The effects of aging on visual memory: evidence for functional reorganization of cortical networks

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Abstract

Recent evidence suggests that the mature human brain is capable of substantial functional reorganization following injury. The fact that the brain retains a great deal of plasticity raises the possibility that cortical reorganization may occur during normal aging. We examined this issue by using positron emission tomography (PET) to measure the brain activity associated with short-term memory for simple visual attributes in young and old observers. A two-interval forced choice procedure was used to measure spatial frequency discrimination thresholds for sine wave gratings presented at different inter-stimulus intervals (ISI). Memory load was manipulated by varying the duration of the ISI and by presenting an irrelevant masking stimulus in the middle of the ISI. Old and young observers performed the experiment equally well. However, the neural systems correlated with good performance differed for the two age groups. The results support the hypothesis that the functional networks that underlie visual memory undergo reorganization during aging. © 2001 Published by Elsevier Science B.V.

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1. Introduction

How are psychological processes instantiated in the brain? One classical technique for addressing this issue is to measure how damage to different parts of the brain affects behaviour. Using this approach, several studies have shown that focal lesions often produce deficits in specific aspects of visual perception (Huxlin & Merigan, 1998; Merigan, Freeman, & Meyers, 1997; Merigan, 1996; Merigan & Pham, 1998; Newsome & Paré, 1988; Newsome & Wurtz, 1988; Pasternak & Merigan, 1994) and memory (Greenlee, Lang, Mergner, & Seeger, 1995; Greenlee, Rischewski, Mergner, & Seeger, 1993; Markowitsch, 2000; Zola & Squire, 2000). For example, Newsome and Paré (1988) found that lesions to visual cortical area MT reduced the performance of monkeys in a motion discrimination task, but not in an orientation discrimination task. Based on the specificity of the induced deficit, Newsome and Paré argued that activity in MT contributes selectively to motion perception. However, Newsome and Paré also found that the effects of MT lesions were not permanent: over a period of several days, monkeys fully recovered their ability to discriminate motion. The transient nature of the deficit suggested that the pathways subserving motion perception were reorganized after the lesion. Indeed, there is now substantial evidence that sensorimotor pathways in the mature brain are capable of extensive reorganization following injury (Buonomano & Merzenich, 1998; Kaas, Florence, & Jain, 1999; Liepert et al., 2000).

The fact that the mature brain retains a surprising degree of plasticity has implications for theories of cognitive aging. It is generally agreed that performance on a wide range of perceptual and cognitive tasks declines with age, and that age-related changes are much greater in some tasks than in others (Grady & Craik, 2000). Within the area of memory, for example, age differences are very small in priming tasks, but are very large in episodic retrieval tasks (Balota, Dolan, & Ducheck, 2000). What are the biological underpinnings of these deficits? One possibility is that priming and episodic memory tasks tap into different sets of neural structures that support different memory systems (Tulving & Schacter, 1990), and that these systems age at different rates. For example, visual priming is associated with neural activity in extrastriate areas (Schacter & Buckner, 1998), whereas episodic memory is thought to be linked to activity in frontal areas (Lepage, Ghaffar, Nyberg, & Tulving, 2000). The effects of aging are not uniform throughout the brain (Anderson & Craik, 2000), so it is reasonable to suggest that the differential effects of aging in priming and episodic retrieval tasks reflects the structural integrity of extrastriate and frontal areas in old adults. Note that, according to this view, the failure to find a difference between old and young people in priming tasks means that the same neural circuitry underlies priming in both age groups. This interpretation of a null result is entirely appropriate, but the results reported by Newsome and Paré (1988) and others suggest that it may not always be correct. Specifically, demonstrations of plasticity in the adult brain raise the possibility that functional networks may be reorganized during normal aging, and therefore that the same behaviour in young and old adults may be controlled by different neural networks.

There are, of course, many neuroimaging (i.e., PET and fMRI) experiments that have found different patterns of brain activation in young and old adults engaged in the same task (Grady & Craik, 2000). Moreover, analyses of the functional interactions among brain regions – as revealed by interregional covariances of activity – suggest that age modifies the functional interactions subserving episodic and working memory (Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997; Esposito, Kirkby, Van Horn, Ellmore, & Berman, 1999; Grady et al., 1995; Grady, McIntosh, Rajah, Beig, & Craik, 1999). Both observations are consistent with the view that cortical circuits undergo substantial modification during normal aging. However, most neuroimaging studies of cognitive aging have measured brain activity in tasks on which there are group differences in performance, and therefore it is difficult to determine if differences in activity are due to the effects of age or to the effects of task difficulty. For example, it is possible that young observers would exhibit the same pattern of brain activation as old observers if the task was made more difficult (e.g., by shortening stimulus duration). Such a result would indicate that the group differences in brain activation reflected task difficulty rather than age (although the group difference in performance would, of course, still need to be explained). An additional complication is that most studies of memory have used stimuli like words and faces, which can be encoded in a variety of ways. Thus, even in memory tasks where young and old observers perform similarly, group differences in brain activation might reflect group differences in encoding and retrieval *strategies* rather than reorganization of the brain (Grady et al., 1999). With these issues in mind, we have chosen to measure brain activity in a visual memory task designed to produce equivalent performance in young and old observers and to minimize the number of effective encoding and retrieval strategies. Showing group differences in brain activity in such a task would bolster the argument that the human brain undergoes functional reorganization during normal aging. Tests involving sensory memory often show relatively small effects of aging (Balota et al., 2000), and so we have examined the effects of aging in a visual memory task.

2. Experiment 1: Preliminary psychophysical investigation

Traditionally, studies of visual memory have used words or pictures as stimuli. Such stimuli are semantically rich in the sense that a variety of conceptual encoding strategies could be used to represent items in memory. Our goal was to use procedures that restricted the range of potential encoding strategies, and therefore we adopted the stimuli and methods normally used in visual psychophysics to examine how simple visual attributes are stored in memory (Magnussen, 2000; Magnussen & Greenlee, 1999). The rationale behind this approach is that attributes such as orientation, spatial frequency, and direction of motion, are fundamental building blocks of visual perception (De Valois & De Valois, 1988; Graham, 1989), and therefore they might also be important for low-level visual memory. Memory for these attributes usually is measured in a two-interval forced choice (2-IFC) discrimination task, in which observers are asked to make a judgement about two

briefly presented patterns separated by a variable inter-stimulus interval (ISI). A discrimination threshold can be obtained by varying the difference between the patterns. When care is taken to ensure that observers must compare the patterns in the two intervals to perform the task accurately, the memory for an attribute can be inferred by examining how threshold varies as a function of the ISI. Moreover, the number of potential encoding and retrieval strategies is greatly reduced because the patterns lack semantic content and vary along a single, well-defined dimension, and therefore one can be reasonably certain that the memory being studied is perceptual in nature.

Our work has focused on how spatial frequency is encoded in memory. Several studies have shown that, in young observers, spatial frequency memory remains remarkably good even for ISIs as long as one minute. For example, Bennett and Cortese (1996) reported that spatial frequency discrimination thresholds for sine wave gratings remained roughly constant as the ISI was increased from 200 ms to 1 minute. Although spatial frequency memory is robust, it can be interfered with by presenting a pattern during the ISI. The magnitude of this so-called memory masking effect depends on the frequency of the masking stimulus (Bennett & Cortese, 1996; Magnussen, Greenlee, Asplund, & Dyrnes, 1991), a result which has been interpreted as showing that spatial frequency is represented in memory by an array of mutually inhibitory, frequency-tuned channels (Deutch & Feroe, 1975; Magnussen et al., 1991). Experiment 1 examines if spatial frequency memory is organized similarly in old and young observers.

2.1. Methods

Twenty-four young (17–30 years of age) and 24 elderly (60–85 years of age) observers from the University of Toronto Vision Lab Participant Pool took part in this experiment. All observers were in good health, and none suffered from any ocular disease. Observers were paid for their participation.

Stimuli were vertical sine wave luminance gratings, with average spatial frequency set to 1.9 cycles/deg, and contrast set to 20% (10–20 times greater than detection threshold). Grating contrast was modulated by a circular envelope that had a diameter of 5.25°; contrast was 20% within the envelope and zero elsewhere. Spatial frequency discrimination thresholds were measured with a 2-IFC procedure. Two gratings were each presented for 210 ms, separated by an ISI of 2400 ms. The observer's task was to indicate, by pressing one of two response buttons, which interval contained the higher spatial frequency (thinner bars). The observer was informed that the higher spatial frequency could appear in either stimulus interval with equal probability. A tone sounded at the end of the trial if the observer's response was incorrect.

