than simply being coactive, RSC actually drove activity in AThal of good but not poor learners while people viewed a permanent landmark.

These two regions both contain neurons which display tuning to the direction an animal's head is facing (Section 1.3; Chen et al., 1994b; Taube, 1995; Vann et al., 2009). It is

therefore particularly interesting that in this experiment the RSC also showed increased interaction with a third head-direction cell containing region, the subiculum (Taube et al., 1990), when good learners viewed a permanent landmark (at an albeit lower statistical threshold). Therefore, these three regions, which have consistently been shown to be densely interconnected and functionally related in rodents (Sections 1.3, 1.4, 1.5 and 1.8), were all interacting in accordance with a person's ability to learn and respond to information about permanent landmarks.

It is also interesting to note that the subiculum is directly implicated with RSC in the spread of pathology in Alzheimer's dementia (George et al., 2014). This provides further evidence that the disorientation usually present in the early stages of Alzheimer's dementia, could be a consequence of aberrant processing in RSC, one of the first regions to show pathological change in the condition (Section 1.7; Pengas et al., 2010, 2012). The profound disorientation and dense amnesia commonly associated with lesions to RSC (Section 1.6; Maguire, 2001a; Vann et al., 2009) could also be explained by RSC playing a crucial role in forming reliable representations of the surrounding environment by ensuring they are centred upon permanent features. I suggest that the identification and processing of permanent landmarks in RSC, as well as its interactions with related regions such as AThal and the subiculum, could form a fundamental part of environmental computations, impacting upon a person's more general spatial abilities such as navigation.

7.4.5 Accuracy of the spatial information provided by landmarks

I found that the HC was more active when people viewed landmarks which provide relevant spatial information about external cues. However, for landmarks which could not be used to locate treasure, HC had increased functional coupling with the RSC. There was also increased activity in ITC when there was no reliable landmark-treasure relationship and ITC also displayed increased functional connectivity with RSC for uninformative landmarks. Thus, for landmarks with no meaningful spatial relationship to other items, both HC and ITC interact more with RSC.

My previous experiments have indicated that whereas RSC is responsive to features intrinsic to landmarks themselves (i.e. their permanence), the HC appears to contain more detailed information related to knowledge of the precise spatial relationships between

them (see Section 7.7.2 of this chapter, as well as Experiments 3 and 4). ITC is believed to play a role in object perception (Zhang et al., 2011; Sato et al., 2013) and so, like RSC, seems to process features which are more intrinsic to an item itself. I therefore propose that these results reflect HC using landmarks which provide accurate spatial information to help map the relationships between different environmental cues. When this is not possible, however, and landmarks cannot be used to reliably locate other items, the reduced engagement of HC and increase in its interaction with RSC could represent a shift in emphasis towards processing intrinsic features of the landmarks themselves, such as their permanence in order to assist performance; a process which is perhaps also reflected in increased ITC activity.

Responses in the ACC were also linked to the accuracy of information provided by a landmark. The region has not previously been implicated in processing specific properties of landmarks. It's involvement in this experiment's task therefore perhaps instead reflected the variability in treasure locations and processing of errors introduced in the third testing phase task (Brown and Braver, 2005; Behrens et al., 2007), which had not been present in the first task when landmarks were shown on their own.

7.4.6 Conclusions

It has not previously been possible to determine whether RSC truly processes landmark permanence or whether the responses in fact reflect more complex computations related to using these reliable environmental cues to localise specific places. Here, I dissociated these two landmark attributes to investigate which the RSC processes and how this may relate to a person's ability to learn new spatial information. In the first testing phase task, RSC and more posterior parts of POS were more engaged when people viewed permanent than transient landmarks. However, only activity in RSC could be used to decode the permanence of landmarks using MVPA. Responses in the HC were linked to whether or not a landmark was relevant for locating a target and how far away that target was. Activity in RSC was also related to a person's ability to acquire the new landmark information and the RSC of good, but not poor, learners drove responses in AThal while viewing a permanent landmark.

In the third testing phase task, the HC was more active while people viewed images of landmarks providing accurate spatial information, whereas ITC was more engaged by those which did not. For uninformative landmarks, both the HC and ITC regions displayed increased functional coupling with RSC.

HC, therefore, appears to handle detailed information about the spatial relationships between items (Section 5.7.3; Maguire et al., 2006). In everyday life, this process could serve to construct and maintain representations of spatially coherent scenes (Hassabis and Maguire, 2009; Mullally and Maguire, 2013). RSC, on the other hand, is responsive to a feature intrinsic to individual landmarks, their permanence and a person's ability to acquire important new spatial information is directly linked to processing of landmark permanence by RSC and its influence upon other related brain areas.

Chapter 8: Experiment 6

Exploring the scope of permanence processing in RSC

8.1 Introduction

The RSC and PHC play well-established roles in processing some aspect of scenes and during spatial tasks (Sections 1.10.3 and 1.10.4; Epstein, 2008; Spreng et al., 2009). Indeed both are commonly labelled as "scene-selective" (Dilks et al., 2011; Golomb et al., 2011; Nasr et al., 2011, 2013). However, as already described, there is debate about precisely what information they process in the service of these cognitive functions.

In PHC, "scene-selective" activity could emerge from representations relating to the inherent sense of space that scenes evoke (Kravitz et al., 2011a; Mullally and Maguire, 2011). Other proposals posit that PHC processes the geometric layout of a scene (Epstein and Kanwisher, 1998; Henderson et al., 2008; Wolbers et al., 2011), lower level visual properties (Peyrin et al., 2004; Rajimehr et al., 2011) or some combination of multiple factors (Troiani et al., 2012; Zeidman et al., 2012).

For RSC, various accounts suggest it may help localise and orient a scene within wider environmental representations (Section 1.10.3; Park and Chun, 2009; Epstein and Vass, 2014; Hindley et al., 2014a); make spatial comparisons (Section 1.10.4; Nasr et al., 2013) or translate between allocentric and egocentric representations of space (Section 1.11; Byrne et al., 2007; Vann et al., 2009). However, my previous experiments suggest RSC involvement in this broad range of spatial tasks could in fact more simply reflect the use by these tasks of permanent landmarks (Chapters 3-7). These permanence representations can develop rapidly for completely novel, alien landmarks (Chapters 5-7) and operate in both large- and small- scale space (Chapter 6-7). However, to date, permanence has only been considered in terms of spatial processing. This leaves important questions regarding the scope and purpose of these representations untested. In the present study, I investigated whether brain regions which code for permanent landmarks might also have wider-ranging representations of non-spatial aspects of a scene.

Responses analogous to "scene-selectivity" have been demonstrated when people read sentences describing concrete, rather than abstract, situations (Wallentin et al., 2005; Wang et al., 2010). Here, I built upon this principle and created a set of three different types of sentence to investigate the scope of neural permanence representations. The first type of sentence described scenes containing a permanent or transient object – this was designed to be directly analogous to the landmark experiments I have already described. The second type of sentence also described scenes but focussed instead upon permanent or transient *actions*, rather than on landmarks. Finally, there were sentences about abstract concepts, which were unlikely to evoke an image of a scene but which still varied in terms of their permanence. Participants read these sentences while undergoing fMRI scanning and performed an incidental vigilance task. This allowed me to examine responses to spatial (landmarks) and non-spatial (actions) aspects of scenes, as well as non-scenes, all in the context of varying permanence.

Given the results of my previous experiments, I had a clear hypothesis that RSC would code for the permanence of spatial scene features. Also, given the deep-seated role RSC seems to play in processing scenes, I hypothesised it would not be engaged by abstract, non-scene sentences. How RSC would handle non-spatial scene sentences was an open question, but would provide valuable insights into the parameters within which RSC operates.

8.2 Methods

8.2.1 Stimuli

I first created a set of 344 sentences. There were 3 different types of sentence and within each sentence type there were descriptions of things which were either permanent or transient, giving a total of 6 sentence categories (Figure 59). The first sentence type described scenes and explicitly referred to a spatial feature or item which was either permanent or transient (e.g. category 1 - permanent: "Everybody uses the village post-box" and category 2 - transient: "People walk past the pile of rubbish"). The second type again described scenes, but this time referring to permanent or transient actions happening within the scene (e.g. category 3 - permanent: "The chef always creates

complex dinners" or category 4 - transient: "The drummer misses some performances"). The third and final type of sentence described abstract concepts, not concrete scenes, which were permanent or transient (e.g. category 5 - permanent: Humans are capable of enduring friendships" or category 6 - transient: "The climate is constantly changing").

	Permanent	Transient
Spatial scene	'Everybody uses the village post-box' 1	'People walk past the pile of rubbish' 2
Non-spatial scene	'The chef always creates complex dinners' 3	'The drummer misses some performances' 4
Abstract, non-scene	'Humans are capable of enduring friendships' 5	'The climate is constantly changing' 6

Figure 59 Example sentences from each of the six categories.

This collection of sentences was first rigorously characterised in a behavioural ratings experiment (Section 8.2.3) and then an optimal closely-matched set of 300 were selected for use in the fMRI study (Section 8.2.4).

For both the ratings and fMRI experiments, sentences were displayed in black, size 50, Calibri font, in the centre of a screen with a grey background.

8.2.2 Participants

Twenty healthy, right handed participants, who all had normal or corrected to normal vision and could read and speak excellent English (10 females, mean age 22.2 years, SD 3.2) took part in the behavioural ratings experiment.

Thirty-two healthy, right-handed participants, none of whom had taken part in the ratings study, took part in the main fMRI experiment (16 females, mean age 21.6 years, SD 3.9). All had normal vision and could read and speak excellent English.

All subjects in both experiments gave written informed consent in line with local research ethics committee policy.

8.2.3 Behavioural ratings experiment

The ratings experiment served two purposes: to ensure the 6 sentence categories used in the main fMRI experiment were matched according to a range of different features, but also to characterise properties of the sentences which could themselves be investigated in the fMRI experiment.

There were two rounds of questioning in which participants rated different features of the sentences. In each round, all of the 344 sentences were presented in a randomised order, one after the other for 4 seconds and each was immediately followed by some questions.
The first round of questioning sought to characterise the imageability of the sentences and vividness of any image they evoked. For each sentence, participants were first asked: "Does this sentence bring an image of an item or scene into your mind's eye?" to which they could reply with one of three options: "*No image"*, an image of a "*Single item"* or image of a *"Full scene"*. If they indicated that the sentence did bring an image to mind (either of an item or a scene) they were then asked whether this image was *"Weak"* or *"Strong"*.

When designing the sentences, I aimed to ensure that they all referred to ordinary, everyday items and that the descriptions were clear and unambiguous. I tested whether this was the case in the second round of questioning. Participants were again shown the sentences one at a time in a different order. For each one they first rated: "Is the thing described in the sentence ordinary?" and chose either "*Ordinary*" or "*Out of the ordinary*". After giving this response, participants were then asked "Does anything else, not mentioned in the sentence, come to mind?"; they indicated either "*Yes*" or "*No*", and if the former (i.e. that something else did come to mind) they were then asked what it was that came to mind.

After collecting this set of ratings, I used them to help select an optimised set of 300 sentences which were closely matched across the 6 categories (50 sentences per category).

I first excluded any sentences which were consistently considered unusual by the 20 participants (>5 "*Out of the ordinary*" ratings). Any sentences describing a scene (categories 1-4) which more than 7 (i.e. more than a third of the 20 participants) people said brought no image to mind were also excluded along with abstract non-scene sentences (categories 5 & 6) which more than 7 subjects said brought an image to mind. I finally excluded any sentences which more than 2 people said brought to mind something else which was not mentioned in the sentence.

The matching between the 6 categories was confirmed by a series of two-way ANOVAs with two levels for permanence (permanent and transient) and three levels of sentence type (spatial scene, non-spatial scene and abstract non-scene). The results were as follows: percentage of sentences regarded as ordinary (main effect of permanence: $F_{1,294}$ = 1.141, p = 0.3; main effect of sentence type: $F_{2,294}$ = 2.865, p = 0.06; interaction: $F_{2,294}$ = 0.406, p = 0.7); number of sentences where anything else came to mind (main effect of permanence: $F_{1,294}$ = 0.191, p = 0.7; main effect of sentence type: $F_{2,294}$ = 0.191, p = 0.8; interaction: $F_{2,294}$ = 2.479, p = 0.09); percentage of sentences which brought an image into the mind's eye (main effect of permanence: $F_{1,294}$ = 0.005, p = 0.9; main effect of sentence type: $F_{2,294}$ = 1155.068, p < 0.001; interaction: $F_{2,294}$ = 0.918, p = 0.4) - note that a significant difference between scene (categories 1-4) and non-scene (categories 5 & 6) sentences was expected as the sentences were specifically designed to have different imageability.

The sentence categories were further matched for objective, physical properties of the words they contained, namely the number and length of words: mean number of words (main effect of permanence: $F_{1,294}$ = 0.071, p = 0.8; main effect of sentence type: $F_{2,294}$ = 0.176, p = 0.8; interaction: $F_{2,294}$ = 0.045, p = 1.0); mean word length (main effect of permanence: $F_{1,294}$ = 0.070, p = 0.8; main effect of sentence type: $F_{2,294}$ = 1.180, p = 0.3; interaction: $F_{2,294}$ = 0.409, p = 0.7).

I also matched the sentences for word frequency to ensure that the sentences did not differ in the amount of rare or uncommon words they contained. For this, I used a frequency list generated from the 100 million word British National Corpus (Kilgarriff, 1997). Specifically, the 6 categories were carefully matched for the mean word frequency of their low-frequency words (those with a frequency less than 0.025%) (main effect of permanence: $F_{1,294} = 0.576$, $p = 0.4$; main effect of sentence type: $F_{2,294} = 0.081$, $p = 0.9$; interaction: $F_{2,294} = 0.000$, $p = 1.0$).

This left me with a set of thoroughly characterised sentences, which were rigorously matched for a wide range of conceptual, perceptive, linguistic and physical features.

8.2.4 Stimuli and task for the fMRI experiment

For the fMRI experiment, in addition to the optimised set of 300 sentences from the ratings study, I included 50 extra nonsensical sentences to serve as the basis of the incidental vigilance task (e.g. “Looking through murky with market planning”). While undergoing fMRI scanning, participants were presented with images of the 350 sentences one at a time and performed a simple vigilance task. They were instructed to read each sentence carefully and press a button if the sentence they were reading was “complete and utter nonsense”. This ensured that they paid attention to the sentences and their meaning, but without drawing attention to any particular feature of them. No mention was made about any of the key differences between the sentences and there were no instructions that they should try to picture what was being described. This ensured that participants were completely naïve to the key manipulations of interest which was crucial to allow an unbiased assessment of neural responses for the different sentences categories.

