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**Research Report**
**Age-effects on associative object–location memory**
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**ABSTRACT**

Aging is accompanied by an impairment of associative memory. The medial temporal lobe and fronto-striatal network, both involved in associative memory, are known to decline functionally and structurally with age, leading to the so-called associative binding deficit and the resource deficit. Because the MTL and fronto-striatal network interact, they might also be able to support each other. We therefore employed an episodic memory task probing memory for sequences of object–location associations, where the demand on self-initiated processing was manipulated during encoding: either all the objects were visible simultaneously (rich environmental support) or every object became visible transiently (poor environmental support). Following the concept of resource deficit, we hypothesised that the elderly probably have difficulty using their declarative memory system when demands on self-initiated processing are high (poor environmental support). Our behavioural study showed that only the young use the rich environmental support in a systematic way, by placing the objects next to each other. With the task adapted for fMRI, we found that elderly showed stronger activity than young subjects during retrieval of environmentally richly encoded information in the basal ganglia, thalamus, left middle temporal/fusiform gyrus and right medial temporal lobe (MTL). These results indicate that rich environmental support leads to recruitment of the declarative memory system in addition to the fronto-striatal network in elderly, while the young use more posterior brain regions likely related to imagery. We propose that elderly try to solve the task by additional recruitment of stimulus–response associations, which might partly compensate their limited attentional resources.

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## 1. Introduction

One of the most common memory complaints of elderly is that they are unable to remember the location of household objects, like keys (e.g. Jonker et al., 1996).

These complaints are part of an age-related episodic memory decline (for review, see Hedden and Gabrieli 2004), in particular of contextual memory. For instance, elderly show problems remembering which of two experimenters presented a target (McIntyre and Craik 1987, Schacter et al., 1994), what gender the presenter was (e.g. Simons et al., 2004), or what the target's case format was (e.g. Kausler and Puckett 1981) and what colour the target was presented in at study (Park and Puglisi 1985, see Spencer and Raz 1995 for a review). Given that item memory stays generally intact (Craik and McDowd 1987) (for a recent meta-analysis, see Old and Naveh-Benjamin 2008), it was hypothesised that elderly are impaired at binding contextual elements into a coherent episode, also called the associative deficit (Naveh-Benjamin 2000). Adding to the age-related associative deficit is the so-called resource deficit (Craik and Byrd 1982), which posits that a lack of cognitive, in particular attentional resources, makes it difficult to use self-initiated processes.

With age, several brain structures essential for self-initiated processes (the fronto-striatal network) and associative memory (the Medial Temporal Lobe; MTL) deteriorate structurally with age. Foremost, lateral prefrontal cortex volume decreases around 5% per decade, starting at age 20 (Raz et al., 2005, Resnick et al., 2003). Decline in the basal ganglia is also apparent, for instance, caudate volume declines with 0.75% per year (Raz et al., 2005). Similar decline is observed in the hippocampus (0.79%), but age-related degeneration of the frontal lobe is the most prominent.

Next to structural decline, also age-related functional decline is observed. For instance, the hippocampus, which is well known to be involved in encoding and retrieval of between-domain associations (Mayes et al., 2007), often shows decreased activation in elderly during encoding (e.g. Mitchell et al., 2000) and retrieval (e.g. Cabeza et al., 2004). Furthermore, elderly show reduced performance on several memory tasks, like cued recall (e.g. Craik and McDowd 1987), source memory (e.g. Wegesin et al., 2000) and associative memory (Chalfonte and Johnson 1996, Glisky et al., 2001, Naveh-Benjamin 2000; Naveh-Benjamin et al., 2003, 2004). Implicitly imposing strategic processing during encoding enhances source memory performance (Wegesin et al., 2000). However, explicitly imposing strategic processing during encoding and retrieval does not entirely eliminate the associative deficit (Naveh-Benjamin et al., 2007). This indicates elderly probably not only have problems with self-initiation (like implementing strategies), they might also be unable to optimally use the strategies that are offered to them (Dunlosky and Hertzog 1998).

The MTL and fronto-striatal network are known to interact with each other (e.g. Poldrack and Packard 2003, Poldrack and Rodriguez 2004). This has been observed in stimulus-response learning (Poldrack et al., 1999), but also in object-location associative memory (Iaria et al., 2003). Since the MTL and fronto-striatal network interact, they might also be able to

compensate for each other. This was for instance observed in patients with specific damage to the caudate nucleus by Voermans and colleagues (2004). They showed that activation of the right hippocampus compensated for gradual functional degradation of the caudate nucleus in a route recognition task. In healthy young adults, an increased interaction was found between the caudate and hippocampus. This indicates that the hippocampus can compensate for reduced caudate processing when necessary.

Here we aim to investigate if elderly show compensatory activity in the fronto-striatal network in an object-location associative memory retrieval task, where the demand on self-initiated processing is manipulated during encoding only. Following the concept of resource deficit, elderly probably have difficulty using their declarative memory system when demands on self-initiated processing are high, which can be established by offering little contextual information (or so-called environmental support (Craik et al., 1987)). The task used is the same as used by De Rover et al. (2008). They investigated self-initiated processes in an fMRI study using an episodic memory task for sequences of object-location associations in a grid. Here, the structure of the sequence during encoding could implicitly influence the representation used at retrieval. During encoding, either all the objects were visible simultaneously (rich environmental support) or every object became visible transiently (poor environmental support). They found that young adults adapted their representation used at retrieval to the encoding cues available. Rich environmental support during encoding rendered activation in regions related to mental imagery (Wheeler et al., 2000), such as the fusiform gyrus, the lingual gyrus and cuneus during retrieval, in addition to areas generally found active during retrieval tasks. In turn, poor environmental support during encoding rendered activation in the globus pallidus and thalamus during retrieval; structures that are generally involved in memory where temporal information is crucial (Ivry and Spencer 2004, Packard and Knowlton 2002, Vakil et al., 2000).