Two spatial frequencies, f and $(f + \Delta f)$, were presented on each trial. Pilot experiments determined a set of four spatial frequency increments (Δf) around the threshold range, and on each trial, one Δf value was selected randomly and added to the target frequency, f. Each Δf was presented 25 times, yielding a total of 100 trials in a single block. A computer recorded the percentage of correct responses for each

Δf, and a cumulative normal function was fit to the results. An observer's discrimination threshold was defined as the size of Δf needed to respond correctly on 80% of the trials.

Thresholds were measured in two conditions. In the simple memory condition, no masking stimulus was presented, and during the ISI the observer viewed a uniform blank field. In the memory masking condition, a sine wave grating was presented for 210 ms in the middle of the ISI. The spatial frequency of the mask was 0.5, 1, or 2 times f. Observers were told they must look at the mask, but that it was irrelevant to the task and could be ignored. All observers were tested in both conditions.

The base frequency, f, was varied randomly across trials to ensure that observers based their discriminations on a comparison of the patterns in the two intervals. Frequency randomization was accomplished by multiplying f and Δf by a number, r, selected from a uniform random distribution ranging from -0.25 to 0.25 log units. A different value of r was selected on each trial. If a mask was presented, then the mask frequency also was multiplied by r. The initial base frequency was 1.9 cycles/deg, so after multiplication f ranged from 1.1 to 3.4 cycles/deg. This range of randomization was much larger than discrimination thresholds, and so the effects of randomization were noticed easily by the observers. The randomization procedure ensured that a different frequency was presented on each trial, so that observers could not base discrimination on a comparison of a stimulus in only one interval with a stored representation of f. Instead, to perform accurately, observers needed to store the frequency of the first stimulus in memory to be compared with the second stimulus.

2.2. Results and discussion

The results are shown in Fig. 1. Weber fractions $(\Delta f/f)$ are plotted on the vertical axis and the ratio of the mask and target frequencies is shown on the horizontal axis. The left-most points on the graph indicate discrimination thresholds measured without a mask and thus serve as a baseline. In this plot, the amount of memory masking is depicted by a vertical shift of the data points above the baseline. Similar results were obtained in both age groups: substantial memory masking occurred when the mask frequency was higher or lower than thetarget frequency, but no masking occurred when the masking target frequencies were identical. There was no significant difference between old and young observers.

The results of this preliminary experiment suggest that spatial frequency memory does not change significantly with age. At least for the one ISI tested, older observers retained spatial frequency information over this short retention interval as well as young observers, and the pattern of memory masking was the same in both age groups. This result is consistent with previous reports that perceptual memory does not change significantly with age (Balota et al., 2000).

Most importantly, the result of this preliminary experiment provided us with an appropriate paradigm with which to ask: what are the brain mechanisms that
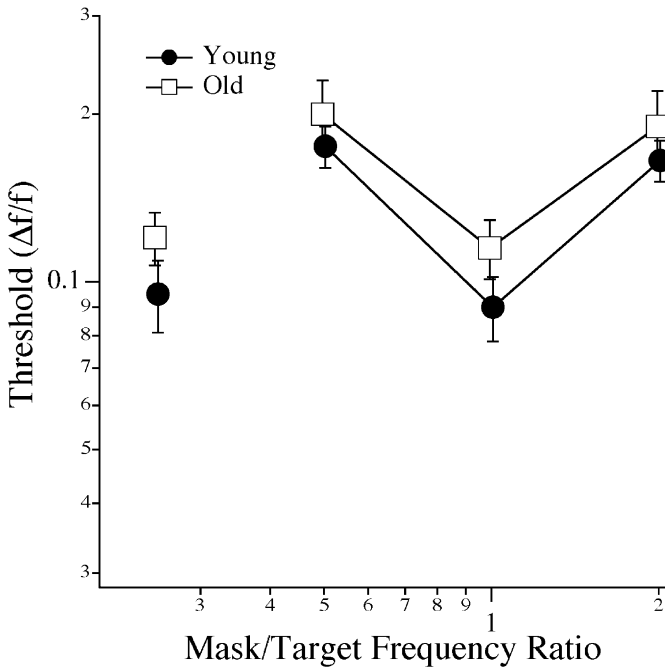
Fig. 1. Spatial frequency discrimination thresholds in old and young observers plotted as a function of the relative frequency of the mask. The mask was presented for 210 ms in the middle of the ISI, which was 2400 ms. The average frequency of the target stimuli was 1.9 cycles/deg. The symbols on the left side of the graph are thresholds measured without a mask. Error bars represent ±one standard error.

underlie perceptual memory? The next experiment addresses the issue of whether and how those mechanisms change with age. Does spatial frequency memory remain constant with age because old and young brains process information in the same ways? Or do old brains undergo functional reorganization consistent with the notion of evolving compensatory mechanisms throughout our lifetimes?

3. Experiment 2: Combining PET and psychophysics

The logic of this study was essentially the same as that in our initial behavioural experiments, except that psychophysical measures were combined with neuroimaging using positron emission tomography (PET). Some methodological details were changed due to constraints of the PET protocol (e.g., additional control tasks were required, only a limited number of experimental conditions could be included, and results needed to be combined across minute-long blocks of time). The key methodological differences are summarized below. For complete methodological details see Della-Maggiore et al. (2000) and McIntosh et al. (1999), where some of these results have been described previously.

3.1. Methods

Ten young (20–30) and nine old (60–79) new observers recruited from the University of Toronto Vision Lab Participant Pool took part in the experiment. As in our preliminary experiment, observers were required to discriminate two sine wave gratings from one another by deciding which interval had the higher spatial frequency (thinner bars). However, whereas all stimuli were presented in the fovea in Experiment 1, here stimuli were presented in the near periphery. In one interval, a grating was presented 5.25° to the left of fixation, and in the other interval a grating was presented 5.25° to the right of fixation. The side on which the high-frequency grating appeared and the interval in which it appeared were randomized from trial to trial. Only the simple memory condition was included (i.e., there were never any masking stimuli), and ISIs of either 500 or 4000 ms separated grating stimuli.

Psychophysical testing was conducted over two sessions, separated by about 24 h. Testing on Day 1 identified the stimuli that observers would see on Day 2, when PET measurements were made concurrent with psychophysical testing. The goal was to ensure that during scanning observers were tested only with Δf values straddling their 80% correct threshold level for each condition. This strategy equates task difficulty – as indexed by response accuracy – across participants and conditions, eliminating that factor as a possible confounding source of differences in brain–behaviour relationships.

On Day 2, PET scans of regional cerebral blood flow (rCBF) were taken while observers performed the 2-IFC frequency discrimination task. As on Day 1, observers were asked to attend to each pattern, and then respond by pressing one of two buttons to indicate which side contained the higher spatial frequency pattern. We also included a zero ISI condition, in which both patterns were presented simultaneously. For each ISI, observers also performed a control task in which the two spatial frequencies presented on each trial were identical to each other, but spatial frequency was varied across trials as in the experimental conditions. In the control conditions, observers were asked to attend to each pattern and then press both response buttons at the end of each trial. The purpose of the control trials was to enable us to factor out age-related changes in brain activity that were not specifically related to visual memory (e.g., viewing visual stimuli, making motor responses, etc.) in standard subtraction analyses (see below). ISI was held constant within a single PET scan. To ensure that enough trials were included at each ISI so that a reliable rCBF signal would be obtained, we required participants to make all of their responses within 1500 ms after the presentation of the second grating stimulus. This time limit was in effect during the pre-testing on Day 1 as well, so that testing was as similar as possible on the two days.

PET scans were obtained using a protocol described elsewhere (Cabeza et al., 1997). Briefly, PET scans were obtained after a bolus injection of 40 mCi [^{15}O] H_2O for each scan. Images were acquired over 60 s using a GEMS-Scanditronix PC2048-15B head scanner (in-plane resolution 5–6 mm), and measurements began when the bolus tracer arrived to the head. Each scan lasted one minute, and the inter-scan interval was 11 min. Radioactive counts were used as an indirect indication of rCBF.

All observers' images were spatially transformed to facilitate inter-subject averaging and identification of common areas of change. For each observer, all image volumes were registered to the initial scan to correct for head motion across the experiment. The images were then transformed to an rCBF template conforming to a standard brain atlas space (Talairach & Tournoux, 1988) and smoothed with a 10 mm isotropic Gaussian filter to reduce individual anatomic variability (SPM95; see Friston, 1995). Voxel values within a transformed image volume were then expressed as a ratio of the average counts for all brain voxels within a scan. There were no group differences in whole brain average counts, which justifies the ratio adjustment.

3.2. Results and discussion

3.2.1. Behaviour

The behavioural results from Day 2 are shown in Fig. 2. Young and old thresholds did not differ at either ISI. Average response time was approximately 1 s and did not differ across groups or ISI.