I specifically designed the nonsense sentences so that their first few words could potentially form a meaningful sentence (e.g. “Looking through murky”) so that it was not immediately obvious if a sentence was nonsense. This ensured that participants had to read sentences in full to establish their meaning. In this way, I could be confident that everyone was reading all the sentences in their entirety. The 50 nonsense sentences were also completely matched with the 6 categories (of the optimised experimental set of 300) for the length, number and frequency of their words (mean word length: $F_{6,343} = 0.826$, $p =$

0.6; mean number of words: $F_{6,343} = 0.410$, $p = 0.9$; mean word frequency: $F_{6,343} = 0.571$, $p = 0.8$).

The 350 sentences were presented one at a time for 4 seconds each in a pseudorandomised order, to ensure an even distribution of the 6 categories and nonsense sentences across the whole scanning period. There was a 2 to 4 second jittered interval separating the sentences during which a black fixation cross was shown in the centre of a grey background. Participants pressed a button with their right index finger if they thought the sentence they were reading was nonsense and were instructed to do nothing for sentences they thought were sensible. Pressing the button caused the trial to immediately end and move on to the next inter-trial fixation period. All nonsense sentences and any extra trials on which subjects pressed the button were removed from the fMRI analysis. The 350 trials were split into 3 scanning runs of approximately 13.5 minutes each.

Immediately after scanning was completed, participants were debriefed. The key aim of this debriefing session was to ascertain whether or not they had become aware of the key differences between sentences while performing the incidental vigilance task. Participants were first asked, “Did you notice anything in particular about the sentences?” If they did not articulate any of the differences, participants were then asked more specifically: “Did you notice any definite pattern in what the sentences described or were they just random?” Finally, they were presented with a list of twelve different possible ways in which the sentences might have varied and were instructed to identify *one* of the options they thought was correct. Eleven of the options were incorrect foils (e.g. “type of font the sentences were written in”) and there was only 1 correct option (“described either permanent or transient things”). Participants then had to indicate how confident they were in their selection (*Guessing*, *Not confident*, *Fairly confident*, *Very confident*).

The precise experimental paradigm described in this section was tested in a pilot study with three subjects (none of whom took part in the fMRI experiment; 2 female, mean age 23.3 years, SD 1.5). All three subjects felt there was sufficient time to read the sentences in full within the time allocated on each trial. They all indicated that they took in the meaning of sentences and were able to accurately identify the nonsense catch trials. After completing the experiment, none of the three subjects were aware that the sentences

varied in terms of their permanence. I therefore did not feel it necessary to make any changes to the experimental paradigm before proceeding to the full fMRI experiment.

8.2.5 Scanning parameters and preprocessing

T2*-weighted echo planar images (EPI) with BOLD contrast were acquired on a 3T whole body MRI scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany). I used a 32-channel head receive coil and the standard RF transmit body coil. Scanning parameters were optimised for the hippocampus and surrounding tissue whilst still achieving whole brain coverage: 48 oblique axial slices angled at −45° from the axial to coronal plane (as defined in Weiskopf et al., 2006), 2.5 mm thickness (with inter-slice distance factor 20%), repetition time TR = 3.36s (slice TR = 70 ms), echo time TE = 30 ms, echo spacing 500 µs, matrix size = 64×74, 13% oversampling in the PE direction, excitation flip angle = 90°, in-plane resolution 3 mm×3 mm, field of view FoV = 192 mm×192 mm phase encoding (PE) in the anterior-posterior direction. For reduction of signal loss in the hippocampal region, slices were angulated and a z-shim gradient moment of +0.6 mT/m*ms was applied (Weiskopf et al., 2006). The first 6 'dummy' volumes from each scanning run were discarded to allow for T1 equilibration effects. Field maps were acquired with a standard manufacturer's double echo gradient echo field map sequence (short TE = 10 ms, long TE = 12.46 ms; 64 axial slices with 2 mm thickness and 1 mm gap yielding whole brain coverage; in-plane resolution 3mm×3mm). A 3D MDEFT T1-weighted structural scan (Deichmann et al., 2004) was acquired for each participant with 1 mm isotropic resolution. FMRI data were analysed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images were bias corrected, realigned and unwarped (using the field maps), normalised to a standard EPI template in MNI space with a resampled voxel size of 3×3×3mm and smoothed using an 8mm FWHM Gaussian kernel.

8.2.6 Whole brain fMRI contrasts

After preprocessing, I performed a series of whole brain univariate fMRI analyses using the GLM. Each trial was modelled as the full 4 seconds that a sentence was on display.

In the first instance, I examined for fMRI responses in relation to the interaction between whether a sentence describes a scene (categories 1-4) or non-scene (categories 5 & 6) and

its permanence. I then performed a second interaction analysis, but this time only considering scene sentences, to assess for responses which were sensitive to permanence and whether sentences described a spatial (categories 1 & 2) or non-spatial (categories 3 & 4) aspect of a scene.

I then examined responses related to descriptions of scenes, their spatial properties and strong imagery, independent of whether what was being described was permanent or transient. I therefore performed contrasts of scene (categories 1-4) versus abstract, non-scene sentences (categories 5 & 6). I also contrasted fMRI responses to spatial scene (categories 1 & 2) and non-spatial scene (categories 3 & 4) sentences.

As described above, prior to the fMRI study, a different group of participants (n = 20) rated various features of each sentence (see Section 8.2.3). Every subject in this behavioural rating experiment indicated whether each sentence brought an image into their mind's eye and if so whether it was a strong or weak image. I used these ratings to look for regions, anywhere in the brain, which become more engaged for sentences which consistently bring a vivid image to mind. Specifically, for each sentence, I took the number of people (out of 20) who indicated that it brought a "strong" image to mind and used this as a parametric regressor for a whole brain GLM analysis.

I then examined responses to the three contrasts in relation to the permanence of what a sentence described. To do this, I first performed separate analyses of permanent and transient sentences. I contrasted permanent scenes (categories 1 & 3) with permanent non-scenes (category 5), permanent spatial scenes (category 1) with permanent non-spatial scenes (category 3) and permanent sentences parametrically modulated by the strength of imagery. I then repeated the same with the transient sentences. I also directly compared permanent and transient scene sentences (categories 1 & 3 versus 2 & 4) as well as the parametric strength of imagery regressors for permanent and transient sentences. I also separately contrasted permanent and transient spatial (category 1 versus 2) and non-spatial scene (category 3 versus 4) sentences. For all the permanent versus transient sentences contrasts described, I also performed corresponding analyses to look for any regions which might be more active for transient sentences.

For each of the contrasts described above, regressors of interest were convolved with the HRF (see those sections for the precise contrasts made in each univariate analysis). In each case, a separate regressor was made for the nonsense sentences and any trial on which the button was pressed (i.e. those which a participant thought was nonsense); this and individual movement regressors were treated as covariates of no interest. Subject-specific parameter estimates pertaining to each regressor of interest (β) were calculated for each voxel. Second level random effects analyses were run on these parameter estimates (collapsing across scanning runs) using one-sample t-tests.

For all contrasts outlined in Sections 8.3.2 and 8.3.3, I report any fMRI activations that survived a whole brain FWE corrected threshold of $p < 0.05$. In Section 8.3.4, for the separate comparisons of permanent and transient sentences, I again report all fMRI activations that survived a whole brain FWE corrected threshold of $p < 0.05$. For the direct comparisons between permanent and transient trials, given the more subtle differences expected between these two conditions and my strong hypotheses regarding engagement of RSC in this condition, I report all fMRI activations which survived a whole brain uncorrected threshold of $p < 0.001$ in the RSC and $p < 0.05$ (FWE corrected) for the rest of the brain. For the transient vs permanent contrasts I had no clear prior hypothesis regarding which brain regions might be activated (unlike RSC for the opposite contrast) and so they are reported at a whole brain FWE corrected threshold of $p < 0.05$.

8.2.7 Connectivity analyses

For any regions shown to be engaged by scenes, their spatial properties and strong imagery (i.e. all those reported in Section 8.3.3), I then examined how they may interact with other brain regions in relation to the permanence of what is being described. I used each of the clusters identified in the univariate analyses (at a threshold of $p < 0.05$ FWE corrected) as seed regions in gPPI analyses (Section 2.8.1). Specifically, I looked for any brain areas which had increased functional coupling with the seed regions on permanent compared to transient trials. The precise contrast used for each seed region corresponded to the univariate contrast from which they were derived. For example, for a region specifically responsive to scenes (i.e. categories 1-4 versus 5 & 6), the gPPI analysis compared permanent and transient scene sentences (categories 1 & 3 versus 2 & 4). For a region responsive to just spatial scenes (categories 1 & 2 versus 3 & 4), the PPI analysis

compared permanent and transient spatial scenes (category 1 versus 2) and so on. I report any significant results at a whole brain uncorrected threshold of $p < 0.001$ for the RSC (given my specific prior hypotheses regarding permanence processing in this region) and $p < 0.05$ FWE corrected for the rest of the brain.

I then examined the dynamics of key interactions between regions identified in the gPPI analyses using DCM (Section 2.8.2). I specifically investigated the permanence based causal influence between brain regions already shown to have permanence-related interactions with one another (from the gPPI analyses). I used stochastic DCM (Daunizeau et al., 2012) which accounts for endogenous fluctuations in brain activity; this is of particular relevance here as my participants were not directly viewing or experiencing what was described in the sentences, so much of the network's activity will have been driven by endogenous brain processes (rather than purely external experimental manipulations).

The design matrix used for the DCM analysis contained two main regressors: one for all scene sentences (categories 1 to 4) and a second for just permanent scene sentences (categories 1 & 3). The first was to be used for the models' input (the DCM C matrix) and the second for modulatory connections (B matrix). DCM10 was used for the analysis and I assumed there to be reciprocal endogenous connections between the regions as well as self-connections (A matrix). I compared all plausible models of interaction between the regions. These differed in the connections which were modulated by permanence (B matrix) and the region which received the system's driving input (C matrix) (see Figure 63 for exact model architectures). Each of the models' predicted haemodynamic responses were fitted to the actual fMRI data in each subject and compared using a random effects bayesian model comparison to establish the most likely "winning" model (Stephan et al., 2009).

8.3 Results

8.3.1 Behavioural results

Behavioural responses made by participants while they were performing the task inside the scanner indicate that they successfully maintained attention upon what all 350

sentences were describing. The mean error rate (missed or inappropriate 'nonsense' response) was very low throughout for all participants (mean error rate = 3.1% SD 2.9). After scanning, participants were asked if they noticed any patterns or differences in what the sentences described, none of the 32 participants made reference to being aware of any difference in whether sentences described a scene/something spatial or that half the sentences described something permanent and the other half something transient. When presented with a list of twelve options of ways in which the sentences could have varied, seven of the thirty-two participants correctly identified that the sentences described either permanent or transient things. All of those seven indicated that they only considered this after seeing it on this list of options in the debrief and even then they were not particularly confident in their choice: four stated they were "Not confident", three "Fairly confident" and none were "Very confident". Thus, during fMRI scanning, no participant was consciously aware of the crucial distinction between permanent and transient sentences and even when aided, only 3 could pinpoint the distinction with any confidence. Therefore, any neural responses related to the key features of the sentences are likely to be from automatic, implicit processing.

8.3.2 Neural responses related to the interaction between sentence type and permanence

I first performed an analysis to examine fMRI responses in relation to the interaction between a sentence's permanence and whether it describes a scene or non-scene. At an FWE corrected threshold of $p < 0.05$, no brain region was responsive to this interaction. However, significant activations in bilateral RSC (right: 18, -43, 10, Z = 5.20; left: -15, -52, 13, Z = 4.57) were present at a whole brain uncorrected threshold of $p < 0.001$. A second interaction analysis considered responses in relation to whether a scene sentence described something spatial or not and the permanence of what was being described. No brain regions were responsive to this interaction, even at a reduced threshold.

These results indicate that RSC may be sensitive to the interaction between whether or not a sentence describes a scene and its permanence, but not whether a scene sentence refers to something spatial. I then interrogated responses in relation to sentence type (Section 8.3.3) and permanence (Section 8.3.4) further.

8.3.3 Neural responses associated with descriptions of scenes, their spatial properties and strong imagery

I compared responses to sentences which described any scene (categories 1-4) to abstract, non-scene sentences (categories 5 & 6). As would be expected, this revealed increased activity in parts of cortex traditionally labelled as being "scene-selective", the PHC bilaterally (left: -30, -31, -14, Z = 10.96; right: 33, -28, -11, Z = 6.59) and left RSC (-9, -52, 10, Z = 5.93) (Figure 60A). The PHC cluster in the left hemisphere also extended into the HC, which is not usually considered "scene-selective" in experiments using visually presented images. One other part of the brain which is usually considered as being "scene-selective", the transverse occipital sulcus (TOS), did not shown any increased engagement for scene sentences. The reverse contrast (i.e. categories 5 & 6 vs 1-4) revealed no significant activation at the same statistical threshold, but at a whole brain uncorrected threshold of $p < 0.001$, clusters in medial prefrontal (9, 68, 10, Z = 5.54), parietal (-18, -52, 46, Z = 5.03) and anterior cingulate (-3, 11, -8, Z = 4.78) cortices were more active for abstract, non-scene sentences than those describing scenes.

Within the sentences describing a scene, if the focus was on a spatial aspect of that scene (categories 1 & 2), then the left PHC (-27, -34, -20, Z = 6.69) had greater activity than for non-spatial scene sentences (categories 3 & 4). This indicates that PHC may in particular process spatial aspects of a scene.

Prior to the fMRI study, a different group of participants indicated whether each sentence brought an image into their mind's eye and if so whether it was a strong or weak image (Section 8.2.3). I used these ratings to look for regions, anywhere in the brain, which become more engaged for sentences which consistently bring a vivid image to mind. For sentences which brought a stronger image to mind, increased activity was observed in bilateral PHC (left: -27, -37, -11, Z = 11.42; right: 30, -31, -14, Z = 10.04) and again, the cluster in left PHC extended into parts of HC (Figure 60B). There were also clusters of increased activation in bilateral RSC (left: -9, -49, 7, Z = 6.55; right: 15, -49, 7, Z = 6.28). Therefore, the same regions which are more engaged by scene, rather than non-scene, sentences also have greater activity the stronger the image a sentence brings to mind (Figure 60 parts A and B respectively).

