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Visual attention deficits in Alzheimer's disease: an fMRI study

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Abstract

Cognitive and neuroscience studies indicate that attentional operations are impaired in Alzheimer's disease (AD). Our goal was to define the anatomical areas of activation associated with visual attention processing and to define deficits or changes that may occur in AD patients compared with control group. Thirteen AD patients and 13 age- and education-matched normal controls were tested in two visual search tasks (one was a conjunction task, where feature binding is required. The other was a subset task, where group stimuli is needed without feature binding) using fMRI techniques. After stereotactical normalization, voxel-by-voxel *t* statistics was used to compare activated brain areas between patients and control subjects. Our findings suggest that both search tasks are controlled by partially overlapping cerebral networks, including parietal, frontal and occipital–temporal cortical regions and primary visual cortex. The AD patient group showed less activation in both parietal lobes and the left frontal regions, while increased activation was found in the right frontal lobes and the right occipito-temporal cortical regions with the conjunction task. In the subset task, decreased activation in AD patients was seen in the left parietal lobe and bilateral frontal lobes, while increased activation was seen in both medial temporal lobes. In addition, for the comparison between tasks, The difference is very small for AD patients. Control group showed a higher amplitude in the right prefrontal region, temporal cortical regions and parietal lobe. These results indicate that attention deficits in AD patients may be attributed to both binding problem and grouping inefficiency.

Keywords: Functional MRI; Visual search; Attention; Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease that is the major cause of dementia in older adults. In most cases, AD begins as a memory disorder. Recently, there has been a suggestion that memory deficit is followed by attentional difficulties [2,3,15,19], including both auditory [13] and visual [12] selective processing, visual search [8,22,26,27] and attention shifting [6]. However, attentional impairments have not been examined extensively and identification of the cerebral components and neural basis of attentional deficits is still in its infancy. The purpose of the present functional Magnetic Resonance Imaging (fMRI) study was to define the anatomical areas of activation associated with visual attention processing and to define deficits or changes that may occur in a group of AD patients compared with control group.

Thirteen patients (mean age, 62.6 ± 7.8; eight females and five males) suffering from mild to moderate AD (diagnosed according to NINCDS-ADRDA [19] and ICD-10 criteria [1]) were recruited from our outpatient memory disorder unit. The severity of cognitive impairment was assessed using the Mini Mental State Examination (MMSE) [7] (group mean score, 18.3 ± 4.2). A group of 13 normal subjects (7 females and 6 males) matched for age (mean age 64.5 ± 6.7) and education was recruited from the community. Controls had a mean score of 27.8 ± 2.6 points in the MMSE and no pathological changes on screening T_1 and T_2 structural cranial MR images. Subjects and patients with color blindness were excluded from this study. All subjects signed a written informed consent according to the Declaration of Helsinki (BMJ 1991;

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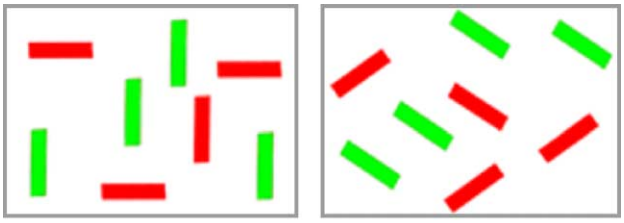

Fig. 1. Diagrammatic representation of the visual search tasks used in the study.

302; 1194) and the experiment protocol was approved by the local research ethics committee.

Each participant completed two types of visual search tasks. One was a conjunction task, where the target was a vertical red bar and the distracters were green vertical and red horizontal bars (Fig. 1a), i.e., two feature classes (e.g. color and orientation) are present in the array and spatial attention and feature binding are required. The other was a subset task, where again two features are present but only one of them is needed in order to group stimuli together (the subset) to allow parallel processing without the need for feature binding [9]. In which the target was a red bar of a particular orientation, among green distracters of the same orientation and red distracters of a different orientation (Fig. 1b). The orientations (0–90° in 10 steps) of the bars changed randomly from trial to trial with a minimum difference of 30° between the two orientations present on any trial. The target was therefore the red bar with the odd-one-out orientation. The visual display subtended a maximum size of 12° horizontally and 8° vertically. Three stimulus set sizes (i.e., the number of bars in each stimulus view) (4, 8 and 12) were randomly varied from trial to trial and the target was present in 50% of trials.

