Recruitment of unique neural systems to support visual memory in normal aging

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The performance of many cognitive tasks changes in normal aging [1–3]. Recent behavioral work has identified some tasks that seem to be performed in an age-invariant manner [4]. To understand the brain mechanisms responsible for this, we combined psychophysical measurements of visual short-term memory with positron emission tomography (PET) in young and old individuals. Participants judged the differences between two visual stimuli, and the memory load was manipulated by interposing a delay between the two stimuli. Both age groups performed the task equally well, but the neural systems supporting performance differed between young and old individuals. Although there was some overlap in the brain regions supporting performance (for example, occipital, temporal and inferior prefrontal cortices, and caudate), the functional interconnections between these common regions were much weaker in old participants. This suggests that the regions were not operating effectively as a network in old individuals. Old participants recruited unique areas, however, including medial temporal and dorsolateral prefrontal cortices. These unique areas were strongly interactive and their activity was related to performance only in old participants. Therefore, these areas may have acted to compensate for reduced interactions between the other brain areas.

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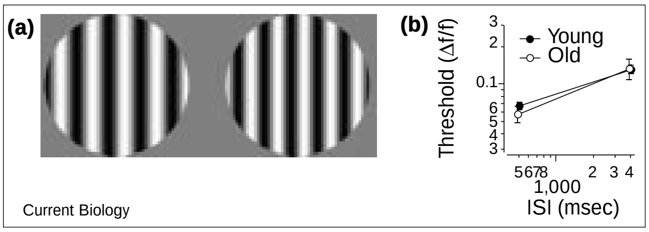
Results and discussion

Participants in our experiments saw pairs of vertical sinusoidal gratings presented successively in time with two different interstimulus intervals (ISIs; Figure 1a). After viewing each pair of gratings, participants pressed one of two keys to indicate which grating had the higher spatial frequency. Grating stimuli resist symbolic coding, thus they are free from complicating factors such as extra-laboratory associations or participants' differing verbal skills [5]. Psychophysical testing was performed in two sessions, separated by about 24 hours. The first day's results identified stimuli that each participant would see on day two, when PET measurements were made concurrently with the psychophysical testing. On day one, the spatial frequency difference (Δf) varied from trial to trial; discrimination thresholds were estimated for each individual. On the second day of testing, the spatial frequency differences were restricted to four values lying near and bracketing the participant's threshold for a given ISI. Restricting stimuli to the vicinity of a participant's threshold equalised task difficulty — as indicated by response accuracy — across participants and conditions, eliminating difficulty as a source of possible differences in brain–behavior relationships.

Figure 1b shows the mean discrimination thresholds determined during the second day of testing. Older participants' thresholds did not differ from those of their younger counterparts for either ISI. An analysis of the variance of participants' thresholds identified only one significant effect. For both groups, thresholds increased with ISI ($p < 0.01$). These results suggested that information about the first stimulus' spatial frequency was lost during the longer ISI, but that the rate of loss was similar in young and old participants. There was also no indication

Figure 1



Stimuli and behavioral results. (a) Comparison of two sine wave gratings differing in spatial frequency by 20% (Δf = 0.2). Stimuli are not drawn to scale. In each experimental trial, each grating was presented successively for 500 msec, with a blank (grey) interval in between of 500 or 4,000 msec. After the second stimulus, an asterisk appeared on the screen, signaling the onset of a 1,500 msec response window. During this time, the participant pressed one of two keys on a numerical keyboard to indicate whether the stimulus with higher spatial frequency (thinner bars) was presented in interval 1 or interval 2. (b) Mean discrimination thresholds (Δf/f) plotted as a function of ISI and age group. Filled symbols show results for young observers; open symbols for old observers. Bars indicate ± 1 standard error.

Table 1

Peak areas for the ISI patterns.