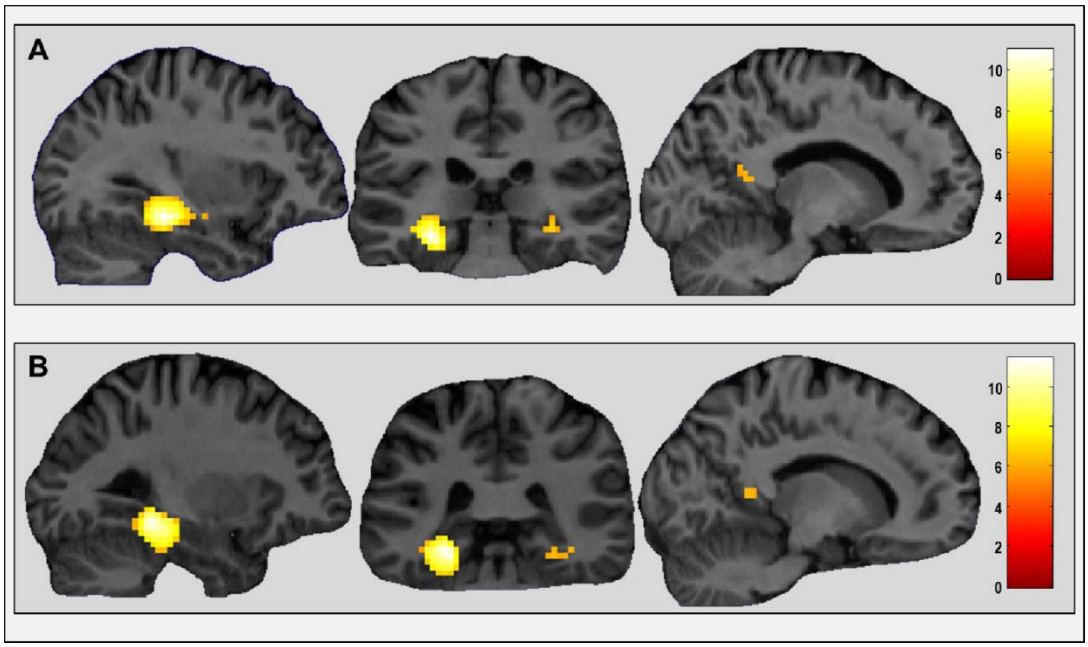

Figure 60 Brain regions engaged by sentences describing scenes and evoking strong imagery. (A) PHC, extending into HC (left and centre panels) and a small cluster in RSC (right panel) show greater activity for scene (categories 1 to 4) than non-scene (categories 5 & 6) sentences. (B) Similar parts of PHC/HC (left and centre) and RSC (right) are more engaged by sentences which consistently evoke a strong mental image. Activations are displayed on sagittal and coronal views of a single representative participant's structural MRI brain scan at a whole brain FWE corrected threshold of $p < 0.05$. The colour bar indicates the Z-scores associated with each voxel.

Thus, PHC, HC and RSC are all engaged when people read a sentence which describes a scene or which brings a strong image into the mind's eye. This response is largest in PHC, where even greater activity is elicited if the scene described has a particular focus on a spatial object rather than a non-spatial feature (e.g. an action). So whereas PHC processing appears to reflect the sense of space evoked by a scene, RSC and HC are perhaps engaged by some other aspect(s).

8.3.4 Neural responses associated with permanence

Having established strong responses to scenes in traditional "scene-selective" cortex, I probed these representations further, taking into account the permanence of what sentences described. For both the measures which demonstrated increased activity within PHC, HC and RSC (scene versus non-scene sentences and parametric strength of imagery), I performed similar analyses, but separating out permanent and transient sentences.

Transient scenes (categories 2 & 4) produced significantly greater activity in PHC (left: -30, -31, -11, Z = 12.52; right: 36, -34, -11, Z = 7.07) and left posterior-lateral parietal cortex (-

45, -76, 34, Z = 10.94) than transient abstract non-scene sentences (category 6); and again, similar to responses seen for all scenes (both permanent and transient together), the cluster in left PHC extended into parts of HC. However, *unlike* combined permanent and transient scenes, transient scenes did not engage RSC more than transient non-scenes; even at a lower statistical threshold of $p < 0.001$ whole brain uncorrected. The same was true using the parametric regressor for strength of sentence imagery: when just considering transient sentences, sentences producing stronger imagery engaged left PHC and HC (-27, -37, -14, Z = 8.25), but not RSC (even at a whole brain uncorrected threshold of $p < 0.001$). So for both measures, if a sentence described something transient, RSC lost responsivity to sentences describing scenes or eliciting strong imagery.

For sentences describing something permanent, a contrast of scenes vs abstract non-scenes (1 & 3 versus 5) revealed increased activity within bilateral PHC/HC (left: -33, -37, -8, Z = 10.77; right: 33, -37, -5, Z = 7.12), bilateral RSC (left: -9, -55, 16, Z = 8.95; right: 9, -52, 19, Z = 6.61), as well as bilateral posterior-lateral parietal cortex (left: -42, -76, 34, Z = 9.04; right: 45, -61, 28, Z = 7.40) and right inferior-lateral parietal cortex (54, -7, 10, Z = 8.85). For sentences describing something permanent, the stronger the imagery it brings to mind, the greater the engagement of left PHC/HC (-27, -40, -14, Z = 9.45), right PHC (30, -31, -14, Z = 7.88) and bilateral RSC (left: -12, -55, 10, Z = 7.80; right: 18, -55, 19, Z = 6.84) it produces.

Whereas PHC and HC are responsive to all scenes, either permanent or transient, RSC is only engaged when the object or action described is permanent. To formally test whether RSC is indeed more responsive to permanent than transient sentences, I directly contrasted fMRI responses to permanent and transient sentences for the two measures. There was significantly greater activity in bilateral RSC (left: -12, -52, 13, Z = 3.92; right: 18, -46, 10, Z = 3.77), but not any other brain region, for permanent compared to transient scene sentences (categories 1 & 3 vs 2 & 4) (Figure 61A). Similarly, when considering the strength of imagery elicited by a sentence (Figure 61B), bilateral RSC (left: -15, -58, 16, Z = 5.33; right: 9, -55, 13, Z = 3.95) was more engaged if it was permanent compared to transient.

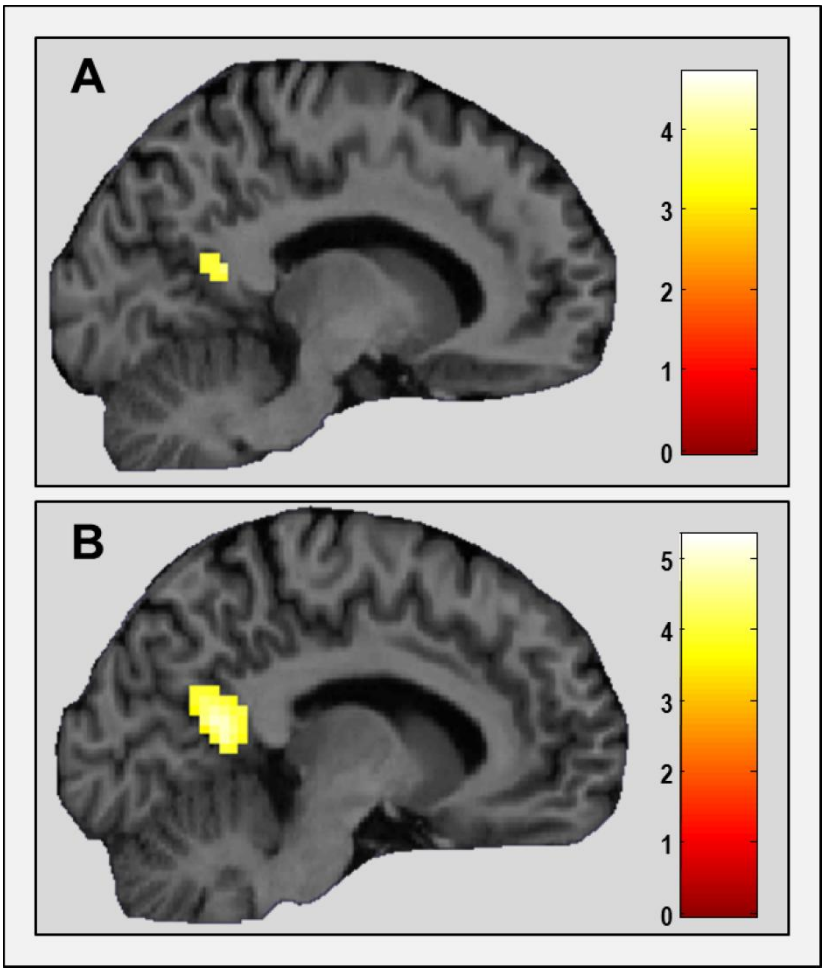

Figure 61 Brain regions responsive to permanence. RSC was more engaged by permanent than transient scenes (A) and also permanent sentences which bring a strong image to mind (B). Activations are shown on sagittal views of a single representative participant's structural MRI brain scan, displayed at a whole brain threshold of p < 0.001 (unc). The colour bar indicates the Z-scores associated with each voxel.

I also directly compared permanent and transient sentences separately for spatial and non-spatial scenes. Despite the low number of trials and power for these contrasts, increased activity in RSC, but no other brain region, was still evident for permanent compared to transient spatial (21, -43, 4, Z = 3.46) and non-spatial (-9, -52, 16, Z = 3.46) sentences (categories 1 versus 2 and 3 versus 4 respectively). For permanent versus transient abstract non-scene sentences (category 5 versus 6), there were no differences in RSC, even at the reduced threshold of p < 0.001 whole brain uncorrected. At this lower threshold, bilateral dorsolateral prefrontal cortex (DLPFC), was more active for permanent than transient non-scene sentences (right: 42, 53, 7, Z = 5.37; left: -51, 44, 4, Z = 4.95), as well as posterior parts of the occipital lobes (right: 15, -85, 10, Z = 5.58; left: -9, -88, 4, Z = 4.93) and the cerebellum (-36, -58, -47, Z = 4.80).

I also compared spatial and non-spatial scenes for permanent and transient sentences separately (categories 1 versus 3 and 2 versus 4 respectively). Here, when the permanence of sentences being compared was the same, PHC was the only region more active for spatial than non-spatial scenes for both permanent (left: -27, -31, -20, Z = 4.83; right: 30, -34, -17, Z = 4.02) and transient (-30, -34, -20, Z = 5.63) sentences (at a whole brain uncorrected threshold of $p < 0.001$).

I also performed similar comparisons to all those mentioned above, but looking instead for brain areas more engaged by transient than permanent sentences. None of these comparisons revealed any significant activation in any brain region.

RSC was therefore consistently more engaged by permanent than transient sentences but only if they described scenes or produced strong mental imagery. This was the case when comparing both permanent and transient spatial items and also non-spatial actions within a scene. Indeed, RSC even appeared to lose all sensitivity to scenes or strong imagery, if what is being described was transient. No similar sensitivity to permanence was evident in PHC or HC; both were more responsive to sentences describing any sort of scene or producing stronger mental imagery irrespective of permanence. For non-scene sentences, DLPFC but not RSC was more active if they described something permanent.

8.3.5 Interactions between brain regions associated with permanence

I then investigated how these brain regions might be interacting with other parts of the brain depending on the permanence of a sentence. I performed gPPI using regions identified in the whole brain univariate contrasts (Section 8.3.3) as seeds. Specifically, I assessed how the interactions with other brain regions might differ for areas shown to be responsive to scenes (bilateral PHC/HC and left RSC), spatial aspects of scenes (left PHC) and strong imagery (bilateral PHC/HC and bilateral RSC) depending on permanence.

The bilateral clusters in PHC (extending into HC) which were more engaged when people read about scenes than non-scenes also displayed greater functional coupling with RSC if the scenes were permanent (-12, -52, 7, Z = 3.98) (Figure 62). For the part of LPHC which was more engaged by spatial than non-spatial scenes, if that spatial scene described a permanent rather than a transient object, then it also had increased functional coupling

with RSC (15, -46, 10, Z = 4.01). Similarly, the bilateral medial temporal lobe region (PHC extending into HC in the left hemisphere) which was more engaged when people read sentences which brought a stronger image to mind, displayed increased functional coupling with RSC (-12, -55, 7, Z = 4.22) if the stronger imagery was of something permanent rather than transient.

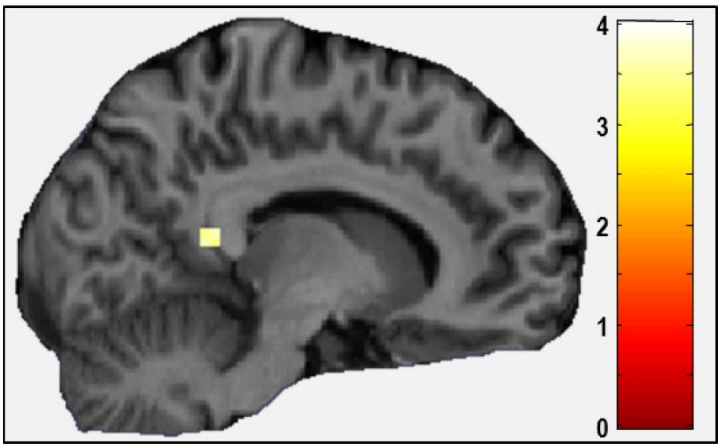

Figure 62 Result from the gPPI analysis. RSC has greater functional coupling with scene-responsive medial temporal lobe regions (PHC and HC) if the contents of the scene were permanent. Similar functional connectivity was also evident for sentences which bring a strong image of something permanent to mind. The activation is displayed on sagittal views of a single representative participant's structural MRI brain scan at a whole brain threshold of p < 0.001 (unc). The colour bar indicates the Z-scores associated with each voxel.

Neither of the PPI analyses using RSC seed regions showed any significant changes in functional coupling for permanent versus transient sentences. This perhaps reflects a lack of any regions, other than itself, which were responsive to permanence.

I also performed equivalent whole brain gPPI contrasts to look for greater functional coupling for transient compared to permanent sentences. No significant interactions were present for any of the seed regions. The changes in functional coupling were specific to permanent trials.

