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Review Article

Spatial memory and navigation in ageing: A systematic review of MRI and fMRI studies in healthy participants

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Highlights

- A marked deficit in allocentric spatial processing in older adults compared to younger controls
- Trend towards egocentric strategies in older adults compared to younger controls
- Majority of studies reported association with volumetric and functional changes in hippocampus

Abstract

Aim: Spatial deficits are widely observed in normal ageing and early Alzheimer's disease. This review systematically examined neuroimaging evidence for structural and functional

differences in the hippocampus (HC) associated with non-pathological age-related changes in allocentric spatial abilities.

Methods: Databases were searched to identify peer-reviewed studies on allocentric spatial processing in normal ageing including MRI or fMRI data. 15 eligible studies were reviewed after applying exclusion criteria and quality assessment.

Results: There was a marked deficit in allocentric spatial processing and trend towards egocentric strategies in older adults when compared to young controls or across the lifespan, associated in the majority of studies with HC volumetric changes, metabolic or microstructural indicators, and underactivity. A few studies reported no significant correlations.

Conclusion: Findings confirm literature supporting an age-related allocentric spatial processing deficit and a shift towards egocentric strategies. A majority of studies implicated HC atrophy, microstructural/metabolic alterations or functional changes in age-related allocentric spatial impairment. More sensitive imaging techniques and ecologically valid spatial tasks are needed to detect subtle changes in the HC and brain's navigational network.

Keywords: neuroimaging; ageing; allocentric spatial processing; spatial memory; spatial navigation

Introduction

Increasingly, countries across the world are dealing with ageing populations, with a quarter of Europe over 60 and the rest of the world except Africa expected to reach that proportion by 2050 – an estimated 2.1 billion people (United Nations Department of Economic and Social Affairs, 2017). This is already resulting in shifting demands in social and medical care to reflect the needs of an older populace, and in the behavioural and neurosciences, there is growing research into the normal and pathological changes in cognition that accompany

ageing, especially given the profound impact of age-related cognitive decline on the health and quality of life for individuals, families and societies (Di Carlo et al., 2000).

Memory decline, although popularly associated with diagnosing dementia (McKhann et al., 1984), has also long been observed in normative ageing (Craik, 1994). The medial temporal lobe (MTL), particularly the hippocampus (HC), play a key role in both episodic memory and the spatial memory and navigational system in humans and other animals (Burgess, Maguire, & O'Keefe, 2002) and is one of the regions most sensitive to the effects of ageing (Lister & Barnes, 2009; Raz et al., 2005). Episodic memory, or the recollection of specific, autobiographical events as opposed to semantic or procedural memory, experiences decline with age (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Nyberg, Backman, Erngrund, Olofsson, & Nilsson, 1996) that is linked to reduced MTL and HC functioning (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2005). Since the HC is also important for spatial memory and navigation, it is not surprising that this capacity deteriorates alongside episodic memory and can potentially serve as a more direct and quantifiable way of assessing HC integrity and episodic memory functioning in healthy older adults compared to traditional cognitive tests or assessments of episodic memory.

Correspondingly, there is a self-reported and observed deterioration in navigational abilities in healthy older adults (P. C. Burns, 1999; Moffat, 2009) which has been garnering interest in a field formerly dominated by psychometric testing and measures such as visuospatial memory and mental rotation, which are not directly translatable to real-life behaviours such as spatial memory and wayfinding (Hegarty, Montello, Richardson, Ishikawa, & Lovelace, 2005). Although there have been early studies using real-world paradigms (Evans, Brennan, Skorpanich, & Held, 1984; Wilkniss, Jones, Korol, Gold, & Manning, 1997), the advent of brain imaging technology and the ability to realistically create virtual environments to assess spatial memory and navigation has led to many more studies investigating this ability in healthy young adults, older adults as well as Alzheimer's Disease (AD) patients.

Furthermore, spatial memory and navigation has been proposed as an early warning sign of AD due to the core role HC atrophy is believed to play in the condition (Bishop, Lu, & Yankner, 2010; Gazova et al., 2012; Monacelli, Cushman, Kavcic, & Duffy, 2003; West,

Coleman, Flood, & Troncoso, 1994). Relevantly, people with Mild Cognitive Impairment (MCI), a category with heightened risk of developing AD (Petersen, 2004), display spatial deficits intermediate between healthy older adults and those with early AD (Serino, Cipresso, Morganti, & Riva, 2014).

Declines in spatial memory and navigation occur during the course of normal ageing due to the impact of age on the hippocampus and can serve as an easily quantifiable estimate of HC functioning, as well as having relevance for conditions like Alzheimer's Disease.

1.1 Spatial reference frames: egocentric, allocentric, cognitive maps

Spatial orientation and navigation is usually conceptualised in terms of two different reference frames – egocentric and allocentric. Egocentric processing is self-to-object and habitual, based on encoding locations and objects in relation to the individual, and retains the same perspective as the initial representation. For example, memorising a certain route by the sequence of left-right turns and where landmarks appear relative to oneself. This form of representation is independent of any higher-level model of the environment. Meanwhile, allocentric processing is object-to-object and based on encoding relationships of objects and environmental characteristics to each other. The related concept of a “cognitive map” (Tolman, 1948) refers to the underlying allocentric representation of the environment that is perspective-independent, allowing more flexible navigation in novel environments. Through exploration, an animal builds a cognitive map of the spatial relationships between different proximal, distal landmarks and any boundaries in a local environment, while also tracking their own location in relation through sensory feedback. The map allows them to navigate efficiently to a certain goal from anywhere in the space through their global knowledge of the interrelationships between different features of the environment. These two frames are sometimes referred to variably as route or survey, non-spatial or spatial; however for consistency this review has kept to the terms egocentric and allocentric. There is considerable evidence suggesting that a deficit in utilising an allocentric reference frame may contribute to the spatial impairment found in older adults and AD patients (Colombo et al., 2017; Gazova et al., 2012; Serino et al., 2014).

In many spatial memory and navigational tasks it is possible to use either an allocentric or egocentric strategy, and individual differences exist in preference and ability (Bohbot, Gupta, Banner, & Dahmani, 2011; Marchette, Bakker, & Shelton, 2011). Indeed, “pure” allocentric or egocentric tasks may be near impossible to design (Ekstrom, Arnold, & Iaria, 2014). However tasks in which performance depends on one representation or the other can shed light on the neural dependencies of spatial memory and navigation in participants and tease out preference for or impairments in either type of processing that occur with ageing. A classic task of spatial memory and hippocampal function, the Morris Water Maze/Task (MWT) (Morris, 1984), was first devised for rodents. Animals had to learn the location of a hidden platform in a circular pool surrounded by distal cues. Allocentric processing is suggested by successful recall of the platform location from novel starting locations, as rodents would have to remember the platform position in relation to the distal cues and work out another path from their new location in the pool. However, researchers have also raised the possibility of non-allocentric solutions due to the MWT’s small-scale setting and issues with generalising to larger environments, which place different navigational demands upon the individual (Ekstrom et al, 2014; Wolbers & Wiener, 2014).

Spatial navigation can utilise an egocentric or allocentric reference frame. Egocentric processing encodes directions and movements in relation to the self. Allocentric navigation depends on a ‘cognitive map’ – a perspective-independent neural representation of proximal, distal landmarks and boundaries of the environment in relation to each other.

1.2 Neural correlates of spatial memory and navigation

The neural correlates of spatial navigation have been extensively studied in animals and humans alike through lesion, cell recordings and behavioural studies. Allocentric navigation is often associated with the HC (Packard & McGaugh, 1996) – a region closely linked to the idea of a cognitive map (O’Keefe & Nadel, 1978), although findings of allocentric processing despite HC damage suggest a non-aggregate network centred on the MTL (Ekstrom et al., 2014) with areas including the parahippocampal (PHC) and retrosplenial (RSC) cortices performing essential functions, such as translating between allocentric and egocentric frames of reference (Byrne, Becker, & Burgess, 2007; Chrastil, 2012), as well as prefrontal

(PFC) and parietal cortices, involved in executive function and route planning in complex scenarios.

The discoveries of a large array of spatially responsive neurons in the HC and MTL have bolstered their connection with allocentric navigation and cognitive mapping, and focused substantial spatial navigation research on these regions. “Place cells” in the HC (Ekstrom et al., 2003; O’Keefe, 1976) fire selectively at specific locations (place fields) in an environment independent of head orientation, and can remain stable for weeks or “remap” if the environment changes (Fyhn, Hafting, Treves, Moser, & Moser, 2007). Grid cells, mainly found in the medial entorhinal cortex (MEC), pre- and parasubiculum (Hafting, Fyhn, Molden, Moser, & Moser, 2005; Jacobs et al., 2013), fire repeatedly across an environment to form a grid-like pattern of equilateral triangles. Border cells are sensitive to the distance and direction of boundaries and are found in the EC, subiculum, pre- and parasubiculum (Lever, Burton, Jeewajee, O’Keefe, & Burgess, 2009; Solstad, Boccara, Kropff, Moser, & Moser, 2008). Other cells underlying the supporting function of *path integration* (estimating one’s location while navigating based on self-motion information) include head direction cells in the dorsal presubiculum (Taube, 2007) and speed cells in the HC and MEC (Kropff, Carmichael, Moser, & Moser, 2015), which depend on environmental cues to correct calculation errors that accumulate over time.

A recent fMRI meta-analysis (Boccia, Nemmi, & Guariglia, 2014) identified a network of active regions in both egocentric and allocentric navigation including the HC, PHC, RSC, caudate nucleus (CN), PFC and parietal cortex, with extended activation in the right superior occipital gyrus, angular gyrus and precuneus for egocentric processing, suggesting that their neural correlates may overlap and interact in complex ways, despite the conventional conceptualisation of HC/allocentric and striatum/egocentric (Goodroe, Starnes, & Brown, 2018). Recent theories about the HC emphasise its role in spatiotemporal binding and more general relational processing (Eichenbaum & Cohen, 2014; Zhang & Ekstrom, 2013).

Spatial navigation involves a large network including the HC, PHC, RSC, PFC, parietal cortex and may overlap for allocentric and egocentric processing. Specialised spatial cells in the HC and MTL, such as 'place cells', 'grid cells' and 'boundary vector cells', may support allocentric navigation, construction of a cognitive map of the environment as well as contextualising navigational experiences across time.