We hypothesise that elderly will not be able to use the environmental support as systematically as the young use it (imagery), due to a lack of attentional resources. To investigate if the elderly use the extra environmental support in the same systematic way as the young, we first conducted a complementary behavioural experiment with unconstrained response order during recall in young and elderly adults, in which the encoding conditions were identical to the ones used in the fMRI experiment, to make sure any differences between conditions during retrieval are exclusively attributable to differences occurring at encoding.

Participants had to encode sets of 9 object-location associations in a 3×3 grid while either a rich environmental encoding structure was provided (all objects visible simultaneously), or while a poor environmental encoding structure was provided (isolated objects becoming visible sequentially). At recall, participants were instructed to reconstruct the grid freely.

To investigate the neural basis of this hypothesised absence of visual imagery in elderly and the putative fronto-striatal support to the declarative memory system, we applied the same task as described above in an fMRI study with young and elderly participants. Besides large overlap in brain

activation between young and elderly participants and conditions (since we investigate only highly educated elderly and there were no perceptual differences during cued-recall), we expected any specific differences to pertain to the support of the putatively impaired declarative memory system in the elderly, namely, more activation in the fronto-striatal network as a function of age.

This study is especially important for people working with elderly, like geriatricians, psychologists and occupational therapists, as the outcomes might be useful being taken into account when designing training and therapy.

## 2. Results

### 2.1. Behavioural experiment

Performance during recall of object location associations without a predefined recall order was well above chance level (11%=1/9 items×100%) in both groups and conditions (environmentally rich, young: mean correct=75.0%, SD=23.1%,  $t_{11}=9.6$ ,  $P<0.0001$ ; environmentally poor, young: mean correct=69.8%, SD=22.6%,  $t_{11}=9.0$ ,  $P<0.0001$ ; environmentally rich, elderly: mean correct=71.1%, SD=22.5%,  $t_{11}=9.3$ ,  $P<0.0001$ ; environmentally poor, elderly: mean correct=64.2%, SD=24.3%,  $t_{11}=7.6$ ,  $P<0.0001$ ). There was no interaction between age and condition ( $F_{(1,22)}=0.12$ , ns.) and no main effect of age on performance ( $F_{(1,22)}=0.26$ , ns.). Performance of both groups was better during recall after environmentally rich encoding ( $F_{(1,22)}=6.40$ ,  $P<0.05$ ).

To investigate whether participants used the spatial structure of the grid during retrieval after environmentally rich or the environmentally poor encoding, we analysed the relation between response order and positions in the grid of the correct answers only. For items encoded in a rich environment, the percentage of correct answers that was relocated in spatially contiguous (adjacent) positions in the grid during retrieval, was above chance level only in young participants (young: mean=134%, SD=28%; one-sample t-test, test value=100%,  $P<0.01$ ; elderly: mean=93%, SD=26%, ns.). For items encoded in a poor environment, the percentage of spatial contiguous correct answers was not different from chance level in both groups (young: mean=99%, SD=44%, one-sample t-test, test value=100%, ns; elderly: mean=90%, SD=39%, ns). This pattern of results indicates that the young used the environmental cues (neighbouring items) to reconstruct the grid after the environmentally rich encoding condition.

### 2.2. fMRI experiment

#### 2.2.1. Behavioural results

During cued recall in the scanner, participants performed significantly above chance level (11%) in both groups (environmentally rich condition, young: mean correct=73.2%, SD=16.2%,  $t_{19}=17.2$ ,  $P<0.0001$ ; environmentally poor condition, young: mean correct=66.7%, SD=15.5%,  $t_{19}=16.1$ ,  $P<0.0001$ ; environmentally rich, elderly: mean correct=51.7%, SD=16.8%,  $t_{19}=10.8$ ,  $P<0.0001$ ; environmentally poor, elderly: mean correct=44.3%, SD=15.7%,  $t_{19}=9.5$ ,  $P<0.0001$ ). Young

adults performed better than the elderly group ( $F_{(1,38)}=19.59$ ,  $P<0.0001$ ). For both groups, performance was better for object–location associations that were studied in a rich than in a poor environment ( $F_{(1,38)}=43.27$ ,  $P<0.0001$ ). No interaction between the factors age and condition was observed ( $F_{(1,38)}=0.16$ , ns.).

#### 2.2.2. fMRI results

Given performance differences between young and old subjects, performance was used as a covariate in all fMRI analyses. However, not considering performance yielded very similar results (not shown) suggesting that differences in performance can hardly explain differences in brain activity observed between young and old subjects.

**2.2.2.1. Cued recall versus rest and main effects.** Following the two encoding conditions, young and elderly participants activated similar brain regions during cued recall relative to the visual fixation condition. In general, these involve the dorsal and ventral visual processing stream extending into the MTL, (pre)motor areas, dorsolateral prefrontal cortex (DLPFC) and the basal ganglia (see Fig. 2). Although the activation patterns from elderly appear generally more extensive compared to the young, a direct contrast between the two age groups shows only specific differences (see Table 1). The left superior temporal lobe (BA 21/22/42) and right basal ganglia (caudate/putamen extending into insula) were stronger activated in elderly than in young participants (main effect of aging; Elderly>Young, in an Age×Condition ANCOVA, see Table 1).