Voxel	Ratio	X	Y	Z	Area	Y–500	Y–4,000	O–500	O–4,000
1	2.78	56	–38	–8	A21–GTM	0.53	–0.76	0.29	–0.58
2	2.39	–20	14	–12	A38–GTM	0.94	–0.71	–0.47	–0.05
3	2.51	14	12	–8	Cpu	0.79	–0.75	–0.63	–0.70
4	2.67	–26	30	0	A45–GFI	0.81	–0.68	0.16	–0.26
5	2.75	24	42	0	A10 GFM	0.78	–0.64	0.47	–0.63
6	2.78	–12	28	8	Cpu	0.82	–0.51	0.60	–0.75
7	2.76	–32	–14	32	A3,2,1 GPO	0.67	–0.90	0.36	–0.08
8	2.41	–48	–64	–16	A19/37 GF	–0.66	0.73	–0.21	0.43
9	2.91	–6	–86	16	A17	–0.64	0.85	–0.49	0.93
10	2.54	4	–86	0	A18 GL	–0.63	0.76	–0.72	0.51
11	2.52	–4	–86	–4	A18 GL	–0.83	0.57	–0.48	0.59
12	2.30	26	–96	4	A18 GO	–0.41	0.69	–0.31	0.55
13	2.34	–28	–86	12	A18 GO	–0.52	0.74	–0.26	0.71
14	2.32	–44	–58	16	A37–GTM	–0.40	0.58	–0.32	0.78
15	2.36	34	–26	16	A40 LPI	–0.65	0.53	0.10	0.48

The ratio is the parameter estimate from the PLS analysis divided by its standard error. Voxel number corresponds to those in Figure 2. Area labels are from the atlas designations [21]. The final four columns show the correlation of the voxel value with threshold in each group. Y, young; O, old; 500 and 4,000 refer to the short and long ISIs, respectively.

of a group or ISI difference in task strategy, as indicated by post-experiment debriefing.

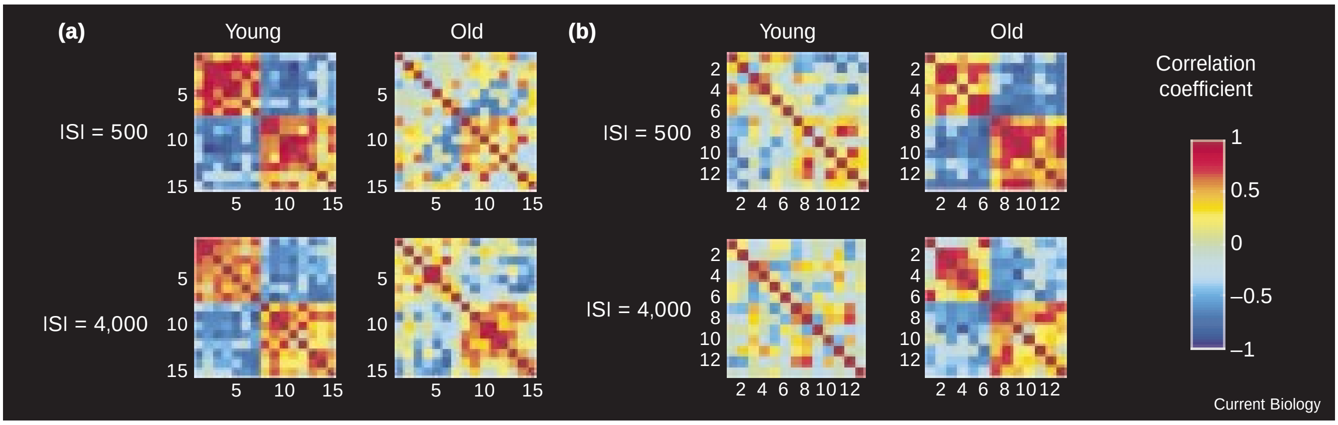
One-minute PET scans of regional cerebral blood flow were taken while participants performed the task on the second day. Within any single scan, the delay between grating stimuli was constant. The image analysis focused on whether the groups' equivalent thresholds were supported by the same neural systems [6,7]. To answer this question a multivariate partial least squares (PLS) analysis was used to identify image-wide patterns of correlation between brain activity and behavior that were either common to or differentiated ISIs and groups [8]. These patterns consist of a singular image within which the voxels are weighted in proportion to the strength and direction (positive or negative) of their brain–behavior correlation. Three reliable patterns were identified through PLS analysis: the first identified brain–behavior relationships that were common across ISIs and groups (Common pattern; $p = 0.10$); the second identified brain–behavior relationships that differentiated ISI only (ISI pattern; $p = 0.004$); and the third pattern identified brain–behavior relationships that distinguished groups (Group pattern; $p = 0.03$). In the Common pattern, dominant-negative weights (related to lower thresholds) were located in ventral occipital cortices and ventral posterior thalamus; peak positive weights (correlated with higher thresholds) were located in left anterior prefrontal and bilateral inferior parietal cortices. This pattern of brain activity might identify an age-invariant system related to discrimination *per se*.