1.3 *Pattern of changes in memory with ageing*

Ageing impacts different types of memory disparately, with working, associative, contextual and spatial memory impaired in older adults (Craik, 1994). This pattern of deficits reflect both general trends such as cognitive slowing and neurobiological changes in the regions of the brain that support respective types of memory, like the MTL and frontal-striatal systems (Buckner, 2004). The deterioration in spatial memory and navigational abilities in older adults has been well-characterised in many studies, the main observations being a decline in allocentric processing, a preference and greater reliance on egocentric strategies, which are relatively preserved (Colombo et al., 2017), and impairments in switching between frames of reference (Harris & Wolbers, 2014) within the context of wider difficulties in set switching associated with the ageing PFC (Meiran, Gotler, & Perlman, 2001).

While more basic visual functions such as distance and object perception are maintained (Lester, Moffat, Wiener, Barnes, & Wolbers, 2017), older adults show impairments in vestibular processing, perception of self-motion and pronounced deficits in path integration (Harris & Wolbers, 2012; Mahmood, Adamo, Briceno, & Moffat, 2009). Along with declines in allocentric spatial working memory linked to the medial PFC (Lester et al., 2017), these disproportionately affect the components of allocentric processing and contribute to poorer spatial navigation performance. In addition, older adults experience greater difficulty in encoding and retrieval of spatial information in long term memory in large-scale environments requiring exploration to fully comprehend (Head & Isom, 2010; Lövdén et al., 2012), prefer proximal to distal cues or boundaries (Moffat & Resnick, 2002; Schuck, Doeller, Polk, Lindenberger, & Li, 2015), and are slower to learn and encode a cognitive map (Daugherty et al., 2015; Moffat & Resnick, 2002). The underlying cellular mechanisms are well elucidated in numerous animal studies (Lester et al., 2017).

Besides from global memory and cognitive decline, ageing specifically affects allocentric processing and the ability to switch between reference frames. Older adults show impairment in several putative components of allocentric processing such as path integration and long-term memory of spatial information.

1.4 Structural and functional changes in the hippocampus with ageing

Although the relationship between hippocampal volume and poorer memory in ageing was unclear in a large meta-analysis (Van Petten, 2004), more recent studies have reported shrinkage of the HC, entorhinal cortex (EC) and PFC with ageing, particularly from middle age onwards (Du et al., 2006; Raz & Rodrigue, 2006) and associations to memory performance were found longitudinally (Rodrigue & Raz, 2004). Besides from the MTL and PFC, other areas in the brain's 'navigational network' such as the caudate nucleus also display significant age-related deterioration (Betts, Acosta-Cabronero, Cardenas-Blanco, Nestor, & Düzel, 2016; Raz et al., 2003). Furthermore, the studies in the meta-analysis mostly utilised verbal memory tasks when declines in episodic and spatial memory are more marked with ageing (Gazova et al., 2012; Hedden & Gabrieli, 2004). Changes to prefrontal functions such as working memory, functional connectivity, long-term potentiation (LTP – the process believed to underlie learning in hippocampal pyramidal cells) in the HC and place cell firing stability may all contribute to the decline in performance of older individuals on allocentric tasks (Lester et al., 2017). A decrease in pattern discrimination and speed of cognitive mapping (i.e. spatial learning) in place cells have been reported in aged rats (Hok, Chah, Reilly, & O'Mara, 2012; Schimanski, Lipa, & Barnes, 2013). Risk and protective factors such as hypertension (Korf, White, Scheltens, & Launer, 2004), cognitive reserve (Buckner, 2004; Tucker & Stern, 2011) and genetic variation (Beaudet et al., 2015) can greatly affect hippocampal integrity and functioning and subsequently, episodic, spatial memory and navigation with ageing.

The MTL, PFC and other regions involved in spatial navigation experience deterioration with ageing, which has been linked to memory decline. Cell atrophy, changes in functional connectivity, decreased efficiency of LTP, poorer pattern discrimination and speed of cognitive mapping all contribute to lower HC functioning as do risk and protective factors.

1.5 *Review rationale and research questions*

There have been several reviews of the impact of ageing on the healthy navigational system (Colombo et al., 2017; Klencklen, Després, & Dufour, 2012; Moffat, 2009). Most recently, Lester et al. (2017) integrated rodent, primate and human data to provide a broad overview of how the navigational system ages across species, examining in detail emerging evidence for underlying cellular mechanisms of age-related changes. In contrast to the theory-driven approach of Lester and colleagues, Colombo et al. (2017) focused on human behavioural data in a systematic review of studies employing allocentric and egocentric spatial paradigms with healthy young and elderly participants, while Boccia et al. (2014) performed a meta-analysis of 24 fMRI studies of healthy young adults navigating novel and familiar environments using egocentric or allocentric strategies.

The reviews mentioned above have defined their remits and approached the evidence from different angles, enriching our understanding of the neural/cellular mechanisms and changes in spatial navigation as the brain ages. However, so far there has not been a systematic review of studies exclusively on spatial memory and navigation in healthy older adults that also examines imaging data. Such a review can further improve our knowledge of how morphological and functional changes in the HC, MTL and other regions occurring with age map onto the widely observed age-related differences in humans, particularly the decline in tasks reliant on allocentric processing. Performing a methodical, systematic search for relevant studies and considering both cross-sectional and longitudinal studies can allow us to track and correlate age-related neural and behavioural changes in spatial memory and navigation in greater detail.

Thus, the current review aims to fill this gap in the existing literature to provide an overview of the MRI and fMRI studies investigating spatial memory and navigation in healthy older

adults and longitudinal studies tracking individuals across time, and summarise the current evidence on neural correlates of age-associated spatial and allocentric deficits. Lastly, it discusses the findings in context of our latest understanding of the ageing navigational system, strengths and limitations of the review and included studies, and suggests directions for future research.

This review's main objectives are:

1. To examine the characteristics of allocentric and egocentric navigation in healthy older adults and age-related differences to younger adults;
2. To review the structural imaging findings on neural changes with ageing, focusing on HC and MTL areas, and the structural and functional imaging evidence on neural correlates of spatial processing in healthy older and younger adults.

Methods

A systematic review was conducted on existing peer-reviewed literature to investigate our current understanding of spatial memory and navigational changes in normative ageing and their structural and functional neural correlates. The PRISMA guidelines for systematic reviews (Moher, Liberati, Tetzlaff, & Altman, 2009) were followed for this paper.

2.1 Inclusion criteria

The inclusion criteria for the review were as follows: (1) the main experimental paradigm assessed spatial navigation and/or memory with regard to allocentric and egocentric referencing, (2) the sample included healthy elderly participants with or without younger control groups, (3) the study reported structural magnetic resonance imaging (MRI) or functional magnetic resonance imaging (fMRI) data for the elderly participants, (4) the study was a full-length article published in a peer-reviewed journal, (5) in English with full text available. As this review aims to examine the neural correlates of changes in spatial memory and navigation accompanying normal ageing, studies comparing healthy elderly to pathological samples or focusing on participants with AD and mild cognitive impairment (MCI) were excluded. Studies involving interventions targeted at spatial navigation and/or

memory were only included if they reported baseline measurements fulfilling the inclusion criteria.

Studies that met the inclusion criteria then underwent formal quality assessment using an appropriate critical appraisal tool. Studies with a rating above 55% were included in the systematic review.

2.2 Search methodology

To identify qualifying studies, a database search was conducted in November 2017. PsycInfo, Ovid MEDLINE and Embase databases were searched for entries containing the following terms in all fields: (“allocentric” or “spatial memory” or “third person perspective” or “egocentric” or “spatial orientation (perception)” or “spatial navigation”) AND (“aging” or “geriatrics” or “gerontology” or “geropsychology” or “human development” or “older adult*” or “elder*” or “age differences”). The detailed search strategy is presented in **Table 1**.

INSERT TABLE 1 HERE

Search terms were purposefully inclusive so that studies employing less common terminology would be found as well. Terms referring to neuroimaging, MRI or fMRI were not included in the database search and studies were assessed for criterion 3 during the screening stage instead, as key papers fulfilling inclusion criteria identified whilst preparing for the systematic review used variable terms to refer to neuroimaging and/or made little mention of imaging data in the title and keywords.

Results

3.1 Search results

The database search produced 4069 articles, which was reduced to 2087 after limiting results to English articles and human studies (**Figure 1**). After removing duplicates 1532 articles remained. A further 17 articles meeting search term criteria were identified in the references section and citation searches (using Google Scholar) of recent reviews and key papers (Beaudet et al., 2015; Colombo et al., 2017; Driscoll et al., 2003; Lester et al., 2017).

The titles and abstracts of these 1549 articles were screened and 20 articles were considered to have met the inclusion criteria. The full-text versions were then assessed to ascertain their eligibility, with five articles being excluded after this step (reasons given in **Figure 1**). The excluded articles are listed in **Appendix 1**. The remaining 15 articles were subject to the formal quality assessment.

INSERT FIGURE 1 HERE

3.2 *Quality assessment*

There are a variety of tools available to researchers for assessing randomised controlled trials or intervention studies (Downs & Black, 1998; Higgins & Green, 2008), however fewer are designed to evaluate experimental or quantitative studies with non-randomised groups or correlational designs, such as those examined in this review. The “Qualsyst” tool (Kmet, Lee, & Cook, 2004) was developed for health science researchers to critically appraise the quality, based on the construct of internal study validity, of quantitative and qualitative studies using a standardised checklist and produces an overall quality score out of 100% for each study. It was selected for this systematic review because it is a general appraisal tool suitable for assessing a wide range of different study designs, as identified papers included cross-sectional as well as longitudinal designs. The authors suggest cut-off points ranging from 55% to 75% depending on the constraints of the systematic review. One rater rated all the papers in this review according to the Qualsyst Manual, which includes descriptions of studies under Yes, Partial and No categories for each checklist item. Although the manual descriptions were detailed, a certain degree of subjective judgment was introduced as the checklist included items such as “Conclusion supported by results?” As the quality scores of the studies ranged from 73-86%, and considering the low number meeting inclusion criteria, all studies were included in the systematic review (**Table 2**). Weaknesses in studies with ‘Medium’ quality (scores <75%) and caveats were mentioned in the Discussion, however given the narrow range, quality ratings could not add significantly to the critical analysis. Detailed scores for the assessed studies are presented in **Appendix 2**.