**Table 1 – Local maxima of the age × condition ANCOVA.**

Region	BA	Z score	Local maxima		
			x	y	z
<i>Main effect of age (ANCOVA: Elderly&gt;Young)</i>					
STG (l)	21/22	4.12	−62	−8	6
STG (l)	42	4.03	−64	−20	8
Putamen		4.34	28	18	10
Insula		3.69	36	16	6
Caudate		3.50	20	22	2
<i>Interaction effect (ANCOVA: Environmentally rich&gt;Environmentally poor &amp; Elderly&gt;Young)</i>					
MTG (l)		4.64	−40	−50	10
Fusiform gyrus (l)	37	4.15	−42	−48	−16
ITG (l)		4.03	−46	−50	−8
Thalamus (r)(pulv.)		4.43	22	−24	10
Parahippocampal gyrus (r)		4.27	38	−24	−20
Brainstem (r)		4.14	6	−40	−10
Internal capsule (l)		4.04	−16	−12	−8
Globus Pallidus (l)		3.86	−22	−18	−6
Thalamus (l) (lp)		3.58	−10	−16	−2
Thalamus (r) (dm)		3.88	4	−10	10
Thalamus (r) (nvl)		3.88	10	−8	4
Globus Pallidus (r)		3.59	18	−4	−6

Stereotaxic coordinates are listed in MNI space. BA=Brodman area; pulv.=pulvinar; lp=lateral posterior nucleus; dm=mediodorsal nucleus; nvl=ventral lateral nucleus.

**2.2.2.2. Condition × Age interaction.** To tackle the question at issue whether there are age-related differences in brain activity indicating compensatory processes we explored age-related differences in brain activation during retrieval between the environmentally rich and environmentally poor conditions by examining the interaction between the factors of condition and age. The Condition × Age interaction (Environmentally rich > Environmentally poor and Elderly > Young, see Table 1 and Fig. 3) revealed effects in the basal ganglia (left and right globus pallidus), thalamus, left fusiform gyrus, left middle temporal gyrus, right parahippocampal gyrus and right hippocampus. In particular the interaction in the basal ganglia and thalamus seems to be driven by stronger brain activation by the elderly after the environmentally rich encoding condition (see Figs. 3A and B, for a graph of the parameter estimates). For instance, elderly have significantly stronger activation in the thalamus than the young after the environmentally rich encoding condition (Post hoc two sample t-test:  $t_{38} = -2.1$ ;  $P < 0.05$ ). In addition, activity in the thalamus is higher after environmentally poor encoding than after environmentally rich encoding in the young (one sample t-test:  $t_{19} = -2.3$ ;  $P < 0.05$ ). In the elderly the reverse is the case ( $t_{19} = 3.4$ ;  $P < 0.005$ ).

In addition, we found an interaction of the factors condition and age in an extended MTL region. To explore this further, we plotted the parameter estimates of the local maximum in the hippocampus ([28 –22 –6], Figs. 3C and D). Elderly showed enhanced activation compared to young during cued recall after environmentally rich encoding (two sample t-test:  $t_{38} = -2.4$ ;  $P < 0.05$ ). Activation in elderly was also enhanced after the environmentally rich encoding condition when compared with the environmentally poor condition (one sample t-test:  $t_{19} = 4.6$ ;  $P < 0.001$ ).

Altogether, generally increased activation during recall in fronto-striatal network and left superior temporal lobe is accompanied by enhanced activation of the declarative memory system in the elderly after environmentally rich encoding.

### 3. Discussion

In this study, we aimed to investigate the effects of aging on object–location memory and their neural underpinnings, by employing two complementary experiments (with identical encoding conditions) involving a task where the retrieval conditions differed only in the way the object–location associations were encoded. Because the test procedures within each experiment were identical for the two conditions at issue, the differences in brain activity or performance were exclusively related to differences occurring at encoding. In other words, one can conclude that differences in performance between conditions in the behavioural experiment are related to differences that occurred at encoding and that differences in retrieval-related activity between conditions in the imaging experiment are related to the very same differences that occurred at encoding.

Behaviourally, despite small subject groups, we found that young are able to use the information from an environmentally rich encoding structure systematically during retrieval;

they used a representation likely to involve mental imagery after environmentally rich encoding. In contrast, environmental support does not result in the use of an imagery-based representation in elderly.

Both age groups benefited from the visibility of all neighbouring objects during the environmentally rich encoding condition, which is reflected by the increased performance on this condition in the behavioural and fMRI experiment. On the brain level, the enrichment of the encoding structure resulted in specific differences between young and elderly subjects. While in young it results in the use of imagery (cuneus) during recall (see De Rover et al., 2008), the elderly engage their declarative memory system (hippocampus, thalamus, fusiform gyrus) to accompany the fronto-striatal network. In general, elderly showed enhanced activation of the basal ganglia (right caudate extending to insula), as we had expected.

During the fMRI experiment, the elderly were outperformed by the young. This is likely to be reflected in the main effect of aging that was observed in the left superior temporal gyrus. The elderly probably had difficulty suppressing task irrelevant input (such as scanner noise) (see also Amedeo and Diaz 1998, Meulenbroek et al., 2004). This idea is in line with studies investigating effects of attention on visual processing (Gisselgard et al., 2003, Petersson et al., 1999a,b, Rouleau and Belleville 1995), which showed that task-irrelevant processing can be suppressed by, for instance, deactivation of the auditory cortex. Hence, one might speculate that elderly participants have more difficulty focusing their attention on task-relevant visual input.