The singular image for the ISI pattern (Table 1) identified negative weights in the medial occipital cortices and positive weights bilaterally in ventral striatum and inferior prefrontal cortex, and right inferior temporal cortex. For both groups, the pattern of brain activity correlated inversely with threshold across the two ISIs (Figure 2a). Thus, for the short ISI, greater activity in occipital and less activity in striatum, inferior prefrontal and inferotemporal was related to a lower threshold. The pattern was completely reversed for the long ISI.

The Group pattern (Table 2) identified brain–behavior correlations that differed between groups, and regions that were differentially related to the short and long ISIs. The corresponding singular image has negative weights in left anterior and medial temporal cortices and more dorsally in occipital cortex. Positive weights were less extensive, and included posterior thalamus and dorsomedial prefrontal cortices. For old participants, the pattern of brain activation correlated negatively with threshold at the short ISI and positively at the long ISI. Thus, at the short ISI, greater activity in temporal and dorsal occipital cortices was related to a lower threshold, whereas greater activity in posterior thalamus and dorsomedial prefrontal cortices was related to a higher threshold (Table 2). This pattern was completely reversed at the long ISI. Moreover, in young participants, this difference between ISIs was reversed and attenuated. Peak voxels, shown in Table 2, showed differential correlations with behavior in the two delay tasks in old participants, whereas in young participants, the voxels either correlated with behavior in only the short delay condition or in neither task.

Our results suggest that the basic functional network supporting performance was similar for the two groups (for example, the ISI effect), but that additional regions were recruited in the old participants (for example, the Group

Figure 2



Differential regional interrelations between young and old participants. 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 1 for (a) and Table 2 for (b). The matrix is symmetric about the main diagonal, which corresponds to the correlation (+1.0) of each voxel with itself.

effect). If this network hypothesis is correct, the interrelations, or functional connections [9], between peak voxels for the ISI pattern should be similar for young and old participants, whereas interrelations between voxels from the Group pattern should be stronger for old participants. Interregional correlations of activity serve as an indication of functional connectivity [10–12]. Figure 2a shows pseudo-colored representations of the correlation matrices of the voxels singled out by the ISI Pattern. For young participants, strong correlations between voxels are obvious in both ISIs. In old participants, correlations among the same brain regions are markedly reduced ($p = 0.05$). Figure 2b shows pseudo-colored representations of the correlation matrices for voxels identified from the Group pattern. Unlike Figure 2a, there is no obvious clustering of voxel correlations for young participants. In contrast, old participants show strong correlations among voxels at both ISIs. By comparing correlation maps across age groups in Figure 2b, one can see that correlations were far stronger in old participants' brains than in the brains of their young counterparts ($p = 0.05$). One intriguing explanation of these results is that the Group pattern might represent the additional areas recruited into the network for old participants to compensate for the lack of coherence between areas identified in the ISI pattern. The strong relationship between the Group pattern voxels and performance in the old participants reinforces this interpretation. For young participants, such recruitment would not

Table 2

Peak areas for the Group patterns.