Each task condition was performed in a separate run during brain imaging. The functional scan followed a classic block design where the stimuli were presented in six blocks (54 s of each block with 12 trials), alternating with fixation periods of 27 s. In both conditions, a single trial proceeded as follows: a central fixation cross (+) was presented for 500 ms, followed by the array of visual stimuli for 3000 ms. A blank interval of 1000 ms intervened between trials. In all task conditions, participants were required to detect predefined target stimuli amid an array of distracting items and respond with a right-hand button press. Participants were instructed to respond as quickly as possible, while avoiding errors. Reaction time (RT) and accuracy were recorded. Before experiment the participants were given enough practice and familiarized with the procedures.

The fMRI experiment was performed using a 1.5-T MRI system (Siemens Sonata, Germany). For functional imaging, 16 slices [(slice thickness = 5 mm, slice gap = 1 mm; flip angle (FA) = 90°; matrix size = 64 × 64; field of view (FOV) = 220 mm × 220 mm)], were acquired using a gradient-echo echo-planar imaging (GE-EPI) sequence with a repetition time (TR) of 4500 ms, and an echo time (TE) of 50 ms. Each functional time series consisted of 108 volumes and lasted 486 s. Additionally, structural three-dimensional data sets were acquired in the same session using a T1-weighted sagittal MP-RAGE sequence (TR = 1900 ms, TE = 3.93 ms; matrix = 448 × 512; thickness = 1.70 mm, gap = 0.85 mm; FOV = 250 mm × 250 mm).

Table 1
Reaction times (mean ± S.D.) and accuracy (percent correct) in the conjunction and subset task in the two subject groups

	Patients	Controls	Between-group significance (P)
Accuracy			
Conjunction	90.36	96.27	<0.01
Subset	87.43	92.29	<0.01
Repeated measure	ns	$P < 0.05$	
RT(ms)			
Conjunction	1241.5 ± 96.4	987.6 ± 84.7	<0.01
Subset	1548.3 ± 87.3	1123.9 ± 78.5	<0.01
Repeated measure	$P < 0.05$	$P < 0.05$	

ns: no significance ($P > 0.05$).

SPM 99 was used for imaging data preprocessing and statistical analysis [10,11]. Functional images were co-aligned with a high-resolution anatomical scan taken in the same session (3D-MPRAGE). Images were transformed into Talairach space [28] and smoothed (effective smoothing for group: 12 mm). The statistical effects of task conditions and subjects were estimated according to the general linear model applied to each voxel in brain space. Statistical comparisions between experimental factors were based on the random-effects model. The different activations between groups and within each group were analyzed using two-way ANOVA. The common brain areas engaged by each search conditions were identified by group analysis between the significant activation in each visual task relative to its baseline. Subsequently a direct voxel-by-voxel t-statistic comparison was performed between the Alzheimer's patients and the healthy elderly. The statistical threshold was set at $P < 0.001$ uncorrected.

Behavioral data: Behavioral accuracy and reaction time (RT) data were summarized in Table 1. The two groups showed higher accuracy in the conjunction task than the subset task ($P < 0.01$), but post hoc comparison revealed that the difference was statistically significant only in the normal controls ($P < 0.05$). The between-group and repeated measure ANOVA revealed that the correction rates of AD patients were significantly lower than the control subjects in both conjunction ($P < 0.01$) and subset ($P < 0.01$) task. The controls responded much faster than the patients in both tasks ($P < 0.01$). The difference of RT reach significance between tasks in both groups.