The putamen and caudate nucleus, in which also a main effect of age was observed, are in the literature often implicated in tasks where stimulus–response learning is involved (Knowlton et al., 1996, Packard and Knowlton 2002). We therefore attribute this effect to the support that the fronto-striatal network gives to the declarative memory system, because attentional resources decline with age.

We observed several interaction effects, which indicate that environmental support results in involvement of the declarative memory system: The medial dorsal nucleus of the thalamus is thought to be involved in the strategic component of declarative memory (Aggleton and Brown 2006), as for instance lesions of the medial dorsal nucleus affect the ability to use retrieval strategies (for a review, see Van Der Werf et al., 2003). Van der Werf and colleagues propose an important role of this nucleus in controlling focus on the memory content. With age, the thalamus seems to stay relatively preserved structurally (for example, see Grieve et al., 2005). The differential activation we observed is therefore probably compensatory and specific, that is, it might be related to the retrieval of additionally encoded information (neighbouring items) in the condition where this information was given (environmentally rich condition).

We also found an interaction effect in the right MTL. Several previous memory studies also observed enhanced activation of the right MTL in elderly (Maguire and Frith 2003, Meulenbroek et al., 2004), which has generally been interpreted as additional spatial processing. No doubt the MTL is involved in spatial processing (Bird and Burgess 2008, Eichenbaum et al., 1999), but this involvement is not exclusive. For

instance, Ekstrom and Bookheimer (2007) observed the hippocampus is equally involved during spatial and sequential retrieval in young subjects. Furthermore, patients with MTL lesions perform poorly on memory tasks for spatial location, temporal order and list discrimination (for a review, see Yonelinas 2002). In addition, it was found that the hippocampus is involved in encoding of between-domain associations (Piekema et al., 2009) and the maintenance of object–location associations (Piekema et al., 2006). These data point to a more general function, namely, retrieval of contextual information. Importantly, young did not show differential activation in the MTL as a result of condition. We therefore think the interaction effect in the right MTL reflects support of the declarative memory system to the fronto-striatal network in the elderly, which is also in line with the observation of Voermans and colleagues (2004) that the hippocampus can compensate for reduced caudate processing when necessary. Future studies may aim to elucidate this finding.

The enhanced activation of the fusiform, middle and inferior temporal gyrus, can probably also be ascribed to the support of the declarative memory system (Cabeza and Nyberg 2000). Classically these areas are involved in object-recognition, identification and categorization (Kondo et al., 2005, Martin and Chao 2001). Possibly, the enhanced activation found in the elderly only after environmentally rich encoding indicates the retrieval of information from neighbouring objects (such as “the adjacent objects were non-living”). This is, however, speculative and needs to be investigated further.

We are aware that the observed performance differences during the fMRI experiment pose a possible confounding effect on the interpretation of the data, especially regarding compensatory effects. The fact that the grid was not reconstructed over the course of the cued recall condition compromised the opportunity to benefit from environmental support. Within the concept of encoding specificity (Tulving and Thomson 1973), this means the retrieval cues were probably less effective in providing access to the stored information. In contrast to the task during fMRI, the behavioural experiment provided more overlap between study and test processing, helping retrieval. This concept is otherwise known as transfer appropriate processing (Morris et al., 1977). Together with the time pressure, this is likely what caused the worse performance in the fMRI experiment in the elderly. Regardless, we think controlling the fMRI data on single-subject and group level for performance levels provided us with sufficiently corrected data.

Applying an associative memory task like ours will likely recruit prefrontal areas like DLPFC. In our study, retrieval of object–location associations compared to visual fixation did activate the DLPFC. However, no significant differences were observed in direct comparison of the recall conditions or the age groups. Probably both conditions engage the DLPFC to the same degree (De Rover et al., 2008, Kessels et al., 2007). The lack of an age-related difference in the DLPFC is more difficult to interpret. One might expect prefrontal activations in elderly to be less asymmetric because of recruitment of contralateral homologous structures, as was found by Cabeza in high-performing adults (Cabeza et al., 2002) and subsequently interpreted in the HAROLD model (Hemispheric Asymmetry Reduction in Older adults) (Cabeza 2002). Some studies report

under-recruitment of prefrontal areas in elderly (Grady et al., 1995, Logan et al., 2002), but then mostly during encoding. The present experiment, however, focuses on retrieval influenced by encoding structure. The most plausible explanation for the lack of differences in the DLPFC is that the demand on the DLPFC is equal across the groups.

In conclusion, our findings demonstrate that environmental support during encoding results in young in the use of imagery during recall, while elderly engage their declarative memory system in addition to the fronto-striatal network. In general, elderly try to solve the task by stimulus–response associations based on single trial learning, because they lack attentional resources.

