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# Distinct resting-state functional connections associated with episodic and visuospatial memory in older adults

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## ABSTRACT

Episodic and spatial memory are commonly impaired in ageing and Alzheimer's disease. Volumetric and task-based functional magnetic resonance imaging (fMRI) studies suggest a preferential involvement of the medial temporal lobe (MTL), particularly the hippocampus, in episodic and spatial memory processing. The present study examined how these two memory types were related in terms of their associated resting-state functional architecture. 3T multiband resting state fMRI scans from 497 participants (60–82 years old) of the cross-sectional Whitehall II Imaging sub-study were analysed using an unbiased, data-driven network-modelling technique (FSLNets). Factor analysis was performed on the cognitive battery; the Hopkins Verbal Learning test and Rey-Osterreith Complex Figure test factors were used to assess verbal and visuospatial memory respectively. We present a map of the macroscopic functional connectome for the Whitehall II Imaging sub-study, comprising 58 functionally distinct nodes clustered into five major resting-state networks. Within this map we identified distinct functional connections associated with verbal and visuospatial memory. Functional anticorrelation between the hippocampal formation and the frontal pole was significantly associated with better verbal memory in an age-dependent manner. In contrast, hippocampus–motor and parietal–motor functional connections were associated with visuospatial memory independently of age. These relationships were not driven by grey matter volume and were unique to the respective memory domain. Our findings provide new insights into current models of brain-behaviour interactions, and suggest that while both episodic and visuospatial memory engage MTL nodes of the default mode network, the two memory domains differ in terms of the associated functional connections between the MTL and other resting-state brain networks.

## 1. Introduction

It is estimated that by 2050, nearly one in four people worldwide will be over 60, with older adults outnumbering children under 14 (WPA, 2015). In a rapidly ageing society, it is becoming increasingly important to understand the biological underpinnings of cognitive function in older age. Decline in episodic memory is often the first clinical presentation in patients with Alzheimer's disease (AD) and amnestic mild cognitive impairment, and the early stages of AD are also characterised by deficits in visuospatial memory (Lange et al., 2002; Serino et al., 2015). Medial temporal lobe structures, particularly the hippocampus, contribute to the processing of episodic memory as well as the representation of spatial information in the brain (Kumaran and Maguire, 2005; Nadel and Moscovitch, 1997; O'Keefe and Nadel, 1978). Reductions in hippocampal volume and impairments in its structural connections to other brain regions are implicated in the episodic and spatial memory deterioration commonly observed in ageing and dementia (Delbeuck et al., 2003; Jack et al., 2004; Serino and Riva, 2014).

Functional magnetic resonance imaging (fMRI) studies have furthered our understanding of the hippocampus' complex role in supporting episodic and spatial memory. Task-based fMRI studies suggest a preferential involvement of hippocampal activity during episodic and

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spatial memory tasks (Hirshhorn et al., 2012; Nadel et al., 2013; Robin et al., 2015; Ryan et al., 2009), but they tell us little about its relevant functional connections, which are usually studied using resting-state fMRI. In the resting-state brain, *i.e.* in the absence of a task, spontaneous activity within the hippocampus is synchronised (functionally connected) with a network of brain regions that together make up the default mode network (DMN). This resting-state network comprises the anterior and posterior cingulate cortices, precuneus, lateral temporal cortex, ventromedial prefrontal cortex, inferior parietal lobule and medial temporal lobe structures (Buckner et al., 2008; Raichle et al., 2001). The DMN is typically engaged at rest and during internally oriented tasks involving autobiographical memory, and is deactivated during cognitively challenging or externally oriented tasks (Andrews-Hanna et al., 2010a; Buckner, 2010; Spreng et al., 2009). Reduced functional connectivity (FC) of the DMN has been linked to memory impairment in AD patients and, not surprisingly, this network is the most frequently studied resting-state network in the context of memory decline. (Allen et al., 2007; Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Ferreira and Busatto, 2013; Hafkemeijer et al., 2012; Mevel et al., 2011; Wu et al., 2011).

Recent evidence suggests that the functional association of DMN with the hippocampus may vary based on cognitive demands. For instance, studies find synchronised activity between the hippocampus and DMN during episodic memory retrieval but not encoding, and between hippocampus and prefrontal networks during episodic but not spatial memory tasks (Andrews-Hanna et al., 2010b; Huijbers et al., 2011; Robin et al., 2015). Moreover, it is not simply functional connectivity (FC) *within* the DMN but its anticorrelations (negative correlation) with other organized resting-state networks like the task-positive dorsal attention network and central executive network (CEN) that may be essential for supporting cognition (Nekovarova et al., 2014; Onoda et al., 2012; Spreng et al., 2016, 2010; Sridharan et al., 2008; Uddin et al., 2009). Graph-theory and whole-brain rs-fMRI based connectomics approaches allow us to expand on the traditional, more focused seed-based or single-network analyses, and examine these intra- and inter-network connections in greater detail (Cole et al., 2010; Smith et al., 2013; van den Heuvel and Sporns, 2013). Such network modelling methods map the "functional connectome" by parcellating the rs-fMRI data into a large number of small distinct brain regions (*nodes*) using (for example) high-dimensionality independent component analysis (ICA), and subsequently estimating the FC (*edges*) as the temporal correlations of node activity. These techniques have provided valuable insights into the organisation of the brain at rest, and functional reorganisation of network connections in ageing and dementia (Chan et al., 2014; Dipasquale et al., 2015; Geerligs et al., 2015; Grady et al., 2016; Sala-Llonch et al., 2015; Schouten et al., 2016; Smith et al., 2015).

