

Task-induced deactivations during successful paired associates learning: An effect of age but not Alzheimer's disease

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Task-induced fMRI deactivations during successful encoding and retrieval of visuospatial paired associates were examined at different levels of task difficulty in younger and older adults (Experiment 1), and older adults with and without mild probable Alzheimer's disease (AD) (Experiment 2). Irrespective of the level of task difficulty, common deactivations (determined through the use of conjunction analyses) were observed in the lateral and medial prefrontal, anterior and posterior cingulate, and temporal brain regions and in the claustrum during both encoding and retrieval in younger and older adults (Experiment 1). In AD patients and healthy older adults, common deactivations were found in posterior cingulate, temporal, and lateral parietal regions and in the insula and claustrum during encoding and retrieval of paired associates (Experiment 2). As task difficulty increased, irrespective of the type of task, the magnitude of task-induced deactivations increased in the medial prefrontal/superior frontal gyrus and middle/posterior cingulate cortex in younger and older adults (Experiment 1), and in the middle cingulate cortex in older adults with and without AD (Experiment 2). In Experiment 1, greater deactivation was observed in the anterior cingulate gyrus in older compared to younger adults during retrieval of paired associates which was attributed to greater suppression of task-unrelated thoughts in the older group. No significant differences in task-induced deactivation, or in the type of relationship exhibited between deactivation and task difficulty, were observed between older adults with and without AD (Experiment 2). It was suggested that this was related to the matching of successful task performance and task difficulty across patient and control groups. Following previous proposals, task-induced deactivations were suggested to underlie a shifting of attentional focus from monitoring of the self and the environment (through attenuation of these activities) to external, goal-directed behaviour.

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Task-induced deactivations in functional magnetic resonance imaging (fMRI) studies can be defined as decreases in the measured BOLD signal response seen during an experimental condition compared with a control condition or baseline resting state. Such deactivations have been reported in the posterior and anterior cingulate, precuneus, inferior parietal, temporal and medial prefrontal cortices, and are independent of the specific cognitive task being performed or imaging modality (e.g., Binder et al., 1999; Hutchinson et al., 1999; Mazoyer et al., 2001; Shulman et al., 1997). They are considered to arise as a consequence of the suspension of task-independent processing that occurs when the brain is at rest or in a passive state, referred to as a default mode of brain function by Raichle et al. (2001), in order to facilitate engagement in focused or goal-directed behaviour (Gusnard and Raichle, 2001; McKiernan et al., 2003). This mechanism is thought to allow attentional resources to be reallocated or diverted from resting-state activities to cognitively demanding tasks. Such resting- or passive-state activities may include monitoring of internal states and external environments, supporting internal thought and episodic memory processes (Greicius et al., 2004; Greicius and Menon, 2004; Gusnard and Raichle, 2001), or planning of future events from past experiences (Binder et al., 1999).

A number of recent fMRI studies have investigated the relationship between task-induced deactivation and cognition. In a study of auditory target detection, McKiernan et al. (2003) observed increases in the magnitude of deactivation as task difficulty increased. Deactivations in the anterior cingulate/superior frontal gyrus were found to be independent of task difficulty manipulations, while deactivations in posterior parietal and posterior cingulate cortices were found to respond to variations in stimulus presentation rate, target discriminability, or memory load. Similar increases in task-induced deactivation with increasing task difficulty have been identified in the subgenual prefrontal cortex during performance of an *n*-back verbal working memory task (Pochon et al., 2002). Further, Chee and Choo (2004) reported

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greater deactivations in left posterior cingulate (BA 31) and medial prefrontal cortices (BA 10) for a verbal working memory task involving maintenance and manipulation than for an easier task that only involved maintenance of information. Demonstration of greater deactivation with increasing cognitive load is consistent with the mechanism of task-induced deactivation proposed by Gusnard and Raichle (2001). The more cognitively challenging a task is, the greater the interruption of ongoing mental activities and reallocation of attentional resources, hence the greater the deactivation in medial prefrontal and posterior parietal/cingulate regions. Thus far, increases in deactivation with increasing task difficulty have been observed in younger adults. Whether or not these same effects are also seen in older adults is as yet unknown.

Task-induced deactivations have also been studied in older adult and neurodegenerative populations, although not in relation to task difficulty. Lustig et al. (2003) examined deactivations associated with performance of a semantic classification task in younger adults and older adults with and without probable Alzheimer's disease (AD). A significant effect of age was found in the medial prefrontal cortex whereby older adults showed less deactivation in this region than younger adults in comparison to viewing a passive, fixation baseline. Within the medial parietal/posterior cingulate cortex, there was a significant group effect. Younger adults displayed significant signal decreases, older adults without probable AD evinced a negligible (non-significant) signal increase, but older adults with probable AD displayed a significant signal increase. Such apparent activation of the medial parietal/posterior cingulate cortex in AD, at a point where deactivation was seen in younger adults, was suggested to be secondary to disruption of medial temporal projections to this region. However, these group differences in deactivation were accompanied by significant between-group differences in classification accuracy (90% for younger adults, 85% for older adults without AD, 80% for older adults with AD). In a study of subjects with mild cognitive impairment, AD patients and healthy controls, Rombouts et al. (2005) recently reported significant group differences in the early phase of the BOLD deactivation response in the anterior cingulate gyrus during face encoding, in the precuneus during the 1-back condition of a verbal n -back working memory task and in the inferior frontal gyrus during a 2-back condition. However, group differences in deactivation responses were again accompanied by significant group differences in response time (RT) and task accuracy, particularly during the harder level of the n -back task.

In both cases, it is difficult to determine the extent to which significant group differences in the deactivation response were due to performance factors or to ageing or AD-related neurodegenerative processes. It is possible that these group differences in deactivation may have occurred due to differing cognitive processes being in operation in subjects performing the task at different accuracy levels. For example, activation of the posterior cingulate/precuneus in AD patients compared to deactivation in younger adults in the Lustig et al. study may have resulted from greater involvement of error detection processes (e.g., Menon et al., 2001) in the former group. Related to variations in error rates, between-group differences in activation/deactivation may have occurred through the utilization of block designs that do not permit post hoc separation of correct and incorrect trials in subsequent statistical analyses. Murphy and Garavan (2004) have shown that the inclusion of both correct and incorrect trials in statistical analyses of imaging data can result in increased rates of false positive and false negative activations. In simulation analyses, they

showed that the number of false positives increased and the number of true positives decreased exponentially as the average number of errors included in the analysis increased from 1 to 12. A final consideration is that differences in the subjective difficulty of the cognitive task may have resulted in differential patterns of brain activity between patient and control groups. Different cognitive processes may be in operation when subjects are performing a task at a subjectively easy compared to harder level, which in turn may be reflected in differing patterns of brain activity with increasing task difficulty, as discussed earlier. Thus, if a patient group is performing a subjectively more difficult task at a lower accuracy level and consequently utilizing different cognitive processes compared to a control group, it is not surprising that group differences in brain activation are observed.

In the current study, task-induced deactivations related to successful learning of visuospatial paired associates problems that varied in difficulty were investigated in separate experiments involving (1) younger versus older adults, and (2) older adults with and without mild probable AD. Visuospatial paired associate learning was chosen as the experimental task since performance on this type of task is known to be impaired in AD (Blackwell et al., 2004; Sahakian et al., 1988; Swainson et al., 2001). There were three main aims of this study. First, to assess the extent to which individuals from different age/disease populations show the commonly reported pattern of task-induced deactivations in medial prefrontal, anterior and posterior cingulate, precuneus and temporal-parietal regions during encoding and retrieval of paired associates. To address this aim, deactivations that occurred irrespective of the task (encoding or retrieval) and group (older vs. younger adults; AD patients vs. elderly controls) were examined using conjunction analyses.

Second, to determine whether and how the magnitude of task-induced deactivation varies with increasing task difficulty in older adults (with and without mild probable AD), in addition to younger adults, and whether this is influenced by age or disease processes. In younger adults, we hypothesized that linear increases in deactivation with increasing task difficulty would be particularly seen in the anterior cingulate cortex/superior frontal gyrus, but also in the middle frontal gyrus, posterior cingulate gyrus, precuneus and occipito-parietal cortex, based on previous findings (McKiernan et al., 2003). A lack of such increases in deactivation with increasing task difficulty in older adults (with or without AD) would suggest a revision of the proposed mechanism underlying task-induced deactivations, as discussed above, with respect to ageing or disease processes.