Thus, for three separate measures, parts of the medial temporal lobe (MTL) which were responsive to scenes, spatial aspects of scenes and strong imagery displayed increased functional connectivity with RSC when what was being described was permanent. When a sentence was permanent, therefore, RSC was not only more engaged, but also interacted more with other scene responsive brain regions.

Having established the functional coupling between RSC and MTL regions, specifically for permanent scenes, I used stochastic DCM to assess the nature of this interaction. The specific regions used in the DCM analysis were the bilateral parts of the MTL (consisting of bilateral PHC, extending into HC in the left hemisphere) which were more engaged by scene than non-scene sentences and the RSC which was more active for permanent than transient scenes. I compared four simple, biologically plausible models of interaction between these two regions. Motivated by the mass-univariate (Sections 8.3.3 and 8.3.4) and gPPI analyses (Section 8.3.5), the DCM analysis considered only scene trials (categories 1 to 4) and investigated how interactions between RSC and MTL were modulated when a scene was permanent (categories 1 and 3). The 4 models' structures (Figure 63) were as follows: Model 1 had RSC as the input region and RSC then driving responses in MTL for permanent scene sentences; Model 2 was the same but in the opposite direction, with input coming through MTL and MTL then driving RSC permanence responses; Models 3 and 4, had bidirectional modulatory connections, but with the driving input to the system coming through RSC and PHC respectively. The winning model was Model 3 and this accounted for an average of 89.5% variance (SD 4.3) in the subjects' fMRI data. This indicates that for permanent scenes, RSC and MTL were modulating each other's responses, but the input to this system came through RSC.

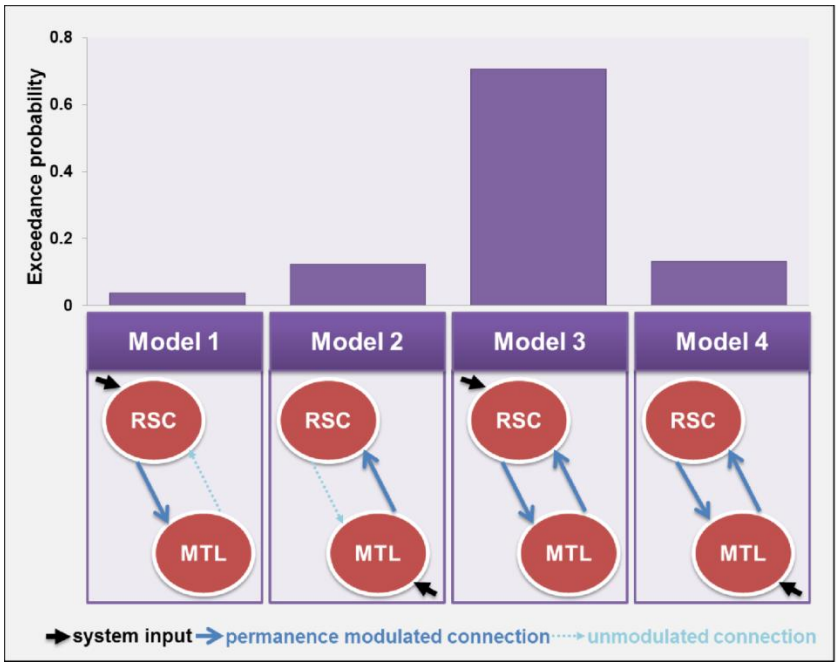

Figure 63 The dynamics of permanence related interactions. Four models of RSC-MTL interaction were compared in a DCM analysis (bottom) with their corresponding exceedance probabilities (above). Model 3 was the winning model, suggesting RSC and MTL mutually modulated each other's activity when a sentence described a scene which suggested permanence, with input to the system coming through RSC.

8.4 Discussion

8.4.1 "Scene-selective" brain areas

When participants read sentences describing a scene, two brain regions traditionally considered to be "scene-selective", the RSC and PHC, became more active. This is consistent with previous demonstrations of these regions processing concrete rather than abstract sentences (Wallentin et al., 2005; Wang et al., 2010). However, RSC was significantly more active for scenes with permanent contents; so much so that if the item or action described within a scene was not permanent RSC no longer displayed any responsivity to those scenes. This suggests that the long-held consensus that RSC is "scene-selective" (Dilks et al., 2011; Golomb et al., 2011; Nasr et al., 2011, 2013) more likely reflects the processing of permanent environmental features. Exactly the same was true when considering how strong an image a sentence brought to mind. The stronger the imagery evoked, the greater PHC and RSC responded. However, whereas PHC activity was insensitive to the permanence of what was being evoked, RSC was only more active if the image being evoked was of something permanent.

Another brain region which is frequently considered "scene-selective" is the TOS, yet here I found no evidence of this region being recruited. This might reflect the nature of the stimuli used. Investigations of scene processing in these regions typically use images of scenes (Dilks et al., 2011; Golomb et al., 2011; Nasr et al., 2011), whereas here the only visual inputs were words. TOS might therefore be involved in a lower-level processing of a scene's visual features. This would also be consistent with its close proximity to posterior visual regions. Any imagery of a scene when reading the sentences could only have been created from purely endogenous representations. This constructive process might perhaps account for the fact that HC, which is not commonly considered scene-selective, was more engaged for scene than abstract sentences (Hassabis and Maguire, 2009; Maguire and Mullally, 2013).

If HC responses truly reflected scene construction, then it follows that they would not differ depending upon what a scene described. This was indeed the case. The same was not true, however, for PHC. Here, activity was significantly greater for sentences explicitly describing spatial features of a scene. This adds further support to the proposal that

activity in PHC reflects a basic level of processing local space (Mullally and Maguire, 2011), while HC engagement arises from the more complex act of constructing and maintaining spatially coherent scene representations (Hassabis and Maguire, 2009; Mullally and Maguire, 2013).

8.4.2 RSC

On first impressions, the responses in RSC could have seemed to be "scene-selective" - there was greater activity in RSC when comparing fMRI responses for all scenes versus non-scenes and for sentences evoking stronger imagery. However, this masks a more nuanced reality. For sentences where the scene or imagery brought to mind was of something transient, there was no longer any difference between activity for scenes and non-scenes in RSC. The scene-selectivity was only manifest within a permanent context. RSC processing of scenes has previously been proposed to centre around translating between allocentric and egocentric representations of space (Section 1.11; Byrne et al., 2007; Vann et al., 2009). However, this cannot account for any differences related to the permanence of scene contents. Therefore, while RSC might play some role when translating between spatial reference frames, this does not appear to constitute a core function of the region.

Instead, the present study provides further evidence that RSC is primarily involved in processing permanent, reliable features encountered in our surroundings. My previous experiments have consistently demonstrated that RSC processes landmarks which remain fixed in a single, permanent location, in real-life (Experiments 1 and 2), virtual reality (Experiment 3) and imagined (Experiment 4) environments. Here, RSC was once again more engaged by permanent than transient items when they are simply described in a sentence. This sensitivity to permanent landmarks did not require using them for any sort of complex spatial manipulation or localising/orientating (Sections 1.10.3 and 1.10.4 and 1.11; Nasr et al., 2013; Epstein and Vass, 2014), just a mere reference to them sufficed.

This experiment was also able to reveal that RSC permanence representations appear to extend beyond the purely spatial domain. RSC was not only more engaged by permanent than transient items, but also for sentences describing a permanent, regular action. The

responsivity to permanence did not, however, extend to more abstract concepts, so at the very least it appears to require some sort of grounding within concrete, tangible settings. The processing of more than just a scene's spatial features warrants further investigation. It remains to be seen just how extensive RSC representations of non-spatial scene elements are. It is possible that they only constitute a minor by-product of a neural system whose primary function is identifying reliable landmarks for mapping environments. However, if RSC permanence processing is indeed more generalised this would have intriguing implications about the nature and scope of the region's overall contribution to cognition. RSC might, for example, help inform more general models of how rare or surprising the events currently being perceived are in order to help optimise representations of environments and behaviour happening within them (Friston, 2010).

8.4.3 Connectivity between permanence responsive RSC and scene-responsive MTL

The specific features of scenes which the different brain regions were responsive to was also linked to the way in which they interacted with one another. I performed a series of gPPI analyses which consistently showed the scene-responsive parts of the MTL (bilateral PHC extending into HC in the left hemisphere) to be interacting with RSC if sentences described something permanent. A DCM analysis indicated that this interaction was bidirectional, with the RSC and MTL mutually influencing one another's activity for permanent scenes, but the input driving the system came through RSC.

This interaction could reflect a system whereby dependable cues are first identified within RSC and then integrated into more detailed internal models of an environment in the MTL. The ongoing exchange of information between the two brain areas could then reflect updating and evaluation of existing neural representations, ensuring their long-term reliability by adapting to what is currently being perceived. In my third and fourth experiments a similar interaction between the RSC and HC was also demonstrated in a purely spatial context. In both instances, RSC was able to rapidly acquire new permanence representations for previously alien spatial cues. RSC-HC interactions were then linked to the calling-upon of detailed knowledge of the specific locations permanent landmarks were positioned within an environment. The present study indicates that the same

network could perhaps contribute to representations of more than just a scene's spatial relationships.

Processing of permanent landmarks in RSC and related brain areas has also been previously associated with a person's ability to navigate and acquire new spatial information (Experiments 1, 2, 3 and 5). Given that the present study had such a straightforward task (reading simple sentences) and minimal variability in subjects' performance, it was not possible to investigate any inter-individual differences here (see also Section 6.4.3 for similar discussion). However, it would be interesting for future work to consider whether a person's ability to learn about the regularity of events and actions happening in a certain place is related to processing within these regions and if so, how this may be linked to more general memory processes.

8.4.4 Processing of non-scene, abstract concepts

None of the "scene-selective" brain areas were engaged when people read the non-scene sentences. Instead, prefrontal cortical regions responded to the abstract concepts. Medial parts of prefrontal cortex were more active for non-scene than scene sentences, but DLPFC was more active when people read abstract sentences describing something permanent compared to transient. This was the only permanent versus transient contrast which did not engage RSC, which I relate to the absence of a concrete spatial setting (Section 8.4.2). It is therefore interesting that a brain region which shares such dense reciprocal connectivity with RSC (Section 1.3; Kobayashi and Amaral, 2003) would instead be more active. However, this dense connectivity is not evident in rodents, only primates.

It is tempting to speculate that this could perhaps reflect a system which has evolved in primates to carry out more abstract conceptual thinking, which still bears some association to lower-level processing of similar themes in the spatial domain. Thus, whereas RSC processes the permanence of things which are physically tangible, the densely connected DLPFC could perhaps 'take-over' for comparable higher-level cognition. However, significant amounts of further work would be required to establish the validity of this conjecture.

8.4.5 Summary

This study builds upon my previous body of work which indicates that RSC specifically processes permanent, stable environmental landmarks in a variety of different circumstances. However, by having participants read simple sentences while undergoing fMRI scanning, I was able to expand upon these findings and establish the generalisability of neural permanence representations. RSC responses not only discriminated between permanent and transient spatial aspects of a scene, but also actions and events occurring within them. This suggests RSC could contribute to a broader array of cognitive tasks than just helping to map environments, and offers intriguing lines for future enquiry.

PHC responses were related to processing spatial aspects of a scene and engagement of HC appeared to reflect the construction of coherent scenes in the mind's eye, irrespective of the scene's contents. These two MTL regions were themselves insensitive to permanence, but displayed greater functional coupling with RSC when a scene described something permanent.

This wide range of responses and interactions between different brain regions all occurred with participants performing a completely incidental task. They had no knowledge of the key differences between the sentences and were simply required to confirm they made sense. This suggests these are fundamental, automatic neural processes and provide further evidence potentially explaining why disruptions to RSC by lesions (Section 1.6; Valentine et al., 1987; Maguire, 2001a; Vann et al., 2009) or in the early stages of neurodegenerative disease (Section 1.7; Villain et al., 2008; Pengas et al., 2010, 2012), can give rise to such profound amnesia and navigation deficits.

Chapter 9: General Discussion

9.1 Overview

Despite the apparent importance of RSC for key aspects of cognition, very little is known about what specific information it processes when carrying out these functions (Section 1.11). The central aim of this thesis was to try to gain experimental control over RSC activity in order to determine what precise contribution it makes (Section 1.12). The results of the first experiment provided an intriguing starting point for me to build upon and explore in a series of subsequent experiments.

In this chapter, I present a synopsis of the results from the six experimental chapters. I consider the response of the RSC especially in relation to landmark permanence, how this interacted with the spatial abilities of participants, and then consider what information may be represented in other related brain regions. I go on to discuss how these results fit with extant theories of RSC function, and in the process discuss my own view of RSC functioning, before reflecting upon the clinical implications and limitations of my results, and finally I outline possible areas which future work could explore.

To minimise the potential for confusion when describing the six different experiments, I refer to them by abbreviated 'nicknames' throughout this chapter as follows:

- Experiment 1 (Chapter 3) = "Landmarks"
- Experiment 2 (Chapter 4) = "Quads"
- Experiment 3 (Chapter 5) = "Fogworld"
- Experiment 4 (Chapter 6) = "Spatial scales"
- Experiment 5 (Chapter 7) = "Orientation"
- Experiment 6 (Chapter 8) = "Sentences"

9.2 RSC

9.2.1 Permanence representations

Across all six of my experiments, the RSC was consistently responsive to the permanence of landmarks. For familiar everyday items, the landmarks experiment demonstrated that RSC is engaged by only the most permanent, non-moving items. However, RSC does not simply activate in the presence of anything permanent, the quads study highlighted that it contains a representation of multiple permanent landmarks which are in view at any given time. These first two experiments both used familiar real-world items. This allowed me to examine responses in a naturalistic setting, but it meant that the landmarks came with semantic and associative "baggage". Consequently, there was the potential for some other feature of the items, which I had not accounted for, to be driving any apparent effects related to landmark permanence. However, the same does not apply for the three subsequent experiments (the fogworld, spatial scales and orientation studies). These each tested "pure", uncontaminated representations of landmark permanence with completely novel items of which people had no prior experience.

The fogworld experiment demonstrated that responses in RSC are highly specific for landmark permanence. Before participants knew which items were permanent, RSC did not respond to any landmark feature; permanence-related responses only emerged when people learned which landmarks never moved. This is entirely consistent with the first two experiments, where RSC also did not respond to any other features of items such as their size or visual salience. The primary purpose of the orientation experiment was to further examine whether RSC may respond to a property of landmarks other than their permanence. Once again, RSC was only engaged by landmarks which remained fixed in a single location, independent of their usefulness for orientation. In the same study, it was possible to classify between the four different types of landmark (according to both their permanence and usefulness), but the subsequent 2-way classifications suggest that this was primarily driven by representations of permanence, rather than usefulness, in RSC. Thus, when it comes to processing landmarks, RSC seems to display a high degree of specificity in responding to only the most permanent environmental cues. The same is not true for the other brain regions which also showed some responsiveness to landmark permanence (see Section 9.3).