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## 4. Experimental procedures

### 4.1. Behavioural experiment

#### 4.1.1. Participants

Twenty-four healthy volunteers participated in the first experiment (12 young adults (De Rover et al., 2008), 6 female; mean age=27.6 years, SD=3.6, range 21–33; 12 elderly participants, 6 female; mean age=61.8 years, SD=3.6, range 59–70). There was no difference in educational level between the young and the elderly (mean number of years of formal education for the young was 17.6, SD=0.5; and 17.3, SD=0.5 for the elderly;  $t_{22}=1.69$ , ns). All but one young and one elderly participant were right-handed as indexed by an Edinburgh handedness index (see also: Oldfield 1971). All elderly participants were high functioning, autonomous community dwellers mostly having an academic degree. The elderly participants, while mostly retired, were all active in cultural pursuits, continuing education or with responsibilities in various associations. None of the healthy elderly had a history of neurological/psychiatric disease or used psychopharmacological drugs and none reported subjective memory problems. Vision was normal or corrected-to-normal in every participant. All participants gave written informed consent according to the Helsinki Declaration and the local medical ethics committee.

#### 4.1.2. Stimulus material and experimental procedure

We selected 117 black-on-white line drawings of common living and non-living objects (Snodgrass and Vanderwart 1980). We randomly chose 9 drawings (5 living and 4 non-living) for the distraction task, 54 drawings (27 living and 27 non-living) for the environmentally rich encoding condition and 54 drawings (27 living and 27 non-living) for the environmentally poor encoding condition. In line with the subsequent fMRI experiment, the behavioural experiment was structured in 12 cycles each including four phases: encoding, distraction, recall test, and visual fixation (Fig. 1). Each cycle started with either an environmentally rich or an environmentally poor encoding condition, in which object–location associations were memorized intentionally, and ended with an object–location cued-recall memory test. During encoding, participants were required to memorize nine objects and their particular location in a 3×3 grid displayed on a computer screen. The participants were instructed to make a living/non-

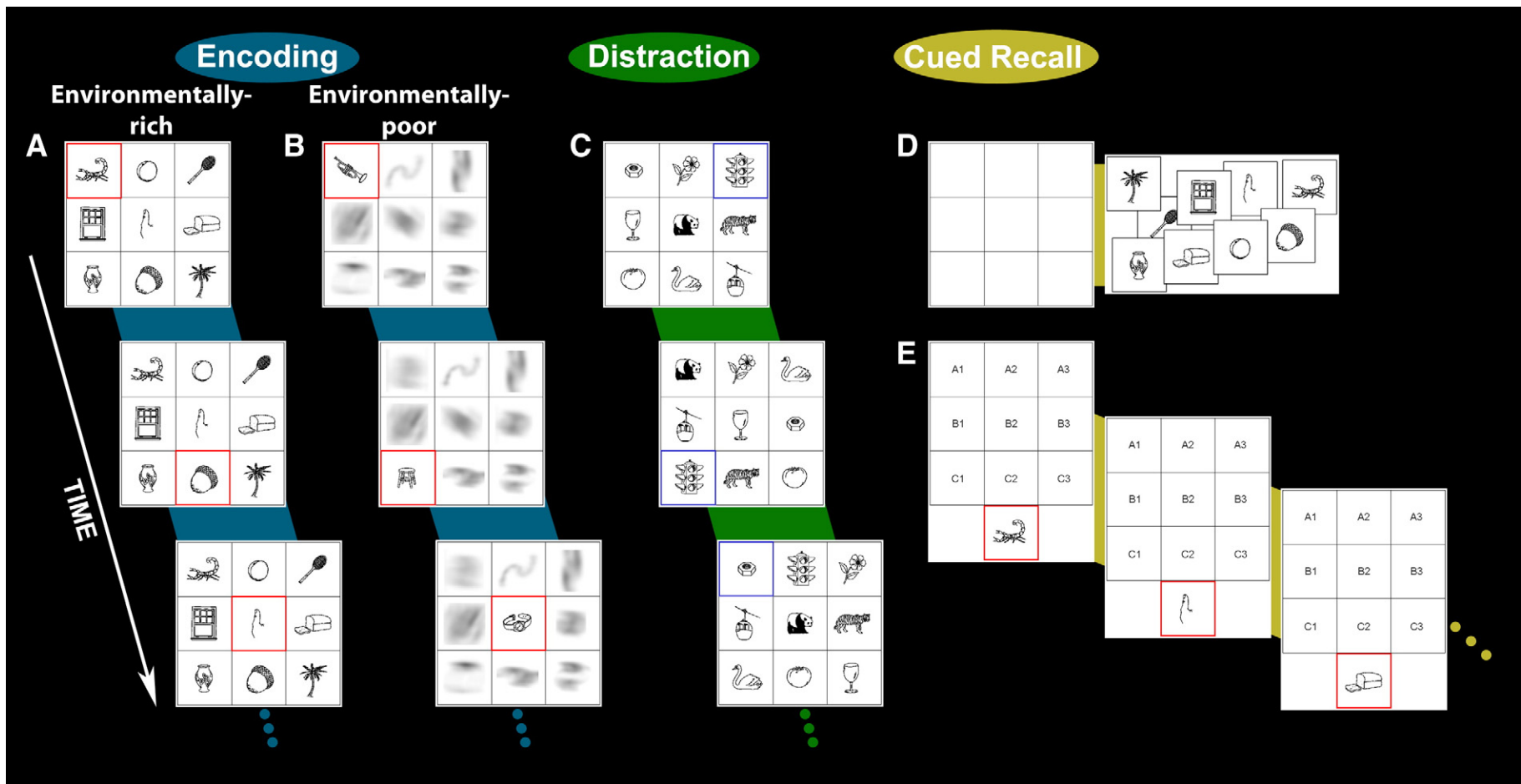


Fig. 1 – Experimental design, demonstrating the timeline of a single cycle. During Environmentally rich (A) or Environmentally poor encoding (B), participants made a living/nonliving judgment about the object in the red frame. (A) During Environmentally rich encoding, all objects were visible simultaneously and continuously. (B) During Environmentally poor encoding, objects were visible one at a time, while others were covered by a non-informative mask. (C) After encoding, participants were distracted with a one-back object memory task. (D and E) Cued recall, followed by a rest period (fixation cross, not shown). (D) In the behavioural experiment, cued recall comprised a paper version of the grid and objects, so participants could freely reconstruct the grid. (E) In the fMRI experiment, objects were presented sequentially below the grid during cued recall and participants indicated the positions by button presses corresponding to the coordinates in the grid. After cued recall, a rest period involving visual fixation was followed by a new encoding phase (randomly A or B).

