Spatial- and object-based attentional deficits in Alzheimer's disease
Relationship to HMPAO-SPECT measures of parietal perfusion

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Summary
The purpose of this study was to investigate the ability of patients with Alzheimer's disease to shift attention between spatial locations and between objects, and to examine the brain regions involved in these cognitive operations using single photon emission computed tomography (SPECT) imaging. A recent study of patients with focal lesions provided evidence that the right and left parietal lobes are differentially involved in shifting selective attention from invalidly cued spatial locations and objects, respectively (Egly et al. J Exp Psychol Gen 1994; 123: 161–77). Accordingly, in Alzheimer's disease patients, we hypothesized that right parietal hypoperfusion on SPECT would be associated with deficits on the spatial-based component of a cued reaction time task, and left parietal hypoperfusion would be associated with the deficits on the object-based component. Attentional performance of Alzheimer's disease patients (n = 29) was compared with age-matched normal controls (n = 17) using a cued reaction time task based on Egly et al. (1994). Regions of interest were defined semi-automatically on SPECT, and were anatomically localized with the aid of co-registered MRI. As hypothesized, in Alzheimer's disease patients, reaction time costs of invalid targets eliciting shifts of attention between spatial locations were selectively correlated with SPECT hypoperfusion in the right superior parietal lobe; while reaction time costs of between-object shifts of attention were correlated with hypoperfusion in the left inferior parietal lobe. These results provide evidence for the specialized roles of the right and left parietal regions in the spatial and object components of attentional shifting respectively, and suggest that the cognitive profile associated with Alzheimer's disease includes both spatial- and object-based attentional impairments.

Keywords: visual attention; Alzheimer's disease; SPECT; neuropsychology; parietal lobe

Abbreviations: AC/PC = anterior commissure/posterior commissure; ANOVA = analysis of variance; AP = anterior–posterior; DRS = (Mattis) Dementia Rating Scale; HMPAO = hexamethylpropylene amine oxime; MMS = Mini-Mental State Examination; OM = orbitomeatal; SPECT = single photon emission computed tomography; srCBF = standardized regional cerebral blood flow

Introduction

Alzheimer's disease is a neurodegenerative disorder of unknown aetiology, and a major cause of dementia in elderly adults. In Alzheimer's disease, deficits in cognitive processes such as memory, language and visual attention are the result of regionally selective neuropathological changes. The neuropathological events that best correlate with the deterioration of cognitive function are the loss of synapses (Terry *et al.*, 1994) and the presence of neurofibrillary tangles (Arrigada *et al.*, 1992). Of interest, with respect to visual attention, is the pathology of the posterior parietal and prefrontal regions. These cortical areas have been hypothesized to form part of a cortical system involved in the focusing, shifting and maintenance of attention over time (Mesulam, 1990; Morecraft *et al.*, 1993; Posner and Dehaene,

1994). Given the topographical distribution of pathology in Alzheimer's disease, it would be predicted that the visual attention system would be damaged early in the disease process.

Recent developments in imaging methodologies, most notably the development of anatomical and functional neuroimaging techniques, provide an opportunity to quantify brain dysfunction in Alzheimer's disease. Both PET and single photon emission computed tomography (SPECT) have been used to index regional tissue dysfunction in the brains of Alzheimer's disease subjects. Based on previous studies, it is known that Alzheimer's disease is associated with the following features on PET and SPECT: (i) reduced perfusion in the parietotemporal association cortices, even early in the disease process (Kumar *et al.*, 1991); (ii) the reduction of perfusion is bilateral, although asymmetry in the degree of hypoperfusion is often observed (Haxby *et al.*, 1985); (iii) in more advanced cases, perfusion in the frontal association cortex is also reduced (Waldemar *et al.*, 1994); (iv) the primary sensory and motor cortical regions are relatively spared (Jagust *et al.*, 1993; Kumar *et al.*, 1991). These PET and SPECT findings are consistent with the topographical distribution of pathological markers and suggest that PET and SPECT can provide an index of the regional distribution of pathology in Alzheimer's disease. If imaging measures of brain dysfunction are combined with measures of cognitive performance, then Alzheimer's disease potentially provides an opportunity to probe the relationship between brain function and cognitive processes (Parasuraman *et al.*, 1992; Penniello *et al.*, 1995). This approach was utilized in this study to examine whether the deficits in orienting selective attention in Alzheimer's disease patients are significantly correlated with indices of regional cerebral blood flow on hexamethylpropylene amine oxime (HMPAO) SPECT imaging.