Thresholds in both groups increased with increasing ISI, suggesting that some information about spatial frequency was lost over time, but that the rate of loss (forgetting) was the same for young and old participants. Previous studies (including our own pilot work), have found no effect of ISI on discrimination thresholds. One
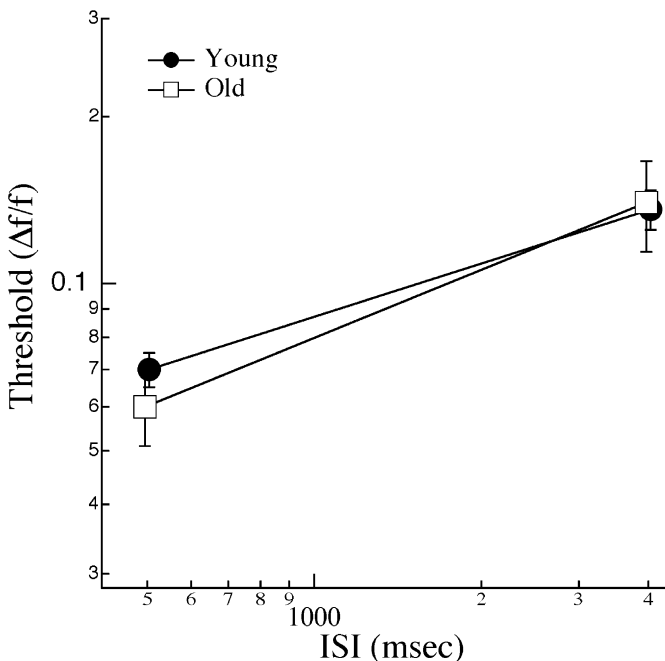

Fig. 2. The behavioural results from Experiment 2. Spatial frequency discrimination thresholds for young and old observers are plotted as a function of ISI.

possible factor contributing to the ISI effect in our experiment is that our stimuli were presented in the near periphery, not in the fovea. If one of the functions of short-term visual memory is to help knit together information across successive fixations, one might expect that memory should be maintained the longest for patterns falling on the fovea, because that is where most visual information is encoded. Information from the periphery may be more important for guiding saccades, but not for maintaining high-fidelity representations of the visual world. In that case, it would make sense for visual memory to fade faster in the periphery than in the fovea. Because other studies typically use foveal presentations, additional work is needed to test this hypothesis.

Another possible explanation of the behavioural results is that they are a by-product of another methodological change to the standard paradigm that was necessitated by the PET procedure. Specifically, in our experiment observers were required to respond within a 1500 ms window. In contrast, in standard visual memory experiments (including our preliminary experiment), trials are self-paced, and observers take as long as they need to make their responses. In one recent study that examined both accuracy and reaction time (Magnussen, Idas, & Myhre, 1998), spatial frequency discrimination thresholds remained relatively constant for ISIs ranging from 1 to 10 s, but response times increased significantly for ISIs greater than 3 s. If more time is needed to perform optimally at ISIs above 3 s, one might expect that performance would decline (thresholds would increase) for longer ISIs when response time is constrained, as in our experiment. Again, additional experiments clearly are needed to test this hypothesis.

Regardless of the cause of increased thresholds, young and old observers' thresholds were affected similarly by ISI. This fact alone might lead one to expect that neural systems operate similarly across the lifespan. However, the results of neuroimaging analyses lead to a completely different conclusion.

3.2.2. Imaging

In this section, we describe the results from two different statistical analyses, one based on subtraction, and another based on covariances. We then present the results of a systems-level neural model.

For the first analysis, we performed a series of contrasts within SPM, and identified voxels showing greater functional signals in one set of conditions than in another. This sort of subtraction analysis, which rests on the assumption of functional localization, is the most common form of analysis in PET and fMRI, and can be thought of as subtracting brain activation under one set of conditions from activation under another set of conditions (different tasks, different subject populations, etc.).

For each observer, the data were collapsed across ISI, and activation measured in the control tasks was subtracted from activation measured in the discrimination tasks. This contrast identified brain regions where rCBF was significantly greater in the discrimination task. Next, these difference scores were compared across age groups. The results of these age-related contrasts are shown in Table 1, which indicates the regions in which task-related rCBF differed significantly across age

Table 1
The stereotaxic coordinates for the peak areas of task-specific activation that differed significantly across age groups[a]

Region	x	y	z
Young > old			
Right insula	42	−6	8
Substantia nigra	−12	−12	−8
Left medial temporal gyrus	−40	−42	8
Old > young			
Right cerebellum/occipital	24	−64	−16
Left superior frontal gyrus	−14	24	36

[a] Area labels are from the atlas designation (Talairach & Tournoux, 1988).

groups. Greater activation was observed in young observers in the right insula and left medial temporal gyrus (BA 21/22), whereas there was more left superior frontal activation (BA 8/32) in old observers than in young ones. Although such an analysis does yield age-related differences in brain activation, it is not clear whether those differences necessarily imply compensatory reorganization. As Grady and Craik (2000) point out, when determining whether compensatory reorganization has occurred, it is not enough to show that older brains exhibit more or less activity in a particular part of the brain; one must also show that the change in activity is associated with improved performance. To argue for compensation one must also understand the output side: the brain–behaviour relationship. One method for doing this would be to look for correlations between performance and activity level in a region of interest across individual observers. However, such an analysis would still be limited because it focuses on localized activity, rather than on the patterns of activity across the entire brain that relate to performance.

Instead, for our second analysis, we used multivariate partial least squares (PLS) to extract image-wide patterns of correlation relating brain activity and behaviour. A full description of PLS is found elsewhere (McIntosh, Bookstein, Haxby, & Grady, 1996). Essentially, PLS analysis enables us to derive commonalities and differences in activity across tasks and groups, based on the covariance between rCBF and behaviour (measured here by spatial frequency discrimination thresholds). In our study, the behavioural PLS identified three reliable, orthogonal latent variables, or patterns of activation across the whole brain, that were related to performance (McIntosh et al., 1999). The first pattern identified regions of activation that were common across both ISIs and age groups. In the common pattern, lower thresholds (i.e., better performance) were associated with high activation in the occipital cortices and ventral posterior thalamus, and low activation in the left anterior prefrontal and bilateral inferior parietal cortices.

The second pattern identified by PLS discriminated performance on the short (500 ms) ISI from performance on the long (4000 ms) ISI. The peak saliences for this ISI pattern are shown in Fig. 3a and Table 2. One can think of each salience as indicating the strength of the association between behaviour and activation in each area.
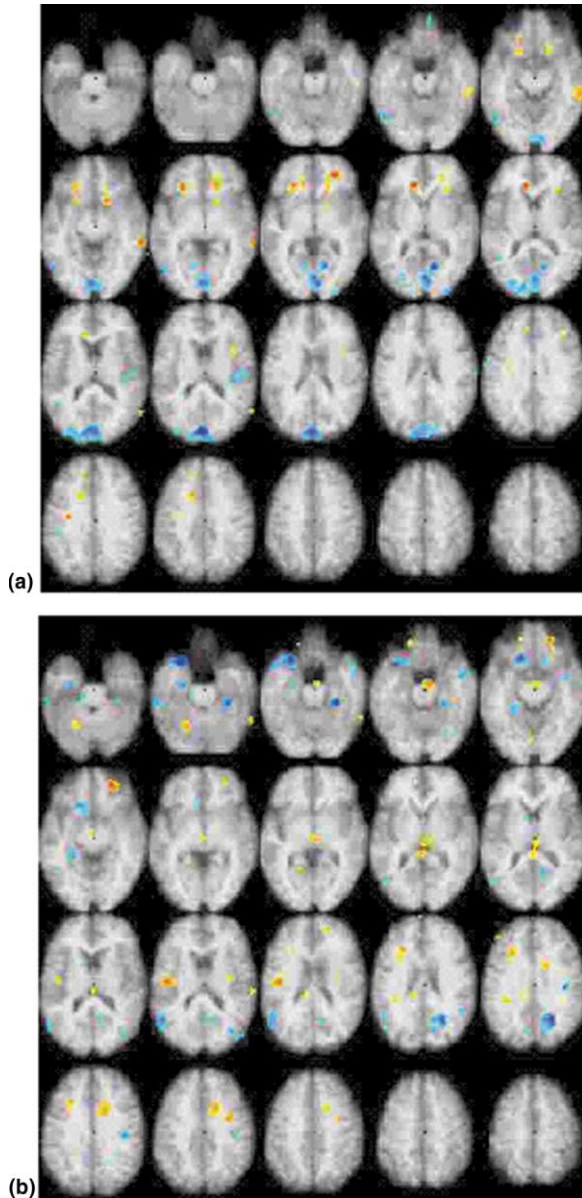
Fig. 3. Results of the PLS analysis of the PET data from Experiment 2 showing the relation between brain activity and behaviour. The ISI pattern and group pattern are shown in panels (a) and (b), respectively. Voxels with significant positive salience (red–yellow) and negative salience (blue–green) are displayed on an axial structural MRI. The MRI is in standard atlas space. In each panel, slices start at −28 mm below the AC–PC line (at the top left) and move in increments of 4 mm to +28 mm (at the bottom right). Left is to the left and the top is anterior. (Adapted from Fig. S1 in the supplementary material for McIntosh et al., 1999).