Ageing is associated with domain-specific changes in cognitive ability, with declines in some but not other cognitive domains (Harada et al., 2013). The present study examined the resting-state functional connections associated with episodic and spatial memory using an unbiased data-driven network-modelling framework applied to 497 participants (60–82 years old) of the Whitehall II Imaging Sub-study. Given the vulnerability of these memory domains in ageing and AD, and task-fMRI evidence of their shared dependence on the hippocampus, we investigated whether, and how these two types of memory are related in terms of the underlying resting-state functional architecture supporting them. Specifically, we examined if associations between memory and resting-state functional connectivity were domain-specific and age-dependent.

## 2. Materials and methods

### 2.1. Participants

Participants belonged to the Whitehall II Imaging Sub-study, and the study protocol and MRI pre-processing pipeline has been described in detail previously (Filippini et al., 2014). Briefly, participants were drawn from the Whitehall II study, a cohort of 10 308 British Civil Servants established in University College London in 1985 and followed-up for over 30 years across 12 waves. For the Whitehall II Imaging Sub-study, 550 participants were randomly selected from the parent study; a battery of cognitive tests was administered followed by an MRI scan at the FMRIB Center, Oxford between 2012 and 2015. rs-fMRI data from 497 participants were used in this analysis. Exclusion criteria were incomplete or poor quality MRI data and/or structural abnormalities on the MRI scan (e.g. large tumours or brain cysts). Informed consent was obtained from all participants.

### 2.2. Verbal memory scores

Cognitive tests were administered by trained psychology graduates and psychiatrists and in the following order: Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT-A and TMT-B), Lexical (letter: "F") and Semantic Fluency (category: "Animals"), Rey-Osterrieth Complex Figure (ROCF) copying, RCF immediate recall, Hopkins Verbal Learning Test (HVLT-R) immediate recall, Boston Naming Test, Digit Span (forward, backward, ascending sequence) and Digit Coding (from the Wechsler Adult Intelligent Scale-IV), HVLT-R delayed recall, RCF delayed recall and Test of Premorbid Function (TOPF) (Filippini et al., 2014). All tests were included in a factor analysis (except the MoCA which is a screening tool for cognitive impairment). Factor analysis was performed using an oblique rotation (direct oblimin in SPSS 21) to allow for correlation between factors. The verbal memory factor (largest factor, accounting for ~36% of the total variance) and visuospatial memory factor (accounting for ~7% of the total variance) were used in this analysis. HVLT-R (immediate and delayed recall) and ROCF (copy, immediate and delayed recall) loaded high on verbal and visuospatial memory factors respectively (Table S1, Supplementary Materials). The HVLT-R is a list learning and free recall task comprising three trials of 12 words and is used to evaluate episodic verbal memory decline in dementia (Shapiro et al., 1999). The ROCF test involves copying a complex geometric figure and reproducing it from memory both immediately and following a delay, and is used to assess visuospatial memory and constructional ability (Shin et al., 2006).

### 2.3. MRI analysis

T1-weighted structural MRI (multi-echo MPRAGE sequence with motion correction) and multiband echo-planar imaging rs-fMRI scans (voxel = 2 mm isotropic, TR = 1.3 s, acquisition time = 10 min 10 s, multi-slice acceleration factor = 6, number of volumes = 460) were acquired. Participants were scanned on a 3T Siemens Magnetom Verio (Erlangen, Germany) scanner with a 32-channel head coil, at the FMRIB Center, Oxford. Data were pre-processed using FSL tools (Jenkinson et al., 2012; Smith et al., 2004) as described in Filippini et al., (2014). Network modelling was performed using FSLNets (Smith et al., 2013).

#### 2.3.1. Pre-processing and group-ICA

T1 images were bias field corrected, brain extracted and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using FSL-FAST. Rs-fMRI data were pre-processed (motion correction, brain extraction, high-pass temporal filtering at 100s, field-map correction) using FSL tools. FIX (FMRIB's ICA-based X-noisefier) was used to remove the artefactual components that reflected non-neuronal fluctuations (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). FIX was trained using the WhII_MB6.RData trained-weights file, which was generated from hand-labelling 25 participants from this study. This training file is available online (http://www.fmrib.ox.ac.uk/datasets/FIX-training/) and described, including the leave-one-out classification accuracy results, in Salimi-Khorshidi et al. (2014). The pre-processed and cleaned rs-fMRI scans were registered to standard space using FNIRT and spatially smoothed using a Gaussian kernel of 6 mm full width at half