The third aim was to examine differences in task-induced deactivation between younger and older adults (Experiment 1) and older adults with and without AD (Experiment 2), matched for successful task performance and/or task difficulty. In Experiment 1, control of successful task performance was achieved by providing participants with multiple attempts to learn correct visuospatial pairings, and by only examining those deactivations associated with successful attempts. While such a strategy may be adequate when comparing groups for whom fairly small performance decrements across groups are predicted, such a strategy is not sufficient when performance decrements are predicted to be large (as in the case of AD patients vs. elderly controls). Therefore, in Experiment 2 task difficulty was additionally controlled by individually adapting levels of cognitive load so that relative increases in task difficulty were approximately equal across groups. To the authors' knowledge, this is the first study in which

it will be possible to attribute potential differences in task-induced deactivation between AD patients and healthy comparison subjects to effects of disease rather than task performance. From previously published data (Lustig et al., 2003), we predicted that age-related differences in deactivation would be seen in the medial prefrontal cortex (less deactivation in older compared to younger adults). Effects of age (deactivation in younger adults, negligible activation in older adults) and neurodegenerative disease (greater activation in AD patients compared to older controls) were predicted in the posterior cingulate cortex/precuneus.

Experiment 1: Younger and older adults

Materials and methods

Participants

Twelve younger adults (6 female, 6 male) and 12 older adults (6 female, 6 male) who were all right-handed participated in the experiment. All volunteers were screened for concomitant serious medical problems and psychiatric history. Age, years of education and test scores on the Mini-Mental State Examination (MMSE, Folstein et al., 1975), National Adult Reading Test (NART, Nelson and Willison, 1991), Beck Depression Inventory (for younger adults, BDI, Beck et al., 1961) and Geriatric Depression Scale (for older adults, GDS, Yesavage et al., 1983) are provided in Table 1. The study was approved by the Cambridge Local Research Ethics Committee and all volunteers provided written informed consent before participating in the experiment.

Materials and procedure

The visuospatial paired associates learning task required participants to remember *what* object appeared in *which* location (out of six possible locations) on a computer screen. Participants were presented with six white squares (locations) on a black

background in which pictures of everyday color objects were presented. During the encoding phase an object appeared in one of the locations for 2.5 s, followed by another object in a different location 0.5 s later, until 3, 4, or 6 objects had been presented. The retrieval phase occurred 1 s after encoding, and in this phase two objects that had been presented during encoding appeared side-by-side in one of the locations for 2.5 s. Participants were required to decide which of the two objects had appeared in that location during encoding by pressing one of two response keys corresponding to a left–right decision. After 0.5 s, another pair of objects appeared in a different location and this continued until memory for all encoded objects had been tested. When the last recognition decision in that problem had been made, there followed a gap of 4 s and then presentation of either the same object–locations if an incorrect recognition decision had been made, or a new set of randomly-chosen object–location pairs. Participants were allowed a maximum of 5 attempts to successfully complete object–location problems. Object–location problems were pseudo-randomly presented such that no more than two problems with the same number of object–locations could appear consecutively in a scan run.

Task difficulty was manipulated by varying the number of objects that could appear in one of 6 locations indicated by the white boxes. For each individual subject, the number of object–location pairs chosen for each level of difficulty was determined during off-line testing and was based on the mean number of attempts taken to successfully complete each type of problem. Task difficulty levels were chosen so that easy, moderately difficult and difficult problems could be successfully completed by all subjects in approximately 1, 1.5 and 2 attempts, respectively. From offline testing, problems comprising 3, 4 and 6 object–location pairs proved to represent desirable levels of task difficulty in all subjects. Task difficulty levels were determined in a practice session that occurred 3–4 days prior to scanning. All subjects received an additional practice session 1 h before

Table 1

Demographic characteristics and neuropsychological test scores for younger and older adults (Experiment 1) and older adults and AD patients (Experiment 2)

	Experiment 1				Experiment 2			
	Younger adults (<i>n</i> = 12)		Older adults (<i>n</i> = 12)		Older adults (<i>n</i> = 12)		AD patients (<i>n</i> = 12)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	28.7	5.3	64.4	3.8	77.3	4.8	77.3	4.9
Years of education	17.9	2.5	14.8	2.5	11.4	3.4	11.3	3.2
MMSE	30.0	0.0	29.4	0.8	29.1	0.9	26.3	2.1
NART errors	10.9	4.1	9.3	4.8	14.4	14.5	12.2	10.7
GDS	–	–	0.8	1.1	1.7	1.4	2.6	1.9
BDI	1.9	2.3	–	–	–	–	–	–
DRS attention	–	–	–	–	12.1	1.6	11.7	1.6
DRS initiation	–	–	–	–	10.3	2.7	6.4	3.3
DRS construction	–	–	–	–	10.0	0.0	10.0	0.0
DRS conceptual	–	–	–	–	11.5	2.8	9.6	2.4
DRS memory	–	–	–	–	12.8	1.3	4.1	3.3
DRS total score	–	–	–	–	12.7	3.4	6.2	2.4
WMS immediate	–	–	–	–	17.6	5.9	8.3	4.0
WMS delayed	–	–	–	–	16.6	6.8	1.0	2.7
Clock drawing	–	–	–	–	0.1	0.3	0.5	0.5
Verbal fluency	–	–	–	–	16.3	5.7	17.5	5.6

For younger adults, *n* = 10 for the MMSE, NART and BDI. For older adults, *n* = 11 for all tests except for the MMSE where *n* = 12. For AD patients, *n* = 12 for the MMSE, 11 for the GDS, WMS and DRS, 10 for Clock drawing and Verbal Fluency, and 9 for the NART. MMSE is scored out of 30, NART is scored out of 45, GDS is scored out of 15, BDI is scored out of 21, WMS is scored out of 25, and Clock Drawing is scored from 0 (no impairment) to 3 (severe impairment). DRS scores are age-corrected scaled scores.

scanning. After the scanning session participants were asked to rate on a 7-point scale ranging from 1 (very easy) to 7 (very difficult) how difficult they found each type of problem to successfully complete.

Image acquisition

Functional and structural data were acquired on the 3 T Bruker scanner at the Wolfson Brain Imaging Centre, Cambridge. In each functional time series, T2*-weighted images depicting BOLD contrast were acquired using an interleaved echo planar (EPI) sequence at 21 whole-brain axial slices (TR = 3020 ms, TE = 27 ms, flip angle = 90°, matrix = 128 × 128, field of view = 25 cm², interslice distance = 5 mm, slice thickness = 5 mm). Seven initial EPI volumes were discarded to allow for magnetic stabilization in each functional time series. Each scan run lasted a maximum of 8 min or until 4 problems at each of the 3 levels of difficulty had been successfully completed. All participants received 3 scanning runs apart from 2 participants who only received 2 scanning runs due to technical difficulties. Imaging data from one younger adult had to be discarded due to problems with fMRI data acquisition. Three-dimensional, high resolution whole-brain axial images were also acquired for each participant.

Image analysis

Using Statistical Parametric Mapping (Friston et al., 1995) and SPM99 software, for each participant, functional data were slice timing corrected using sinc-interpolation, realigned to the first EPI volume of each session, coregistered to the structural T1 weighted image, normalized to MNI space using nonlinear basis functions and parameters determined from individual SPGR images, and smoothed with an 8 mm FWHM Gaussian kernel. At all stages, images were inspected for any problems resulting from the preprocessing procedure.