INSERT TABLE 2 HERE

The 15 studies included 10 studies reporting structural MRI and neurophysiological data (iron accumulation, NAA/Cre levels) obtained with separate imaging, four studies reporting fMRI data obtained from scanning during the experiment, and one study with both MRI and fMRI data (Antonova et al., 2009). Although 'egocentric' was included in the search strategy, studies predominantly focused on investigating allocentric processing in ageing with spatial memory or navigational paradigms.

3.3 *Summary tables of reviewed studies*

Many of the reviewed papers originated from several key research groups, with the radial maze studies led by Bohbot at McGill University, consisting of three studies (Konishi et al., 2013; Konishi, McKenzie, Etchamendy, Roy, & Bohbot, 2017; Konishi & Bohbot, 2013), and the Morris Water Task studies driven by Moffat and Resnick or Raz (for path complexity) at Wayne State University, consisting of two (Moffat, Elkins, & Resnick, 2006; Moffat, Kennedy, Rodrigue, & Raz, 2007) and three studies (Daugherty et al., 2015; Daugherty, Bender, Yuan, & Raz, 2016; Daugherty & Raz, 2017) respectively. Details of the studies and the main findings are presented, separately for MRI and fMRI, in **Tables 3a** and **3b**. The study with both MRI and fMRI data (Antonova et al., 2009) has been included in both tables.

INSERT TABLE 3A AND B HERE

<u>Glossary</u>	
OA: Older adults	YA: Younger adults
HC: Hippocampus	PHG/PHC: Parahippocampal gyrus
EC: Entorhinal cortex	CN: Caudate nucleus
CB: Cerebellum	LPFC: Lateral prefrontal cortex
RSC: Retrosplenial cortex	ACC: Anterior cingulate cortex
OFC: Orbitofrontal cortex	AMG: Amygdala

3.4 *Experimental designs of structural MRI studies*

Eleven studies included structural MRI (sMRI) data on participants, and four studies included other measurements such as magnetic resonance spectroscopy imaging (MRSI), diffusor tensor imaging (DTI) and R2* relaxometry. Eight of the studies had cross-sectional samples while three had intervention or longitudinal data, with one of the longitudinal studies being a follow up (FU) of a large sample from a cross-sectional study two years later (Daugherty et

al., 2015, 2016). Six studies recruited younger controls for comparison to an older adult group and five of those also had imaging data for the younger participants, while three studies had samples with a wide age range and estimated the influence of age in later analyses. Two studies only looked at neural correlates of spatial performance in older adults.

Seven studies (Antonova et al., 2009; Daugherty et al., 2015, 2016; Daugherty & Raz, 2017; Driscoll et al., 2003; Korthauer et al., 2016; Moffat et al., 2007) used virtual reality analogues, presented on computer screens and controlled by keyboard or joystick, of the Morris Water Task (vMWT), a test of spatial memory. They mainly investigated allocentric processing through randomised start points, although individual studies focused on examining different outcome measures. The task starts with a training phase where participants explored and learnt the position of a hidden platform within a circular pool. Distal cues that could be used to encode the platform position allocentrically were located in the larger room enclosing the pool, and once participants located the platform, they were notified of success through a tone and/or the platform appearing. Participants' starting positions and orientations were randomised to discourage egocentric strategies, and there was a time limit imposed on trials. The protocols included probe trials where the platform was removed and participants' search paths were recorded, and some studies had control conditions where the platform was visible.

The four remaining sMRI studies employed a dual-solution navigation task – a 12-armed radial maze (Concurrent Spatial Discrimination Learning Task, CSDLT), whose training phase can either be egocentrically or allocentrically encoded, however distinguishes between the two strategies using probe trials (Konishi & Bohbot, 2013; Konishi et al., 2017), or spatial navigation tasks in complex virtual environments with multiple local and distal landmarks such as zoos (Lövdén et al., 2012), towns (Konishi et al., 2017) or interconnected rooms (Head & Isom, 2010). In the wayfinding (allocentric) conditions, participants were allowed to freely explore the spaces, guided by the experimenters to ensure exposure to all landmarks (Head & Isom, 2010; Konishi et al., 2017), or were required to navigate through the entire environment to search for cued stimuli (Lövdén et al., 2012). The main outcome measures were flexible shortest-route navigation from any landmark to another, and

accuracy in navigating to cued landmarks, which depend on allocentric processing, i.e. the effective formation and maintenance of a cognitive map. Head and Isom (2010) employed route learning as a control condition while the other two studies did not have specific controls.

3.5 Overview of structural MRI findings

3.5.1 Age-related behavioural indicators of differences in allocentric processing

All nine studies comparing spatial task performance between younger adults, usually in their 20s-30s, and older adults (Antonova et al., 2009; Driscoll et al., 2003; Head & Isom, 2010; Korthauer et al., 2016; Lövdén et al., 2012; Moffat et al., 2007) or comprising of samples with a large age range (Daugherty et al., 2015, 2016; Daugherty & Raz, 2017) found pronounced age-related deficits in performance, an outcome that confirms the consensus in wider literature (Colombo et al., 2017). Generally speaking, older adults (OA) tend to travel more circuitous routes, spend more time searching, and be less accurate in recalling the trained location in vMWT, and when required to plan a novel route between two landmarks, deviate more from the optimal distance, as well as successfully locating the cued landmarks less. Three studies from the same researchers (Daugherty et al., 2015, 2016; Daugherty & Raz, 2017) highlighted the additional explanatory power of path complexity, a novel vMWT measure independent from path length and search time, that is quantified by fractal dimensionality, already used in studies of ecological animal behaviour (Gautestad, 2011).

Studies that recruited only OA or those of middle age and above had mixed findings of the effect of age within this group, with three out of four studies reporting null results – two studies that examined the relationship between age and CSDLT performance in OA samples, largely in their 60s, did not find a significant effect of age on performance (Konishi & Bohbot, 2013; Konishi et al., 2017), and neither did a study looking at a subset of participants stratified into middle-aged (40-59 years old) and OA (60-78 years old) find any age-related differences in performance on the vMWT (Korthauer et al., 2016), suggesting that the commonly found significant differences between younger adults (YA) and OA may already be

somewhat established in middle age. In contrast, in a sample of OA aged 55-80 years old in Konishi et al. (2017) there was a significant effect of age on performance on a wayfinding task set in a virtual town, particularly in the distance travelled in excess of optimal routes between two landmarks, and to a lesser degree the accuracy of locating cued landmarks. It is likely that the wayfinding task is more cognitively challenging in comparison to the vMWT and CSDLT, where only one location or choice in a smaller space has to be encoded at one time and there is less demand on abilities such as working memory and executive function, important for encoding and recall of multiple objects scattered in a large-scale space as well as route planning involving knowledge of the possible paths in between. However, it is also important to avoid over-extrapolating from the findings of only three studies and the positive result of one particular study.

The three studies containing longitudinal data reported largely negative results of decline in allocentric processing across time. The interventional study that tested participants at baseline, after 4 months of training on an allocentric “virtual zoo” task, and 4 months post-training (Lövdén et al., 2012) reported consistent marginal improvement in both the YA and OA control walking-only groups that suggested a test-retest effect. However, it is difficult to say whether the short study window (8 months) limited any meaningful findings about deterioration with age. The two longitudinal studies with longer FU periods of two years (Daugherty & Raz, 2017) and 8 years (Korthauer et al., 2016), both employing the vMWT, presented no clear evidence that ageing negatively affects performance on spatial tasks. The first study reported inconsistent intra-individual reliability of vMWT across time and had mixed longitudinal findings: vMWT learning rate and absolute magnitude of improvement declined while reduction in path complexity improved at FU. Lastly, Korthauer et al. (2016) did not find any difference in vMWT performance at FU after 8 years. It should be noted that both studies had samples with a wide age range (baseline age ranges 18-77 and 30-83) which may have occluded any decline in the older participants in overall analyses of the main effect of age, as well as experiencing high dropout rates of about 40%, which the first study handled through statistical estimation of the missing data and the second through controlling for significant difference factors in the regression analyses. There is a clear need for more longitudinal studies of allocentric processing tracking individuals as they grow older,

and minimising participant dropout, in order to elucidate the consistently significant age differences in spatial navigation that has been observed in cross-sectional samples.

Consistent with the literature, there is a pronounced deficit in allocentric processing when comparing young and older adults or across the lifespan. Studies with middle-aged to older adults had mixed findings, with one of four reporting an influence of age in that population. The three longitudinal studies did not find deterioration in performance across time.

3.5.2 Age-related differences in HC and other regional volumes and microstructure

Findings presented a mixed picture of cross-sectional age-related differences in regional volumes of the HC and surrounding areas, with five studies supporting cross-sectional and longitudinal age differences in HC and surrounding regional volumes. Significant cross-sectional age differences were found in bilateral, left, right and posterior HC volumes (Driscoll et al., 2003), total HC volume (Moffat et al., 2007), while age correlated with right HC volume (Konishi et al., 2017) and with smaller HC subfield and EC volumes (Daugherty et al., 2016). Four studies did not report simple comparisons or correlations of regional volumes or biochemistry with age (Daugherty et al., 2015; Head & Isom, 2010; Konishi & Bohbot, 2013; Korthauer et al., 2016) while two studies with only male participants did not find differences in cross-sectional HC volumes or NAA/Cr between YA or middle aged and OA (Antonova et al., 2009; Lövdén et al., 2012). The literature indicates high individual variability in the volume of HC and surrounding regions (HC/PHG) in OA (Van Petten, 2004), as well as many influencing factors on HC/PHC volume such as genetics, health conditions and fitness (Persson et al., 2014; Raz et al., 2005; Raz & Rodrigue, 2006) that may lead to mixed results due to different inclusion criteria, head size normalisation methods and sample heterogeneity. The two studies showing no HC atrophy in males run contrary to a meta-analysis suggesting more age-associated decline in men (Fraser, Shaw & Cherbuin, 2015). It is hard to conclude whether this is a real or random effect given only two studies and contradiction with existing literature, since gender effects of HC atrophy in healthy ageing have not been extensively investigated.

The two studies with longitudinal structural MRI data both found significant differences in HC volume across time. Lövdén et al. (2012) observed declines in left and right HC volumes in the control group consistent with previous longitudinal studies while the intervention group displayed stable hippocampal volumes post-training and 4 months after. Daugherty & Raz (2017) reported significant shrinkage in the HC, PHG as well as CN and CB, but not LPFC, after two years consistent with longitudinal studies, although again there was significant missing MRI data (72/213 and 49/131 at baseline and FU) that was estimated statistically.