Voxel	Ratio	X	Y	Z	Area	Y–500	Y–4,000	O–500	O–4,000
1	3.06	4	–10	–16	MBR	–0.73	–0.20	0.41	–0.54
2	3.66	18	46	–8	A10–GFI	–0.25	0.32	0.76	–0.61
3	3.08	–4	–36	4	THAL	–0.40	0.02	0.76	–0.39
4	3.35	–42	–14	16	A42/22 GTS	–0.81	0.26	0.42	–0.46
5	3.02	–28	20	28	A9–GFM	–0.16	–0.18	0.92	–0.19
6	3.08	28	–4	40	A6–GPRC	–0.03	0.26	0.84	–0.78
7	3.22	–26	–12	–24	A36 GF/GH	0.22	0.22	–0.64	0.71
8	3.70	–30	14	–24	A38–GTM	0.39	–0.33	–0.71	0.79
9	3.83	26	–32	–20	A20–GF/GH	0.08	0.18	–0.85	0.62
10	3.41	–16	20	–12	A11/32 GC	0.81	–0.54	–0.88	0.03
11	3.23	–50	–62	16	A39–GTS	0.47	0.38	–0.53	0.80
12	3.59	22	–58	24	A31–CU	0.77	–0.23	–0.51	0.62
13	3.26	36	–20	28	A3,2,1 GPO	0.35	–0.41	–0.82	0.39

The ratio is the parameter estimate from the PLS analysis divided by its standard error. Voxel number corresponds to those in Figure 2. Area labels are from the atlas designations [21]. The final four columns show the correlation of the voxel value with threshold in each group. Y, young; O, old; 500 and 4,000 refer to the short and long ISIs, respectively.

be necessary because areas from the ISI pattern formed a coherent functional network.

Our results lead to two important conclusions. First, even though participants in both age groups performed at equivalent levels, this equivalence emerged from the use of different brain regions. These findings, along with other recent studies [13–15], challenge the pervasive assumption that similar performance levels across groups indicates that the groups used the same neural system [16]. The neural networks supporting short-term visual memory differed as a function of age. Some differences between groups could reflect age-related modification of functional connectivity between regions [17]. Second, preserved performance with age may reflect a functional, task-related reorganization in the participants' brains [6], even for tasks as basic as spatial frequency discrimination. This reorganization takes two different, but possibly related forms: age-related changes in the brain regions that support visual memory, and age-related changes in the strength of functional coupling between participating regions [13]. Because old observers' performance was related to activity of and interactions between these unique areas (Figure 2b), recruitment of these area may have compensated for reduced interactions among other areas. Prefrontal and medial temporal cortices figured prominently in the collection of regions showing strong interactions in the old participants. Interestingly, in memory tasks in which old participants show a performance deficit, there is a lack of activation of prefrontal and medial temporal areas that are engaged in young participants [18]. Continued exploration of this age-related neural reorganization should identify the conditions that promote or inhibit reorganization, and elucidate whether the reorganization that preserves performance in one task does so at a cost to other behavioral and cognitive operations [19,20].

Supplementary material

Supplementary material including a figure showing the relationship of brain activity and behavior together with additional methodological details is available at http://current-biology.com/supmat/supmatin.htm.