In order to examine positive linear increases in deactivation with increasing task difficulty, the memory load parameter was regressed onto the BOLD response to stimuli onsets and convolved with a canonical hemodynamic response function within the general linear model. Only successful attempts were modeled as regressors of interest; epochs associated with unsuccessful encoding and retrieval were included as two separate covariates of no interest. Epochs associated with encoding were calculated from the onset of presentation of the first object to the offset of presentation of the last object in each object–location problem. Epochs associated with retrieval were calculated from the onset of presentation of the first object to the onset of the decision response time to the last object (or the offset of presentation of the last object if no response was made) in each object–location problem. Epochs lasting 9, 12 and 18 s that corresponded to encoding or retrieval of 3, 4 and 6 object–location problems were treated as two separate regressors (one for encoding and one for retrieval). Seven additional covariates of no interest modeled 6 movement parameters (3 rigid-body translations and 3 rotations) that were obtained during image realignment and a constant term. A polynomial expansion was used to model linear and nonlinear relationships between memory load and the BOLD response: zero-order (standard boxcar), followed by first-order (i.e., linear response) and then second-order (i.e., positive quadratic response) terms were modeled against a resting baseline (the 4 s interval between the end of one successful or unsuccessful attempt at an object–location problem and the next).

To assess task-independent deactivations common to both younger and older adult groups during encoding and retrieval, irrespective of task difficulty, contrast images corresponding to rest > zero-order encoding and rest > zero-order retrieval were generated from parameter estimates for each participant. These were then entered into an analysis of variance (ANOVA), without a constant term, at the second, random-effects level to form statistical parametric maps (SPMs) of the Z statistic. In the ANOVA model, four groups were specified in order to allow conjunctions over older and younger adult groups and encoding and retrieval. Nonsphericity correction was applied over replications in order to account for the fact that 2 contrast images were being taken to the second level from each participant. Corrections were also applied to account for possible correlations between contrast images. Following model estimation, contrasts of [1 0 0 0], [0 -1 0 0], [0 0 -1 0] and [0 0 0 -1] were tested together under the conjunction null hypothesis of no conjunction of effects across groups or tasks by examining the intersection of statistical maps that were individually significant at a given alpha rate (Nichols et al., 2005). It should be noted that the use of the conjunction null approach permitted the conjunction of non-orthogonal contrasts of rest > zero-order encoding and rest > zero-order retrieval that shared a common baseline condition (Nichols et al., 2005).

The above steps were then repeated for contrast images corresponding to 1st-order encoding and retrieval, and 2nd-order encoding and retrieval. Additionally, SPMs of 1st- and 2nd-order contrasts were masked with conjunctions of rest > zero-order encoding and retrieval in older and younger groups in order to ensure that task-induced deactivations were demarcated from activations. Voxel-wise zero-order, masked 1st-order and masked 2nd-order contrasts were thresholded at $P < 0.05$, corrected for multiple comparisons across the whole brain using the false discovery rate (FDR, Genovese et al., 2002), unless stated otherwise.

To examine between-group differences in deactivations, contrast images corresponding to rest > zero-order/1st-order/2nd-order encoding or retrieval were generated from parameter estimates for each participant and entered into analyses of covariance (ANCOVAs) at the second, random-effects level to form statistical parametric maps (SPMs) of the Z statistic. Zero-order, first-order and second-order contrast images associated with encoding and retrieval were assessed in separate analyses. The nuisance covariate entered into ANCOVAs was the mean-centered number of attempts taken to successfully complete the hardest object–location problems for each individual, which was mean-centered separately for each group¹. Between-group differences were assessed within functionally-defined a priori ROIs and across the whole brain. A functional ROI-image comprising four 8 mm spherical regions in the precuneus and posterior cingulate that corresponded to peak locations of group differences in deactivation reported by Lustig et al. (2003) was generated using the WFU PickAtlas ROI toolbox (Maldjian et al., 2003). An 8 mm spherical region in the medial prefrontal cortex in which Lustig et al. reported a significant effect of age was also included in the functional ROI-image. Coordinates for the ROIs were 9 35 40 (BA 31), 7 29 40 (BA 31), 7 49 52 (BA 7), 9 43 44 (BA 7/31) and 1 37 6 (BA 24). In all between-group analyses, SPMs of the z statistic were initially thresholded at $P < 0.001$ (uncorrected for multiple comparisons), then a small volume correction for multiple comparisons was applied within the ROI-image, with only those voxels surviving a corrected height threshold of $P < 0.05$ being subsequently reported. For both within- and between-group analyses, SPM coordinates

were converted from MNI to standard space (Brett et al., 2001) and then deactivations were localized using the Talairach and Tournoux (1988) atlas.

Results

Neuropsychological data

Independent *t* tests were used to examine differences in demographic details and neuropsychological test scores in younger and older adults (see Table 1). As expected, there was a significant age difference between younger and older adults ($t[22] = 18.87, P < 0.0001$). Significant differences in MMSE scores ($t[20] = 2.55, P < 0.05$) and years of education ($t[22] = 3.03, P < 0.01$) were also found between younger and older adults (older adults performed significantly worse on the MMSE and received fewer years of education than younger adults).

Behavioral data

Table 2 presents the mean number of attempts taken to successfully complete object–location problems in a visuospatial paired associates learning task and the mean subjective ratings of task difficulty at each level of memory load. Data were submitted to a mixed-factor analysis of variance (ANOVA) that included a within-subjects factor of memory load (3 vs. 4 vs. 6 object–locations) and a between-subjects factor of group (younger vs. older adults). For the mean number of attempts, the main effects of group and memory load were significant: $F(1, 42) = 19.11, \text{MSE} = 2.73, P < 0.0001$; $F(2, 42) = 14.91, \text{MSE} = 0.57, P < 0.005$, respectively. The group-by-memory load interaction was also significant: $F(2, 42) = 6.53, \text{MSE} = 0.25, P < 0.05$. Post hoc Tukey pairwise comparisons revealed that the mean number of attempts was greater for older compared to younger adults for 4 and 6 object–location problems, but not for 3 object–location problems. There was no difference in the mean number of attempts taken to successfully complete object–location problems of different loads in younger adults. However, in older adults, the

mean number of attempts was greater for 6 object–location problems in comparison to 3 or 4 object–location problems. For the mean subjective ratings of task difficulty, the main effect of group approached significance whereby there was a trend for older adults (3.58) to rate object–location problems as being more difficult than younger adults (2.82): $F(1, 38) = 4.11, \text{MSE} = 9.11, P < 0.06$. The main effect of task difficulty was significant whereby 6 object–location problems (4.86) were rated as being more difficult than 3 object–location problems (1.91): $F(2, 38) = 47.24, \text{MSE} = 45.70, P < 0.0001$. However, the group-by-task difficulty interaction was not significant: $F(2, 38) = 0.18, \text{MSE} = 0.18, P > 0.1$.

Functional imaging data

Areas of common deactivation in younger and older adults

Areas of task-induced deactivations common to both younger and older adults during encoding and retrieval are presented in Table 3 and Fig. 1. A conjunction of zero-order contrasts across task (encoding or retrieval) and group (older or younger adults) revealed deactivations in prefrontal (superior and inferior frontal gyri, medial prefrontal cortex), temporal (superior and middle temporal gyri) and limbic regions (anterior and posterior cingulate cortices), and in the lateral cerebral sulcus and claustrum. No positive linear or quadratic responses to increasing memory load were found to survive a corrected height threshold of $P < 0.05$ in conjunctions of contrasts across both task and group (masked by a conjunction of zero-order contrasts across task and group, thresholded at $P < 0.05$, corrected). To avoid the possibility of making a Type II error, we note that at an uncorrected height threshold of $P < 0.05$, linear increases in deactivation with increasing task difficulty were found in the medial prefrontal cortex/superior frontal gyrus and middle/posterior cingulate cortex in conjunctions across task (encoding and retrieval) and group (younger and older adults). Since analyses were conducted under the conjunction null hypothesis, 1st-order responses were masked by zero-order responses in deactivation, and linear increases in deactivation with increasing task difficulty were predicted in the medial frontal and cingulate cortex, it is unlikely that these results are false positives occurring due to not correcting for multiple comparisons.