Two studies (Driscoll et al., 2003; Lövdén et al., 2012) including measurements of HC NAA/Cre and DTI reflecting metabolic or microstructural alterations supported age-related differences (Daugherty et al. (2017) and Korthauer et al. (2016) did not report direct comparisons), suggesting that more subtle changes in hippocampal synaptic plasticity, neurotransmission, and LTP that are known to affect functions such as cognitive mapping in animals (Lester et al., 2017) may likely contribute to age-related changes in humans as well.

Several studies including other regions of interest (ROI) offered evidence for age differences in caudate nucleus (Daugherty & Raz, 2017; Konishi et al., 2017; Moffat et al., 2007), cerebellar (Antonova et al., 2009; Daugherty & Raz, 2017; Moffat et al., 2007) and prefrontal cortex volumes (Antonova et al., 2009; Moffat et al., 2007), areas that have been implicated in allocentric as well as egocentric or sequence-based navigation (Babayan et al., 2017; Ferbinteanu, 2016; Fouquet et al., 2013).

Five out of 11 studies reported significant age differences in HC volume, metabolic or microstructural indicators, while the rest did not directly compare regional volumes or found no differences. The two longitudinal studies reported shrinkage in line with previous literature. Age differences in CN, CB, PFC were also reported by studies that included other ROI.

3.5.3 *Neural correlates of allocentric spatial memory and navigation in ageing*

All studies examined brain-behaviour correlations in an attempt to characterise the neural (volumetric/metabolic) correlates of allocentric spatial memory and navigation, with the majority of studies finding significant associations between task performance and

hippocampal and parahippocampal areas.

Eight studies reported mixed or positive findings on hippocampal associations with allocentric processing. Driscoll et al. (2003) reported that HC NAA/Cr, but not volume, accounted for a significant amount of variance in vMWT performance, while HC volume, NAA/Cr and age all accounted for significant variance in performance on a non-spatial HC-dependent task. Head and Isom (2010) found a significant age-related impairment in wayfinding (allocentric condition) on a virtual maze task, with HC volume associated with better wayfinding performance and CN volume with route learning (egocentric condition) in the subset of OA scanned; however between-association differences were non-significant. Building on a previous YA study that found correlations between allocentric strategies with HC volume and egocentric strategies with CN volume in CSDLT (Bohbot, Lerch, Thorndyck, Iaria, & Zijdenbos, 2007), Konishi and Bohbot (2013) investigated neural correlates of spontaneous strategy use in an OA sample and found a correlation between right HC volume and allocentric strategy use, but not between CN volume and egocentric strategy use. In a large OA sample, Konishi et al. (2017) found a negative correlation between age, wayfinding ability and HC volume, but again no associations between CN volume and egocentric strategies. Higher right HC volume was correlated with younger age. Wayfinding task performance (allocentric processing) was positively correlated with right, left and total HC volume. CSDLT probe trial performance correlated with left and total HC volume. Neither task correlated with total cerebral or CN volume.

Eight out of 11 structural MRI studies reported mixed or positive findings. Three studies reported significant associations between HC volume and allocentric spatial ability (vMWT performance, wayfinding, radial maze) and one study found an association only with HC metabolism. Little evidence supported the relationship between egocentric processing and CN volume.

Daugherty et al. (2015) demonstrated the additional explanatory power of vMWT path complexity (estimated by fractal dimensionality) as change on this measure significantly correlated with hippocampal areas, while path length did not. HC volume was positively associated with smaller vMWT trial 1 path complexity, shorter search time, and larger path

complexity change across trials, while PHG volume also positively correlated with path complexity change. Greater search time was associated with smaller CB volumes.

Daugherty et al. (2016) examined the relationship between age, HC subfields CA1-2, EC, CA3-dentate gyrus volumes, and vMWT search path length and path complexity, and found that regional volumes were not associated with average path length, complexity, first trial performance or absolute improvement. Independent of age, larger subiculum and EC volumes correlated and trended respectively with greater reduction in path complexity, while CA1-2 volumes correlated with greater reduction in path length but not complexity. In the two year FU of Daugherty et al. (2015), Daugherty and Raz (2017) found that vMWT learning rate and performance declined across time but path complexity improved quicker. Advanced age, higher pulse pressure, smaller CB and CN volumes and greater CN iron were associated with less efficient search paths while path complexity improvement was predicted by lower HC baseline iron and larger PHG volumes. Korthauer et al. (2016) found that total vMWT latency was negatively associated with grey matter volume in right HC, left and right thalamus, right medial OFC, while distance was negatively associated with right HC volume. In middle aged subjects, total latency was negatively correlated with right HC while in OA it correlated with right medial OFC. Total latency negatively correlated with fractional anisotropy in the left and right uncinate fasciculus after controlling for age and speed.

Three studies from the same research group investigated vMWT path complexity (fractal dimensionality) and variously reported that its reduction was associated with HC, PHG, EC and subiculum volumes, while only HC iron and PHG volume predicted path complexity change longitudinally. One of the three found associations between HC grey matter or total volume and vMWT latency and path length, although HC's role is unclear in OA.

Three studies reported no significant associations between hippocampal regions and spatial task performance. Moffat et al. (2007) found a non-significant main effect of HC volume on vMWT performance, where the influence of HC volume was only significant in YA on the first trial, while prefrontal grey, white matter, and CN volumes explained significant variation in vMWT performance independent of age with a trend for CB. As there was no difference found between YA and OA on HC volumes, Antonova et al. (2009) did not perform

correlations with vMWT performance. Lövdén et al. (2012) did not find any significant associations between HC volumes or mean diffusivity with virtual zoo performance in the YA and OA intervention groups, either together or separately.

Three out of 11 studies found no significant correlations between HC volume or microstructure and allocentric spatial processing. One study reported a correlation with CN volumes.

3.6 *Experimental designs of functional MRI studies*

Five papers reported fMRI data on studies of spatial memory and navigation, all cross-sectional designs comparing healthy OA samples, ranging from their late 50s to 70s, with younger control groups in their 20s to early 30s (Antonova et al., 2009; Konishi et al., 2013; Meulenbroek, Petersson, Voermans, Weber, & Fernández, 2004; Moffat et al., 2006; Schuck et al., 2015). Diverse experimental paradigms targeting allocentric processing were employed, including a MWT analogue task “Arena” (Antonova et al., 2009), CSDLT (Konishi et al., 2013), a route learning task (Meulenbroek et al., 2004), a “virtual maze” task requiring flexible landmark-to-landmark navigation (Moffat et al., 2006), and an object location memory task manipulating landmark location and boundaries (Schuck et al., 2015). All participants were trained on familiarisation tasks, e.g. for key presses or joysticks, closely modelled on the experimental paradigms before scanning.

Meulenbroek et al. (2004) showed subjects 14 video sequences of fixed routes through virtual homes of similar size and topography, training them to remember and press the corresponding key of the direction (left, right, straight) signalled by yellow arrows at five decision points. In the recognition condition, the sequences were shown again and subjects indicated by keypress the direction taken. Interspersed with rest periods, the control condition was passive viewing of a straight corridor with arrows. In Moffat et al. (2006), six objects were scattered in a virtual environment (VE) consisting of several rooms and hallways and participants were instructed to fully explore and encode all object locations, aware they would be tested on their “map knowledge” to encourage allocentric encoding. They were required to navigate to specified objects by the shortest of several routes. The

control condition was following a designated path in a visually similar VE using floor markers. Antonova et al. (2009) used “Arena”, a MWT analogue where participants had to navigate to and remember the location of a pole within a circular arena with abstract coloured patterned walls, equivalent to MWT distal cues. After six training trials participants were placed randomly in the arena without the pole and had to navigate to the recalled location. This was interspersed with rest epochs and a visual control period of passively watching static abstract coloured patterns.

Konishi et al. (2013) administered the CSDLT with fMRI to 52 younger and older adults. YA data was published separately (Etchamendy, Konishi, Pike, Marighetto, & Bohbot, 2012). Participants were trained to use the keyboard on a practice VE beforehand and OA were given a mock fMRI scan with a non-transferable CSDLT analogy task for familiarisation. A visuomotor control condition (navigate down one of two arms with an object, no distal environment) was interspersed with CSDLT trials, and participants simultaneously performed a working memory counting task to disrupt learning during the control condition. To investigate landmark (striatal) and boundary (hippocampal) information processing in ageing, Schuck et al. (2015) applied a computational model of boundary processing derived from Burgess & O’Keefe (1996) and a model of landmark processing (Doeller & Burgess, 2008) to generate predictions and compare them to behavioural data on a VR object location task. Male participants navigated in a circular outdoor arena surrounded by walls and distal cues e.g. mountains, clouds, with a landmark (traffic cone) and five randomised objects. During encoding trials, participants navigated from the centre to collect objects (only one appeared at a time) and learn their locations. On feedback trials, six for each object, they navigated to the recalled location of a cued object, with the object then appearing in the real location and collected again. In the three types of transfer trials, the boundary was increased or decreased by 20%, or the landmark was shifted, and participants navigated to recalled locations of cued objects without feedback.

3.7 Overview of fMRI findings

3.7.1 Age-related differences in allocentric processing

Similar to the structural MRI studies described above, four out of five studies found significant age differences in performance on spatial memory and navigation tasks in keeping with findings from numerous other studies without imaging. Meulenbroek et al. (2004), employing video sequences of fixed routes with arrows (active key-pressing and passive observing conditions) for a route training and recall task, reported both groups performed well above chance in route recognition with a slight but significant age-related deficit. Moffat et al. (2006), where participants explored a VE with six randomly located objects and were then assessed on shortest path navigation to objects, recorded significantly reduced speed overall and greater mean number of errors during object location recall for OA. Antonova et al. (2009), utilising the Arena task, a Morris Water Task analogue where participants navigated to and recalled the location of a pole in a circular arena, found that OA were significantly worse at recalling the location compared to YA. Schuck et al. (2015), employing a circular walled virtual environment where participants can encode object locations with reference to boundaries, proximal and distal cues, calculated vectors for displacement between recalled and correct object locations during the final feedback trial and three types of transfer trials and compared them to vectors predicted by the landmark and boundary models. Schuck and colleagues reported that YA performed significantly better, with an age x trial interaction in the feedback phase, i.e. more absolute improvement in YA. YA showed behaviour consistent with the boundary model and a smaller effect of landmark processing, while OA showed the opposite pattern. Visual inspection of vectors showed that YA consistently shifted their remembered locations in response to boundary change while OA did not. The remaining study (Konishi et al., 2013), which used the Concurrent Spatial Discrimination Learning Task (distinguishing between object recall encoded with egocentric versus allocentric/environmental cues), reported similar final performance for both groups on the CSDLT but slower learning for OA, requiring significantly more training trials to reach criterion.