Acknowledgements

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References

1. Craik FIM, Jennings JM: Human memory. In *Handbook of Cognition and Aging*. Edited by Craik FIM and Salthouse TA. New Jersey: Lawrence Erlbaum Associates; 1992:51-110.
2. Kosnik W, Winslow L, Kline D, Rasinski K, Sekuler R: Visual changes in daily life throughout adulthood. *J Gerontol* 1988, 43:63-70.
3. Sekuler R, Sekuler AB: Visual perception and cognition. In *Oxford Textbook of Geriatric Medicine.* 2nd Edition. Edited by Evans JG, Williams TF, Michel J-P, Beattie BL and Wilcock GK. Oxford: Oxford University Press; in press.
4. Bennett PJ, Sekuler AB: *Visual Pattern Analysis in Elderly Observers.* University of Toronto, Dept of Psychology, Vision Research Lab, Toronto, 1992.
5. Bennett PJ, Cortese F: Masking of spatial frequency in visual memory depends on distal, not retinal, frequency. *Vision Res* 1996, 36:233-238.
6. Esposito G, Kirkby BS, Van Horn JD, Ellmore TM, Berman KF: Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation. *Brain* 1999, 122:963-979.
7. Madden DJ, Turkington TG, Provenzale JM, Denny LL, Hawk TC, Gottlob LR, *et al.*: Adult age differences in the functional neuroanatomy of verbal recognition memory. *Hum Brain Mapp* 1999, 7:115-135.
8. McIntosh AR, Gonzalez-Lima F: Large-scale functional connectivity in associative learning: interrelations of the rat auditory, visual and limbic systems. *J Neurophysiol* 1998 80:3148-3162.
9. Friston K: Functional and effective connectivity: a synthesis. *Hum Brain Mapp* 1994, 2:56-78.
10. Horwitz B: Functional neural systems analyzed by use of interregional correlations of glucose metabolism. In *Visuomotor Coordination*. Edited by Ewert J-P and Arbib MA. New York: Plenum Press; 1989:873-892.
11. McIntosh AR, Rajah MN, Lobaugh NJ: Interactions of prefrontal cortex related to awareness in sensory learning. *Science* 1999, 284:1531-1533.
12 Strother SC, Kanno I, Rottenberg DA: Principal components analysis, variance partioning, and 'functional connectivity'. *J Cereb Blood Flow Metab* 1995, 15:353-360.
13. Hazlett EA, Buchsbaum MS, Mohs RC, Spiegel-Cohen J, Wei TC, Azueta R, *et al.*: Age-related shift in brain region activity during successful memory performance. *Neurobiol Aging* 1998, 19:437-445.
14. Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, *et al.*: Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci* 1997, 17:391-400.
15. Grady CL, Maisog JM, Horwitz B, Ungerleider LG, Mentis MJ, Salerno JA, *et al.*: Age-related changes in cortical blood flow activation during visual processing of faces and location. *J Neurosci* 1994 14:1450-1462.
16. Latham K, Barrett BT: No effect of age on spatial interval discrimination as a function of eccentricity or separation. *Curr Eye Res* 1998, 17:1010-1017.
17. Cabeza R, McIntosh AR, Tulving E, Nyberg L, Grady CL: Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport* 1997, 8:3479-3483.
18. Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, *et al.*: Age-related reductions in human recognition memory due to impaired encoding. *Science* 1995, 269:218-220.
19. Grady CL: Brain imaging and age-related changes in cognition. *Exp Gerontol* 1998, 33:661-673.
20. Salthouse TA: Constraints on theories of cognitive aging. *Psychonom Bull Rev* 1996, 3:287-299.
21. Talairach J, Tournoux P: *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Thieme Medical Publishers; 1988.