Table 2

Mean number of attempts taken to successfully complete object–location problems and mean subjective ratings of task difficulty in a visuospatial paired associate learning task in younger and older adults (Experiment 1) and AD patients and older adults (Experiment 2)

Level of task difficulty	Experiment 1				Experiment 2			
	Younger adults ^a		Older adults		Older adults		AD patients	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Mean number of attempts</i>								
1	1.20	0.21	1.39	0.25	1.08	2.39	1.27	2.77
2	1.13	0.09	1.52	0.24	1.17	1.56	1.39	3.89
3	1.28	0.18	1.89	0.47	1.27	2.31	1.75	4.25
4	–	–	–	–	1.45	2.86	2.16	5.43
<i>Subjective ratings of task difficulty^b</i>								
1	1.56	0.87	2.17	0.83	1.86	0.49	–	–
2	2.44	1.23	3.42	1.18	2.91	0.79	–	–
3	4.44	1.89	5.17	0.94	4.66	0.89	–	–
4	–	–	–	–	5.84	1.40	–	–

^a $N = 12$ in all groups except for younger adults in Experiment 1 ($N = 11$ for mean number of attempts, $N = 9$ for task difficulty ratings).

^b Task difficulty ratings for older adults in Experiment 2 were scaled to match the rating scores used in Experiment 1 where 1 = very easy and 7 = very difficult.

Table 3

(i) Areas of common deactivation revealed by a conjunction of zero-order encoding and retrieval across older and younger adults in Experiment 1 ($P < 0.05$ corrected). (ii) Areas of common positive linear increases in deactivation with increasing memory load found in a conjunction of encoding and retrieval across older and younger adults in Experiment 1 ($P < 0.05$ uncorrected)

Brain region	Brodmann's area/ hemisphere	Z score	<i>x</i>	<i>y</i>	<i>z</i>
<i>(i) Zero-order responses in Experiment 1</i>					
Frontal regions					
Superior frontal gyrus	R9	3.67	14	46	34
Inferior frontal gyrus	R47	3.49	46	29	10
	R47	3.38	48	25	1
Medial prefrontal cortex	Mid 10	4.58	0	53	7
	R11	4.11	2	58	15
	R10	4.03	2	65	15
Temporal regions					
Superior temporal gyrus	R22	3.96	59	39	4
Middle temporal gyrus	L39	4.10	51	67	25
	R21	4.01	61	18	6
	L21	3.64	50	14	3
	L21	3.38	55	5	13
Lateral cerebral sulcus/ Superior temporal gyrus	L38	3.49	44	23	1
	L38	3.46	44	16	6
Limbic regions					
Anterior cingulate cortex	Mid 24	3.54	0	26	19
Posterior cingulate cortex	R31/23	5.50	2	47	28
	L30	3.70	4	52	14
	R31	3.41	10	29	36
Other regions					
Clastrum	R	4.19	34	16	1
<i>(ii) Linear increases in deactivation in Experiment 1^a</i>					
Frontal regions					
Medial prefrontal cortex/ Superior frontal gyrus	R10	2.26	4	65	12
	Mid 10	1.85	0	59	6
Limbic regions					
Middle/posterior cingulate cortex	R24/31	2.05	2	22	36

^a First-order responses are masked by a conjunction of zero-order encoding and retrieval across groups ($P < 0.05$ corrected) to ensure that linear increases in deactivation are observed, rather than linear increases in activation.

Between-group differences in task-induced deactivation

After covarying out the mean number of attempts taken to successfully complete the hardest object–location problems for each individual and correcting for multiple comparisons across the whole brain, we failed to find statistically significant differences between younger and older adults in all contrasts. However, in ROI analyses, younger adults were found to deactivate the left anterior cingulate gyrus (BA 24, $z = 3.73$) significantly less than older adults across the average of memory load conditions during retrieval (i.e., zero-order response). We failed to find statistically significant differences in deactivation between older and younger adults in all other

contrasts when applying small volume corrections for multiple comparisons in the ROI-image.

Discussion

Deactivations in superior, inferior and medial prefrontal gyri, superior and middle temporal gyri, anterior and posterior cingulate cortices, and the lateral cerebral sulcus and claustrum were found in younger and older adults during successful performance of a visuospatial paired associates learning task. Deactivations were not found in angular or superior occipital gyri, though they were expected based on previous findings (Mazoyer et al., 2001; Binder et al., 1999). Marx et al. (2004) have demonstrated signal decreases in occipitoparietal regions during an eyes-closed resting baseline relative to a fixation condition that were not observed with an eyes-open resting baseline. Therefore, the lack of deactivations in lateral parietal regions may be related to the use of an eyes-open resting baseline in Experiment 1 but an eyes-closed resting baseline in these other studies.

Task-induced deactivations that increased in magnitude with increasing task difficulty were found in the medial prefrontal cortex/superior frontal gyrus and middle/posterior cingulate cortex during both encoding and retrieval of visuospatial information in younger and older adults, albeit only at an uncorrected height threshold. McKiernan et al. (2003) reported a positive linear relationship between deactivation responses and task difficulty in the anterior cingulate/superior frontal gyrus, middle frontal gyrus, precuneus, posterior cingulate and occipitoparietal cortex in younger adults. However, the anterior cingulate/superior frontal gyrus was the only region to display linearly increasing deactivation with increasing task difficulty that was independent of the type of difficulty manipulation. Therefore, the observation of a linear relationship between deactivation and task difficulty in the medial prefrontal cortex/superior frontal gyrus in both younger and older adults partially supports and extends this previous finding.

It has been proposed that task-induced deactivations result from the interruption of internal, ongoing mental activities such as monitoring of internal states and external environments, planning of future events from past experiences and episodic memory processing that are engaged during resting or passive conditions (Greicius et al., 2004; Greicius and Menon, 2004; Gusnard and Raichle, 2001; Mazoyer et al., 2001; Binder et al., 1999; Shulman et al., 1997). These suspensions of Γ default_ mental processes are thought to occur in order that attentional resources may be reallocated from such mental activities to goal-oriented behavior. It has further been suggested that the greater the cognitive demands (and difficulty) of the goal-oriented behavior, the greater the attentional resources needed, and hence the greater the suspension of Γ default_ mental processes, which is observed as a greater magnitude of deactivation (McKiernan et al., 2003). The medial prefrontal cortex/superior frontal gyrus is the only region that displayed linear increases in deactivation with increasing cognitive demand, irrespective of the type of difficulty manipulation, in McKiernan et al. (2003). It is also one of two regions found to display linear increases in deactivation with increasing task difficulty in Experiment 1 (the other being the middle/posterior cingulate cortex). Thus, it appears that there are regional variations in the deactivation responsiveness to task difficulty. This suggests that while the medial prefrontal cortex/superior frontal gyrus may be involved in diverting attentional resources to the cognitive task at hand, the same cannot be said of

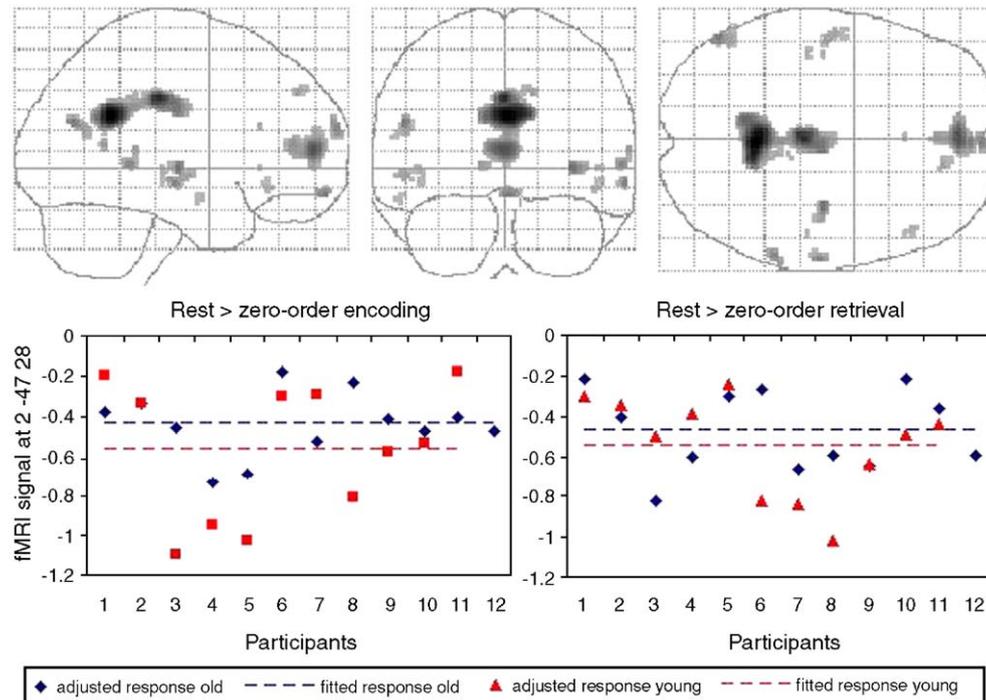


Fig. 1. Regions of brain deactivation in older and younger adults (Experiment 1) during rest > zero-order encoding and retrieval, as revealed by conjunction analyses across task and group. Fitted and adjusted responses are displayed for the global maxima peak voxel in the right posterior cingulate cortex (BA 31/23, 2 -47 28) during rest > zero-order encoding and during rest > zero-order retrieval).

other brain regions that are commonly deactivated under resting or passive conditions such as the inferior and superior frontal, temporal and angular gyri.