Table 2
The stereotaxic coordinates for the peak saliences identified by the ISI pattern[a]

Voxel	x	y	z	Area	Y-500	Y-4000	O-500	O-4000
1	56	−38	−8	A21-GTM	0.53	−0.76	0.29	−0.58
2	−20	14	−12	A38-GTM	0.94	−0.71	−0.47	−0.05
3	14	12	−8	Cpu	0.79	−0.75	−0.63	−0.70
4	−26	30	0	A45-GFI	0.81	−0.68	0.16	−0.26
5	24	42	0	A10 GFM	0.78	−0.64	0.47	−0.63
6	−12	28	8	Cpu	0.82	−0.51	0.60	−0.75
7	−32	−14	32	A3;2;1 GPO	0.67	−0.90	0.36	−0.08
8	−48	−64	−16	A19/37 GF	−0.66	0.73	−0.21	0.43
9	−6	−86	16	A17	−0.64	0.85	−0.49	0.93
10	4	−86	0	A18 GL	−0.63	0.76	−0.72	0.51
11	−4	−86	−4	A18 GL	−0.83	0.57	−0.48	0.59
12	26	−96	4	A18 GO	−0.41	0.69	−0.31	0.55
13	−28	−86	12	A18 GO	−0.52	0.74	−0.26	0.71
14	−44	−58	16	A37-GTM	−0.40	0.58	−0.32	0.78
15	34	−26	16	A40 LPI	−0.65	0.53	0.10	0.48

[a] Area labels are from the atlas designation (Talairach & Tournoux, 1988). The final four columns show the correlation of the voxel value with discrimination threshold in the young (Y) and old (O) groups. 500 and 4000 refer to the short and long ISIs, respectively.

It is important to note that the regions depicted in Fig. 3 show areas that *together* form the ISI pattern, and it is incorrect to think of each salience as a difference score for a particular region. Negative saliences (blue–green in the figure) are seen in the medial occipital cortices, and positive saliences (red–yellow in the figure) bilaterally in ventral striatum and inferior prefrontal cortex, and in right inferior temporal cortex. This ISI pattern was correlated inversely with threshold across the two ISIs. At the short ISI, higher activity in the medial occipital cortex and lower activity in striatum, inferior prefrontal, and inferior temporal cortex was associated with better performance. At the long ISI, the reverse was true. Interestingly, although the ISI pattern was correlated with performance for both young and old observers, the correlations *among different regions* within the ISI pattern of activation were higher in young observers (Fig. 4a). This age-related difference in interregional correlations is consistent with the hypothesis that the functional network underlying this form of short-term visual memory is degraded in older observers.

If this is the case, how did older observers manage to perform as well as younger observers on the task? One possible answer is that older observers recruited new areas of the brain to help them compensate for the weakened state of the primary neural network. Support for this answer comes from the analysis of the third pattern of activation identified by PLS, which differentiated performance of old observers from young observers. The peak saliences for this group pattern are shown in Fig. 3b and Table 3. Negative saliences were found in the left anterior and medial temporal cortices and more dorsally in occipital cortex, and positive saliences in the posterior thalamus and dorsomedial prefrontal cortices. For old observers, the group pattern

correlated negatively with threshold at the short ISI, and positively with threshold at the long ISI. Thus, higher activity in temporal and occipital cortex and lower activity in thalamus and prefrontal cortex was associated with lower thresholds (better
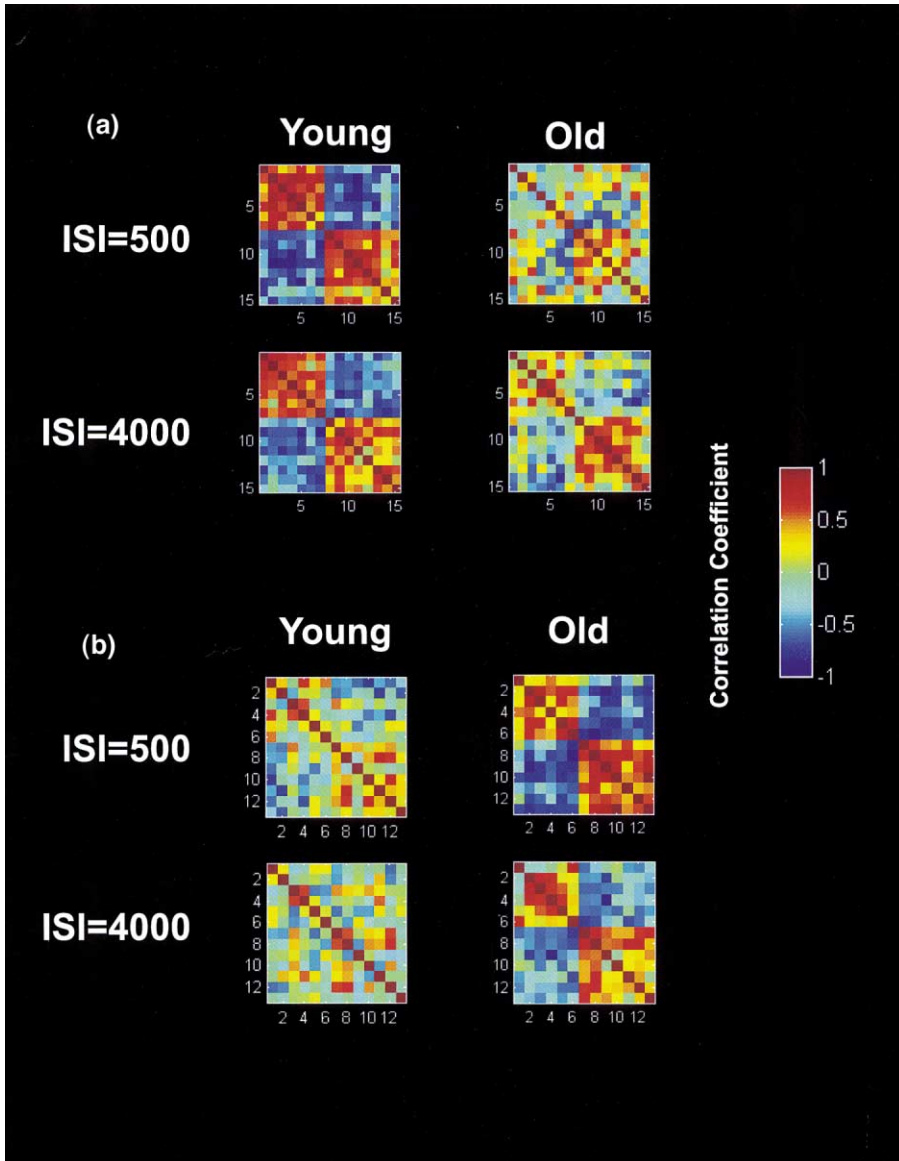