FMRI results: The general network of brain areas involved during visual search was defined by group analysis of brain activations in both task conditions relative to the visual fixation baselines, in each group of AD patients and subjects. A large number of cortical regions were activated (see

Table 2
Anatomical regions activated during the conjunction task ($P > 0.001$)

Age-matched controls					AD patients				
Region (Brodman area)	Voxels	*X*	*Y*	*Z*	Region (Brodman area)	Voxels	*X*	*Y*	*Z*
L-precuneus (BA18)	27717	−26	−68	44	L-superior parietal lobule (BA7)	13813	−36	−42	62
L-superior parietal lobule (BA7)	27717	−32	−56	50	L-inferior occipital gyrus (BA18)	13813	−20	−104	0
L-postcentral gyrus	27717	−50	−32	50	R-superior parietal lobule (BA7)	5280	32	−66	50
R-superior parietal lobule (BA7)	8070	32	−60	48	R-medial occipital gyrus (BA19)	5280	34	−94	6
R-frontal eye fields (BA6)	4030	32	−6	64	R-inferior parietal lobule (BA40)	5280	38	−48	44
R-inferior frontal gyrus (BA47)	4030	56	16	2	R-medial frontal gyrus (BA 10)	1090	44	50	−4
L-basal ganglia	1444	−16	−14	14	L-medial frontal gyrus (BA 46)	476	−48	42	20
R-basal ganglia	1444	18	0	18	L-medial frontal gyrus (BA10)	476	−36	60	12
R-thalamus	1444	14	−6	12	R-inferior temporal gyrus (BA37)	213	44	−64	−14
R-medial frontal gyrus (BA 10)	279	42	56	8	R-inferior frontal gyrus (BA45)	114	30	26	2
R-inferior frontal gyrus (BA46)	279	50	46	14					

Tables 2 and 3 and Fig. 2a–d), including parietal, frontal, occipital–temporal cortical regions and primary visual cortex, as well as several subcortical structures.

The AD patient group showed less activation in both parietal lobes and the left frontal region, while increased activation was found in the right frontal lobe and the right occipito-temporal cortex (OTC) with the conjunction task (Fig. 2e). With the subset task, less activation in AD patients was revealed in the left parietal lobe and both frontal lobes, while more activation was present in the right medial temporal lobe (Fig. 2f).

An image map showing the difference of activations was derived by subtracting the subset task from the conjunction task, The normal controls showed a higher amplitude in the right prefrontal lobe, both temporal cortical regions and parietal lobes (Fig. 3). The difference between tasks is very small for AD patients, including bilateral parietal lobes, the left occipital–temporal cortical region and the left primary visual cortex (Fig. 4).

Here we examine the difference between visual search, in a conjunction search, two types of distracters are used, each type sharing one feature in common with the target stimulus. As spatial attention is important in conjunction tasks [30,31], the more distracters there are in the array, the longer the viewer takes to find the target or indicate its absence. This is known as serial search, since each stimulus or small clusters of them must be processed in turn until the target is either found or excluded. Subset search has been suggested as one way of allowing the selection of a particular feature (e.g. color) to be processed in parallel, without interference from other features (e.g. orientation). In this task, there are again two types of distracters (e.g. orientation and color) but only one feature has constant and known invariables (e.g. color always red). The second feature varies from trial to trial (e.g. the distracter/target orientation changes). The task is therefore to search through the array for the sole red target with a particular orientation among green distracters of the same orientation and red distracters of a different orientation [9].

In the present experiment, we recorded differential cortical activation during a conjunction search task and a subset search task and compared activations between tasks in both groups. Consistent overlap of cortical activity during conjunction search and subset search was found in the parietal, frontal and occipital–temporal cortical regions, primary visual cortex and several subcortical structures, including FEF (frontal eye field) and anterior and posterior IPS (intraparietal sulcus) [4,5]. In addition, each search task may involve specific mechanisms since the different search

Table 3
Anatomical regions activated during the subset task ($P > 0.001$)