As Gusnard and Raichle (2001) note, deactivations in different cortical regions comprising the *default network* may underlie different cognitive processes. It has been suggested that deactivation of the medial prefrontal cortex/superior frontal gyrus is associated with attenuation of internal, self-focused attention (engaged when monitoring one's own mental state, for example), which allows attentional resources to be diverted to external, goal-directed behaviour. A linear relationship between task-induced deactivations and cognitive load can be predicted if it is assumed that greater attenuation of self-focused attention (observed as greater deactivation) occurs as task demands, and hence the requirement for attentional resources, increase. The authors further argue that *Factivity* in the posterior cingulate/precuneus in the resting state may reflect monitoring of the external environment, and suggest that this "broad information-gathering activity" may be interrupted (observed as deactivation) should focused attention be needed. Thus, linear increases in deactivation with increasing task difficulty in the middle/posterior cingulate cortex may be expected if it is again assumed that the need for externally-focused attention increases with increasing task-related cognitive demands. Further, if it is assumed that these demands are met by the switching of attention from the external environment to goal-directed behaviour, and observed in the form of increasing deactivation. Finally, the authors suggest that *Factivity* of lateral temporoparietal regions in the default resting state may underlie conscious awareness of the environment. Thus, deactivations in temporoparietal regions may reflect a degree of attenuation of conscious awareness of the environment when engaging in goal-

directed behaviour. Increases in deactivation with increasing task difficulty were not found in lateral temporoparietal regions in Experiment 1 suggesting that this function is unrelated to the diversion of attentional resources, and related simply to the performance of goal-directed behavior.

Turning to between-group differences in task-induced deactivations, age-related differences in task-induced deactivation were predicted in the medial prefrontal cortex (less deactivation in older compared to younger adults) and posterior cingulate cortex/precuneus (deactivation in younger adults, negligible activation in older adults). However, in the current study, younger adults were found to deactivate the left anterior cingulate gyrus significantly less than older adults during successful retrieval, an opposite effect to that predicted, and no significant differences were found in the posterior cingulate cortex/precuneus. In a recent study, McKiernan et al. (2006) observed a positive relationship between task-induced deactivations and the frequency of task-unrelated thoughts occurring during an auditory target detection task. As the number of self-reported task-unrelated thoughts decreased, the magnitude of deactivation in the left anterior cingulate and posterior parieto-occipital cortex, fusiform and middle frontal gyrus increased. A similar relationship between the frequency of task-unrelated thoughts and regional cerebral blood flow has been demonstrated in the left prefrontal and anterior cingulate cortex (McGuire et al., 1996). Therefore, greater deactivation of the left anterior cingulate gyrus in older compared to younger adults in Experiment 1 may be related to greater suppression of task-unrelated thoughts in the former group. Older adults may have needed to suppress task-unrelated thoughts to a greater degree than younger adults in order that attentional resources could be diverted to successful performance of the paired associates learning task.

A lack of significant differences in deactivation in the posterior cingulate cortex/precuneus between younger and older adults may be related to the fact that only encoding and retrieval trials associated with 100% recognition accuracy were included as regressors of interest in imaging analyses in Experiment 1. Encoding and retrieval trials associated with incorrect attempts were included as regressors of no interest in design matrices. Lustig et al. reported differences in deactivation that were accompanied by significant differences in semantic classification accuracy between younger and older adults in a block design in which correct trials could not be separated from incorrect trials. This meant that a greater proportion of incorrect trials were included in the estimation of the hemodynamic response function during semantic classification in older compared to younger adults. The inclusion of incorrect with correct trials in imaging analyses is known to increase the rate of false positive and false negative activations, and decrease the rate of true positives, by changing the shape of the impulse response function (Murphy and Garavan, 2004). In one particular demonstration of how false positives can occur, the impulse response function was found to flatten in older but not younger adults in the inferior parietal lobule during the performance of a response inhibition task due to the inclusion of greater errors in the older compared to younger group (average of 6.3 vs. 1.9 errors). Therefore, between-group differences in task-induced deactivation in the posterior cingulate cortex/precuneus observed by Lustig et al. may have resulted from a failure to control for differences in task performance, and the subsequent inclusion of incorrect trials in data analyses, rather than age-related processes.

Experiment 2: older adults and AD patients

Greater deactivation of the left anterior cingulate gyrus in older compared to younger adults was found in Experiment 1, and was posited to reflect greater suppression of task-unrelated thoughts in older compared to younger adults. It was suggested that this may have occurred in order that attentional resources could be diverted to successful performance of the paired associates learning task. The need for older adults to suppress task-unrelated thoughts to a greater extent than younger adults may be related to the fact that there was a trend for older adults to rate object–location problems as being more subjectively difficult overall than younger adults. Therefore, in Experiment 2, an attempt was made to equate the difficulty of the task across AD patient and control groups, in addition to matching groups for successful performance. Task difficulty was controlled by individually adapting levels of cognitive load so that relative increases in task difficulty were approximately equal across groups. A failure to replicate between-group differences reported by Lustig et al. was anticipated since no significant differences in deactivation in the posterior cingulate cortex were found in comparisons of younger and older adults in Experiment 1 when controlling for the potential confound of successful task performance.

Materials and methods

There are a number of methodological differences between Experiment 1 and Experiment 2 since the experiments were not intentionally designed for between-experiment comparisons, and

were conducted at different time-points. Methodological differences include the type of scanner (3 T vs. 1.5 T), version of image processing software (SPM99 vs. SPM2), type of retrieval task (recognition and selection out of 2 objects vs. recognition), object presentation times (2.5 s vs. 5 s), inter-trial intervals (4 s vs. 7.5 or 10.5 s) and intra-trial intervals (1 s vs. 6 s interval between encoding and retrieval). These differences arise from either the experiments being conducted at different time-points or from the experiment being designed with dementia patients' ability to perform cognitive tasks in mind. However, these methodological differences were not considered to be problematic since this study examined task-independent deactivations (i.e., those deactivations that are not dependent on particular characteristics of the cognitive task, imaging modality or image processing software) rather than task-dependent deactivations. For a further discussion of the distinction between task-independent and task-dependent deactivations, see Gusnard and Raichle (2001).

Participants

Twelve patients who satisfied NINCDS-ADRDA (McKhann et al., 1984) criteria for mild probable AD and twelve healthy, older adults participated in the experiment. Each group comprised 5 male and 7 female participants, and all volunteers were right-handed apart from two patients with AD and three healthy, older adults. All volunteers were screened for concomitant serious medical problems and psychiatric history. Seven of the patients with mild probable AD were receiving acetylcholinesterase inhibitor treatment. The study was approved by the joint Research Ethics Committee of the Institute of Psychiatry and South London and Maudsley Trust. All volunteers provided written informed consent before participating in the experiment. Table 1 provides details of age, years of education and test scores for the MMSE, NART, GDS, Dementia Rating Scale (DRS-2, Mattis, 2001), Wechsler Memory Scale immediate and delayed story recall (WMS, Wechsler, 1997), Clock Drawing test (Sunderland et al., 1989) and Verbal Fluency for the letter *s*.