Four out of five fMRI studies found significant age differences in performance on spatial memory and navigation tasks, including route learning and object location memory in simple and complex environments. One study reported slower acquisition for OA in a radial maze but no difference in final performance.

3.7.2 *Age-related differences in functional activation during allocentric processing*

Generalising from the fMRI studies, there are fairly consistent findings regarding reduced activity in OA of the HC and parahippocampal areas during spatial tasks, with one study reporting a positive association between HC/PHG activation and task performance (Moffat et al., 2006). Two studies observed increased activation in frontal areas such as the ACC in OA (Meulenbroek et al., 2004; Moffat et al., 2006).

Meulenbroek et al. (2004) reported activation of a neural network involved in spatial memory and navigation in both groups (dorsal and ventral visual streams) during the task, and diminished activation in dorsal and ventral visual processing streams, posterior fusiform, parahippocampal and parietal areas in OA during route encoding, which they inferred as the neural basis of the small age-related deficit in route encoding, as these areas are known to support memory formation of complex visual stimuli with a spatial component (Ekstrom et al., 2003; Weis, Klaver, Reul, Elger, & Fernández, 2004). OA also had undiminished anterior parahippocampal activity compared to YA, thought to indicate an abolished familiarity signal, diminished perisylvian deactivation during encoding and stronger activation of the ACC during route recall, hypothesised to be related to failure to inhibit distractions and irrelevant information.

Moffat et al. (2006) also found increased activation in frontal and striatal areas, including the ACC and medial frontal cortex, which may be due to a more general compensatory shift from medial temporal regions supporting navigation to reliance on frontal areas (Gutchess et al., 2005), and reduced activation in the HC, PHG, retrosplenial cortex and parietal areas in OA, again consistent with existing fMRI literature on memory in OA (Daselaar et al., 2005).

Furthermore, superior spatial navigation task performance was associated with increased activation in the posterior PHG, RSC and precuneus, supporting the hypothesis that the

observed age-related impairment in spatial tasks is underpinned by reduced functionality in these areas.

Antonova et al. (2009) found that for encoding versus rest, YA had greater activation in the bilateral HC, left PHG, right anterior frontal pole and dorsolateral PFC (DLPFC), while OA had greater activation of the corpus striatum. During retrieval, YA activated the medial temporal lobe structures and right DLPFC while OA activated the anterior medial cingulate gyrus. Despite no difference in hippocampal volumes, there was age-related attenuation in HC and perirhinal activity for encoding and retrieval, although the difference did not survive between-group analysis of variance. The authors noted the concordance of their findings on age-related attenuation of HC/PHG activity with previous studies and suggested that the performance deficits seen in OA are due to subtler changes in neurogenesis and functional connectivity in the HC rather than atrophy.

Two studies focused on the dissociation between hippocampal and striatal systems, thought to support allocentric and egocentric navigation respectively (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003), and found generally attenuated HC and increased striatal activity in OA (Konishi et al., 2013; Schuck et al., 2015). Konishi et al. (2013) reported a time effect with HC being recruited early on in the encoding phase by YA while CN activated towards the end, more so in OA. The authors hypothesised that ageing creates preference and reliance on the caudate/striatal system of stimulus-response learning due to reduced cognitive resources (Iaria et al., 2003; Nadel & Hardt, 2004), and explain their results within the characterisation of the hippocampal and striatal systems being fast, resource-intensive and slower acting (i.e. developed through experiencing reward contingencies) respectively (van der Meer, Johnson, Schmitzer-Torbert, & Redish, 2010). Schuck et al. (2015) reported largely similar results and manipulated boundaries and landmarks associated with each system to demonstrate OA reliance on proximal cues and insensitivity to distal elements such as boundaries. However, they also found that OA landmark processing was related to HC activity in addition to striatal areas (putamen) and the thalamus, suggesting HC function may be altered by ageing. Interestingly, high-performing OA in both studies also activated

hippocampal in addition to striatal areas, suggesting that HC involvement in OA may either indicate allocentric strategies or supplement landmark-based/egocentric learning.

All five fMRI studies reported reduced HC and PHG activity in OA during allocentric tasks. OA had more activation in frontal or striatal areas in all studies, while one study observed a positive association between HC activation and performance.

3.8 Differences in results based on sample sizes and gender ratios

The three largest studies had above 90 participants (Daugherty et al., 2015; Daugherty & Raz, 2017; Lövdén et al., 2012) and the three smallest had below 32 (Antonova et al., 2009; Driscoll et al., 2003; Korthauer et al., 2016). Three studies had only male participants (Antonova et al., 2009; Lövdén et al., 2012; Schuck et al., 2015) while six studies had majority female participants ranging from 66-72% (Daugherty et al., 2015, 2016; Daugherty & Raz, 2017; Head & Isom, 2010; Korthauer et al., 2016; Moffat et al., 2007).

There was no clear pattern among studies of different sizes. Both large and small studies reported a mix of positive (Daugherty et al., 2015; Daugherty & Raz, 2017; Korthauer et al., 2016) and negative (Driscoll et al., 2003; Lövdén et al., 2012) findings of associations between HC/PHC and allocentric processing. Antonova et al. (2009) reported no MRI but significant fMRI associations with the HC. Male-only studies (Antonova et al., 2009; Lövdén et al., 2012; Schuck et al., 2015) reported significant fMRI and non-significant MRI findings, while findings from female-heavy studies (MRI only) were consistent with the overall sample.

Discussion

4.1 Allocentric processing in old age

With reference to the two main objectives of the review, it is possible to conclude for the first that in agreement with the overall findings in wider research, healthy older adults show a consistent performance gap compared to young adults in spatial tasks in almost all measures collected by the studies examined, including Morris Water Maze analogues and

wayfinding in virtual mazes. The only exception is the study by Konishi et al. (2013) that found similar final performance between OA and YA but a slower learning rate in OA. Older adults take longer, more complex paths, spend longer searching and are less accurate in learning MWT platform or virtual environment landmark locations. These differences appear to be driven by general factors including slower processing and movement speed, poorer working memory and executive functioning for demands including route planning, as well as spatial and navigational characteristics such as primarily egocentric and local landmark-based strategies (Bohbot et al., 2012; Schuck et al., 2015) and difficulty in selecting or switching to an allocentric reference frame when the task necessitates it (Harris, Wiener, & Wolbers, 2012; Harris & Wolbers, 2014; Wiener, Condappa, Harris, & Wolbers, 2013).

In this review, studies involving only middle aged (MA) and OA and longitudinal studies reported ambiguous results and were unable to clarify the trajectory of how observed cross-sectional age differences develop. There were three studies that looked at OA only or examined MA and OA, with two null results and one reporting a significant age effect, and it may be that the studies are underpowered due to small sample sizes or the tasks used may not be sensitive enough to identify subtle changes. Alternatively, the significant age deficits may have started developing before or around middle age; however that is at odds with reported trends in HC, MTL, prefrontal and striatal atrophy, which increases in older age (Raz et al., 2005), as well as purely behavioural cross-sectional studies that point to an older threshold for significant deterioration (Carelli et al., 2011; Gazova et al., 2013). The three longitudinal studies had short time windows and/or significant participant attrition that appeared non-random, possibly affecting findings if lower-performing subjects or those with greatest age-related decline in spatial ability dropped out. Given the difficulties of conducting rigorous longitudinal studies, there is a clear need for more resources to be invested, perhaps including allocentric spatial tasks as a standard measure in large cohort studies of ageing, especially considering the importance of spatial memory and navigation deficits as an early indicator of dementia (Gazova et al., 2012).

It may be difficult to infer with certainty egocentric or allocentric ability from tasks as they are rarely “purely” either and ones usually characterised as allocentric can involve egocentric

computations and conversions between reference frames (Ekstrom et al., 2014). It is also important to note that allocentric representations are intrinsically bound up with egocentric processing when navigating – translating “map-like” spatial knowledge into perspective-dependent viewpoints, body and head movements (Byrne et al., 2007).

Notwithstanding, the current review’s findings are consistent with a recent review of 20 allocentric/egocentric behavioural studies of healthy older adults (Colombo et al., 2017), which also reported an age-related performance gap in conditions favouring allocentric strategies or requiring switching reference frames, while pointing to preserved egocentric abilities in older adults.

4.2 Neural correlates of spatial processing: MRI, fMRI and other measures

Although a more nuanced understanding is emerging of the neural basis of spatial navigation as a network phenomenon (Ekstrom et al., 2014), the reviewed studies mostly focused on the HC and parahippocampal areas when analysing relationship with behaviour due to its longstanding association with the cognitive map and allocentric navigation.

Several main findings can be surmised: (1) Total (and right) HC volume, as well as to a lesser extent PHG areas, correlate with performance on allocentric-dependent navigational tasks in six out of 11 studies, while mixed results were reported on the subgroup of studies that investigated correlation of navigational performance with CN volume and HC biochemical/microstructural estimates, (2) Attenuated activation of the HC and PHG in all five fMRI studies, and increased activation in striatal areas or frontal areas in OA during spatial tasks in three and two studies respectively, accompany age-related deficits, (3) High-performing OA appear to activate the HC in addition to striatal areas in contrast to low-performing OA in a study that performed the sub-analysis.

Thus, the 15 studies offered moderate and strong support respectively for age-related reductions in HC/PHG volume and activity that to a large extent correspond with enduring OA performance deficits in spatial navigational tasks usually conceptualised as allocentric or “hippocampal-dependent”. Three of the studies found significant associations between performance and the right HC, thought to support memory for specific locations in

environments (Burgess et al., 2002; Maguire, Frackowiak, & Frith, 1997). This naturally evokes the hypothesis that the OA performance gap is mediated by a shift away from allocentric strategies towards reliance on egocentric, proximal landmark-based or response strategies, contributing to their poor performance. In accordance with the HC hypothesis of spatial navigation, this shift towards extra-hippocampal strategies would be driven by the age-associated neural and functional deterioration of the HC/PHG areas, and decreased HC-PFC connectivity.