Fig. 4. Differential regional interrelations between young and old observers. Correlations among peak voxels from (a) ISI pattern and (b) group pattern. Correlation values are color-coded red (positive) or blue (negative). Values on the vertical and horizontal axes correspond to the voxel numbers in Table 2 for (a) and Table 3 for (b). The matrix is symmetric about the main diagonal, which corresponds to the correlation (+1.0) of each voxel with itself. (Adapted from Fig. 2 in McIntosh et al., 1999).
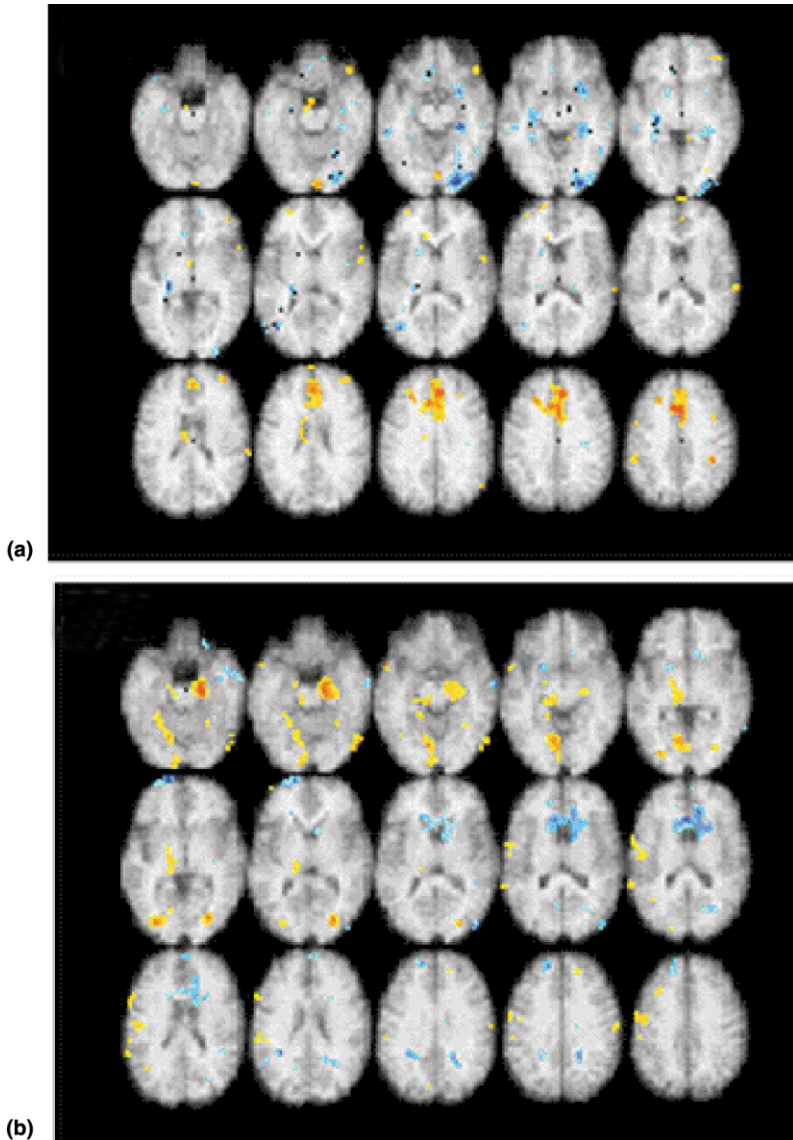
Fig. 5. Results of the seed-voxel PLS analysis of the PET data from Experiment 2 showing the relation between brain activity in each voxel and the activation in a seed voxel located in the right hippocampal region (RHIPP). PLS identified two patterns of activation that differentiated old and young observers. One pattern ((a) LV1) was strongly correlated with RHIPP activity in old observers, but not young observers. The other pattern ((b) LV2) was strongly correlated with RHIPP in young observers, but not old observers. Voxels with significant positive salience (red–yellow) and negative salience (blue–green) are displayed on an axial structural MRI. The MRI is in standard atlas space. In each panel, slices start at −28 mm below the AC–PC line (at the top left) and move in increments of 4 mm to +28 mm (at the bottom right). Left is to the left and the top is anterior. (Adapted from Fig. 1 in Della-Maggiore et al., 2000).

Table 3
The stereotaxic coordinates for the peak saliences identified by the group pattern[a]

Voxel	x	y	z	Area	Y-500	Y-4000	O-500	O-4000
1	4	−10	−16	MBR	−0.73	−0.20	0.41	−0.54
2	18	46	−8	A10-GFI	−0.25	0.32	0.76	−0.61
3	−4	−36	4	THAL	−0.40	0.02	0.76	−0.39
4	−42	−14	16	A42/22 GTS	−0.81	0.26	0.42	−0.46
5	−28	20	28	A9-GFM	−0.16	−0.18	0.92	−0.19
6	28	−4	40	A6-GPRC	−0.03	0.26	0.84	−0.78
7	−26	−12	−24	A36 GF/GH	0.22	0.22	−0.64	0.71
8	−30	14	−24	A38-GTM	0.39	−0.33	−0.71	0.79
9	26	−32	−20	A20-GF/GH	0.08	0.18	−0.85	0.62
10	−16	20	−12	A11/32 GC	0.81	−0.54	0.88	0.03
11	−50	−62	16	A39-GTS	0.47	0.38	−0.53	0.80
12	22	−58	24	A31-CU	0.77	−0.23	−0.51	0.62
13	36	−20	28	A3;2;1 GPO	0.35	−0.41	−0.82	0.39

[a] Area labels are from the atlas designation (Talairach & Tournoux, 1988). The final four columns show the correlation of the voxel value with discrimination threshold in the young (Y) and old (O) groups. 500 and 4000 refer to the short and long ISIs, respectively.

performance) at the short ISI, and the reverse was true for the long ISI. For young observers, the difference between ISIs was reversed and attenuated: greater activity in temporal and occipital cortex, and lower activity in thalamus and prefrontal cortex, was associated with higher thresholds (poorer performance) at the short ISI, and there was only a small correlation between brain activity and threshold at the long ISI. As was found with the ISI pattern, there was an age-related difference in the pattern of correlations among the brain regions within the group pattern (Fig. 4b). However, in this case the interregional correlations were stronger in old observers than young observers. If the strong interregional correlations are an indication of a working functional network, then the PLS analysis suggests that a new network has emerged for old observers that is not present for young observers. One interpretation of this result is that old brains recruit new areas of the brain (i.e., the group pattern) to perform the task to compensate for a lack of coherence among areas within the primary network used by young brains (the ISI pattern).

   To better understand the way in which the neural system underlying short-term visual memory might change with age, we next used PLS to examine if the functional connections between the right hippocampal region (RHIPP, $x = 20, y = -18, z = 12$) with the rest of the brain were the same in young and old observers (Della-Maggiore et al., 2000). This so-called seed-voxel PLS is conceptually identical to the behaviour PLS, except that activity in RHIPP is used as a covariate instead of behaviour. RHIPP was selected as the seed because there was a significant negative correlation between activation in that region and threshold that did not vary across ISI and age

group: in all groups and conditions, increased activation in RHIPP was associated with lower threshold. The seed-voxel PLS identified two significant patterns of activity that were correlated with RHIPP activity and which differentiated old and young observers. The first pattern was highly correlated with RHIPP activity in old observers at both ISIs ($r = -0.85$ and -0.97 for the short and long ISI, respectively), but not in young observers ($r = 0.09$ and 0.19 for the short and long ISI, respectively). Conversely, the second pattern was correlated with RHIPP in young observers ($r = 0.9$ for both the short and long ISI), but not in old observers ($r = 0.02$ and 0.22 for the short and long ISI, respectively). The peak positive (red–yellow) and negative (blue–green) saliences – which represent the association between activation in each voxel and activation in RHIPP – for these two patterns are shown in Fig. 5. For the first pattern (labelled LV1 in the figure), activity in left superior frontal gyrus (BA 9/46) and middle cingulate gyrus was positively related to activity in RHIPP, whereas activity in the temporal gyrus, inferior temporal gyrus, and caudate nucleus was negatively related to RHIPP activity. The second pattern (labelled LV2 in the figure) drew on different structures: peak positive saliences were found in hippocampus and bilateral fusiform gyrus, and peak negative saliences were found in left superior frontal gyrus (BA 10) and bilateral posterior cingulate gyrus. The results of this analysis provide very strong support for the hypothesis that functional connections with RHIPP change significantly with age. The results are all the more surprising when one recalls that activation in RHIPP itself did *not* differ across groups or ISI.

Della-Maggiore et al. (2000) examined the interregional correlations among the regions in the two patterns identified by the seed-voxel PLS. Consistent with the results from the seed-voxel PLS, the interregional correlations obtained for the peak voxels in the first pattern were much stronger in old subjects than in young subjects, whereas those obtained for the peak voxels in the second pattern were much stronger in young subjects than in old subjects. To evaluate whether the pattern of interregional correlations were memory-specific, Della-Maggiore et al. (2000) compared the correlations found in the 500 and 4000 ms ISI conditions with the correlations among the same voxels measured during the zero ISI (i.e., simultaneous presentation) condition. For old subjects, but not for young subjects, the brain patterns showing high interregional correlations in the 500 and 4000 ms ISI conditions differed significantly from those in the simultaneous presentation condition. Thus, the pattern of activation found in old subject, but not young subjects, was sensitive to the memory component (i.e., ISI) of the task.

Although seed-voxel PLS identifies patterns of correlations among brain regions, it does not specify how those correlations arise. One possibility is that correlated activity in two regions reflects a direct anatomical connection between them. Another possibility is that the two regions are connected indirectly: for example, they both may receive inputs from a common, third region. Finally, correlated activity might reflect some combination of direct and indirect connections. Covariance structural equation modelling (CSEM) is a technique that can be used to distinguish among these alternatives. CSEM is a form of path analysis that takes as its input the interregional correlations and known anatomical connections among a set of brain

regions. It then computes the set of path coefficients – or functional strengths – for the anatomical connections that provide the best fit to the observed interregional correlations. Hence, CSEM combines interregional correlations and anatomical data to create biologically plausible models of functional cortical networks of interregional interactions.