Materials and procedure

The visuospatial paired associates learning task was very similar to that used in Experiment 1 apart from the following. During encoding and retrieval phases an object appeared in a white box for a maximum of 5 s, and there was a gap of 6 s between encoding and retrieval phases. In the retrieval phase a single object appeared in one of the locations and subjects were required to decide whether this had been presented in that location during the encoding phase. A baseline rest period of 7.5 s (if the attempt was unsuccessful) or 10.5 s (if the attempt was successful or if there had been 5 successive failed attempts) followed each retrieval phase. Furthermore, some modifications were made to the task in order to better enable patients with AD to successfully perform the task while being scanned. The number of white boxes or locations could vary from problem to problem (rather than a fixed number of locations being displayed), and subjects were given the verbal instruction “remember” during encoding and were asked the question “was this here” during retrieval in order to remind them of task requirements. During the retrieval phase a picture of the 2-

button response box that included response key labels appeared in the centre of the screen in order to remind subjects of what the response keys represented.

Four types of object–location problems corresponding to 4 levels of cognitive load that increased in difficulty were individually identified for each subject in practice sessions that occurred in the days prior to the first scanning session. Levels of cognitive load were adapted on an individual basis so that relative increases in task difficulty were equal across groups (individuals in each group received problems ranging from easy through to difficult), though absolute difficulty varied across groups (since a difficult problem for a patient may be easy for a healthy control). Object–location combinations were chosen based on the mean number of attempts taken to successfully complete each type of problem. Object–location combinations were chosen so that easy, moderately easy, moderately difficult and difficult problems could be successfully completed by all participants in approximately 1, 1.5, 2 and 2.5 attempts, respectively. On average, patients with AD received 2.0, 2.5, 3.4 and 3.5 objects in 4.3, 3.5, 5.7 and 4.8 locations, while healthy older adults received 2.0, 3.0, 4.0 and 5.0 objects in 3.3, 4.2, 5.1 and 6.0 locations, respectively. Practice session for patients with AD occurred 6–7 days, 3–4 days and 1 h before the first scan, and 3–4 days and 1 h before the second scan, while healthy older adults received practice sessions 3–4 days and 1 h before the first scan, and 1 h before the second scan. After the first scanning session participants were asked to rate on a 5-point scale ranging from 1 (very easy) to 5 (very difficult) how difficult they found each type of problem to successfully complete.

Image acquisition

Imaging data were acquired on the 1.5 T General Electric Neuro-optimized Signa LX Horizon system at the Maudsley Hospital, London. Functional data sensitive to the blood oxygenation level dependent signal (BOLD) were acquired using an interleaved echo planar sequence at 16 axial slices (TR = 2000 ms, TE = 40 ms, flip angle = 90°, matrix = 64 × 64, field of view = 240 mm², slice thickness = 7 mm, interslice distance = 0.7 mm). Each scanning run lasted 308 s and in each time series the first 4 EPI volumes were discarded to allow for magnetic stabilization. Each subject received 8–10 scanning runs over two 1-h scanning sessions (separated by approximately 1 week), apart from two patients with AD who received 5 runs in a single scanning session due to dropout. Two scanning sessions were administered to ensure sufficient data acquisition for each of the 4 different levels of task difficulty without undue demands on the subjects. Three-dimensional, high resolution whole-brain axial images were also acquired for each subject.

Image analysis

Apart from a few small differences, a similar analysis strategy to that employed in Experiment 1 was used for the analysis of imaging data from AD patients and older adults. The imaging analysis software used was SPM2. In the preprocessing stage, functional data were unwarped to correct for motion-related variance (rather than including motion parameters in the design matrix) and data were normalized into MNI space using affine transformations. Encoding or retrieval epochs corresponding to 2, 3, 4 and 5 object–location problems lasted 11, 16.5, 22 and 27.5 s, respectively. Low-frequency noise was removed using a 128 s high

pass filter. The 6 s interval between encoding and retrieval phases was treated as an additional covariate of no interest.

Results

Neuropsychological data

In older adults and AD patients, significant differences were found for scores on MMSE ($t[22] = 4.24, P < 0.001$), WMS Immediate Story Recall ($t[20] = 4.36, P < 0.0001$), WMS Delayed Story Recall ($t[20] = 13.15, P < 0.0001$), DRS Initiation ($t[20] = 3.08, P < 0.01$), DRS Memory ($t[20] = 8.14, P < 0.0001$), DRS Scaled Total Score ($t[20] = 5.18, P < 0.0001$) and Clock Drawing ($t[19] = 2.16, P < 0.05$). Patients with AD performed significantly worse on the MMSE, DRS Initiation and Memory sub-scales, DRS overall and clock drawing, and remembered fewer items on immediate and delayed story recall than older controls. There was no significant difference in age between older adults with and without AD ($t[22] = 0.04, P > 1$).

Behavioral data

The mean number of attempts taken to successfully complete object–location problems and the mean subjective ratings of task difficulty are presented in Table 2. For the mean number of attempts, data were submitted to a mixed-factor ANOVA that included a within-subjects factor of task difficulty (levels 1 vs. 2 vs. 3 vs. 4) and a between-subjects factor of group (AD patients vs. older adults). The main effects of group and task difficulty were significant: $F(1, 22) = 11.12, MSE = 3.77, P < 0.005$; $F(3, 66) = 20.08, MSE = 1.90, P < 0.0005$, respectively. The group-by-task difficulty interaction was also significant: $F(3, 66) = 3.88, MSE = 0.37, P < 0.05$. Post hoc Tukey pairwise comparisons revealed that AD patients made a significantly greater mean number of attempts per problem than older adults at the hardest level of task difficulty¹. For patients with AD, the mean number of attempts was significantly different across all levels of task difficulty, apart from between the two easiest levels of difficulty. Significant differences in the mean number of attempts were only found between the easiest and hardest levels of difficulty in older adults. Ratings of subjective task difficulty at each of the levels of memory load were only collected from older controls since AD patients did not provide reliable reports. Data were submitted to a one-way ANOVA that included a within-subjects factor of task difficulty (levels 1 vs. 2 vs. 3 vs. 4). The main effect of subjective task difficulty rating was significant: $F(3,33) = 41.69, MSE = 19.19, P < 0.0005$. Level 4 problems were rated as being subjectively more difficult than level 1 problems.

Functional imaging data

Areas of common deactivation in older adults and AD patients

Data were analyzed using the same method of conjunction analyses employed for the examination of task-induced deactivations in younger and older adults (Experiment 1). Table 4 and Fig. 2 present common areas of deactivation in older adults and AD

¹ A nuisance covariate of the number of attempts taken to successfully complete the hardest object–location problems was included in all between-group analyses due to the occurrence of between-group behavioral differences at the hardest level of difficulty during scanning.

Table 4

(i) Areas of common deactivation revealed by a conjunction of zero-order encoding and retrieval across AD patients and elderly controls in Experiment 2 ($P < 0.05$ corrected). (ii) Areas of common positive linear increases in deactivation with increasing memory load found in a conjunction of encoding and retrieval across AD patients and elderly controls in Experiment 2 ($P < 0.05$ uncorrected)

Brain region	Brodmann's area/ hemisphere	Z score	x	y	z
<i>(i) Zero-order responses</i>					
<i>Temporal regions</i>					
Lateral cerebral sulcus/ transverse temporal gyrus	R41	3.43	44	24	19
<i>Parietal regions</i>					
Angular gyrus	L39	2.99	48	64	35
Supamarginal gyrus	L39	2.97	50	62	33
<i>Limbic regions</i>					
Posterior cingulate cortex	R30	5.92	8	50	17
<i>Other regions</i>					
Clastrum	L	4.08	34	12	1
Insula	R	3.05	42	6	0
	L	3.01	34	17	16
<i>(ii) Linear increases in deactivation^a</i>					
<i>Limbic regions</i>					
Middle cingulate cortex	L31/24 L24	2.23 1.80	8 2	8 10	41 41

^a First-order responses are masked by a conjunction of zero-order encoding and retrieval across groups ($P < 0.05$ corrected) to ensure that linear increases in deactivation are observed, rather than linear increases in activation.

patients that were identified from comparisons of a resting condition with zero-order and first-order responses during successful encoding and retrieval of visuospatial paired associates. A conjunction of zero-order contrasts across task (encoding or retrieval) and group (older or younger adults) revealed deactivations in the posterior cingulate cortex, angular and supramarginal gyri, lateral cerebral sulcus/transverse temporal gyrus, insula and claustrum that occurred irrespective of cognitive load. Unlike Experiment 1, there was a failure to find deactivations in the prefrontal brain regions common to AD patient and elderly control groups during encoding and retrieval. Similar to Experiment 1, no positive linear or quadratic responses to increasing memory load were found to survive a corrected height threshold of $P < 0.05$ in conjunctions of contrasts across both tasks and groups (masked by a conjunction of zero-order contrasts across task and group, thresholded at $P < 0.05$, corrected). However, at an uncorrected height threshold of $P < 0.05$, a linear increase in deactivation with increasing task difficulty was found in the middle cingulate cortex during encoding and retrieval in AD patients and controls, slightly anterior to that observed in older and younger adults in Experiment 1. It is unlikely that this finding is a false positive occurring as a result of not correcting for multiple comparisons, for reasons outlined in Experiment 1 and due to the fact that it is in a similar location to that found in Experiment 1.