living decision on each object and to respond verbally in order to ensure active participation and good recall performance. In the environmentally rich encoding condition, a red frame moved through the grid in a fixed pseudorandom order highlighting each item for 3 s, one item at a time, on which the living/non-living decision was made (Fig. 1A). The complete grid-display with all nine objects was visible during the entire encoding phase providing an environmentally rich encoding context, in which each item location could easily be associated with neighbouring objects and the entire grid. The environmentally poor encoding condition was identical to the environmentally rich study condition except that each object was only transiently visible for 3 s, highlighted by the red frame while all other items were hidden by non-informative masks (Fig. 1B). Thus, this condition did not provide simultaneously the entire grid with all objects as an associatively rich spatial structure and its structure was therefore relatively environmentally poor.

To overwrite potentially maintained working memory of the previous encoding phase, we introduced a one-back object memory distraction task (Fig. 1C, Baddely 1995). Participants were shown a 3×3 grid with nine novel objects. In this distraction condition, the sequential, random movement of a blue frame over each grid-box was accompanied by a random rearrangement of objects within the grid every 3 s. For each object highlighted by the blue frame, participants had to indicate whether this object was identical to the one shown previously in the blue frame independently of the location within the grid over nine successive trials. To parallelise this experiment as much as possible with the subsequent fMRI experiment, we included a visual fixation phase that was equally timed to the other phases (such that every phase lasted 27 s). During this condition a white, central fixation cross on a black background was displayed. Participants were instructed to attentively fixate the cross.

During the recall phase, which was identical for the environmentally rich and the environmentally poor encoding cycles, participants were presented with a 3×3 grid on cardboard, without drawings, as well as the studied objects each printed on a small paper card and provided at once in random spatial positions outside the grid (Fig. 1D). Participants were instructed to put the cards on the 3×3 grid on the positions studied during the encoding phase in any order.

Before the actual experiment, participants practiced the task with two cycles (one environmentally rich and one environmentally poor study condition) with additional line drawings, which were not otherwise used during the experiment. Participants were comfortably seated at a desk with a computer monitor for stimulus presentation and the 3×3 grid in front of them. We used a video camera to record the responses made by the participants for further analysis.

#### 4.1.3. Data analysis

First, the recall performance was analysed per individual, by dividing the number of correct answers by the total number of answers. Next, to investigate if participants used the environmental cues during recall, we analysed the correct answers only.

Specifically, we analysed the relationship between the spatial structure of the grid and the recall order chosen by the

participants, in order to determine whether participants used the spatial structure of the grid during retrieval in either of the two conditions (see De Rover et al., 2008, for details of the analysis). In short, the number of successive correct answers in contiguous positions in the grid (Fig. 1: for instance B1 followed by B2 or A1 would be a contiguous answer, but B1 followed by C3 is a non-contiguous answer) was counted per subject and cycle. This number was expressed as a percentage of the chance level, which was calculated as the number of contiguous correct answers divided by the total number of correct answers available in the grid (taking into account that response options decrease with every placement of an object) and set at 100%.

For example, consider a cycle containing only two successive correct answers (B1 followed by A1). The chance that the next correct answer after B1 is in a contiguous position is 0.375, because there are three available contiguous answers following B1: A1, B2 and C1, divided by eight available answers (all 9 positions except B1). The chance level of contiguous correct answers would then be set at 100%, so in this example 0.375 contiguous correct answers are expected by chance. Since the actual number of contiguous correct answers in this example cycle is 1, the percentage of contiguous correct answers is  $1/0.375 \times 100\% = 267\%$  of chance level ( $=0.375 = 100\%$ ) for this particular example cycle.

## 4.2. fMRI experiment

### 4.2.1. Participants

Forty healthy volunteers participated in the second experiment (not included in the behavioural experiment; 20 young participants (De Rover et al., 2008), 10 female; mean age=25 years, SD=4, range 19–33; 20 elderly participants, 10 female; mean age=65 years, SD=4.6, range 60–74). There was no difference in education level between the two age groups (mean duration of formal education young 18 years (SD=2) and elderly 17 years (SD=0.6),  $t_{38} = 1.55$ , ns). All participants were right handed as indexed by an Edinburgh handedness index (Oldfield 1971). All remaining subject characteristics were identical to the ones described for the behavioural experiment, except for the fact that 4 elderly were on anti-hypertensive medication. The structural MRI investigations did not show any evidence for anatomical abnormalities atypical for age.