Age-matched controls					AD patients				
Region (Brodman area)	Voxels	*X*	*Y*	*Z*	Region (Brodman area)	Voxels	*X*	*Y*	*Z*
R-cuneus (BA18)	25312	32	−92	4	R-superior parietal lobule (BA7)	14313	30	−68	56
R-medial frontal gyrus (BA9)	25312	52	14	42	R-superior parietal lobule (BA7)	14313	12	−66	60
R-superior parietal lobule (BA7)	25312	28	−56	50	R-medial occipital gyrus (BA19)	14313	56	−60	−14
L-medial occipital gyrus (BA19)	638	−52	−66	−10	R-superior frontal gyrus (BA 6)	1267	34	4	60
L-inferior occipital gyrus (BA19)	638	−44	−78	−4	R-inferior frontal gyrus (BA44)	1267	46	8	28
L-medial occipital gyrus (BA18)	638	−36	−58	−16	R-medial frontal gyrus (BA9)	1267	56	14	34
L-thalamus	556	−18	−18	16	L-medial occipita	1149	−52	−68	−60
R-basal ganglia	556	−14	−26	−4	L-inferior temporal gyrus (BA37)	1149	−60	−52	−14
L-thalamus	556	−12	−16	6	L-medial frontal gyrus (BA 46)	225	−46	34	24
L-inferior frontal gyrus (BA45)	272	−32	22	2	R-medial frontal gyrus (BA 46)	216	50	38	26
L-inferior frontal gyrus (BA45)	272	−40	14	6	R-cingulated cortex (BA 32)	216	4	22	38
L-medial temporal lobe (BA28)	272	28	−20	−6	R-frontal eye fields (BA6)	216	8	14	44

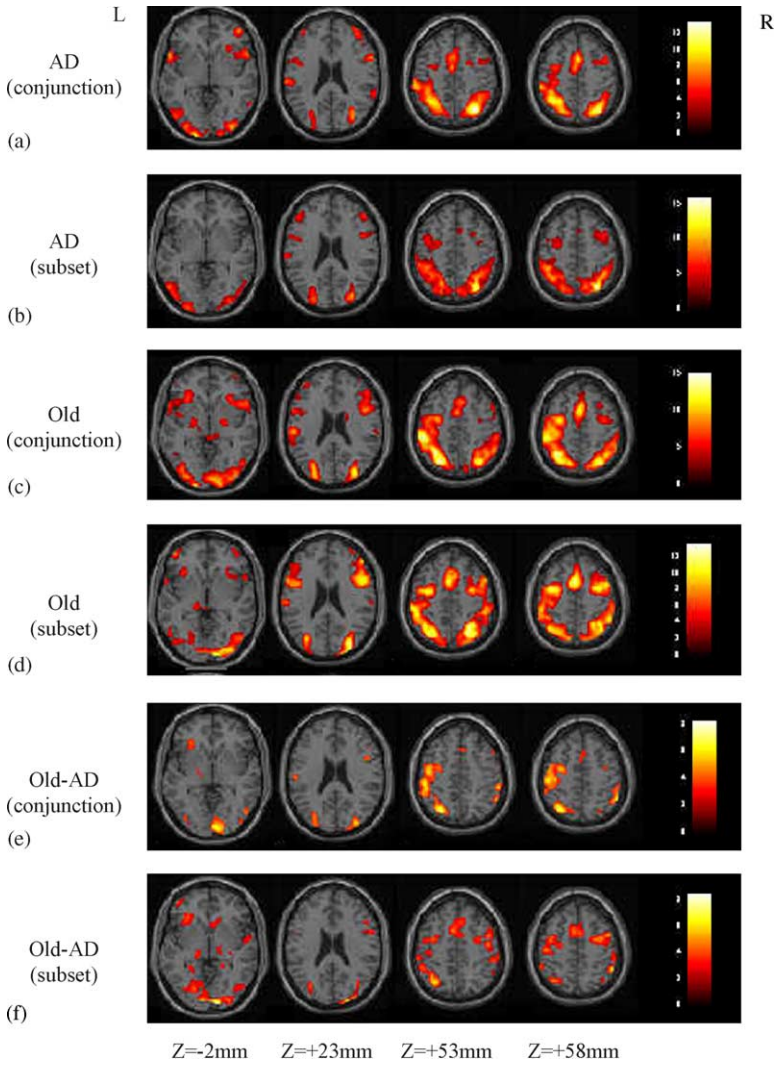

Fig. 2. Averaged brain activation involved in the different conditions (conjuction and subset task) of the two groups (AD patients and controls) (a–d) and the comparison between groups for the different conditions (e and f). Note: R designates the right hemisphere and L designates the left hemisphere.