Between-group differences in task-induced deactivation

Covarying the mean number of attempts taken to successfully complete the hardest object–location problems, we failed to find

statistically significant differences between AD patients and older adults in all contrasts when correcting for multiple comparisons across the whole brain. Furthermore, no significant differences in deactivation between AD patients and older adults were found when applying small volume corrections for multiple comparisons in the ROI-image.

Discussion

Task-induced deactivations were found in lateral parietal and posterior cingulate cortices, lateral cerebral sulcus/transverse temporal gyrus and the claustrum during successful encoding and retrieval of visuospatial paired information in older adults with and without AD. Deactivations were observed in the majority of regions commonly implicated in the default network, apart from in the medial and lateral prefrontal cortex (though these were observed in Experiment 1). The failure to find common deactivations in prefrontal brain regions in Experiment 2 may be related to the difference in age between older adults in Experiments 1 and 2. The average age of older adults in Experiment 1 was 64.4 years, whereas in Experiment 2, the average age of older adults with and without AD was 77.3 years. A significant age-related decline in metabolic rate, as measured by fluorodeoxyglucose (FDG) uptake, in lateral and medial prefrontal regions has previously been demonstrated in the resting brain (Herholz et al., 2002), together with an age-related reduction in regional cerebral blood flow (rCBF) in the anterior cingulate cortex (Martin et al., 1991; Schultz et al., 1999). Furthermore, Lustig et al. (2003) reported a significant correlation between deactivation and age in the medial prefrontal cortex in their healthy older group (average age 76.1 years) such that deactivations decreased towards positive activations as age increased. Therefore, decreasing rCBF and metabolic rate with increasing age may have resulted in the failure to find task-induced deactivations in the lateral and medial prefrontal cortex in older adults in Experiment 2. Clearly, the implications of age-related reductions in prefrontal deactivations and the effect that this has on the performance of goal-directed behaviour warrant further investigation.

Deactivations that increased in magnitude with increasing task difficulty were found in the middle cingulate cortex during encoding and retrieval in AD patients and older adults, albeit at an uncorrected height threshold. This linear response in the middle cingulate cortex was slightly anterior to that found in Experiment 1 in younger and older adults during encoding and retrieval of paired associates, as can be seen in Fig. 3. In contrast to Experiment 1, there was a failure to find a linear relationship between task difficulty and deactivation in the medial prefrontal cortex/superior frontal gyrus in older adults and AD patients. However, this is not surprising given the lack of zero-order deactivations in the medial prefrontal cortex, noted above. The proposed mechanism underlying the increase in deactivation with increasing task difficulty in the middle cingulate cortex is the same as that posited for the middle/posterior cingulate cortex in Experiment 1. As for the posterior cingulate cortex, it is suggested that deactivation of the middle cingulate cortex reflects monitoring of the external environment which is suspended in order to allow attention to be focused on external goal-directed behavior. As the difficulty of the task increases, attenuation of external environment monitoring increases, and so the magnitude of deactivation increases.

Though greater activation of the posterior cingulate cortex/precuneus was predicted in AD patients compared to older adults

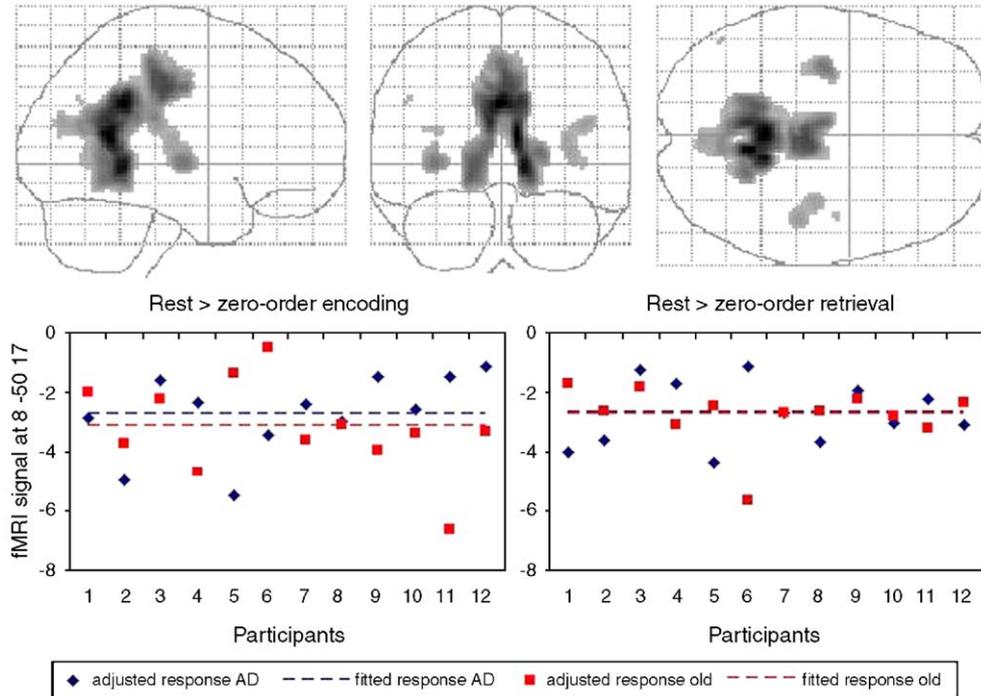
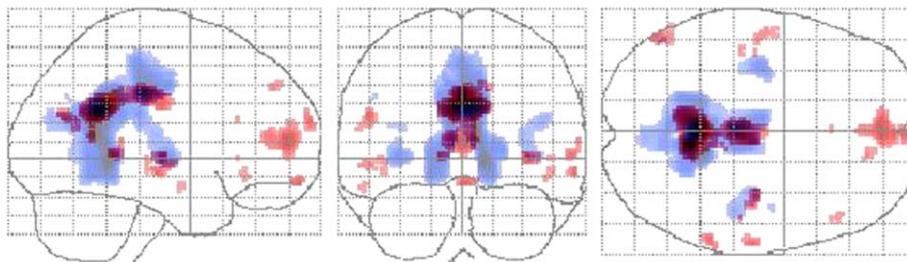


Fig. 2. Regions of brain deactivation in AD patients and older adults (Experiment 2) during rest > zero-order encoding and retrieval, as revealed by conjunction analyses across task and group. Fitted and adjusted responses are displayed for the global maxima peak voxel in the posterior cingulate cortex (BA 30, 8 52 16) during rest > zero-order encoding and during rest > zero-order retrieval).

based on the findings of Lustig et al. (2003), no evidence for such an effect of disease was found in Experiment 2. This may be due to the smaller number of participants in Experiment 2 (12 elderly controls and 12 patients with AD) compared to the Lustig et al. study (27 elderly controls and 23 patients with AD). However, this may also be related to the facts that successful task performance was matched across groups, and incorrect attempts at object–location problems were excluded from analyses in Experiment 2. In the Lustig et al.