For highly familiar landmarks (such as in the first two experiments), RSC responses were all-or-nothing (Figure 23B), depending on whether or not an item *never* moves. This all-or-nothing response would be valuable for identifying only the most stable cues to centre reliable topographical representations around. However, the fogworld experiment indicates that RSC is not just simply more active for permanent landmarks; as people learned which landmarks were permanent, responses in RSC directly tracked the emergence of this knowledge, i.e. the better people knew which landmarks were the most stable, the greater their RSC responses differed between permanent and transient landmarks. Therefore, rather than fine-grained variability in the extent of RSC activation reflecting how permanent an item is, my experiments instead suggest it may relate to *how well* people know the permanence of landmarks. In normal everyday circumstances this may not always be important given that people are likely to have a clear (if not always accurate) idea about the permanence of landmarks they encounter. However, investigating the emergence of *de novo* permanence representations in a novel alien setting in the fogworld experiment, revealed this subtlety in RSC function. This fine-grained variation in RSC responses while a person is still learning which landmarks are reliable cues could provide additional useful information about how dependable subsequent representations based upon them might be. This could in turn also be used to help ascertain whether more information is needed to ensure the reliability of environmental representations. Although these suggestions are consistent with data from the fogworld experiment, more work is needed to substantiate and refine these ideas further.

The spatial scales experiment also demonstrated specificity in RSC for only the most permanent landmarks. Here, the MVPA analysis revealed subject-specific activation patterns in RSC which only helped identify permanent, not transient, items. This was only evident while people recalled landmarks in large scale space; perhaps indicating that the more immersive nature of imagining landmarks within large rather than small-scale settings produces more prominent permanence representations in RSC. This makes intuitive sense given that it more closely mirrors how we experience landmarks in normal everyday life. However, that is not to say that RSC is insensitive to the permanence of items in small scale, two-dimensional space. The same study also found RSC to be significantly more active when people imagined permanent than transient landmarks across both large and small scale recall trials. This was not the case when considering large

and small scale space individually. Therefore, RSC responses when imagining in small scale space must have contributed in some way to the permanence-related activity. The orientation study provides further evidence that items experienced only in small scale space can elicit significant permanence-related responses in RSC. This highlights that RSC is not simply "scene-selective", it contains detectable permanence representations for items in simple two-dimensional spatial arrays. RSComp has also been found to be similarly responsive in tasks which do not involve any sort of complex scene setting (Nasr et al., 2013).

Indeed, all the experiments presented in this thesis provide further evidence that RSC does not simply process scenes (Section 1.10.3; Park et al., 2007; Ward et al., 2010; Golomb et al., 2011; Nasr et al., 2011, 2013; Troiani et al., 2012). In the landmarks, quads, fogworld and orientation experiments, there was no 'scene' to speak of in any of the stimuli which elicited strong RSC responses; they were all single landmarks devoid of background context. One could argue that in the fogworld and orientation experiments subjects will have recalled the 'scene' where landmarks were experienced and not just the item itself. However, I believe any potential differences in the 'sceneness' of permanent and transient landmark representations will have been minimal. If trials had been longer than a few seconds then subjects might have started to think about precisely *where* landmarks were located, but these experiments were specifically designed to assess rapid, automatic responses to intrinsic features of the landmarks themselves. The questions which followed landmark images in the fogworld and orientation experiments also specifically primed subjects to think about the specific properties of landmarks. Furthermore, none of the landmarks in my first two experiments had been previously seen in any location, yet RSC was still engaged by only the most permanent items. In the spatial scales experiment, the large scale recall condition involved people imagining a landmark within a scene of sorts, but these were highly minimalistic scenes and only represented half of all trials. However, the most in depth examination of RSC's scene related responses came from the final experiment.

On first impressions, the sentences study appeared to reveal scene selectivity in RSC. However, further interrogation of the data exposed this as an oversimplification. RSC was more active when people read a sentence describing a scene with permanent contents. Indeed if the scene contents were transient and unreliable, RSC lost any scene-related

responsivity. Thus, RSC appears more sensitive to the permanence of individual elements *within* a scene rather than the scene itself. This is an important consideration given the large number of studies in which the way the region is defined is based upon "scene-selectivity" (Section 1.10.3). Voxels identified with functional localisers in this way include much wider parts of more posterior cortical regions. This further highlights how inappropriate it is for the RSComp region to be named so similarly to RSC proper.

Results reported from RSComp might originate from completely different parts of the brain to anatomical RSC, yet there is still an overwhelming tendency for the different 'cortex' and 'complex' areas to be discussed interchangeably (e.g. Ranganath and Ritchey, 2012; Vass and Epstein, 2013). This is not to say scene selective localisers should be replaced with some sort of "permanence selective" equivalent, rather that much greater caution should applied when interpreting results from functionally and anatomically defined brain regions. The similarity between their names should not necessarily be confused for similarity in function.

Rather than RSC activity reflecting the processing of high level representations of an environment (Park et al., 2010; Henderson et al., 2011; Fairhall et al., 2014) or performing complex spatial computations (Byrne et al., 2007; Epstein and Vass, 2014), it is instead responsive to a single property of individual items. I propose that RSC involvement in the wide range of complicated cognitive functions with which it has been associated could reflect processing at a much more basic, fundamental level. Specifically, I believe that RSC helps identify the most stable and reliable cues in our surroundings upon which dependable neural representations of environments can be constructed by other brain regions which are densely connected to RSC (see Section 9.3).

In section 1.2 of Chapter 1, I highlighted the diversity in RSC anatomy across different species. Human RSC constitutes a much smaller proportion of the entire cortical surface than in other species. I believe this could be a reflection of the basic function I am proposing RSC performs. This could explain why, through the course of human evolution, RSC has not expanded to the same extent as other brain areas which are involved in higher-level cognition, like the prefrontal cortex. However, despite the significant between-species differences, the proposal that human RSC codes for landmark permanence could also explain results of experiment in rodents.

Lesions to rat RSC produce navigational deficits in both radial-arm (Cooper and Mizumori, 2001; Vann and Aggleton, 2002, 2004; Keene and Bucci, 2009) and water mazes (Sutherland et al., 1988; Whishaw et al., 2001; Harker and Whishaw, 2002, 2004; Vann and Aggleton, 2002; Vann et al., 2003; Lukoyanov et al., 2005; Cain et al., 2006) and they appear to particularly impact upon the use of cues in the external room rather than those inside a maze itself when the two are put in conflict with one another (Vann and Aggleton, 2002, 2004, 2005; Vann et al., 2003; Pothuizen et al., 2008). This would all be consistent with RSC-lesioned animals being unable to identify and use the most reliable environmental cues to guide their navigation; they perhaps instead unsuccessfully try to use inappropriate cues.

Proposing RSC is primarily involved in processing landmark permanence might seem at odds with the behaviour of RSC head directions cells (Chen et al., 1994b; Cho and Sharp, 2001). These neurons do not simply respond to certain types of landmark, but actually code for more detailed spatial information. However, coding of directional information is certainly not a ubiquitous feature of all RSC neurons; only ~8% of cells show sensitivity to head direction (Chen et al., 1994b) and of these, many are also modulated by other factors (e.g. running velocity). It is not known what proportion of human RSC neurons, if any, have similar spatial properties, but this does highlight that permanence may not be the only thing to which RSC is responsive. RSC perhaps plays some sort of role in helping tether head direction and other spatial representations to stable environmental cues. This suggestion is somewhat speculative, especially in the context of human RSC, but the more important point is that RSC is likely to do more than simply identify permanent landmarks. It could also have influence in some downstream processing of that information, possibly in conjunction with other more specialised regions (see Section 9.3). This could help explain why, for example, RSC lesions impact upon the control that visual landmarks, but not self-motion cues, have upon thalamic head direction cells (Clark et al., 2010).

So how does RSC determine whether a landmark is permanent and which cues does it use to do so? It appears to be highly adaptable, utilising whatever is the dominant overarching spatial structure in a given circumstance. In the fogworld experiment, this fundamental background structure was provided by the wider virtual reality environment and the paths embedded within it. However, in the spatial scales and orientation experiments there was no such explicit three dimensional construction to organise representations around. In

those circumstances, the permanence of cues could be determined by whether or not their position remained constant relative to a different, much simpler, dominant spatial assembly, namely a computer screen. However, landmarks do not need to be inserted within these surroundings to elicit permanence responses. The fact that most of my experiments found RSC responding to images of isolated, individual landmarks suggests permanence seems to be processed as inherent to individual items based upon inferences made from past experience of similar landmarks in both the real-world (landmarks, quads and sentences experiments) and novel, alien environments (fogworld, spatial scales and orientation experiments).

Another potentially broader function of RSC was highlighted in my final experimental chapter. The sentences study intriguingly hinted at RSC involvement in processing information beyond the spatial domain. RSC was more active while people read a sentence describing permanent or dependable actions and behaviours, not just landmarks. The representations did not extend as far as more abstract concepts; RSC activity was dependent upon there being some sort of grounding within a concrete scene setting. This draws some interesting parallels with the 'scene construction theory' which I will discuss in greater depth in Section 9.4.2. All five of my other experiments considered exclusively spatial representations, but there is evidence from elsewhere that RSC may be involved in other non-spatial tasks (Nelson et al., 2014). It is also not clear how this might relate to the suggestion that RSC is more active while making judgements about your own personality traits than those of others (Moran et al., 2006; Van Buuren et al., 2010). This could perhaps reflect a more reliable, dependable knowledge of your own personal character. It will be interesting for future work to establish the scope of these non-spatial processes and what they may indicate about RSC's overall contribution to cognition.

RSC could, for example, perhaps play a more general role in processing environmental uncertainty and expectations (Moran et al., 2013). Indeed, another way of conceptualising permanent landmarks is as environmental cues which possess low entropy and centring representations of space upon them could be seen as a way of minimising free energy (Friston, 2010). In this regard, RSC might be considered a crucial region for ensuring the brain codes information with optimal efficiency. This is of course speculative, but RSC's sensitivity to permanent landmarks could nonetheless provide a useful and naturalistic framework for future experiments to explore more general ideas in relation to predictive

coding (Rao and Ballard, 1999), the Bayesian brain hypothesis (Knill and Pouget, 2004) and the free-energy principle (Friston, 2010).

9.2.2 Relationship with spatial abilities

A second consistent theme in my experiments is the association between responses in RSC and a person's ability to navigate effectively and with other spatial tasks. This was again specifically related to processing the permanence of landmarks. In the landmarks experiment, people who self-identified as poor navigators were not only less reliable at characterising the most permanent, 'never' moving, items, but also had reduced activation in their RSC when viewing these same landmarks. This seemed a surprising result at first, but replicating the behavioural findings in an independent set of subjects suggests it was a robust effect. However, there were still two potential criticisms which needed addressing. First, using a self-report questionnaire might not be the best measure of a person's true navigation ability. Second, there could possibly have been some misunderstanding of the meaning of the permanence question asked to participants (How often would you expect the position of this object to change in everyday life? *Very Often - Never*). One possible source of confusion was for items which have moving parts but do not change their location, like a tree or a windmill. However, I took great care when explaining the task to participants to ensure they understood that the question referred to whether or not the whole items changes its location and not whether it moves within that place.

I addressed both of these potential limitations in the fogworld experiment. Here I used a more direct, objective measure of navigation, getting participants to actually navigate within fogworld. The alien landmarks were also devoid of moving parts, which removed the possibility of any misunderstanding as to what was meant by permanence. With these added controls, poor performers were again found to have a specific deficit at learning whether landmarks were permanent or transient (despite having no problems recognising them), with an associated reduction in how well their RSC responses discriminated between the two landmark types.

How then do well educated, intelligent participants fail to recognise that landmarks like a tree or stadium stand never move in normal everyday life (see Figure 25 for more

examples)? I believe this reflected the nature of the task I used. People rated the permanence of hundreds of items (683 in the ratings study) one after another. As such, they did not tend to deliberate over their responses for prolonged periods of time. The ratings they gave instead reflected immediate and automatic responses to the landmarks and this is where the deficit became apparent. I have little doubt that if forced to give more effortful consideration of their permanence responses, poor navigators would likely have been equally as consistent as good navigators. Indeed, when explicitly instructed to rate the navigational utility of landmarks, a less elementary feature, good and poor navigators did not differ in their agreement. That is not to say that the ratings of poor navigators were less reliable in general, indeed they showed absolutely no deficit when it came to rating any other features of the landmarks and even the permanence of items which change their location. The difference between good and poor navigators was highly specific for only the most permanent, 'never' moving items, where the initial "gut reaction" of poor navigators was unreliable. Thus, in processing permanence information, the poor navigators appear to be 'falling at the first hurdle', with knock-on effects for their navigation ability because the basis of any representation of an environment are the most stable features within it. This has some interesting parallels with the spatial deficits brought about by lesions and neurodegenerative disease to RSC which I will discuss in Section 9.5.

The quads and orientation experiments found further differences related to a person's spatial abilities. The quads study demonstrated that RSC responses of poor navigators are less informative about whether a majority or minority of landmarks being viewed are permanent. The orientation experiment revealed that the better people had learned the permanence and usefulness of landmarks, the more that activity in their RSC could be used to classify that same information. The RSC of good learners was also interacting more with AThal when people viewed a permanent landmark, which I will discuss in greater detail later in the chapter (Section 9.3.4).

Neither the spatial scales nor the sentences study found any comparable link between RSC responses and spatial abilities. Why might this have been? These two experiments were unique in that they measured fMRI responses while people imagined or read about a scene or landmark rather than viewing an image of landmarks. So there were no apparent differences between the RSC responses of good and poor navigators when elicited by

purely internally generated representations; they only became apparent when assessing automatic responses while people perceived visually presented landmarks. Differences between good and poor navigators/learners might therefore only arise in how their RSC processes external spatial information. Although, as I discussed within their respective chapters (Sections 6.4.3 and 8.4.3), there was less individual variability in task performance in these experiments; they were specifically designed so that subjects would be performing at close to ceiling levels. These tasks also did not have a measure with which to compare good and poor performers. In the fogworld and orientation experiments, the tasks included specific, objective performance measures whereas the landmarks and quads studies used real-world stimuli and so were more appropriate to be considered in relation to the SBSOD scale (Weisberg et al., 2014).