In the context of our experiment, CSEM was used to construct a model of the functional networks corresponding to the two latent variables identified by the seed-voxel PLS. The regions identified by the seed-voxel PLS constituted the nodes in the network, and the paths among the nodes included all mono-synaptic connections that have been identified based on the neuroanatomy of non-human primates (Arikuni, Sako, & Murata, 1994; Bachevalier, Meunier, Lu, & Ungerleider, 1997; Gloor, Salanova, Olivier, & Quesney, 1993; Knierim & Van Essen, 1992; Petrides & Pandya, 1988). Because the seed-voxel PLS identified two latent variables that were correlated with RHIPP activity in old and young observers, a different model was created for each latent variable. The path coefficients for each latent variable are shown in Fig. 6.

There were two main results. First, the patterns of interregional correlations found by the seed-voxel PLS could be well fit by a functional network based on known anatomical connections among the regions. Second, consistent with the interpretation of behavioural and seed-voxel PLS analyses, the functional networks derived for old and young observers differed significantly (Della-Maggiore et al., 2000). Significant differences across groups were assessed by comparing models in which path coefficients were constrained to be equal between groups (i.e., the null model) with those in which the coefficients were allowed to differ (i.e., the alternative model). The comparison of models was done by subtracting the goodness-of-fit χ^2 value for the alternative model from the χ^2 value for the null model. If the alternative model has a significantly lower χ^2 value, then the models are statistically different between groups. The comparison for the model built using the peak voxels from the first latent variable revealed a significant difference in effective connectivity between groups ($\chi^2_{\text{diff}}(12) = 64.85; P < 0.005$). As Fig. 6(a) shows, the strength of the connections in this network was much higher in old subjects than in young subjects. The model built using the peak voxels from the second latent variable also showed a significant difference in effective connectivity between groups ($\chi^2_{\text{diff}}(20) = 41.08; P < 0.005$). This network, shown in Fig. 6(b), consisted of more posterior regions than the one depicted in Fig. 6(a), and the strength of the connections in the young subjects was much higher than in their old counterparts. These results suggest that the functional connectivity among brain regions changes as a function of age.

4. General discussion

The psychophysical results of Experiments 1 and 2 showed that memory masking of spatial frequency is similar in magnitude and stimulus specificity in young and old observers, and that memory for spatial frequency is maintained with equal fidelity across the two age groups. Old and young adults performed a spatial frequency
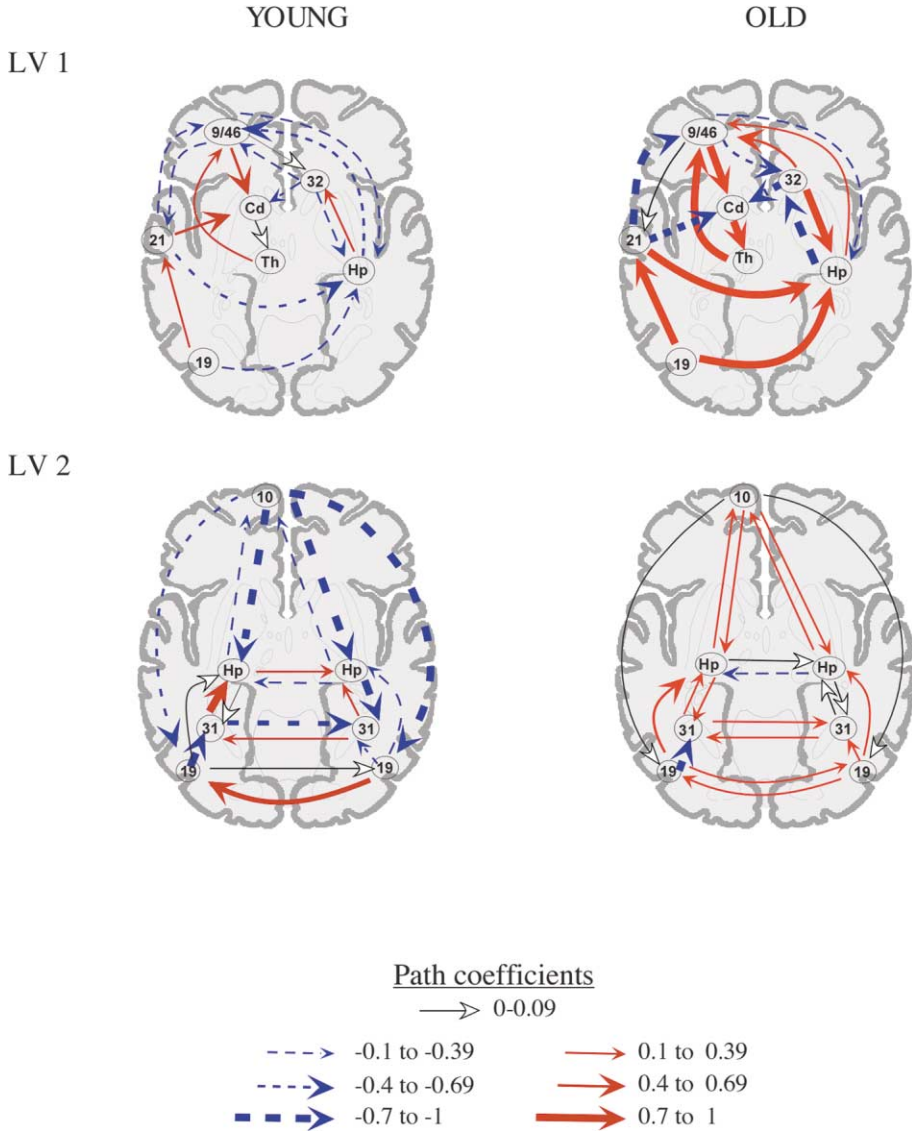
Fig. 6. Schematic illustration of the functional networks derived from covariance structural equation modelling (CSEM). The plots show the path coefficients derived for the young and old observers for the set of regions in the two latent variables (LV1 and LV2) identified by the seed-voxel PLS. The magnitude of the path coefficients is represented by the thickness of the lines. For LV1, path coefficients were higher in old observers, whereas coefficients for LV2 were higher in young observers. The group differences for both latent variables were significant. (Adapted from Fig. 3 in Della-Maggiore et al., 2000).

discrimination task with equal accuracy and response time, over a range of retention intervals. Although a typical interpretation of these behavioural results might be that the neural system underlying visual memory remains unchanged as a function of age,

the results from our neuroimaging analyses (Experiment 2) suggest otherwise. Our analyses indicated that different patterns of activation were correlated with performance in old and young subjects.

Taken as a whole, our findings suggest that you can teach an old brain new tricks: the results are consistent with the idea that the old brain reorganizes itself, building new functional connections across brain regions to compensate for weakened connections in the neural network used by younger brains. In the case of our experiments, this putative compensatory reorganization equates performance in the two age groups, but this need not always be the case.

An alternative hypothesis is that the different pattern of neural activity in young and old observers reflects differences in encoding strategies. However, our stimuli and the methods were designed to minimize the number of potential encoding and retrieval strategies available to observers. Moreover, no age differences were found when observers were asked to describe their strategy and to comment on the subjective difficulty of the task in a debriefing session after the PET measurements. Thus, although we cannot conclusively rule out the possibility that young and old observers used different strategies, we think it is unlikely.

The age-related cortical reorganization suggested by our results is likely limited in the extent to which it can compensate for other age-related neuronal changes. Thus, visual memory in elderly observers may be deficient in ways not revealed by our experiment. For example, other visual dimensions besides spatial frequency – orientation, movement, depth, and color – obviously must be maintained in memory for brief periods, yet we know little about how memory for such features changes with age. In addition, it may be the case that functional reorganization for one task may actually impair performance on another task – resulting in destructive reorganization rather than compensatory reorganization. For example, if older observers rely on the hippocampus to perform a relatively simple visual memory task like that in our experiments (Della-Maggiore et al., 2000; McIntosh et al., 1999), then that region might be less available for more complex memory tasks. There is some evidence to support this idea: Grady et al. (1995) found hippocampal activation during a face encoding task in young, but not old, subjects. Thus, the reorganization we observe in older brains may help to explain not only why performance is maintained as a function of age in the case of visual memory, but also why age-related deficits are obtained in a variety of other tasks with greater memory and attentional demands. Given the potential significance of this idea, additional research is clearly required to fully determine the conditions in which functional reorganization that enhances performance on one task may impair performance on others.

4.1. Understanding the stimulus and task

We purposely designed a memory task that was much simpler than the conditions in which visual memory normally operates. In our task, observers had to retain information about only one visual dimension (i.e., spatial frequency). In normal viewing conditions, however, different fixations will produce images that vary across many dimensions: the images will differ simultaneously in orientation, spatial

frequency, color, movement, and depth. There is some evidence that young observers maintain accurate representations of two or three features simultaneously in visual memory (Chua, 1990; Greenlee & Thomas, 1993; Vincent & Regan, 1995), but we do not know how well four or more dimensions can be stored, nor do we know whether the capacity of visual memory changes with age. Also, in our experiment observers were able to bring all of their attentional resources to bear on the visual memory task, whereas in naturalistic situations they would often have to divide attention among several tasks simultaneously. To generalize our findings to everyday conditions, it will be necessary to measure visual memory in tasks where observers must divide their attention across two or more tasks. Finally, objects typically have meaning far beyond simply "fat bars" and "thin bars". We do not yet fully understand which semantic contexts support or impair visual memory in the elderly. Obviously, these important issues must be addressed in future studies before a complete picture of visual memory in the elderly emerges.