### 4.2.2. Stimulus material and experimental procedure

The fMRI experiment was identical to the behavioural experiment except for: (1) to obtain sufficient power; the second experiment consisted of 20 instead of 12 cycles (Fig. 1). The 20 cycles were separated into two runs of 10 predefined cycles each, which were counterbalanced across participants. Every phase (encoding, distraction, cued recall or rest) lasted 29.7 s (9 items 3.3 s each). We selected 189 black-on-white line drawings (9 drawings [5 living and 4 nonliving] for the distraction task, 90 drawings [45 living and 45 non-living] for the environmentally rich encoding condition and 90 drawings [45 living and 45 non-living] for the environmentally poor encoding condition); (2) responses during encoding, distraction and recall were made by appropriate button presses; (3) During the recall task, participants were presented with the

3×3 grid without drawings. The participants could read the coordinates of each grid box, A1, A2, ... , C3 in the corresponding box. The encoded objects were shown one at a time below the grid in random order (Fig. 1E; 3.3 s per item). Participants were instructed to indicate the coordinate in which the object was presented during the study phase by an appropriate combination of left and right hand button presses.

Before going into the scanner, participants were first thoroughly trained at indicating the different locations in the grid with button presses, to avoid any age-related differences correlated to motor function. Next, they practiced the task in four cycles (two environmentally rich and two environmentally poor study conditions) with additional line drawings, which were not otherwise used during the experiment.

We used the Presentation software ([www.neurobs.com](http://www.neurobs.com)) to present the stimuli and recorded the responses made by the participants. Stimuli were back-projected via an LCD-projector onto a translucent screen that participants viewed through a mirror mounted on the head coil. Participants responded with two optical key devices, one in each hand. The subject's head was immobilized in order to reduce head motion during fMRI data acquisition. The behavioural responses the participants made while in the scanner were analysed for accuracy. The use of different retrieval structures during recall was analysed in the behavioural experiment and thus not further analysed in the fMRI experiment. This approach was chosen, because it allowed us to predefine the response order during recall in the scanner, so that differences in brain activity would not be confounded by any differences in responses.

#### 4.2.3. Data acquisition

Whole head T2\*-weighted EPI-BOLD fMRI data were acquired with a Siemens Sonata 1.5T MR scanner using an interleaved slice acquisition sequence (volume TR=2.93 s, TE=40 ms, 90

degree flip-angle, 37 axial slices, slice-matrix size=64×64, slice thickness=3.5 mm, no slice gap, FOV=224 mm, isotropic voxel-size=3.5×3.5×3.5 mm<sup>3</sup>). High-resolution structural MR images were acquired with a T1-weighted MP-RAGE sequence (volume TR=2.25 s, TE=3.93 ms, 15 degree flip-angle, 176 sagittal slices, slice-matrix size=256×256, slice thickness=1 mm, voxel-size=1×1×1 mm<sup>3</sup>).

#### 4.2.4. MR Image preprocessing and statistical analysis

Image preprocessing and statistical analysis was done with the SPM5 software ([www.fil.ion.ucl.ac.uk](http://www.fil.ion.ucl.ac.uk)). Functional EPI-BOLD images were realigned and the subject-mean functional MR images were co-registered with the corresponding structural MR images using mutual information optimization. These were subsequently spatially normalized (i.e., the normalization transformations were generated from the structural MR images and applied to the functional MR images) and transformed into standardized MNI space defined by the SPM5 MNI T1 template, and finally the functional images were convolved with an isotropic 3D spatial Gaussian filter kernel of 8 mm (Hayasaka and Nichols 2003, Petersson et al., 1999a, b). The fMRI data were proportionally scaled to account for global effects and analysed statistically using the general linear model and statistical parametric mapping (Friston et al., 1994). The linear model included convolved explanatory variables (box-car regressors of the recall phase) modelling the experimental conditions in a blocked fMRI design. The explanatory variables were temporally convolved with the canonical hemodynamic response function provided by SPM5. The realignment parameters were added to the model as regressors of no-interest. Furthermore, to correct for performance differences between cycles within a subject, performance for each cued recall phase was included in the model by parametric modulation of the modelled recall