The few studies investigating HC biochemical (NAA/Cr, iron) or DTI measurements reported mixed results, which along with the considerable difficulty in translating age differences into meaningful inferences about neural microstructure and metabolic damage (Alexander, Lee, Lazar, & Field, 2007; Daugherty & Raz, 2015), restricts interpretation. Similarly, extra-hippocampal correlates of spatial navigation were only investigated in seven out of 11 MRI studies, limiting significance of findings. The caudate nucleus (CN, striatum) was the most popular region, given its purported role in response-based navigation. CN volumetric correlations with spatial task performance were non-significant in four studies (Daugherty et al., 2015; Konishi & Bohbot, 2013; Konishi et al., 2017; Korthauer et al., 2016) with two positive associations with route-learning or longer vMWT path length (Daugherty et al., Head and Isom, 2010) and one positive association with better vMWT performance (Moffat et al., 2007). Three out of five fMRI studies found increased striatal activation in OA accompanying their bias toward egocentric strategies. There is also moderate evidence (seven of 15 studies) across MRI and fMRI results supporting an association between reduced integrity/volume and increased activity in frontal regions and OA spatial task performance that may be mediated by factors such as poorer spatial working memory, attentional deficits, executive functioning and goal planning. The route planning that is required in large virtual mazes recruits the RSC to monitor routes during navigation, mediate between egocentric and allocentric processing, and PFC for unexpected detours in addition to the HC (Spiers & Maguire, 2006).

4.3 Strengths and limitations of spatial tasks and study methodology

All the reviewed studies aimed to investigate the neural correlates of allocentric processing

in ageing and older adults, however it is based on an assumption that better performance on the tasks corresponds to allocentric processing. As Ekstrom et al. (2014) pointed out, almost all tasks involve a mix of egocentric and allocentric representation or may be solved using different approaches, and ultimately involves translation into an egocentric viewpoint (Byrne et al., 2007) – thus it may be more accurate to use a continuous index to estimate which reference frame predominates (Marchette et al., 2011). For instance, despite Meulenbroek et al. (2004) presenting their task as a measure of allocentric processing, the five directions could conceivably be encoded semantically in working memory or procedurally as a sequence of egocentric movements, and the lack of participant agency in terms of navigation decisions might also have affected encoding (Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012). In fact, another study (Head & Isom, 2010) employed a similar procedure as an egocentric control for the allocentric condition of wayfinding. Hence limitations such as task variance and the subjective labelling of conditions as ego- or allocentric need to be taken into account when interpreting findings.

Although commonly regarded as a measure of allocentric processing or cognitive mapping, it is actually difficult to pinpoint the specific processes involved in solving the allocentric MWT due to the small scale of the space that conceivably allows successful recall of the platform location using sensory matching, encoding self-to-environmental cue relations at goal location in earlier learning trials, or multiple distal-cue-to-platform encoding without self-localisation within an allocentric reference frame (Wolbers & Wiener, 2014). This problem of defining what constitutes allocentric navigation also occurs in other “vista” scale spaces (Montello, 1993) that can be perceived from a single location, although dual-solution tasks such as the CSDLT purport to distinguish between the use of reference frames. Further, the computations performed in an allocentric vista space task merely constitute a subset of the processes involved in navigating “environmental” scale spaces, employed by a third of all reviewed studies. In environmental scale spatial navigation, self-localisation in addition to goal localisation is necessary and higher demands are placed on working memory (knowledge of the junctures between two landmarks) and executive functioning (novel route planning, route monitoring and re-planning). Both the hypothesised overall decline in computational resources (Craik, 1986) and reduction in processing speed (Salthouse, 1996)

that occur with ageing disproportionately impact frontal functions such as executive planning and working memory in addition to allocentric navigation, which requires more attentional resources (K. D. Wilson, Woldorff, & Mangun, 2005) and is considered less automatic and elementary than egocentric processing (Pouliot & Gagnon, 2005). A hippocampal-cortical (PFC, medial temporal, medial parietal cortex) network may underlie prospective goal-directed navigation (Brown et al., 2016) and the dorsomedial striatum (DMS) may play a role in supporting flexible, HC-based navigation (Brown & Stern, 2014; Ferbintineau, 2016). Again, these changes would be more apparent in environmental scale versus vista scale spatial tasks due to the multivariate cognitive demands and higher likelihood of overlapping routes of the former. However, a disadvantage of environmental scale tasks is the lack of standardisation, as most paradigms are formulated by individual research groups, rarely directly replicated, and vary considerably in size of the environment, protocol, and number and type of stimuli. In comparison, the experimental properties and outcome measures of MWT have been well validated through numerous studies. However, the concordance of findings implicating HC volume and attenuated activity across studies using the MWT, radial mazes and larger scale spaces does reinforce the consensus of the hippocampus's key role in processing contextual and temporal information to support allocentric navigation.

Lastly, only one reviewed study (Head & Isom, 2010) interviewed about actual strategy use and considered it in the analyses, or included comparison conditions aimed at tapping into egocentric strategies systematically. The control condition in the MWT does not require much spatial learning including egocentric, since the goal (platform) is always visible to the participant. Thus, the caveats of the differences in task parameters and what specific processes they are measuring have to be held in mind when understanding the findings.

4.4 Interpretation

In the reviewed studies, OA appear to be more heavily utilising habitual or route-based strategies and an egocentric-predominant (proximal landmark-based) approach. These two are often equated in the literature, however may be subserved by distinct regions (dorso-lateral striatum (DLS) vs. RSC and parietal areas). Furthermore, the DMS/ventral striatum have been linked to HC-dependent, allocentric processing requiring flexible modulation with

habitual responses (Goodroe et al., 2018), the HC to accessing episodic memories during route-based navigation, and even compensating for CN dysfunction respectively (Brown & Stern, 2014; Cabral et al., 2014; Voermans et al., 2004), and the PHC, separate of the HC, may be crucial to certain categories of allocentric processing (Bohbot et al., 1998). Such complexities may go some way towards explaining findings such as Moffat et al. (2007)'s significant correlation of CN and vMWT, or additional HC activation in high-performing OA in Schuck et al. (2015), in addition to the overall conclusion of significant HC volumetric and functional correlations to allocentric performance in simple tasks like vMWT and navigation in more complex environments.

Indeed, the majority of studies' focus on the HC or discrete brain regions may have obscured disruption in functional connectivity in a wider navigational network including the HC, RSC and PFC resulting in (set) switching difficulties (Carelli et al., 2011; Harris et al., 2012; Morganti and Riva, 2014) and age-related working memory and executive functioning declines reflecting in allocentric difficulties, which require more cognitive resources (Iaria, Palermo, Committeri, & Barton, 2009; Klencklen et al., 2012; Moffat et al., 2007).

4.5 Strengths and limitations of review and included studies

The current review systematically and comprehensively examined all studies investigating the impact of age on allocentric processing in spatial memory and navigation and the relationship to hippocampal and other regional volumes and activity. One strength is that the reviewed articles were similar in experimental design and paradigms used, with the majority employing the MWT and others using radial mazes or larger and more complex virtual environments with multiple landmarks, allowing results to be generalised more easily across studies. Furthermore, the quality assessment tool produced a narrow range of scores indicating the overall quality of the reviewed studies is fairly homogenous and of an acceptable standard, although a third of studies fell just below the 'High' threshold, mostly due to small sample sizes, lack of information about participant selection/control and incomplete reportage of statistical variance. Therefore, scores from the assessment tool was of limited use in eliminating studies of poor quality or in determining the emphasis of the review given such a narrow range.

However, a related and significant limitation is the relatively small number of eligible studies and that papers from two research groups constituted over half of the studies, which is a likely contributing factor to the uniformity of spatial paradigms and quality scores. On the other hand, choosing broader inclusion criteria would restrict the specificity of conclusions due to study heterogeneity. It is important to bear this limitation in mind when interpreting our findings as reflecting a set of similarly designed and implemented studies from which it is possible to draw narrower conclusions about the relationship between age, HC volume, activity or microstructure, and performance on allocentric spatial navigation tasks.

In terms of study design, there were three studies including or scanning OA only that would have been strengthened by inclusion of young comparison groups, while the two long-term studies suffered significant and non-random dropout limiting the applicability of findings. The performance measures and factors entered into regression analyses also varied considerably across studies, with some focusing on conventional outcomes including distance and length of time while others investigated change rates, path complexity, and consistency with model predictions. Besides from the HC, there was heterogeneity in the ROI selected, making it difficult to compare findings as different regions were included in analyses. As is typical in neuroscience research, the studies were often underpowered with sample sizes too small for the number of predictors entered. Thus, it is necessary to be cautious when interpreting and ascribing meaning to increasingly complex interrelationships between multiple regional/functional measures and task performance. The varied imaging methodology due to technological advances and different protocols also introduces variance to the results.

The virtual reality tasks in the reviewed studies have the obvious advantage of greater ecological validity compared to pen and paper tests for assessing real-life spatial memory and navigation, allowing experimenters to collect much more detailed and extensive data regarding participant behaviour. Studies incorporating both real and computer versions of egocentric/allocentric spatial tasks report strong correlations in performance and similar predictive and differentiating power (Burgess et al., 2002; Serino et al., 2014), and the same neural networks and regions are likely recruited. However, key differences remain between

VR and real-life spatial tasks, including gaps in proprioceptive and self-motion feedback using joysticks or keyboards versus exploring by walking, and the lack of sensory immersiveness of computer screens compared to a real world environment. Furthermore, the advantage of being able to investigate functional activation during spatial navigation using VR tasks is counterbalanced by the reduced ecological validity due to immobilisation in a scanner during testing.

4.6 *Relevance to neuropathological ageing: MCI and AD*

An important question stemming from this review would be the relevance of its findings to the clinical population of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) patients. The early topographical and spatial deficits noted in AD and amnesic MCI (aMCI), a heightened at-risk state, appear before significant clinical impairment (Serino et al., 2014) and have been linked to the accumulation of plaques, tangles and accompanying neuronal loss and atrophy first starting in MTL regions – the entorhinal cortex, HC (Braak, Braak & Bohl, 1993; Du et al., 2001; Khan et al., 2014) and RSC (Viček & Laczó, 2014).