Although some might view this lack of realism as a limitation of the psychophysical approach to memory used here and elsewhere (Cornelissen & Greenlee, 2000; Greenlee et al., 1993, 1995; Magnussen & Greenlee, 1992; Magnussen et al., 1991; Magnussen, Greenlee, & Thomas, 1996), we believe it has several advantages over traditional methods. First, as noted previously, using simple stimuli and tasks restricts the set of potential encoding and retrieval strategies, and therefore increases the likelihood that differences in brain activity reflect true reorganization of functional networks. Second, it is easy to see how the task used in our experiments could be altered systematically to approach the complexity of naturalistic conditions. For example, it would be relatively straightforward to increase the number of attributes that need to be remembered on each trial (e.g., contrast, orientation, spatial frequency), to increase the complexity of the stimulus by combining multiple sine wave gratings, or to require observers to integrate information across multiple fixations (Hayhoe, Lachter, & Feldman, 1991; Hayhoe, Bensinger, & Ballard, 1998). Finally, this approach could potentially allow memory researchers to take advantage of, and integrate their findings with, the considerable knowledge gained from psychophysical and physiological experiments about how simple patterns are represented by perceptual mechanisms (Kahana & Bennett, 1994; Kahana & Sekuler, 1999). Models that have been used to explain the detection and discrimination of simple patterns may also account for the identification of letters (Solomon & Pelli, 1994) and faces (Gold, Bennett, & Sekuler, 1999a,b), so a psychophysical approach to memory could be extended to include more naturalistic patterns, too.

It is also important to point out that the psychophysical task used in the current experiment is not really all that simple. Consider what is required for an observer to perform spatial frequency discrimination: the observer must understand the goal of the task (i.e., maximize the number of correct responses), gather evidence about the (visual) environment, and use that evidence to make a decision. To gather evidence efficiently, observers must focus attention at the stimulus location at the appropriate time, and maintain vigilance for the duration of the experiment. Also, observers may use the feedback provided at the end of each trial to change how they gather evidence or how it is used to select a response. In other words, even simple visual discrimi-

nation tasks engage an ensemble of important processes that probably are used in many naturalistic situations, and which activate many cortical and sub-cortical structures besides occipital cortex (Dupont et al., 1998; Greenlee, Magnussen, & Reinvang, 2000; Orban et al., 1998; Orban & Vogels, 1998). Thus, we would suggest that it is reasonable to view simple psychophysical tasks as useful tools for studying the neural bases of *cognition*. This view also is consistent with recent evidence showing that perception and cognition are strongly associated (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994; Schneider & Pichora-Fuller, 1999).

4.2. Functional localization vs. neural context

Historically, two implicit assumptions have guided neuroimaging research (Savoy, 2001). First, a particular mental process is linked to a particular part of the brain. Second, differences in brain activation imply differences in psychological processing (Culham, He, Dukelow, & Verstraten, 2001; Op de Beeck, Wagemans, & Vogels, 2001), Our work is based on a different set of assumptions, in which there is not a localized, one-to-one relationship between brain and behaviour, and instead mental processes occur via functional interactions across many areas of the brain. According to this view, one must consider the effective connectivity within the brain, not just localized regions of increased activity for one group or one condition, to fully understand those processes,

What advantage is gained by the using covariance analyses instead of the more standard subtraction technique? In its simplest form, any task can be conceptualized as a series of black-box stages: (i) input (the stimulus and task demands), (ii) brain activity, and (iii) output (the response, performance). In this context, subtraction typically focuses on the input side: the link between a task and brain activation. The standard subtraction technique highlights only the localized regions in which task differences are seen. One does not obtain a full picture of the whole neural system involved in a task, or the extent to which that system is related to performance. Covariance analyses, such as PLS, enable us to obtain a fuller picture, telling us how activity in one brain region correlates with activity in other regions across the brain, and how activity across the brain correlates with behaviour. This type of analysis enables us to examine links across any of the three stages, rather than limiting our analyses to the input side. Covariance analyses have further value added by examining the data in the context of a plausible neural model. Although, based on statistical covariance techniques, one can understand the extent to which distinct brain regions interact with one another, neural modelling enables us to determine the nature of those interactions (e.g., which are direct and which are indirect?).

For example, in our study, both the seed-voxel PLS and the CSEM analysis found that different functional networks were associated with activity in RHIPP in young and old observers, despite the fact that RHIPP activity *itself* did not differ between groups. Additional analyses suggested that the functional role of RHIPP and related brain areas also changed with age. Specifically, Della-Maggiore et al. (2000) found that activation of the RHIPP-related network was linked to the memory component of the task for old observers, but to the visual discrimination component of the task

for young observers. This result reinforces the idea that the function of an area depends not only its activity, but also on activity in other regions – in other words, the neural context in which activation occurs (McIntosh, 2000).

The fact that young and old observers performed similarly (both in terms of response accuracy and latency) in our task makes it unlikely that the information processing steps involved in encoding, storing, and discriminating spatial frequency differed dramatically across groups. Yet, the neural networks that were associated with performance did differ, suggesting that the same information processing was done by different sets of brain regions in young and old observers. This result raises the issue of when it is safe to assume that differences in brain activity correspond to differences in psychological processing and, more generally, what sort of hypotheses should be used to link neural responses and behaviour (Teller, 1984). Our results suggest that one should be cautious when concluding that different patterns of activation (or different degrees of activation in a given region) necessarily imply differences in mental processing.

References

Anderson, N. D., & Craik, F. I. M. (2000). Memory in the aging brain. In E. Tulving, & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 411–425). New York: Oxford University Press.

Arikuni, T., Sako, H., & Murata, A. (1994). Ipsilateral connections of the anterior cingulate cortex with the frontal and medial temporal cortices in the macaque monkey. *Neuroscience Research*, *21*(1), 19–39.

Bachevalier, J., Meunier, M., Lu, M. X., & Ungerleider, L. G. (1997). Thalamic and temporal cortex input to medial prefrontal cortex in rhesus monkeys. *Experimental Brain Research*, *115*(3), 430–444.

Balota, D. A., Dolan, P. O., & Ducheck, J. M. (2000). Memory changes in healthy older adults. In E. Tulving, & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 395–409). New York: Oxford University Press.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging?. *Psychology and Aging*, *12*(1), 12–21.

Bennett, P. J., & Cortese, F. (1996). Masking of spatial frequency in visual memory depends on distal, not retinal, frequency. *Vision Research*, *36*(2), 233–238.

Buonomano, D. V., & Merzenich, M. M. (1998). Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience*, *21*, 149–186.

Cabeza, R., McIntosh, A. R., Tulving, E., Nyberg, L., & Grady, C. L. (1997). Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport*, *8*(16), 3479–3483.

Chua, F. K. (1990). The processing of spatial frequency and orientation information. *Perception & Psychophysics*, *47*(1), 79–86.

Cornelissen, F. W., & Greenlee, M. W. (2000). Visual memory for random block patterns defined by luminance and color contrast. *Vision Research*, *40*(3), 287–299.

Culham, J., He, S., Dukelow, S., & Verstraten, F. A. J. (2001). Visual motion and the human brain: What has neuroimaging told us? *Acta Psychologica*, *107*, 69–94.

De Valois, R. L., & De Valois, K. K. (1988). *Spatial vision*. New York: Oxford University Press.

Della-Maggiore, V., Sekuler, A. B., Grady, C. L., Bennett, P. J., Sekuler, R., & McIntosh, A. R. (2000). Cortiolimbic interactions associated with performance on a short-term memory task are modified by age. *Journal of Neuroscience*, *20*(22), 8410–8416.

Deutch, D., & Feroe, J. (1975). Disinhibition in pitch memory. *Perception and Psychophysics*, *17*, 320–324.

Dupont, P., Vogels, R., Vandenberghe, R., Rosier, A., Cornette, L., Bormans, G., Mortelmans, L., & Orban, G. A. (1998). Regions in the human brain activated by simultaneous orientation discrimination: A study with positron emission tomography. *European Journal of Neuroscience*, *10*(12), 3689–3699.

Esposito, G., Kirkby, B. S., Van Horn, J. D., Ellmore, T. M., & Berman, K. F. (1999). Context-dependent, neural system-specific neurophysiological concomitants of ageing: Mapping PET correlates during cognitive activation. *Brain*, *122*(Pt 5), 963–979.