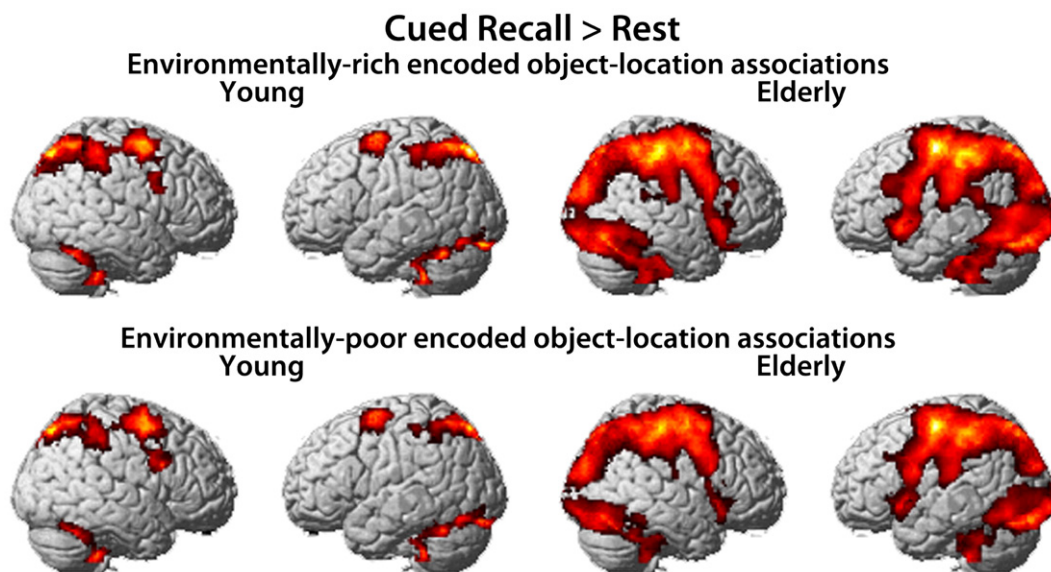
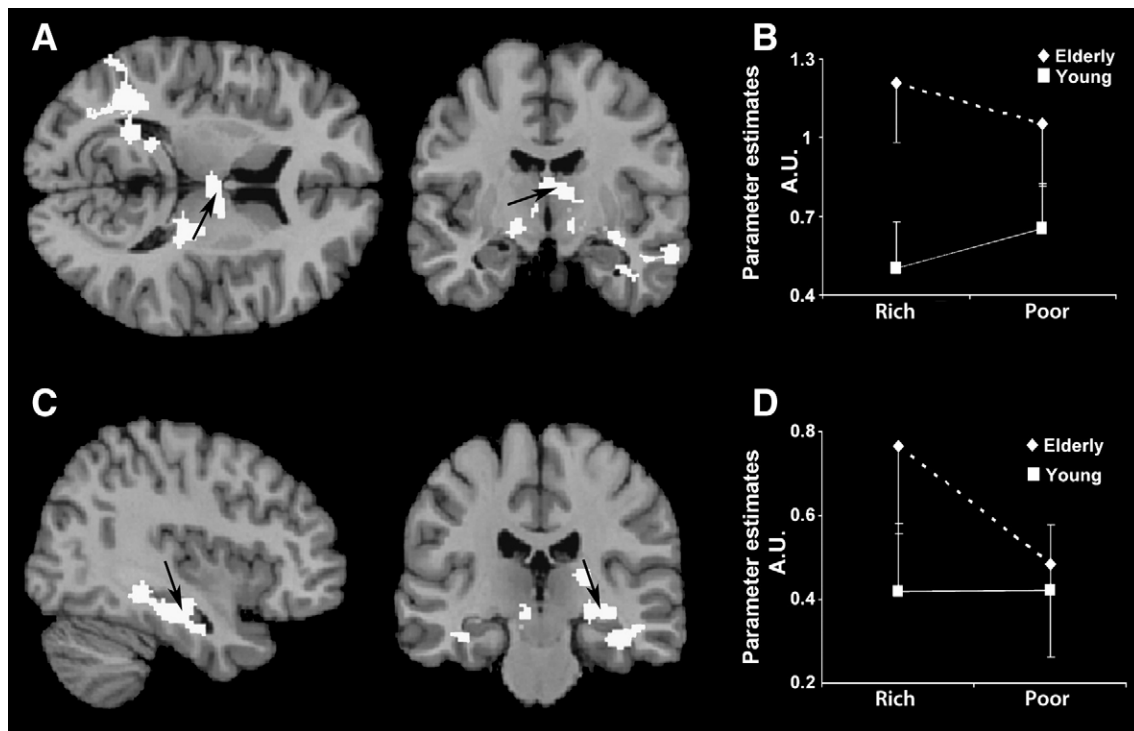


Fig. 2 – Brain regions activated during recall of environmentally richly encoded object–location associations (first row) or recall of environmentally poorly encoded object–location associations (second row) compared to rest condition (visual fixation) in Young participants (left columns) and Elderly participants (right columns). Activations are shown on an individual brain rendered in 3D; only significant clusters are shown ( $P < 0.05$  FWE corr.).





**Fig. 3 – Interaction effects (Environmentally rich versus Environmentally poor and Elderly versus Young), showing a transverse and a coronal view of the cluster of activation in the thalamus (A;  $z = 10$  and  $y = -10$ ) and a sagittal and coronal view of the cluster of activation in the right hippocampus/parahippocampal gyrus (C;  $x = 38$  and  $y = -24$ ), indicated by arrows. Parameter estimates (in arbitrary units; A.U.) of the local maxima are shown in (B) ( $[x\ y\ z] = [4\ -10\ 10]$ ) and (D) ( $[x\ y\ z] = [28\ -22\ -6]$ ). The parameter estimates show that the interaction effects are mainly driven by relatively enhanced activation in elderly during the recall of environmentally richly encoded object–location associations. Activations are shown superimposed on a high resolution T1-weighted volume (rcolin.nii (Holmes et al., 1998)). Error bars represent standard errors of the mean.**

phases. A temporal high pass filter of 128 s was applied to account for various low-frequency effects.

To visualise overall activation per condition in each age group (Fig. 2), two Condition versus Rest contrast images were made for each subject, which were subsequently subjected to a second level random effects analysis (one-sample *t*-test; every age group/condition separately).

In the statistical analysis, relevant contrasts (each recall condition separate, no baseline) corresponding to the hypotheses were used to generate contrast images for each subject, which were subsequently subjected to a second-level random effects analysis ( $2 \times 2$  ANCOVA with Age as between-subject factor, and Condition as within-subject factor. Subject performance was a covariate, to control for group differences). Results from the random effects analyses were initially thresholded at  $T = 3.20$  ( $P = 0.001$ , uncorrected) and the supra-threshold cluster-size was used as the test statistic. Only clusters significant at  $P < 0.05$  corrected for multiple non-independent comparisons based on the family-wise error rate (Worsley et al., 1996) are reported (Fig. 3).

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