Serino et al. (2014) outlined the mainly allocentric and viewpoint translation-related deficits observed when comparing aMCI and early AD patients to healthy older controls, hypothesising that early HC and RSC neuropathology may impair the spatial and temporal “mental frame syncing” supported by these regions. Indeed, the RSC is relatively conserved in healthy elders when compared to MCI (Nestor et al., 2003). This was further discussed by the same research group in Colombo et al. (2017), who contrasted the allocentric and switching deficits between young and older adults, and OA and AD/MCI as neurologically distinct, with age-related allocentric impairments a result of frontal-striatal circuit deterioration (Buckner, 2004), reduced executive function and working memory rather than MTL-related. It is thus possible to say that performance on “allocentric” tasks such as MWT decline from youth to old age, with an even greater impairment in AD/MCI patients – with allocentric measures serving as a valid predictor in both situations. The subtler role HC/MTL plays in the age-related allocentric deficit can be seen in the high concordance of reduced HC activity versus more mixed results in HC volumetric correlations. This suggests that the well-characterised additional AD neuropathology in the HC/EC is causing the allocentric

performance gap between AD/MCI and OA, while the age-associated allocentric decline may be multifactorial, with MTL/HC shrinkage and functional decline as one contributor, but also relate to lower processing speed, computational resources with age; reduced WM, executive functioning due to PFC deterioration, declining frontal-striatal and frontal-HC connections, and CN atrophy affecting goal-directed behaviour in spatial tasks (Goodroe et al., 2018).

4.7 Conclusion and future directions for research

Spatial navigation in complex environments is an ancient and essential ability for survival that has been garnering a lot of attention in the last few decades in context of the neurobiological changes that occur with ageing. Human behavioural research inspired by animal behavioural neuroscience, and more recently structural and functional imaging of the brain, have revealed its crucial connection with the HC, as well as revealing a network incorporating the wider MTL, RSC, PFC, striatum and parietal cortex. This systematic review examined all studies that investigated the role of age in allocentric spatial navigation and its neural correlates. The results show a pronounced deterioration of spatial memory and navigation with normal ageing on tasks that depend on encoding distal environmental cues and require formation of a cognitive map, as well as reasonable evidence linking the deficit to age-related alterations in HC morphology and attenuated activation.

Despite the barriers and resource demands, more rigorous longitudinal studies of spatial navigation and neuroimaging should be conducted to investigate how these age differences evolve and are interrelated over time. Information should be collected about spontaneous allocentric or egocentric strategy use and individual tendencies, through self-report or interviews, and care taken to control for this variable in tasks where either or a mixture can be used. The development of more ecologically valid paradigms set in large scale spaces is also important as there are a broader set of demands that may not be fully reflected in standard paradigms such as the Morris Water Maze. The advent of commercially available immersive virtual reality (iVR) with its ability to track movement is another significant advance beyond computer-based VR tasks used to date in spatial navigation research, as experimental paradigms can be hugely improved in ecological validity both in terms of highly

convincing three dimensional visual and audio input, responsiveness to head movements, and by incorporating self-motion and proprioceptive feedback.

In light of the rapidly growing research into the functions supported by different hippocampal subfields and surrounding regions of the medial temporal lobe such as the entorhinal (Deshmukh & Knierim, 2011) and parahippocampal cortex (Bohbot et al., 1998; Vann, Brown, Erichsen, & Aggleton, 2000), there is a clear need for more studies focusing on examining associations between multiple spatial task outcomes with HC/PHG subfield volumes and activity in older adults, to validate the many promising results from animal studies.

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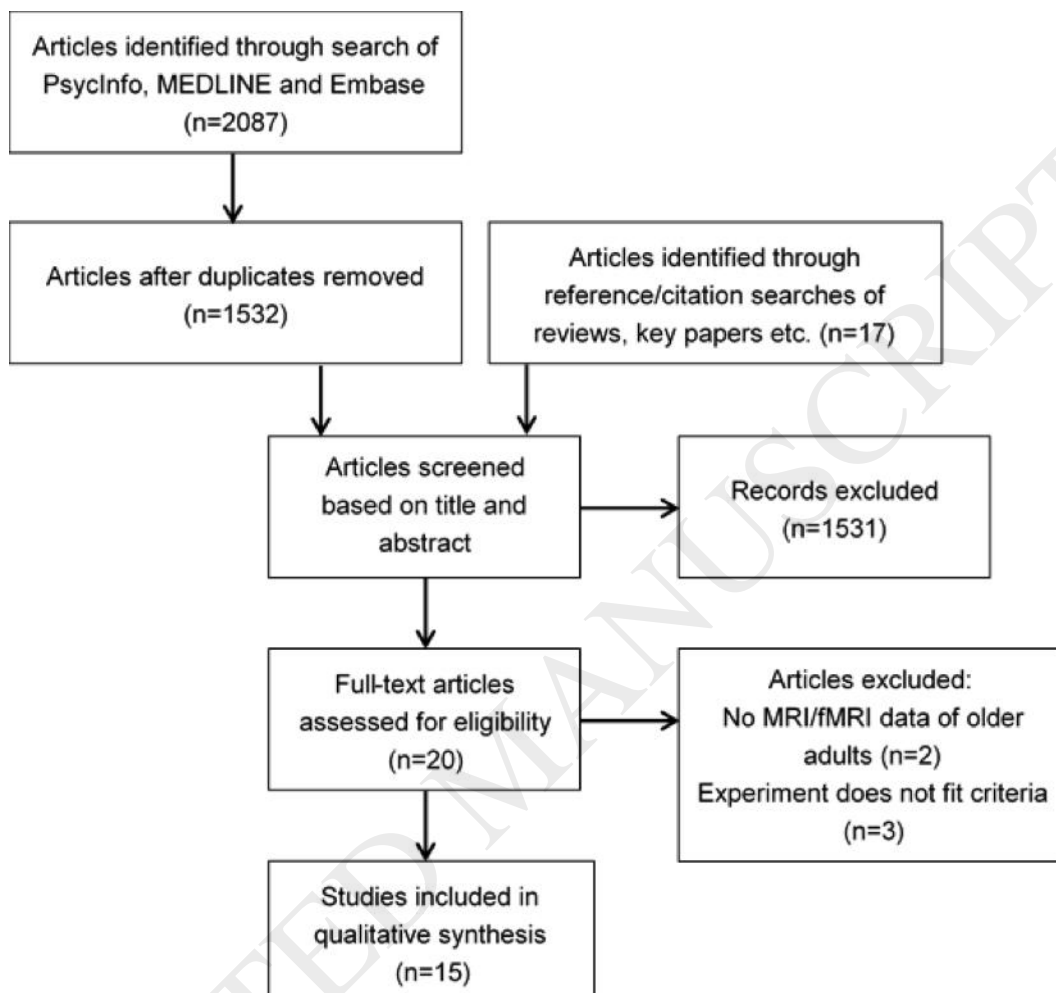
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Figure Captions

Figure 1. Flow chart of selecting papers for review following PRISMA guidelines













Tables

Table 1. Search terms

	Terms	Results
1	allocentric.mp.	3524
2	"spatial memory".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	33455
3	"third person perspective*".mp.	637
4	egocentric.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	7776
5	"spatial orientation (perception)"/	7081
6	"spatial navigation".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	4556
7	1 or 2 or 3 or 4 or 5 or 6	51677
8	aging/ or geriatrics/ or gerontology/ or geropsychology/ or human development/	596290
9	"older adult*".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	167415
10	elder*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	746865
11	age differences/	73122
12	8 or 9 or 10 or 11	1382167
13	7 and 12	4069
14	limit 13 to english language	3977
15	limit 14 to human	2087
17	remove duplicates from 15	1532

Table 2. *Quality ratings*

Study Author(s)	Year	Type	Overall Score	Quality
Driscoll et al.	2003	MRI	0.73	Medium
Meulenbroek et al.	2004	fMRI	0.77	High
Moffat et al.	2006	fMRI	0.82	High
Moffat et al.	2007	MRI	0.86	High
Antonova et al.	2009	MRI/fMRI	0.73	Medium
Head and Isom	2010	MRI	0.77	High
Lövdén et al.	2012	MRI	0.81	High
Konishi et al.	2013	fMRI	0.77	High
Konishi and Bohbot	2013	MRI	0.73	Medium
Daugherty et al.	2015	MRI	0.77	High
Schuck et al.	2015	fMRI	0.77	High
Daugherty et al.	2016	MRI	0.77	High
Korthauer et al.	2016	MRI	0.82	High
Daugherty and Raz	2017	MRI	0.73	Medium
Konishi et al.	2017	MRI	0.82	High

Study Author(s)	Year	Sample (N)*	Study Design	Sample characteristics	Mean age (SD or range)	Female (%)	Imaging modality
Driscoll et al.	2003	32	Cross-sectional with comparison group	16 younger adults (YA), 16 older adults (OA), non-APOE $\epsilon 4$ allele carriers 	YA: 26.1 (20-39) OA: 77.6 (60-85)	YA: 50 OA: 50 	MRIMRSI (HC NAA/Cre)
Moffat et al.	2007	68	Cross-sectional with comparison group	32 younger adults, 36 older adults 	YA: 24.5 (0.91) OA: 68.5 (0.92)	YA: 75 OA: 67 	MRI
Antonova et al.	2009	20	Cross-sectional with comparison group	10 younger adults, 10 older adults 	YA: 23.6 (1.78) OA: 72.14 (5.33)	N/A 	MRI (VBM) fMRI
Head and Isom	2010	47	Cross-sectional with comparison group	29 younger adults, 63 older adults with MRI data for 47 OA 	69.9 (8.55)	72.3 	MRI (VBM)
Lövdén et al.	2012	91	Randomised intervention with comparison group	44 younger adults, 47 older adults 	YA: 26.0 (2.8) OA: 65.0 (2.8)	All male 	MRI DTI
Konishi and Bohbot	2013	45	Cross-sectional, single group	Older adults only 	64.38 (4.0)	51.1 	MRI (VBM)
Daugherty et al.	2015	139	Cross-sectional, single group	Age range from 18-77 	48.52 (15.85)	66.2 	MRI
Daugherty et al.	2016	65	Cross-sectional, single group	Age range from 19-75 	44.99 (16.31)	67.7 	MRI
Korthauer et al.	2016	22	Longitudinal & cross-sectional with comparison group	51 recruited at 8-year FU, 22 with MRI: 9 middle-aged, <60 (MA), 13 older adults, >60 (OA) 	Baseline: 59.7 (30-83) MA: 50.8 (40-59) OA: 67.9 (60-78)	MA: 66.7 OA: 53.8 	MRI DTIMRSI (NAA/Cre)
Daugherty and Raz	2017	213 (131)	Longitudinal, single group	2-year FU sample from Daugherty et al. (2015) aged 18-77 at baseline. n=40 had hypertension 	Baseline: 51.27 (15.52) FU: 55.74 (14.28)	74.0 	MRIR2* relaxometry
Konishi et al.	2017	49	Cross-sectional, single group	107 older adults (55-80), subset (n=49) with MRI 	66.04 (4.41)	55.1 	MRI