Supplementary material

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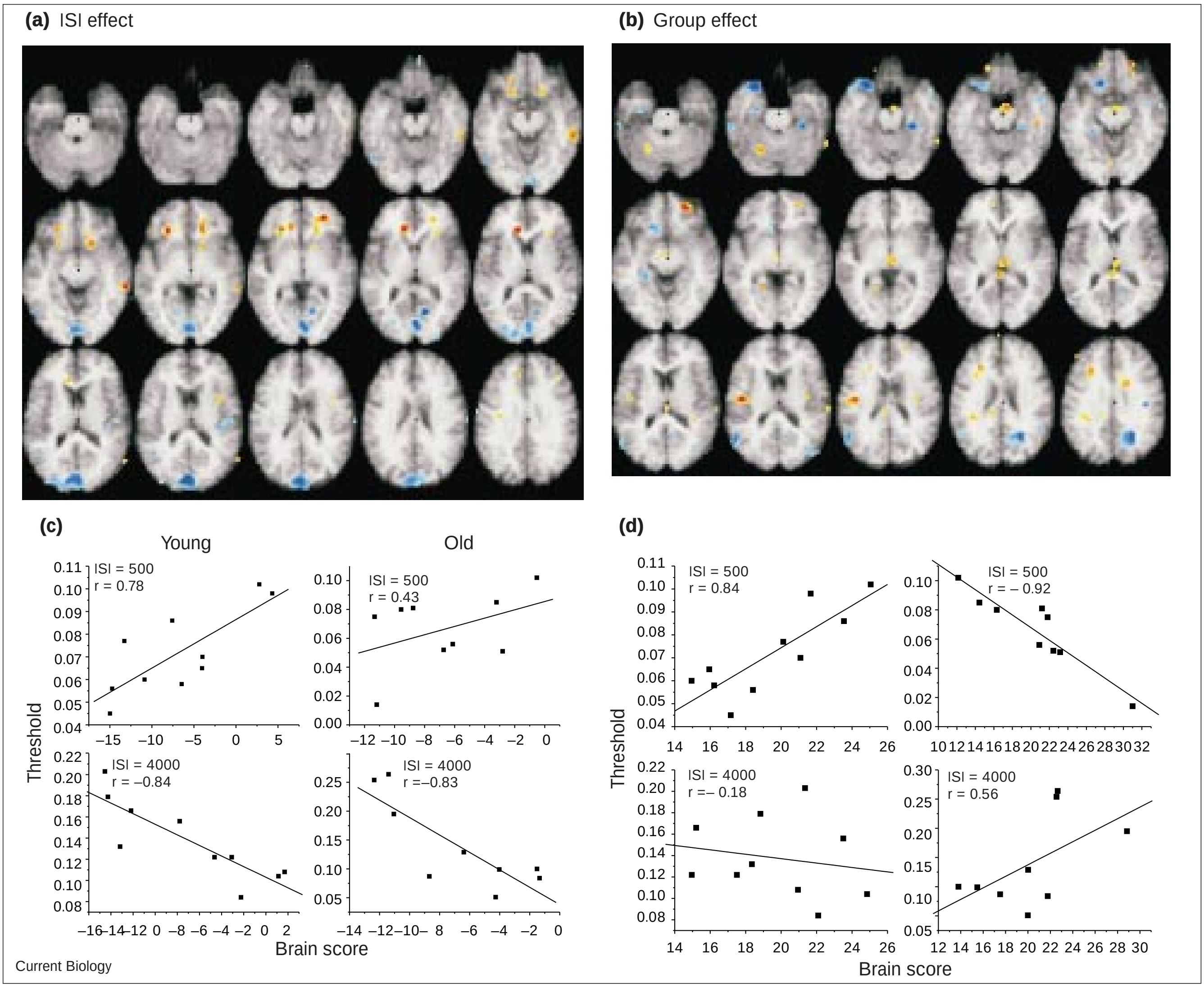
Figure S1



Relationship of brain activity and behavior. **(a)** ISI and **(b)** Group patterns from PLS image analysis. **(c,d)** Scatterplots show the relationship between individual participant's threshold (Δf/f) and the brain scores derived from the singular image. Voxels most strongly related to the pattern in the scatterplots are shaded either red (positive weight) or blue (negative weight) on an axial structural MRI. The MRI is in standard atlas space [S11]. Slices start at –28 mm below the AC–PC line at the top left slice and move in increments of 4 mm to +28 mm at the bottom right. Left is to the left and the top is anterior in the image. In (c,d) the correlation coefficient (r) between threshold and scores is displayed within each plot. Dominant voxels contributing to the brain scores are listed in Tables 1 and 2.

Supplementary materials and methods

Participants

Ten young (mean age = 23; range = 20–30), and nine older participants (mean age = 65; range = 60–79) were recruited from the University of Toronto Vision Laboratory subject pool. All gave informed consent in accordance with the Institutional Review Boards of the University of Toronto and Baycrest Centre. Subjects were in good health and scored in the normal range for their cohort on the Mini-mental status exam and Mill Hill vocabulary test.