study, AD patients performed significantly worse than older controls who performed significantly worse than younger adults on the semantic classification task (80.3 vs. 85.4 vs. 90.0 percentage accuracy, respectively). This is in comparison to older adults with and without AD in Experiment 2 who all performed at 100% accuracy levels. In the discussion of Experiment 1, we noted the importance of separating correct from incorrect trials in imaging analyses. Murphy and Garavan (2004) have shown that the number

CONJUNCTION OF REST > ENC0 AND REST > RET0 IN EXPERIMENT 1 AND 2



CONJUNCTION OF ENC1 AND RET1 IN EXPERIMENT 1 AND 2

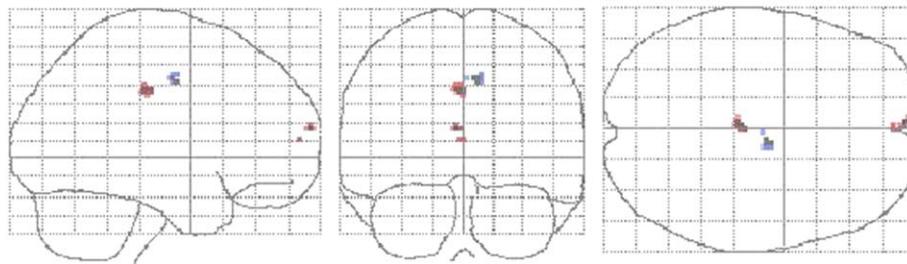


Fig. 3. Brain regions displaying zero-order (top) and linear 1st-order (bottom) responses in deactivation during encoding and retrieval in younger and older adults (Experiment 1, depicted in red), and in older adults with and without AD (Experiment 2, depicted in blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5

Task-induced deactivations that occurred irrespective of level of task difficulty, and linear increases in task-induced deactivations with increasing task difficulty revealed by a conjunction of encoding and retrieval trials across younger and older adult groups (Experiment 1), and AD patient and older adult groups (Experiment 2)

Brain region	Younger and older adults		AD patients and older adults	
	REST > ENC0 + RET0	ENC1 + RET1 ^a	REST > ENC0 + RET0	ENC1 + RET1 ^c
<i>Frontal regions</i>				
Superior frontal gyrus	(
Inferior frontal gyrus	(
Medial prefrontal cortex	((
<i>Temporal regions</i>				
Superior temporal gyrus	(
Middle temporal gyrus	(
Transverse temporal gyrus			(
<i>Parietal regions</i>				
Supramarginal gyrus			(
Angular gyrus			(
<i>Limbic regions</i>				
Anterior cingulate cortex	(
Middle cingulate cortex		((
Posterior cingulate cortex	((
<i>Other regions</i>				
Lateral cerebral sulcus	((
Insula			(
Clastrum	((

^a Masked by a conjunction of REST > ENC0+RET0 across respective groups (older and younger groups in Experiment 1 or AD patient and control groups in Experiment 2). A linear contrast identified regions in which deactivations increased with increasing task difficulty.

of false positives increases and the number of true positives decreases exponentially as the number of errors included in simulation analyses increases from 1 to 12. The percentage accuracy values reported by Lustig et al. (2003) approximate to an average of 7.2, 10.5 and 14.2 errors being made in the younger adult, older adult, and AD patient groups, respectively². Therefore, it is possible that deactivation of the posterior cingulate/precuneus in younger adults, negligible activation in older adults and positive activation in AD patients may simply be a product of an increasing errors being included in imaging analyses leading to increases in false positives. Alternatively, a trend from deactivation to activation in the posterior cingulate/precuneus with increasing error rates may reflect the increasing involvement of error-detection processes since the posterior cingulate/precuneus has been found to be activated during error processing but not response competition, inhibition or selection (Menon et al., 2001). Thus, this demonstrates the importance of matching task performance across patient and control groups when attempting to examine the influence of disease-related processes on brain activations or deactivations.

² Since the actual number of errors was not provided in Lustig et al. (2003) an average of 10.5 and 14.2 errors was calculated from the facts that there were 2 functional runs, each lasting 180 s (not including the first 10 s of the run), and in each run there were alternating fixation blocks (each comprising 9 trials) and active blocks (each comprising 12 trials with 2 s duration and 0.5-s intertrial interval). The total number of each type of block was not reported in the paper, but if it is assumed that each block lasted 30 s then this would result in 36 active trials per functional run, thus 72 active trials in total. The average number of errors was calculated using this total number of trials and the reported accuracy percentages.

Summary of Experiments 1 and 2

The current study examined task-induced deactivations in younger and older adults (Experiment 1) and older adults with and without mild probable AD (Experiment 2) during successful performance of a visuospatial paired associates learning task in which object–location problems were varied in cognitive load. Table 5 and Fig. 3 present a summary of the results of Experiments 1 and 2. In conjunctions of contrasts across tasks (encoding and retrieval) and groups (older and younger adults/AD patients and controls), deactivations in the posterior cingulate cortex and temporal cortices (extending to the posterior lateral cerebral sulcus), previously reported in younger adults (e.g., Binder et al., 1999; Hutchinson et al., 1999; Mazoyer et al., 2001; Shulman et al., 1997) were confirmed in younger adults and additionally observed in older adults with and without AD. Deactivations in lateral and medial prefrontal regions were replicated in both younger and older adult groups in Experiment 1, but not in AD patient and control groups in Experiment 2. This was posited to be a product of the age difference between older adults in Experiments 1 and 2 (average difference of 12.9 years), and the fact that rCBF and metabolic rate are known to decrease with increasing age in these regions. In contrast, deactivations in angular and supramarginal gyri were found in older adults with and without AD in Experiment 2, but not in younger and older adults in Experiment 1. It was suggested that such deactivations were not found in Experiment 1 as a result of using an eyes-open rather than an eyes-closed resting baseline. However, an eyes-open resting baseline was also used in Experiment 2. Therefore, additional task-related factors that varied across experiments as a result of them not being intentionally designed for between-

experiment comparisons (e.g., the length of baseline conditions) may have influenced lateral parietal deactivations in Experiment 1.

In a further extension of previous findings (Chee and Choo, 2004; McKiernan et al., 2003; Pochon et al., 2002), positive linear relationships between cognitive load and deactivations during encoding and retrieval were located in the medial prefrontal cortex/superior frontal gyrus and middle/posterior cingulate cortex in older and younger adults, albeit only at an uncorrected height threshold. Based on previous proposals (McKiernan et al., 2003; Gusnard and Raichle, 2001), the mechanism underlying deactivations in the medial prefrontal cortex/superior frontal gyrus is posited to be one in which internal, self-focused attention is attenuated in order to focus attention on external, goal-directed behaviour. A similar mechanism is proposed for deactivations in the posterior cingulate/precuneus in which monitoring of the external environment is interrupted so as to focus attention on goal-directed behaviour. McKiernan et al. suggested that attentional input is required to keep brain regions *Active* in the resting or passive state and that regions become deactivated when attentional input is required for other non-default activities. Therefore, a dual approach to re-allocating attentional resources from default activities to goal-oriented behaviour is proposed for younger adults, at the minimum, and young–older adults, at the maximum. As the demand for externally-focused attention increases with increasing task-related cognitive demands, there is greater deactivation of the medial prefrontal cortex/superior frontal gyrus (reflecting switching of attention from the self to external goal-directed behaviour), and greater deactivation of the middle/posterior cingulate cortex (reflecting switching of attention from the external environment to goal-directed behavior).

An effect of age was found in the anterior cingulate gyrus, in the opposite direction to that predicted, whereby younger adults produced less deactivation than older adults. It was concluded that greater difficulty in successfully completing harder problems may have resulted in older adults attenuating self-focused attention to a greater degree than younger adults, so that attentional resources could be used to focus on successful task performance. Contrary to predictions based on previously reported findings, no significant differences in task-induced deactivation in the posterior cingulate cortex/precuneus were observed between younger and older adults, and between older adults with and without AD. It was suggested that this may be a product of matching successful task performance and relative difficulty of the task across groups in the current study and, as such, illustrates the importance of controlling for this factor when imaging ageing or neuropsychiatric populations. In conclusion, an understanding of task-induced deactivations, in conjunction with the more commonly reported task activations, is necessary in order to fully characterize the effects of ageing and AD-related neuro-pathological processes in the brain.

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