YA: younger adult; OA: older adult; FU: follow up; MRI: magnetic resonance imaging; MRSI: magnetic resonance spectroscopy imaging; VBM: voxel based morphometry; DTI: diffusion tensor imaging

* Sample size with both behavioural and imaging data

Table 3a. Summary of structural MRI studies

Primary spatial paradigm	Screening and Cognitive tests	Main findings
Virtual Morris Water Task (vMWT) (Hamilton and Sutherland, 1999), Transverse Patterning Discrimination Task (TPDT)	Extensive battery of cognitive measures in ageing study, MMSE	Age-related deficits in both hippocampal tasks. Age-related reduction in HC volume & NAA/Cr levels. Correlation between HC volume and performance on vMWT was non-significant after controlling for age and HC activity. Significant contribution of HC volume to TPDT performance after controlling for age and HC activity.
Virtual Morris Water Task (vMWT) (Moffat and Resnick, 2002)	7 tests grouped into Processing Speed, Working Memory, Spatial Memory and Executive Control indices	Age-related reduction in left PFC, HC, CN, CB, PFW volume. Age-related deficits in vMWT first trial, learning and search accuracy. Non-significant correlation between HC volume and vMWT performance. vMWT performance correlated with CN, PFW volume, executive function, working and spatial memory.
Virtual task (MWT analogue) requiring encoding and recall of location of pole in a circular arena using distal environmental cues	MMSE screen for OA WASI, OA significantly higher IQ	Age-related deficit in accuracy of location recall. No age-related reduction in HC volume, but several other regions larger in YA incl. PFC, PHG, left CN and CB. Attenuation of HC and perirhinal activation in OA during encoding and retrieval accompanied by poor task performance.
Virtual maze with landmarks and wallpaper recall measures (Hartley et al., 2003): wayfinding condition allowed free exploration, route learning condition prescribed path taken	Short Blessed Test for gross cognitive impairment	Age-related deficits in wayfinding and route learning. HC volume significantly associated with wayfinding performance. CN volume significantly associated with route learning performance. However no significant difference between above two associations and other ROI.
Virtual zoo linked to treadmill, participants were required to search for cued animals	Large neurocognitive battery including measures of allocentric ability	Age-related decline in navigation significantly improved by 4-month training and somewhat maintained 4m post-test. Improvement did not transfer to allocentric paper task, which did not correlate with baseline VR performance. No age differences in HC volume, higher diffusivity for OA. HC size/MD not associated with VR performance.
Concurrent Spatial Discrimination Learning Task (CSDLT), a 12-arm radial maze with objects in half the arms. Differentiates allocentric or egocentric strategies.	MMSE, MoCA screen Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Task (RO)	CSDLT performance (allocentric strategy use) positively correlated with right HC volume, but RAVLT and RO performance did not. CN volume not negatively correlated with CSDLT. Increased HC volume covaried with increased right OFC, AMG, PHG volumes.
Virtual Morris Water Task (vMWT) (Moffat and Resnick, 2002)	MMSE and Center for Epidemiological Study Depression Questionnaire (CES-D)	Age and sex-related increases in time and path complexity. Age-related deficit in first trial but no effect on learning across trials. Smaller HC volume associated with higher path complexity and greater travel time. HC and PHG volume associated with change in path complexity i.e. learning.
Virtual Morris Water Task (vMWT) (Moffat and Resnick, 2002)	MMSE and Center for Epidemiological Study Depression Questionnaire (CES-D)	Age-related reduction in HC subfields and EC. Age-related deficit in learning speed and overall performance. Subiculum and EC was associated with faster decrease in path complexity, while CA1-2 associated with faster path shortening. HC subfield volumes did not contribute to overall age-related poor performance.
Virtual Morris Water Task (vMWT)	Extensive neurocognitive battery: Memory, Attention, Executive Functioning, Language, Visuospatial tasks	No age-related decline at FU of any vMWT measures. vMWT latency correlated with right HC, medial OFC and thalamus after controlling for demographics. vMWT latency correlated with right HC and thalamus only in MA, and with right mOFC in OA. Bilateral UF FA significantly correlated with latency after controlling for age, speed.
Virtual Morris Water Task (vMWT) (Moffat and Resnick, 2002)	MMSE and Center for Epidemiological Study Depression Questionnaire (CES-D)	Learning rate and absolute improvement (path length, PL) declined, but reduction in path complexity (FD) improved, all worse in OA at FU. CN, HC, PHG, CB significantly reduced at FU. Greater CN iron, smaller CB and CN volume predicted longer PL, great HC iron and smaller PHG associated with more variable FD. Iron accumulation, not HC volume, predictive of longitudinal decline.
Virtual wayfinding task: required to navigate from one landmark to another in virtual town (n=107, MRI n=49), CSDLT (n=93, MRI n=47)	MMSE screen MoCA	Age-related reduction in right HC and CN volume. Age negatively correlated with wayfinding but not CSDLT performance. MoCA correlated with HC volume, wayfinding performance independent of age, and CSDLT performance. Generally, wayfinding and CSDLT performance correlated with HC volume.

HC: hippocampus; PHG: parahippocampal gyrus; EC: entorhinal cortex CN: caudate nucleus; PFC: prefrontal cortex; CB: cerebellum; PFW: prefrontal white matter; OFC: orbitofrontal cortex; AMG: amygdala; UF: uncinate fasciculus; ROI: region of interest; FA: fractional anisotropy; MD: mean diffusivity; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; WASI: Wechsler Abbreviated Scale of Intelligence











Study Author(s)	Year	Sample (N)*	Study Design	Sample characteristics	Mean age (SD or range)	Female (%)	Imaging modality
Meulenbroek et al.	2004	40	Cross-sectional with comparison group	20 younger adults, 20 older adults 	YA: 23 (2.8) OA: 63 (7.2)	YA: 50 OA: 50 	functional MRI
Moffat et al.	2006	51	Cross-sectional with comparison group	30 younger adults, 21 older adults 	YA: 27.07 (5.46) OA: 68.43 (5.56)	YA: 50 OA: 52.4 	functional MRI
Antonova et al.	2009	20	Cross-sectional with comparison group	10 younger adults, 10 older adults 	YA: 23.6 (1.78) OA: 72.14 (5.33)	N/A 	MRI (VBM) functional MRI
Konishi et al.	2013	52	Cross-sectional with comparison group	23 younger adults, 29 older adults 	YA: 23.8 (3.8) OA: 64.2 (4.7)	YA: 60.9 OA: 48.3 	functional MRI
Schuck et al.	2015	48	Cross-sectional with comparison group	26 younger adults, 22 older adults 	YA: 28.1 (3.9) OA: 67.2 (3.9)	All male 	functional MRI
YA: younger adult; OA: older adult; MRI: magnetic resonance imaging; VBM: voxel based morphometry * Sample size with both behavioural and imaging data							

Table 3b. Summary of functional MRI studies. In the bar graphs, younger adults (YA) are represented by blue, older adults (OA) by red and longitudinal samples by orange. In the pie charts, male and female OA are represented in the outer circle by blue and red; male and female YA in the inner circle by light blue and pink respectively.

Primary spatial paradigm	Screening and Cognitive tests	Main findings
Video sequences of fixed routes through virtual homes and with arrow cues at intersections during encoding; participants asked to recall left, right or straight during recognition. Control condition had repeated travel down empty corridor with arrows.	Nil	Small but significant age-related deficit in route recognition. Stronger activation in YA in posterior fusiform/PHC areas, and weaker recognition-related activity in anterior PHC possibly linked to route encoding advantage in YA. OA showed higher activity in left perisylvian region and ACC, possibly related to attentional deficits.
Virtual building with 6 objects dispersed, participants asked to navigate shortest route to recalled location of objects	Nil	Age-related deficit in object location recall. OA showed reduced activation in posterior HC, PHC gyrus, RSC, parietal regions and greater frontal lobe (ACC, medial frontal cortex) activation. Increased navigational accuracy is associated with greater activation in posterior PHC gyrus, RSC and precuneus overall. Strategy use was not assessed.
Virtual task (MWT analogue) requiring encoding and recall of location of pole in a circular arena using distal environmental cues	MMSE for OA WASI, OA significantly higher IQ	Age-related deficit in accuracy of location recall. No age-related reduction in HC volume, but several other regions larger in YA incl. PFC and PHG. Attenuation of HC and perirhinal activation in OA during encoding and retrieval accompanied by poor task performance.
Concurrent Spatial Discrimination Learning Task (CSDLT), a 12-arm radial maze located in a larger environment, with objects in half the arms. Distinguishes between use of allocentric or egocentric strategies.	MMSE screen MoCA	OA slower acquisition to criterion but matched YA performance. YA had HC activation in beginning of learning, OA had CN activation at end of learning. OA using spatial strategy had HC activation in learning while OA using response strategy had CN activation, suggesting a shift to response strategies accounts for age-related deficits.
Object location task - 5 objects in a virtual circular arena, boundary and landmark conditions manipulated to investigate influence on recalled object locations	Nil	Age-related deficit in object location recall and learning rate. YA performance predicted by a boundary-processing model and OA showed no significant influence of boundary manipulations. Greater HC/PHC activity associated with boundary model predictions. Greater CN activity in OA associated with landmark processing (using lenient threshold). Additional HC activity for landmark learning in high-performing OA.
HC: hippocampus; PHC: parahippocampal cortex; ACC: anterior cingulate cortex; RSC: retrosplenial cortex; CN: caudate nucleus; MWT: Morris Water Task; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; WASI: Wechsler Abbreviated Scale of Intelligence		