tasks produce different magnitudes of activation in some brain areas of the network, right prefrontal cortex and FEF responded at a higher amplitude during the subset search and the left IPS responded at a higher amplitude during the conjunction search. In keeping with the results of previous lesion and functional imaging [2,4,5,15,25], the observed activations during conjunction and subset search most likely reflect covert selective attention. The differential fMRI responses of posterior parietal areas and the FEF should not be contaminated by sensory activation of parietal and FEF neurons. Saccadic eye movements are also unlikely to account for the recorded differential activations [5,26].

This experiment was concerned with the ability of AD patients to perform two types of what, for healthy people, would be efficient visual search tasks. We found that the AD patients searched significantly more slowly and made more errors compared with the controls on both tasks. In our previous study [14], we also found that less resource-demanding capabilities, tapped by the simple feature search, remained relatively preserved in AD. Therefore, the result may arise because there is some damage to general attentional mechanisms in AD, and thus any attention-related task is affected. We found that with the conjunction task less activation in AD patients was demonstrated in the bilateral parietal lobes and the left frontal region, while increased activation was found in the right frontal lobe and the right occipito-temporal cortical region. In the subset task, less activation in AD patients was revealed in the left parietal lobe and bilateral frontal lobes, while increased activation was present in the right medial temporal lobe.

Given that parietal lobe dysfunction is a known pathological characteristic of AD, of particular interest in this study was the involvement of the posterior parietal cortex, which has an established role in orienting spatial attention [18,21,23] and which is critically involved in visual search [4,5,18]. Therefore, this may suggest that there are impairments in some cognitive processes associated with spatial attention in AD patients. Several interpretations about the nature of pari-

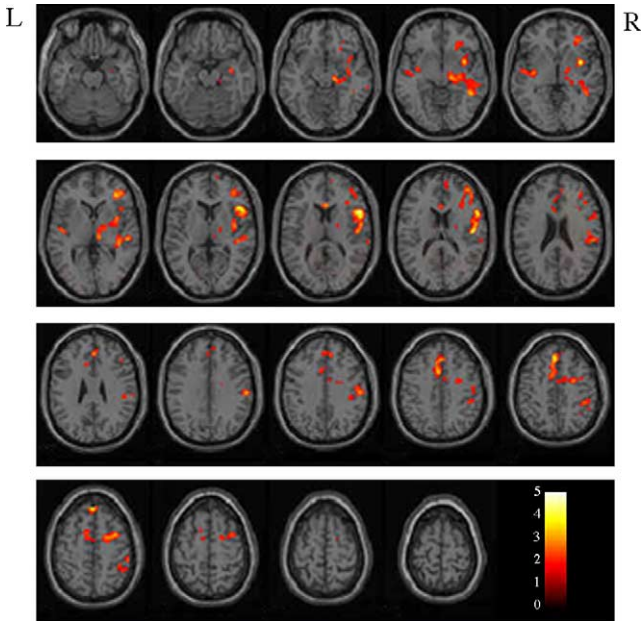

Fig. 3. Cortical activation for the conjuction task compared to the subset task in the controls. Note: R designates the right hemisphere and L designates the left hemisphere.

etal involvement during visual search are possible. Firstly, the parietal cortex could be involved in directing attention serially toward successive locations for the purpose of integrating the constituent features of individual items. In this interpretation, parietal activation reflects both spatial attention and feature binding mechanisms [27,29]. Secondly, the right parietal cortex is not responsible for both selective attention and feature binding, but rather is involved in selecting spatial locations which contained a particular feature variable (such as the color red). When target items can be segmented from neighboring distracters via similarity grouping, detection may not rely on spatial integration. These effects of distracter similarity are reflective of the role of perceptual grouping in visual search and constitute new evidence that it is not the mere search for conjunction targets that activates the superior, posterior parietal lobe [16,32]. Rather, it is the failure of grouping mechanisms to preattentively segment target from distracter items and the subsequent need for feature binding that engages superior parietal cortex. In the absence of these grouping relations, search is mediated by superior parietal-motor regions associated with spatial selection [23]. The binding of features itself is presumably mediated by other areas such as the temporal cortex of the ventral processing stream, which has been suggested to be involved in object representation. Thus, the posterior parietal lobe in visual search may not be bind-specific but rather reflect more general attentional mechanisms.