Previous experiments using the SBSOD questionnaire have found that scores are correlated with PHC and HC resting state functional connectivity (Wegman and Janzen, 2011) and that PHC and putamen responses show greater differences between novel and familiar places or novel and familiar viewpoints of a single place in good compared to poor navigators (Epstein et al., 2005). However, unlike my first two experiments, neither found any relationship between navigation ability and the RSC. This is a common theme in experiments investigating navigation ability. Previous studies which have found differences in the brains of good and poor navigators, related to both navigation (Maguire et al., 2000; Hartley et al., 2003; Ohnishi et al., 2006; Woollett and Maguire, 2011) and processing space more generally (Epstein et al., 2005; Janzen et al., 2008; Baumann et al., 2010; Wegman and Janzen, 2011) have tended not to implicate the RSC at all. Instead, parts of the medial temporal lobes, most notably HC but also PHC, have repeatedly been shown to have differences in terms of fMRI activity (Hartley et al., 2003; Epstein et al., 2005; Ohnishi et al., 2006; Wegman and Janzen, 2011) and structure (Maguire et al., 2000; Woollett and Maguire, 2011; Wegman et al., 2013) for good and poor navigators. The only example of which I am aware which reports RSC activity to be related to performance in a spatial task in fact mislabels a more posterosuperior cortical region as RSC (Wolbers and Buchel, 2005).

Another commonly reported navigation-related difference is between the sexes, where males tend to outperform females in spatial tasks (Moffat et al., 1998; Sandstrom et al., 1998; Montello et al., 1999; Waller, 2000; Coluccia and Louse, 2004; Hegarty et al., 2006).

However, I found no performance differences in relation to the sex of participants in any of my experiments. It has been suggested that sex-based navigation differences might be related to the different strategies adopted by males and females, with females tending to use local route cues compared to more global representations of the wider environment in males (Lawton, 1994; Grön et al., 2000; Chai and Jacobs, 2009, 2010). It is possible therefore, that my experiments' specific, more restricted task demands might have masked differences which could have been present during navigation by free exploration. Even in the fogworld experiment's volitional navigation task, although the test itself involved free exploration of the environment, the learning prior to it was constrained.

More general large variation is consistently found in people's ability to acquire spatial knowledge from environments (Allen et al., 1996; Blajenkova et al., 2005; Fields and Shelton, 2006; Hegarty et al., 2006; Ishikawa and Montello, 2006; Wen et al., 2011; Weisberg et al., 2014), much like the fogworld experiment, but this has never implicated RSC. Similar differences are also evident in how people perceive spatial properties of an environment and the strategies they use when navigating (reviewed in Wolbers and Hegarty, 2010; see also Ishikawa and Nakamura, 2011). However, no previous experiments have considered these variations in relation to the permanence or stability of surrounding cues. I believe this explains why they have never been connected to RSC.

My experiments have only been able to reveal differences in RSC processing related to spatial abilities by examining representations at a basic, fundamental level. This is most evident in the fogworld experiment which assessed completely *de novo* representations acquired in a highly 'stripped back', alien setting. In these circumstances, I found that a person's ability to navigate through the environment after extensive learning within it bore no relation with their self-reported navigation ability in the real world according to the SBSOD scale. The SBSOD scale was similarly unreliable at predicting performance and the amount of information people learned in the spatial scales and orientation experiments. This may appear a completely counter-intuitive result at first, but I believe there are multiple reasons why this was the case.

Although I tested fogworld with a navigation task, the learning period was not explicitly navigational. Subjects were instead shown videos travelling through the environment and their ability to subsequently navigate through it themselves was dependent on how much

they had been able to learn by passive viewing. There were also explicit task instructions during the learning phase, subjects were focussed on learning to recognise landmarks and identify whether or not they were permanent. If subjects had instead been specifically learning to navigate around the environment by self-directed, free movement, SBSOD scores might have perhaps been a better predictor of the amount of information they were able to acquire. This would have been inappropriate for the purposes of my experiment, however, as I needed to maintain strict control over the amount of exposure the subjects had to each landmark. The spatial scales and orientation experiments were similarly not explicitly testing navigation but more general learning of spatial information. It would have been interesting to get the fogworld experiment's participants to rate the permanence of the real-world landmarks used in my first study and compare the responses of good and poor performers in the post-scan navigation task. However, this experiment was already demanding enough and contained numerous elements; time simply did not permit me to add another task.

It is also perhaps worth noting that in the landmarks and quads experiments, subjects completed the SBSOD questionnaire after completing all of the tasks, whereas in my other four experiments, the SBSOD was always filled out before starting commencing the main experiment. This may seem inconsequential, but a person's self-reported sense of direction (although not using the SBSOD) has been shown, at least in one study, to provide a more reliable estimate of performance on spatial tasks when asked at the end of testing compared with the start (Heth et al., 2002).

Some people also question whether navigation in virtual reality provides a true reflection of the real process, given its lack of actual locomotion and the associated proprioceptive feedback (Taube et al., 2013). However, a person's ability to navigate within real-world environments and highly similar virtual simulations of them is usually closely related (Koenig et al., 2011), so it is probably not the virtual reality aspect of my experiments which accounted for the difference. Instead, it more likely reflects the fundamentally different nature of what was being tested in the fogworld, spatial scales and orientation experiments compared to the landmarks and quads experiments.

Unlike my first two experiments, the rest of my experiments which found no significant effects relating to SBSOD scores used completely novel, alien items and environments,

rather than real-world landmarks. A person's ability to navigate within everyday settings (as measured by the SBSOD scale) and their responses to highly familiar real-world landmarks while performing an incidental task (as in the sentences and quads experiments) could be quite independent of their ability to adapt and rapidly learn new information in completely alien settings. These might reflect two quite separate abilities. Even so, the single consistent finding which remains constant across the dissimilar circumstances is that the ability of people to characterise the permanence of landmarks is linked to how their RSC responds to them.

In other words, it is not that some people have an inherent general deficit at navigating in both novel and familiar circumstances, but rather that in either situation, those who cannot process permanence efficiently typically fall down. People who are less reliable at characterising permanent real-world landmarks are subsequently impaired at wayfinding in the real-world, whereas those who cannot flexibly learn the permanence of new items struggle to navigate in these more unfamiliar settings. The behavioural importance of permanent landmarks has been demonstrated in both rodents (Biegler and Morris, 1993, 1996) and humans (Burgess et al., 2004), where an absence of stable environmental cues severely impacts upon performance in spatial tasks. Therefore, similar to my conclusions discussed in Section 9.2.1, RSC processing of permanence appears to form a core, fundamental part of spatial computations.

9.3 Other brain regions

9.3.1 POS

In the fogworld experiment, a region in the parieto-occipital sulcus (POS), more superior and posterior to the RSC, also developed increased activity for permanent compared to transient landmarks as subjects learned this information. However, unlike RSC, before landmark permanence was known, this POS region responded to a different aspect of the landmarks. In the early stages of learning, POS was more active while people viewed landmarks which they subsequently recognised better at the end of scanning. It is not possible to determine whether the increased POS activity early on might have been a cause of better recognition of landmarks or whether it was instead responding to some

particular feature which those memorable items shared. Either way, the sensitivity of POS responses switched to landmark permanence later on in the learning phase.

The spatial scales experiment demonstrated that activity within the same POS region could be used to classify the permanence of landmarks, but only when they are imagined in large scale space. POS was not, however, implicated in any of the landmarks, quads or sentences experiments. So in contrast to RSC, POS is only responsive to landmark permanence in certain circumstances.

In Chapter 5, I discussed how the POS results from the fogworld experiment could be consistent with a function commonly ascribed to the RSComp, namely using landmarks to orientate and localise. In that experiment, I proposed that the POS's initial response to memorable landmarks and subsequent switch to the permanent ones reflected processing of the most appropriate cues for orienting. However, with this interpretation, in the orientation experiment, one would have expected POS to have responded to usefulness rather than permanence. The opposite was instead true. To account for this apparent discrepancy, I propose that the POS region is perhaps involved in using landmarks for orienting and localising, but preferably uses permanent landmarks to do so.

In the fogworld experiment, when people did not know the permanence of landmarks, POS had to use some other feature of the items to identify which would be best to orientate. In these circumstances, the most memorable landmarks proved the best option. However, when the permanent landmarks were revealed as the more reliable cues, POS responses switched to centre around these instead. In contrast to the fogworld experiment, the orientation experiment scanned people after learning was over and so they were very familiar with the permanent landmarks. In normal circumstances, permanent landmarks would commonly also be the most reliable to use for orienting, but when I artificially dissociated the two features in the orientation experiment, POS showed a preference for permanence.

An alternative explanation for the responses in POS across all six experiments could be that it is only engaged when new information is learned about landmarks (as was the case in the fogworld, spatial scales and orientation studies) and not by highly familiar, real-world items (as in the landmarks, quads and sentences studies). In other words, perhaps

POS is important for learning rather than simply perceiving recognisable cues. However, there are several reasons why I believe this is unlikely. If the POS region described in my experiments is comparable to the RSComp, both of which are located superior and posterior to RSC proper, this interpretation would be completely at odds with the region's apparent role in processing familiar real-world scenes (Epstein et al., 2007a, 2007b; Vass and Epstein, 2013) and tasks using long-term spatial knowledge (Rosenbaum et al., 2004, 2007). It also provides little explanation for the POS's responsivity to landmark permanence.

Thus, while RSC has a highly specific, universal response to the permanence of items, POS seems to also primarily process permanent landmarks, but not at such a basic, fundamental level. POS instead appears to only process permanent landmarks when they are located in a specific place. This would explain why the region was implicated in the fogworld, spatial scales and orientation studies but not the landmarks, quads or sentences studies, where items were not associated with a specific spatial location. When landmarks are associated with specific places and the permanence is not known (as was the case in early parts of learning in the fogworld experiment), POS still seeks to localise with landmarks, but has to do so using some other feature of environmental cues as a proxy for permanence before that becomes apparent.

It is interesting to note that despite POS and RSC processing similar information in many of my experiments, none of the gPPI connectivity analyses revealed any evidence of functional coupling between the two regions. Indeed, there is also minimal evidence of shared structural connectivity between these two areas (Section 1.3). In the fogworld experiment, both POS and RSC interacted with similar, but not identical, parts of anterior HC. Perhaps, therefore, information flow between the regions is not direct and instead occurs in conjunction with other mutually connected brain areas.

9.3.2 HC

Similar to the POS, the HC was not implicated in either of the first two experiments which explored responses to the simple perception of isolated, real-world landmarks. HC was only engaged when landmarks were embedded within a wider spatial context. In the fogworld experiment, the HC developed responses to permanent landmarks, but only late

on in the learning process. At the same time, more detailed activation patterns developed in the HC relating to how well people knew where permanent landmarks were located. So the HC appears to have been involved in processing more detailed spatial information about landmarks, information which the permanent but not transient landmarks possessed (i.e. where within fogworld they were located). The same was also true of permanent landmarks in the spatial scales study. In both cases, unlike the landmarks and quads experiments, HC selectively responded to permanent landmarks now that they were associated with extra spatial information. The sentences study was subtly different, however, as here the locations of both permanent and transient parts of a scene will have been imagined in relation to other items. As such, there was no difference in HC responses for permanent and transient sentences. Instead HC was only more active for scene sentences when compared to abstract sentences which had no concrete spatial setting.

The experiment in which HC responses differed most significantly from any other region was the orientation study. This experiment highlighted the particular importance for HC in processing the spatial relationships between items. Subject-specific HC activation patterns could be used to decode the relevance of landmarks for orienting rather than permanence; responses could also be used to classify whether a landmark's associated treasure was distant or nearby, as well as the region being more active for landmarks associated with a more distant treasure location. This coding of the distance between a landmark and its associated treasure location has interesting parallels with studies which have found similar representations in the HC and wider parts of the MTL relating to the distance a person is from a goal location while navigating (Spiers and Maguire, 2007a; Morgan et al., 2011; Sherrill et al., 2013; Howard et al., 2014). However, in some instances HC activation has been shown to increase for closer, rather than further, goal locations (Viard et al., 2011). In the final task of the orientation experiment, if a landmark did not provide useful information about the location of a paired treasure chest HC displayed reduced activity. Furthermore, for landmarks which had no informative spatial associations, HC interacted more with RSC, which perhaps reflected more attention to processing properties intrinsic to a landmark (e.g. permanence).

RSC and HC also interacted with one another in the spatial scales experiment, with RSC driving permanence-related responses in the HC. Here, people were imagining landmarks

rather than being presented images of landmarks. This was also true of the sentences study, where RSC and the MTL region (which included parts of the HC) again showed functional coupling. Therefore, when people were generating representations of scenes using purely endogenous processing, RSC and the HC interacted with one another and in both instances DCM analyses indicated that RSC provided the input to the system.

The HC, therefore appears to play a role in processing more detailed, fine-grained information about the spatial relationships between items rather than features of the landmarks themselves. It seems that RSC might provide information about the most permanent, reliable landmarks in an environment and HC could in turn use this information to form more detailed representations of the surrounding environment. If no permanent cues are available, HC can still play a role in processing the spatial relationships between landmarks for navigation, just not in conjunction with RSC. Indeed HC, but not RSC, has been found to be active during navigation to specific locations using cues which change position from trial to trial (Baumann et al., 2010; Wegman et al., 2014). RSC instead seems finely tuned only for spatial operations based upon permanent environmental cues. I discuss this proposal in greater depth and link it with the scene construction theory in Section 9.4.2.

9.3.3 PHC

In the quads study, PHC behaved in a similar way to the RSC, with both coding for the number of permanent landmarks in view. In both the landmarks and fogworld experiments too, PHC also showed increased activation when people viewed more permanent landmarks. However, there were differences in the nature of these permanence representations when compared with RSC. In the landmarks experiment, PHC was not selectively responsive to just the most permanent landmarks (as RSC was); it instead showed a less specific linear increase in activation in line with how often the items changed their location in everyday life (Figure 23A, Section 3.3.2). New permanence representations also took longer to develop in PHC than RSC in the fogworld experiment. Therefore, while PHC was responsive to the permanence of items in a number of the experiments it does not appear to be a core function of this region as seems to be the case for RSC. Indeed, in the sentences and orientation studies there was no evidence of any sort of permanence representation.