Psychophysical task

Two gratings with spatial frequencies of f and f + Δf were presented sequentially in each trial [S1]. Grating contrast was modulated by a circular envelope that had a diameter of 5.25°: contrast was 20% within the envelope and zero elsewhere. The circular grating patches were presented on the horizontal meridian 5.25° to the left or right of a central fixation point. The side on which the higher frequency grating appeared was randomized across trials; we also randomized which grating appeared first, right or left. The base frequency, f, varied randomly across trials across a $\pm$ 0.25 log unit range centered on 1.9 cycles per degree. This low spatial frequency range minimized contrast sensitivity differences related to age [S2]. The large randomization in f across trials was greater than frequency discrimination thresholds, ensuring that participants based their judgments on a comparison of the two gratings, rather than comparing each grating to a standard frequency built up over trials [S1,S3]. Discrimination thresholds were estimated by fitting Weibull functions to each participant's data for each ISI and determining the Δf that produced correct responses in 80% of the trials. On the second day of testing, values of f varied from 5% below discrimination threshold to 5% above, in 2.5% increments. Accurate responses were obtained in 79.2% of trials across all subjects on the second day, confirming that discrimination thresholds were similar on both days of testing.

Image analysis

Details of our PET protocol and postprocessing of images have been published elsewhere [S4]. The PLS analysis has also been explained elsewhere [S5,S6] and we provide only the essential details here. The covariances of psychophysical threshold with the PET images were computed within each of the two ISIs, across participants and between groups. Singular value decomposition of these covariance maps produces latent variables containing scan profiles and singular images. The scan profiles index changes in the covariances of behavior with the regions identified in the singular image across scans and between groups. The significance of the scan profiles within and between groups was assessed using permutation tests, where group membership was randomly assigned on each permutation [S7,S8] and scan profiles from the permuted data set evaluated against a set of contrasts coding for group effects, ISI effects and the group by ISI interaction [S6]. The stability of voxel weights within a singular image was assessed with bootstrap estimation of standard errors [S9,S10], where peak voxels with singular image weights greater than twice the estimated standard error are considered reliable. Brain scores were created from the dot product of the singular image and each participant's image. Scatterplots of behavior by brain scores within each scan visualize those points in the experiment when brain–behavior correlations are similar and when they differ. Group differences in the voxel correlation matrices displayed in Figure 3 were also assessed using permutation tests.

Supplementary references

S1. Magnussen S, Greenlee MW, Asplund R, Dyrnes S: Stimulus-specific mechanisms of visual short-term memory. *Vision Res* 1991, 311:1213-1219.
S2. Sekuler R, Owsley C: The spatial vision of older humans. In *Aging and Human Visual Function*. Edited by Dismakes K, Sekuler R, Kline D. New York: A.R. Liss; 1982:185-202.
S3. Bennett PJ, Cortese F: Masking of spatial frequency in visual memory depends on distal, not retinal, frequency. *Vision Res* 1996, 36:233-238.
S4. McIntosh AR, Lobaugh NJ, Cabeza R, Bookstein FL, Houle S: Convergence of neural systems processing stimulus associations and coordinating motor responses. *Cereb Cortex* 1998, 8:648-659.
S5. McIntosh AR, Bookstein FL, Haxby JV, Grady CL: Spatial pattern analysis of functional brain images using Partial Least Squares. *Neuroimage* 1996, 3:143-157.
S6. McIntosh AR, Gonzalez-Lima F: Large-scale functional connectivity in associative learning: interrelations of the rat auditory, visual and limbic systems. *J Neurophysiol* 1998 80:3148-3162.
S7. Edgington ES: *Randomization Tests*. New York: Marcel Dekker; 1980.
S8. Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ: Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Trans Med Imaging* 1999, 18:32-42.
S9. Efron B, Tibshirani R: Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy. *Stat Sci* 1986, 1:54-77.
S10. Braun AR, Balkin TJ, Wesensten NJ, Gwadry F, Carson RE, Varga M, *et al.*: Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. *Science* 1998, 279:91-95.
S11. Talairach J, Tournoux P: *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Thieme Medical Publishers; 1988.