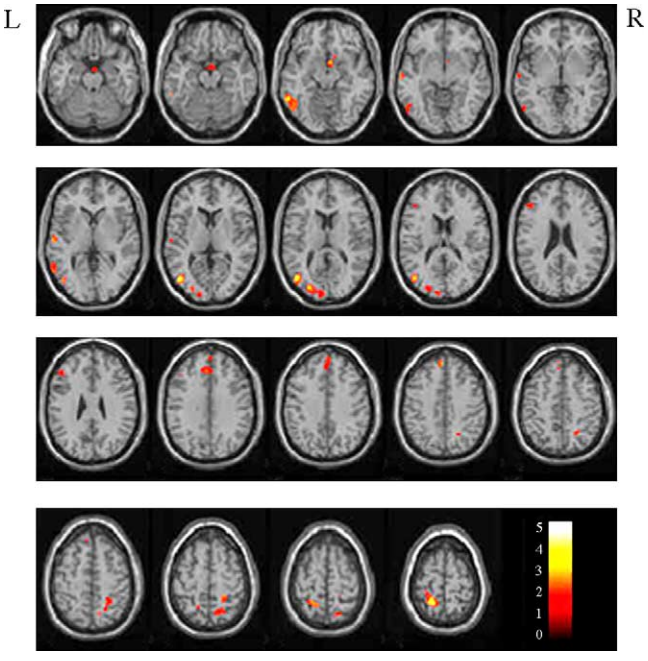

Fig. 4. Cortical activation for the conjuction task compared to the subset task in AD patients. Note: R designates the right hemisphere and L designates the left hemisphere.

Other possibly relevant brain regions are the anterior cingulate cortex, thought to be involved in selecting target information from distracting information [17,23] and frontal lobes, thought to be involved in resolving response conflict, both of which may also be abnormal in AD. Disconnection between frontal and posterior parietal areas may mediate the selective disruption of attentional function in AD.

We also compared the conjunction search with subset search. In this comparison, the normal controls showed a higher amplitude in the right prefrontal lobe, temporal cortical regions and parietal lobes compared with the AD patients, the difference between tasks in AD patients is very small, which suggests attention deficits in AD patients may be attributed to both binding problem and grouping inefficiency. It was not possible in the present study to be certain which, if any, of these factors could account for the significantly impaired search performance on the search task in AD. Thus, further work is required to be able to decide these possibilities.

Another finding of our study is a double dissociation between patients and controls concerning their differential activation of the dorsal and ventral visual stream. Patients showed significantly less activation in the dorsal stream (SPL), while they revealed higher task-related activity in the right OTC compared with controls. This shows that in AD, ventral and dorsal visual pathways are not only differently damaged at the input side as demonstrated during passive visual stimulation [20], but these differences remain during active engagement of these regions [24]. Thulborn et al. [29] also reported reduced parietal cortex activation in the right hemisphere in AD patients during an eye movement task. They interpreted their finding as being a correlate of reduced spatial attention caused by AD. On the one hand, disruptions of intercortical signal flow and direct cortical damage may lead to reduced activity. On the other hand, impaired processing capacities can lead to higher cognitive effort and thus to

increased activation of cortical regions subserving task processing or to the additional activation of regions initially not involved in the task [25,26].

In summary, the current study demonstrates that AD patients have a particular impairment in the conjunction and subset search tasks. There is less activation mainly located in the parietal cortex, with anterior cingulate cortex and frontal lobe dysfunction. This finding is consistent with previous experimental studies [8,27]. Based on the present results together with previous cognitive evidence, we suggest attention deficits in AD patients may be attributed to both binding problem and grouping inefficiency. Our results also agree with the idea that visual search information of AD patients provides an important source for unraveling the pathophysiology processes of this neurodegenerative disease.

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