Friston, K. J. (1995). Statistical parametric mapping: Oncology and current issues. *Journal of Cerebral Blood Flow and Metabolism*, *15*, 361–370.

Gloor, P., Salanova, V., Olivier, A., & Quesney, L. F. (1993). The human dorsal hippocampal commissure: An anatomically identifiable and functional pathway. *Brain*, *116*(Pt 5), 1249–1273.

Gold, J., Bennett, P. J., & Sekuler, A. B. (1999a). Identification of band-pass filtered letters and faces by human and ideal observers. *Vision Research*, *39*(21), 3537–3560.

Gold, J., Bennett, P. J., & Sekuler, A. B. (1999b). Signal but not noise changes with perceptual learning. *Nature*, *402*, 176–178.

Grady, C. L., & Craik, F. I. M. (2000). Changes in memory processing with age. *Current Opinion in Neurobiology*, *10*(2), 224–231.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., Pietrini, P., Schapiro, M. B., & Haxby, J. V. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science*, *269*(5221), 218–221.

Grady, C. L., McIntosh, A. R., Rajah, M. N., Beig, S., & Craik, F. I. (1999). The effects of age on the neural correlates of episodic encoding. *Cerebral Cortex*, *9*(8), 805–814.

Graham, N. V. S. (1989). *Visual pattern analyzers*. New York: Oxford University Press.

Greenlee, M. W., Lang, H. J., Mergner, T., & Seeger, W. (1995). Visual short-term memory of stimulus velocity in patients with unilateral posterior brain damage. *Journal of Neuroscience*, *15*(3 Pt 2), 2287–2300.

Greenlee, M. W., Magnussen, S., & Reinvang, I. (2000). Brain regions involved in spatial frequency discrimination: Evidence from fMRI. *Experimental Brain Research*, *132*(3), 399–403.

Greenlee, M. W., Rischewski, J., Mergner, T., & Seeger, W. (1993). Delayed pattern discrimination in patients with unilateral temporal lobe damage. *Journal of Neuroscience*, *13*(6), 2565–2574.

Greenlee, M. W., & Thomas, J. P. (1993). Simultaneous discrimination of the spatial frequency and contrast of periodic stimuli. *Journal of the Optical Society of Amercia A. Optics and Image Science*, *10*(3), 395–404.

Hayhoe, M., Lachter, J., & Feldman, J. (1991). Integration of form across saccadic eye movements. *Perception*, *20*(3), 393–402.

Hayhoe, M. M., Bensinger, D. G., & Ballard, D. H. (1998). Task constraints in visual working memory. *Vision Research*, *38*(1), 125–137.

Huxlin, K. R., & Merigan, W. H. (1998). Deficits in complex visual perception following unilateral temporal lobectomy. *Journal of Cognitive Neuroscience*, *10*(3), 395–407.

Kaas, J. H., Florence, S. L., & Jain, N. (1999). Subcortical contributions to massive cortical reorganizations. *Neuron*, *22*(4), 657–660.

Kahana, M. J., & Bennett, P. J. (1994). Classification and perceived similarity of compound gratings that differ in relative spatial phase. *Perception & Psychophysics*, *55*(6), 642–656.

Kahana, M. J., & Sekuler, R. (1999). In visual recognition memory, interference reflects proximity in multidimensional stimulus space. *Investigative Ophthalmology and Visual Science*, *40*(4), S752.

Knierim, J. J., & Van Essen, D. C. (1992). Visual cortex: Cartography, connectivity, and concurrent processing. *Current Opinion in Neurobiology*, *2*(2), 150–155.

Lepage, M., Ghaffar, O., Nyberg, L., & Tulving, E. (2000). Prefrontal cortex and episodic memory retrieval mode. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(1), 506–511.

Liepert, J., Bauder, H., Wolfgang, H. R., Miltner, W. H., Taub, E., & Weiller, C. (2000). Treatment-induced cortical reorganization after stroke in humans. *Stroke*, *31*(6), 1210–1216.

Lindenberger, U., & Baltes, P. B. (1994). Sensory functioning and intelligence in old age: A strong connection. *Psychology and Aging*, *9*(3), 339–355.

Magnussen, S. (2000). Low-level memory processes in vision. *Trends in Neurosciences*, *23*(6), 247–251.

Magnussen, S., & Greenlee, M. W. (1992). Retention and disruption of motion information in visual short-term memory. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *18*(1), 151–156.

Magnussen, S., & Greenlee, M. W. (1999). The psychophysics of perceptual memory. *Psychological Research*, *62*(2–3), 81–92.

Magnussen, S., Greenlee, M. W., Asplund, R., & Dyrnes, S. (1991). Stimulus-specific mechanisms of visual short-term memory. *Vision Research*, *31*(7–8), 1213–1219.

Magnussen, S., Greenlee, M. W., & Thomas, J. P. (1996). Parallel processing in visual short-term memory. *Journal of Experimental Psychology. Human Perception and Performance*, *22*(1), 202–212.

Magnussen, S., Idas, E., & Myhre, S. H. (1998). Representation of orientation and spatial frequency in perception and memory: A choice reaction-time analysis. *Journal of Experimental Psychology. Human Perception and Performance*, *24*(3), 707–718.

Markowitsch, H. J. (2000). Neuroanatomy of memory. In E. Tulving, & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 465–484). New York: Oxford University Press.

McIntosh, A. R. (2000). From location to integration: How neural interactions form the basis for human cognition. In E. Tulving (Ed.), *Memory, consciousness, and the brain: The Tallinn conference*. Philadelphia: Psychology Press.

McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage*, *3*(3 Pt 1), 143–157.

McIntosh, A. R., Sekuler, A. B., Penpeci, C., Rajah, M. N., Grady, C. L., Sekuler, R., & Bennett, P. J. (1999). Recruitment of unique neural systems to support visual memory in normal aging. *Current Biology*, *9*(21), 1275–1278.

Merigan, W., Freeman, A., & Meyers, S. P. (1997). Parallel processing streams in human visual cortex. *Neuroreport*, *8*(18), 3985–3991.

Merigan, W. H. (1996). Basic visual capacities and shape discrimination after lesions of extrastriate area V4 in macaques. *Visual Neuroscience*, *13*(1), 51–60.

Merigan, W. H., & Pham, H. A. (1998). V4 lesions in macaques affect both single- and multiple-viewpoint shape discriminations. *Visual Neuroscience*, *15*(2), 359–367.

Newsome, W. T., & Paré, E. B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *Journal of Neuroscience*, *8*(6), 2201–2211.

Newsome, W. T., & Wurtz, R. H. (1988). Probing visual cortical function with discrete chemical lesions. *Trends in Neuroscience*, *11*(9), 394–400.

Op de Beeck, H., Wagemans, J., & Vogels, R. (2001). Can neuroimaging really tell us what the human brain is doing? The relevance of indirect measures of population activity. *Acta Psychologica*, *107*, 323–351.

Orban, G. A., Dupont, P., De Bruyn, B., Vandenberghe, R., Rosier, A., & Mortelmans, L. (1998). Human brain activity related to speed discrimination tasks. *Experimental Brain Research*, *122*(1), 9–22.

Orban, G. A., & Vogels, R. (1998). The neuronal machinery involved in successive orientation discrimination. *Progress in Neurobiology*, *55*(2), 117–147.

Pasternak, T., & Merigan, W. H. (1994). Motion perception following lesions of the superior temporal sulcus in the monkey. *Cerebral Cortex*, *4*(3), 247–259.

Petrides, M., & Pandya, D. N. (1988). Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *Journal of Comparative Neurology*, *273*(1), 52–66.

Savoy, R. (2001). History and future directions of human brain mapping and functional neuroimaging. *Acta Psychologica*, *107*, 9–42.

Schacter, D. L., & Buckner, R. L. (1998). Priming and the brain. *Neuron*, *20*(2), 185–195.

Schneider, B. A., & Pichora-Fuller, M. K. (1999). Implications of perceptual deterioration for cognitive aging research. In F. I. M. Craik, & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (pp. 150–175). Mahwah, NJ: Erlbaum.

Solomon, J. A., & Pelli, D. G. (1994). The visual filter mediating letter identification. *Nature*, *369*(6479), 395–397.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme Medical Publishers.

Teller, D. Y. (1984). Linking propositions. *Vision Research*, *24*(10), 1233–1246.

Tulving, E., & Schacter, D. L. (1990). Priming and human memory systems. *Science*, *247*(4940), 301–306.

Vincent, A., & Regan, D. (1995). Parallel independent encoding of orientation, spatial frequency, and contrast. *Perception*, *24*(5), 491–499.

Zola, S. M., & Squire, L. R. (2000). The medial temporal lobe and the hippocampus. In E. Tulving, & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 485–500). New York: Oxford University Press.