PHC was also responsive to various other features of items, like their size and visual salience, in the landmarks experiment but not the fogworld experiment. This is consistent with the idea that PHC is particularly engaged by visual and spatial qualities which are unique to familiar, real-world items or scenes (Troiani et al., 2012). But what might it be about these real-world stimuli which PHC processes? A potential indication comes from how PHC responded in my last three experiments.

The spatial scales experiment demonstrates that PHC activity is sensitive to the way in which a landmark is imagined. When people were imagining permanent landmarks, PHC patterns of activations could be used to decode whether it was being recalled in large or small scale space. PHC responses also contained information relating to whether a subject imagined a landmark to their left or right, but only for large scale recall trials; a result which perhaps reflects something comparable to the behaviour of "spatial view cells" which have been found in the same region in macaques (Robertson et al., 1998). The sensitivity of PHC to the spatial scale a landmark is experienced in is further highlighted by the orientation experiment. Here, when people only ever viewed the items in small scale two dimensional space, PHC was not found to be responsive to any property of the landmarks. PHC was therefore particularly responsive to real-world landmarks (landmarks and quads experiments) and those experienced in large scale, three dimensional space (fogworld, spatial scales experiments). Both of these factors could be accounted for by the sense of surrounding space that items evoke.

Indeed, Mullally and Maguire (2011) have proposed that PHC is responsive to an awareness of local surrounding space. They introduced the concept of items being either space-defining (evoking a strong sense of surrounding space) or space-ambiguous (do not evoke a sense of surrounding space) and found that PHC was more engaged by space-defining than space-ambiguous items. Published in the same journal issue, another study provided further evidence that PHC is strongly responsive to spatial aspects of real-world scenes (Kravitz et al., 2011a). Both real-world landmarks and those experienced in large scale space may have produced a greater sense of surrounding space in my experiments. Furthermore, Mullally and Maguire (2011) established that the frequency with which an item changes position in everyday life is related to how space-defining it is, with more permanent items tending to evoke a stronger sense of surrounding space. The second

property of items which determines how space-defining they are is their perceived real-world size (Mullally and Maguire, 2011). My landmarks experiment also showed PHC responding in a linear fashion to real-world items which were larger and more space-defining. The responsivity of PHC to permanent landmarks late on in the fogworld experiment could perhaps have reflected these landmarks beginning to evoke a sense of the specific space they occupy within the environment, even when they were viewed in isolation on a plain background. Perhaps, then, the PHC's responsivity to the permanence of items in some of my experiments was secondary to an associated sense of the surrounding space they evoked.

My final experiment provided further evidence in favour of this theory. In the sentences study, PHC was not only more active for scene than abstract sentences, but activity was specifically greater for spatial than non-spatial scenes. There was no responsivity to the permanence of what was being described, only the spatial aspects of scenes. Instead, when people imagined a scene with permanent contents, PHC interacted more with RSC which is more sensitive to the permanence information.

9.3.4 AThal

In the landmarks and orientation experiments there were some interesting results relating to anterior parts of the thalamus in conjunction with the RSC. To be clear from the outset, when I refer to AThal I am not speaking with the anatomical precision necessary to refer to specific nuclei (e.g. the anterior thalamic nuclei). The fMRI clusters of activation were too large to identify individual nuclei. I instead make reference to broader parts of the anterior thalamus which will include different nuclei, but RSC does share connectivity with numerous different nuclei in AThal of both primates (Buckwalter et al., 2008) and rodents (Wright et al., 2010; Jankowski et al., 2013), so I believe this is justified.

Responses in AThal differed according to the spatial abilities of participants. In the landmarks study, good navigators had greater AThal activity when viewing images of permanent everyday items and this was associated with more reliable identification of permanent landmarks. Similarly, when people viewed permanent landmarks in the orientation experiment, the better they had learned the permanence of those landmarks,

the more their RSC interacted with and drove permanence-related responses in AThal. None of my other experiments revealed significant results in AThal. So why might this be?

The landmarks and orientation studies were the only two in which people viewed images of single landmarks which they knew to be permanent. The fogworld experiment was similar in that participants viewed images of single landmarks. However, in that instance, they were only fully aware of which landmarks were permanent towards the end of scanning, so it was perhaps underpowered to reveal subtle differences between the AThal of good and poor learners. In the quads experiment, participants viewed multiple landmarks at once, most often with a mixture of permanent and transient items. The spatial scales and sentences studies measured fMRI responses for internally generated representations of landmarks rather than when viewing images. Therefore, similar to RSC, differences between responses in AThal of good and poor performers appear to be related to a basic, automatic level of processing of external, visual stimuli.

AThal engagement in relation to permanence was specifically related to comparisons between good and poor navigators. Moreover, I only ever found dissimilarity in activation of the AThal of good and poor performers in association with related RSC differences. Thus, a person's spatial abilities were linked to processing in their RSC independent of AThal (e.g. in the fogworld experiment) but the opposite was never true (no experiments demonstrated differences in AThal but not RSC). I therefore propose the relationship between AThal responses and people's spatial abilities came about as a downstream effect of variations in RSC permanence processing. This is also consistent with the result from the orientation experiment where the DCM analysis showed RSC influencing AThal responses for permanent landmarks in good but not poor learners.

It is not clear precisely how this may relate to the significant literature from work with rodents, which indicates that lesions to parts of AThal can bring about a variety of changes in RSC (Section 1.8). My findings do, however, confirm close functional links between the two brain regions in humans also, in addition to their structural connectivity (Section 1.3). The resolution afforded by whole brain fMRI scanning meant that it was not possible for me to investigate interactions between specific cortical layers or subregions of RSC and nuclei in the AThal. However, if this were ever possible, it would be interesting to consider given the consistent finding in rodents that lesions to anterior thalamic nuclei have a

particular impact upon superficial layers of RSC area 29 (Garden et al., 2009; Amin et al., 2010; Mendez-Lopez et al., 2013).

9.4 Relating RSC permanence processing to theories of its function

In Section 1.11 of Chapter 1, I outlined various extant proposals of what the function of RSC might be. I will now discuss the conclusions I have drawn from the results of my six experimental chapters in relation to these main theories of RSC function, and then I propose my own account of RSC functioning.

9.4.1 Orientation/localisation

One possible alternative explanation for the results of my first four and final experiments is that the RSC's apparent responsivity to landmark permanence instead reflected the fact that only items fixed in a set spatial location could be used to localise or orient oneself in space (Epstein and Vass, 2014). One argument against this interpretation is that in the landmarks and quads studies, images always showed landmarks in isolation, completely devoid of any background context. Thus, there was no extra spatial information which could be used to perform any sort of localisation or orienting. The fogworld and orientation experiments similarly assessed responses to isolated landmarks devoid of any background context (although it is possible that these representations included extra residual information about the locations landmarks had been experienced in, see Section 9.2.1). Furthermore, in the landmarks, quads and sentences experiments, participants were engaged in completely incidental vigilance tasks; they were simply looking for small dots which happened to occasionally appear on images of the items or checked that sentences made sense, with no idea that the content of what they were viewing was at all relevant. These tasks required no active spatial calculations to be made, which has previously been suggested to be a key determinant of RSC's level of activity (Epstein et al., 2007b). Therefore, orienting and localising in space does not appear to be necessary to engage RSC. Nor are these processes sufficient to elicit responses in RSC. When people navigate to specific locations using cues which change position from trial to trial (i.e. which are not permanent), RSC does not appear to be involved (Baumann et al., 2010; Wegman et al., 2014).

However, it was still important to formally test how RSC responses are influenced by landmark permanence independently of using their use for orientating and localising. This is what I did in the orientation experiment. Dissociating the two factors provided further evidence that it is the permanence of landmarks which specifically relates to activity in RSC. As I discussed in Section 9.3.1, the results across my six studies are more consistent with POS, not RSC, playing a role localising landmarks. However, even POS did not show any sort of sensitivity to whether landmarks could be used for localising treasure in the orientation experiment.

Another aspect of this theory is the suggestion that the orienting/localising function is centred on a sparse representation of vectors between particularly prominent or well-travelled locations (Epstein and Vass, 2014). This is consistent with the initial responsivity of POS to memorable landmarks in the fogworld experiment, in that they were perhaps particularly prominent landmarks. However, it then switched to instead become more active for permanent landmarks. No other results from any of my other experiments are consistent with this proposal. Instead, RSC (and POS) tended to be responsive to a large number of different landmarks, irrespective of their prominence or familiarity. Only the permanence of landmarks appeared to exert any influence upon whether or not RSC was engaged and every permanent item seemed to be treated in the same way.

Rather than a core function of the RSC being orientation and localisation, I instead believe its apparent role in these processes is explained by their reliance upon environmental representations which are themselves centred around permanent, stable cues. This draws some parallels with a theory based primarily upon evidence from rodents (Yoder et al., 2011). Yoder and colleagues note that the control landmarks have over head direction cell firing is disrupted by RSC lesions (Clark et al., 2010) and suggest RSC therefore plays some role in using visual landmarks to control spatial signals. What I am instead proposing is that the key role RSC plays in such a process actually comes at an earlier stage. The work in this thesis suggests that rather than using landmarks to control spatial signals, RSC instead helps identify the most appropriate, permanent landmarks to base these spatial representations upon. Other connected brain regions, such as the HC and POS, can then use this information to carry out the more complex operations. If there really is a region which is specifically involved in combining different spatial cues to localise and orient

within an environment, then it may form a different part of the RSComp (the area that most of the evidence backing this theory comes from) compared to the RSC proper.

9.4.2 Scene construction

A second proposal is that RSC forms part of a network which carries out the process of 'scene construction' (Hassabis and Maguire, 2007, 2009; Maguire and Mullally, 2013). In Section 1.11, I outlined how scene construction theory is potentially consistent with the RSC's involvement in a wide range of cognitive tasks, but lacks specificity about the precise contribution that RSC makes to the network. In order to construct and maintain spatially coherent scene representations which remain dependable over time, it is important for them to be based upon stable environmental cues. The RSC's involvement in the act of scene construction could therefore reflect the identification and handling of permanent landmarks.

Such an involvement in the construction and maintenance of coherent scene representations could explain the RSC's engagement in a wide variety of different fMRI experiments:

- when people navigate, but only when spatial information is manipulated, updated and integrated into topographical representations (Spiers and Maguire, 2006, 2007a);
- as people process more extensive representations of familiar environments (Wolbers et al., 2004; Sugiura et al., 2005; Epstein and Higgins, 2007; Epstein et al., 2007a; Iaria et al., 2007) and perform tasks requiring the use of long-term spatial knowledge (Rosenbaum et al., 2004, 2007; Epstein et al., 2007b);
- when spatial elements of a scene rather than the simple identity of its contents are processed (Henderson et al., 2008, 2011; Kravitz et al., 2011b; Harel et al., 2012; Troiani et al., 2012; Park et al., 2014);
- when a task requires simulation of spatial information which is not immediately visible (Galati et al., 2010) – this could also apply for rodents navigating in the dark (Cooper and Mizumori, 1999; Cooper et al., 2001; Whishaw et al., 2001; Pothuizen et al., 2008);

- during 'default mode' internally-directed thought (Raichle et al., 2001; Fox et al., 2005; Buckner et al., 2008) or mind wandering (Mason et al., 2007);
- and finally when imagining a viewpoint relative to stable room cues (Lambrey et al., 2012; Sulpizio et al., 2013).

It also provides a potential explanation for deficits seen in RSC-lesioned rodents at integrating different types of cue into coherent spatial representations (Lukoyanov and Lukoyanova, 2006; Keene and Bucci, 2008a, 2008b, 2008c; Robinson et al., 2011; Hindley et al., 2014a).

Perhaps the clearest example of the extent to which this kind of spatial imagery engages RSC comes from the use of the method of loci memory mnemonics (Maguire et al., 2003), which expressly exploits this cognitive machinery in order to optimise memory recall. This can also extend beyond visual scene representations, and RSC similarly processes haptic 'scenes' (Wolbers et al., 2011). RSC has even been implicated in auditory hallucinations where there are sounds acting as inappropriately "permanent landmarks" within a wider auditory scene (Kumar et al., 2014). The sentences experiment highlighted this potential wider extent of permanence representations, so long as they are grounded within some sort of scene setting. RSC is not, however, engaged for very similar tasks involving navigation or manipulating spatial, scene representations when they depend upon the use of table-top toys (Janzen and van Turennout, 2004; Janzen and Weststeijn, 2007; Wegman and Janzen, 2011) or objects which change location from trial to trial (Baumann et al., 2010; Wegman et al., 2014).

9.4.3 Translation

RSC lesions do not impair the ability of rats to form hippocampal allocentric representations of space, it only modifies them, causing place cell 'remapping' (Cooper and Mizumori, 2001). This is inconsistent with the proposal that RSC is necessary to mediate the 'translation' between ego- and allocentric information (Burgess et al., 2001a; Byrne et al., 2007; Vann et al., 2009). If this were the case, RSC lesions would prevent the formation of new allocentric spatial representations from egocentric inputs. Instead, allocentric processing in the MTL is only changed, not abolished, after removing RSC function. Similar modification, but not removal, of allocentric representations is brought about when rodents see an object change location; this causes landmarks to lose their

influence upon hippocampal place cell (Knierim et al., 1995; Jeffery, 1998; Jeffery and O'Keefe, 1999) and thalamic head direction cell (Knierim et al., 1995) activity.

Most, if not all, of the evidence which points toward a role for RSC in translating between spatial coordinate reference frames could alternatively be explained by the region being involved in scene construction centred upon permanent landmarks. Any translation of purely allocentric spatial representations into an egocentric frame of reference could, almost by definition, necessitate a process of scene construction. The same cannot be said for conversions in the opposite direction however (ego- to allocentric). As I outlined in Section 1.11, all sensory inputs to the body's receptors are, by their very nature, egocentric. It follows then that forming any allocentric representations from this egocentric input will require some form of translation between the two, independent of any sort of scene construction. If RSC is truly necessary for translating between different spatial information then RSC lesions would lead to an inability to form any new allocentric representations of space. However, as previously noted, this does not appear to be the case, RSC lesions only modify and do not eradicate allocentric spatial representations (Cooper and Mizumori, 2001) and there appears to be a particular impact upon the influence exerted by salient landmarks with relative sparing of self-motion cue use (Clark et al., 2010). Indeed, there is a dearth of evidence for RSC being involved in translating egocentric to allocentric information at all (I cannot find a single example). The vast majority of evidence in support of RSC 'translation' theory comes from allocentric representations being used for egocentric tasks, which likely involves an element of scene construction. In order to substantiate the idea that RSC coordinates translation between the two frames of reference, it will be important for studies to provide empirical evidence of RSC being involved in forming or altering allocentric representations from egocentric inputs.

Rather than RSC being involved in translation *per se*, I propose it is only important for 'translating' spatial information which is derived from permanent landmarks. This is consistent with the fact that RSC is more active while people make judgements about the locations of items relative to parts of buildings than small objects (Committeri et al., 2004; Lambrey et al., 2012; Sulpizio et al., 2013). Stable environmental cues are processed in most instances of episodic memory recall, navigation, scene processing or imagination of future and fictitious events. When permanent landmarks are not immediately available,

allocentric representations of space can still be formed (Knierim et al., 1995; Jeffery, 1998; Jeffery and O'Keefe, 1999), they just do not engage RSC (e.g. sentences and spatial scales experiments; Janzen and van Turennout, 2004; Janzen and Weststeijn, 2007; Baumann et al., 2010; Wegman and Janzen, 2011; Wegman et al., 2014) and are less effective (Biegler and Morris, 1993, 1996; Burgess et al., 2004).

9.4.4 The permanence hypothesis

I believe that RSC is not primarily involved in performing complex, high level computations in relation to orienting and localising landmarks or translating spatial information. Its engagement in these processes could instead reflect a much more basic, fundamental level of operation due to the fact that these processes operate upon permanent environmental cues. My experiments indicate that RSC is engaged when we view, imagine, recall or are simply exposed to permanent landmarks in any way. I propose that the RSC is crucial for identifying the most stable, reliable cues in our surroundings and that this helps optimise the dependability of neural representations of environments. Interactions with other brain regions connected with RSC, such as the HC, can then build upon this information to form more detailed, spatially coherent, spatial representations (Section 9.3). This account is closest in alignment with scene construction theory (Section 9.4.2; Hassabis and Maguire, 2007, 2009; Maguire and Mullally, 2013), but rather than merely noting its involvement in the process, here I offer an specific important functional contribution that RSC makes.

No previous theories about RSC function have considered its possible relationship with a person's spatial abilities, but I propose that the efficiency with which a person processes the permanence of landmarks forms a key part of their ability to navigate and orient within environments (Section 9.2.2). Deficits in behavioural and RSC responses to permanent landmarks could cause people to 'fall at the first hurdle' as the very basis of an environmental representation is the most stable features within it.

I will now discuss my ideas about RSC permanence processing in relation to the possible aetiology and management of the clinical conditions with which this region is commonly linked.

9.5 Clinical implications

RSC dysfunction is commonly associated with memory deficits and disorientation. As I described in Chapter 1 (Section 1.7), RSC is one of the first brain regions to show atrophy (Pengas et al., 2010; Tan et al., 2013) and metabolic pathology (Minoshima et al., 1997; Nestor et al., 2003a; Chetelat et al., 2008; Hashimoto and Nakano, 2014; Lee et al., 2014) in the earliest stages of Alzheimer's dementia and its prodromal stage, MCI. These changes in RSC are specifically associated with deficits in acquiring new spatial information (Pengas et al., 2012) and more general disorientation is a common early symptom. People with more debilitating lesions involving their RSC are often densely amnesic and display a so-called topographic disorientation, whereby they cannot derive spatial information from environmental landmarks which they can otherwise recognise (Section 1.6; Valentine et al., 1987; Obi et al., 1992; Takahashi et al., 1997; Aguirre et al., 1998; Alsaadi et al., 2000; Maguire, 2001a; Greene et al., 2006; Osawa et al., 2006; Ino et al., 2007).

Given these links between RSC dysfunction and impairments at navigation and processing spatial information, it is tempting to draw parallels between the similar relationship between RSC activity and individual differences in spatial abilities found in several of my experiments and discussed in Section 9.2.2. Differences between the good and poor navigators/learners in my experiments seemingly arose from a basic, fundamental level of processing external spatial information in RSC. Poor navigators had a diminished ability to register the permanence of the most stable landmarks, both behaviourally and in terms of their RSC responses. This could conceivably represent a less extreme version of the changes brought about by more overt RSC dysfunction. It also provides a new way to conceptualise the deficits associated with RSC lesions and Alzheimer's dementia.

The topographic disorientation produced by RSC lesions is commonly suggested to arise from an inability to extract directional information from landmarks, specifically implicating the action of head direction cells in the pathophysiology (Takahashi et al., 1997; Clark et al., 2010). I instead propose that the defective processing might arise at an earlier step than this. Aberrant permanence processing in the RSC might be getting people off to a bad start, preventing them from reliably identifying the most dependable landmarks to build more detailed spatial representations upon. This would leave the ability to recognise and identify landmarks relatively intact, as is often the case, while obstructing key

(permanence) information being available for more advanced spatial operations. Any resultant representations formed of an environment would subsequently be less reliable. This generalised chaotic processing of the surrounding environment could also explain the wider episodic memory problems associated with RSC pathology, which purely directional impairments cannot easily accommodate.

This proposal is speculative, but it offers a new perspective from which to consider and directly test the pathophysiology of RSC dysfunction. Investigating permanence processing in the context of MCI and Alzheimer's dementia could be particularly useful. The early pathological changes seen in RSC could perhaps give rise to specific deficits in a person's ability to characterise the permanence of landmarks and produce associated alterations in fMRI responses while they view them (in a similar way to that seen in the landmarks and fogworld experiments). If this were the case, then it is possible that tests could be designed to detect much sought-after early signs to assist in the prompt diagnosis of the condition, before more overt impairments become apparent.

Further experiments could also explore whether the presence of aberrant permanence processing at diagnosis might be related in some way to the likelihood or rate that people might progress from MCI to Alzheimer's disease. Studying patient populations with neurodegenerative disease presents numerous methodological challenges and trying to establish deficits which are specifically associated with Alzheimer's dementia are particularly difficult. For example, normal age-related cognitive decline might well be associated with reduced efficient processing of landmark permanence. This in itself could be instructive about spatial representations in ageing, but would make studying these processes in relation to neurodegenerative pathology more complex. Despite these methodological difficulties, investigating permanence processing in the context of Alzheimer's dementia could uncover useful new information for understanding the aetiology of the disease and potentially provide new diagnostic and prognostic markers.

RSC related permanence processing could also be considered in the context of treatment, not just diagnosis, of Alzheimer's dementia. If RSC pathology were indeed associated with specific deficits in processing landmark permanence, it would be interesting to consider whether some sort of intervention could be designed to improve outcomes, or at least slow the effects of further decline. At the end of Section 9.2.2, I outlined how, according

to my experiments, the ability of a person to learn and characterise the permanence of landmarks might be crucial in determining how well they can perform spatial tasks. Therefore, training people to better recognise and focus upon the permanence of landmarks could perhaps be used to improve both behavioural and RSC functionality more generally. This training could use simplified versions of the fogworld experiment, two-dimensional desktop tasks (similar to the spatial scales and orientation experiment learning phases) or even everyday landmarks (as in my first two experiments). This could provide a relatively simple means to investigate whether any benefits can be gained from getting people to do explicit permanence related tasks to see if any benefits can be gained in terms of function and RSC engagement. My experiments demonstrated large variation in permanence processing in young, healthy samples and so any intervention would ideally take these pre-morbid abilities into account. It would be instructive to compare any potential improvements with baseline abilities to see, for example, if a greater response rate is seen in people who were initially either good or poor navigators. However, the only reliable way to achieve this would be with a resource-intensive long-term longitudinal study following participants from before the emergence of pathology – otherwise it might be difficult to ascertain the efficiency of a person's premorbid permanence processing.

Given the specific association between responses to permanent landmarks and a person's more general navigational and spatial abilities, it could also be useful to investigate whether some form of permanence training could be used in non-patient populations. For example, could simply getting people to focus on and practise rating or learning landmark permanence bring about some improvement in their navigation or other spatial abilities? Alternatively, more intensive training on specific strategies focusing on topographical relationships between permanent items might be required. These sorts of interventions would be instructive in themselves, as they could reveal whether poor navigators may have inherent limitations which cannot be overcome, possibly caused by a less responsive RSC. Otherwise, RSC activity might only be reduced in poor navigators because they are not attending to permanent spatial cues sufficiently, which would presumably be more amenable to successful intervention. These sorts of studies could reveal valuable new insights about whether the relationship between permanence processing and more general spatial abilities reflects individual variation at a fundamental, basic level or in the cognitive strategies people adopt.

One final clinical condition which is worth consideration in the context of permanence processing is diencephalic amnesia. Nuclei in AThal have been implicated in the pathophysiology of diencephalic amnesia. Damage to the same nuclei can also cause alterations in RSC function (see Section 1.8). This has led to suggestions that disruption to the neural circuits connecting AThal and RSC could account for some of the memory deficits which are present in this condition (Garden et al., 2009; Vann and Albasser, 2009). There are very few experiments which describe functional links between the AThal and RSC in humans. It is interesting then that interactions between these two regions were associated with a person's spatial abilities in two of my experiments. Head direction cells in the anterodorsal thalamus of rats have previously been shown to be under greater influence from stable background cues than foreground objects which change their position (Zugaro et al., 2001). It would therefore be interesting to further explore this link between landmark permanence and more general spatial representations in AThal; especially given the potential clinical implications.

9.6 Limitations and future directions

Throughout the course of my PhD, I have attempted to characterise the nature of permanence representations in the RSC as comprehensively as possible. In my six experiments, I aimed to examine the processing of landmark permanence in a range of different domains, using a variety of stimuli and tasks. These all produced consistent results, but there are still numerous questions remaining which warrant further work in the future.

The primary explanation I provide for much of the RSC's involvement in a range of different cognitive tasks is that it reflects processing of permanent cues during scene construction. The sentences and spatial scales experiments provide a basis for some of the assertions I make, but I did not formally test how permanence links with more complex processes such as episodic memory recall, navigation and imagining fictitious and future events. Most of my experiments used simplified tasks, testing responses to single landmarks or basic descriptions of scenes. This was mainly to maximise experimental control over the stimuli and limit the potential impact of other confounding factors on any apparent permanence representations. However, it could now be instructive to examine the importance of permanence in the context of richer environments and scenes, more

akin to what we experience in everyday life. This will be challenging, but more formal testing of the links between scene construction and the permanence of cues involved could be highly instructive. It would be particularly interesting, for example, to determine whether constructing or navigating through a 'scene' which consists of only transient items engages RSC or not.

In Section 9.4.3 I discussed how there is limited evidence of RSC being involved in converting egocentric spatial information into an allocentric representations, as 'translation' theory would suggest. It could therefore be instructive to test the relative importance of translating or the nature of what is being translated upon RSC responses. The spatial scales experiment partially addressed this question, but it only demonstrated the importance of a landmark being permanent when converting allocentric information to imagine landmarks from an egocentric perspective. Further work could also test similar translation of information learned in an exclusively egocentric setting and tested allocentrically (e.g. learn the permanence of landmarks by exploring a large scale environment, like in the fogworld experiment, and then test map-like representations of that information). That said, it might be difficult (or even impossible) to prevent people from re-imagining landmarks from the first-person perspective they initially encountered them in when trying to recall the information using an allocentric test. If this were the case, it would perhaps demonstrate the intrinsic importance of scene construction for these types of task.

In Section 1.10.6 of Chapter 1, I described a study in which spontaneous RSC activity during an "offline" period between learning and recalling new information was linked to the accuracy of recall (Staresina et al., 2013). This presents another exciting line for further enquiry. The permanence-related responses in RSC reported in this thesis seem to reflect a basic, automatic level of processing, not requiring any conscious attention to the permanence of a landmark. It would therefore be interesting to take this a step further and explore representations of permanent and transient landmarks in "downtime" between tasks and see how this might relate to memory of the items in general, but also comparing good and poor navigators. For example, would there be more spontaneous reactivation of permanent than transient landmark representations? If so, does this differ between good and poor navigators? It would also be interesting to consider this in the context of other "offline" mental states such as during 'default mode' or sleep; the former

would be of particular relevance given that it is associated with greater RSC activation (see Section 1.10.2).

Another area for further experimentation would be to test permanence processing and its impact upon more general spatial abilities in non-human species. For example, experiments in rodents could examine the effects of highly specific RSC lesions upon how landmarks are processed, and explicitly target the role played by permanence. In rodents it would also possible to investigate any potential subtle differences between RSC subregions.

It would be interesting also to attempt to develop ways to study different RSC subregions in humans. One approach would be to use high resolution and/or high field MRI scanning to establish morphologically distinct areas, although this would be a big challenge. Alternatively, RSC subregions could be defined based upon functional and structural connectivity with other brain areas, but again it may be difficult to achieve the resolution necessary to subdivide the relatively small human RSC.

Finally, as I discussed in Section 9.5, it would be useful to examine how RSC processing of permanence translates into patient populations both diagnostically and considering potential rehabilitative approaches. Additionally, further work could establish whether or not some form of permanence "training" could be used to improve people's navigational ability more generally.

9.7 Summary

Previous accounts of RSC function have suggested the region performs relatively complex spatial computations to translate between different types of spatial representation or to orientate within environments. The results of the experiments presented in this thesis instead suggest RSC is involved at a more basic, fundamental level; processing permanent landmarks whenever they are viewed, recalled, imagined or experienced in any way. More detailed spatial representations could then be formed through interactions with other brain regions connected with the RSC. The HC appears important for processing more detailed spatial relationships between environmental cues, whereas the POS seems to be involved in localising and orienting, but only with permanent landmarks. PHC was more

sensitive to the spatial aspects of a scene and the sense of space evoked by landmarks. Processing of permanent landmarks in RSC is also linked to a person's spatial abilities, in conjunction with the AThal.

At the start of this thesis, I referred to the fact that in the year before the start of my PhD there were more than 93 PubMed listed papers mentioning the "hippocampus" for every one mentioning "retrosplenial". At the time of writing, mid-way through 2014, this figure is just under 59. It is clear then that there is a growing interest in trying to understand more about the RSC. To achieve this, the work in this thesis suggests that in addition to examining responses within RSC itself, it will be just as important to consider its interactions with the much wider network of brain regions with which it shares dense connectivity. This will hopefully uncover significant new insights into a number of crucial cognitive functions which depend upon RSC.

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