To study attentional orienting without accompanying eye movements, a spatial cueing paradigm can been used (Posner, 1980; Posner *et al.*, 1984). With this paradigm, subjects are asked to maintain fixation on a central point and to respond by pressing a key to the appearance of a target at a peripheral location on a computer display. The target is preceded by a cue that summons attention either to the target location (i.e. a valid cue) or to the wrong location (i.e. an invalid cue). Cues can be either an abrupt visual onset or a centrally presented arrow-shaped stimulus. Responses to targets on valid and invalid trials require the same perceptual and motor processing but differ in their attentional requirements. Spatial cueing tasks have been used repeatedly and successfully in normal subjects to show that targets presented at validly cued locations are responded to more rapidly than targets appearing at invalidly cued locations (Posner, 1980). There is a consensus that the response-time difference between trials with valid and invalid cues results from the additional time required for the subject to reorient attention from the incorrectly cued location to the correct target location on invalid trials (Posner, 1980; Eriksen and St James,
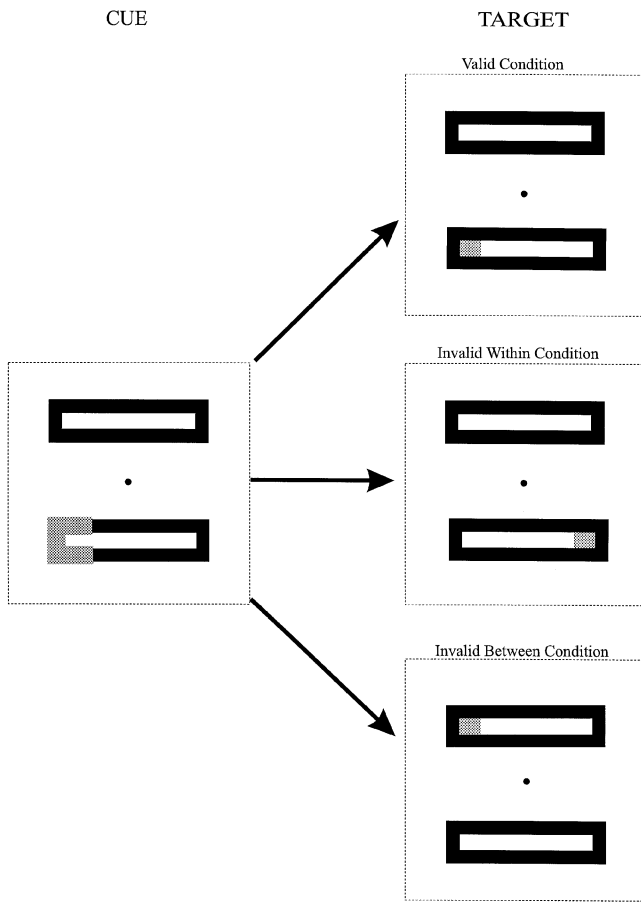
1986). The effects of cue validity on response times are robust, and cueing has also been shown to modulate scalp electrical activity in humans (Mangun and Hillyard, 1987) and the excitability of neurons in non-human primates (Mountcastle *et al.*, 1987).

When subjects with brain damage following cerebrovascular injury are tested on the spatial cueing task, different deficits are found depending on the loci of the lesions (Posner *et al.*, 1984; Rafal and Posner, 1987). Subjects with damage to the parietal lobe are impaired in their detection of targets in the contra-lesional visual field, but only when they are first miscued (by an invalid cue) to the ipsilesional visual field (Posner *et al.*, 1984). These same subjects show almost normal reaction times to contra-lesional targets that are validly cued, which indicates that they are able to shift attention to the contra-lesional field. Based on the deficit seen in parietally-damaged stroke patients on the spatial cueing task, it has been postulated that the parietal lobe is selectively involved in shifting or 'disengaging' attention from previously attended locations in the contra-lesional field.

Further studies have shown that the 'disengage deficit' is more common after damage to the right compared with the left parietal lobe, and is often related to a more general attentional deficit in which the patient fails to respond or orient to stimuli presented contralateral to the brain lesion (i.e. unilateral neglect) (Morrow and Ratcliff, 1988). These clinical observations along with more recent PET studies (Corbetta *et al.*, 1993, 1995) provide converging evidence that the right posterior parietal lobe in humans is specialized for directing attention to spatial locations and may also be specifically involved in disengaging selective attention.

A study by Egly *et al.* (1994) helped to delineate the respective attentional functions of the right and left parietal regions further. They developed an elegant paradigm in which shifting of attention could occur either between spatial locations enclosed within a single object or between spatial locations located in separate objects. The objects consisted of two rectangles that appeared either above and below or to the left and right of a central fixation point. The two rectangles were identical in size and were positioned so that the internal distance between ends of a single rectangle was equal to the perpendicular distance between the ends of the two rectangles (Fig. 1). Cueing was accomplished by brightening (i.e. changing from grey to white) the end of the rectangle. The subject's task was to press a key whenever a target (a square) was detected at one of the four rectangle ends.

This experiment had two conditions: (i) valid trials, in which the target appeared at the cued end of the rectangle and (ii) invalid trials, in which the target appeared at an uncued end of one of the rectangles. On invalid trials the target appeared either at the end of the rectangle opposite to the cue (i.e. invalid-within) or at the end of the uncued rectangle (i.e. invalid-between) (Fig. 1). The two invalid cue conditions allowed for the separate calculation of spatial and object reaction time costs. By comparing reaction time on valid and invalid-within trials it was possible to determine

CUE   TARGET

Fig. 1 Stimulus display for the Egly paradigm. Examples of cue and target displays are shown for valid, invalid-within object and invalid-between object conditions.

the cost of shifting attention spatially from the invalid cue location to the target location (Fig. 1). Additionally, the cost of shifting attention between objects, controlling for the spatial component of the shift, could be derived by comparing reaction times on the invalid-within and invalid-between conditions.

To examine how spatial and object shifts of attention were affected by brain damage, Egly *et al.* (1994) tested a group of stroke patients with either right or left parietal lesions. They found that both groups of stroke patients showed abnormally elevated reaction times to invalidly cued targets in the contra-lesional visual field. For patients with right-parietal lesions, however, the deficit in shifting attention was not affected by the object properties of the stimulus display. In contrast, for patients with left parietal lesions, the reaction time cost of shifting attention between contra-lesional spatial locations was disproportionately elevated only when the cue and target locations were contained in separate objects. The results seemed to suggest that the right and left parietal lobes are, to some extent, differently specialized for shifting attention between spatial locations and objects, respectively.

Egly's finding may also help explain why bilateral parieto-

occipital lesions are associated with simultagnosia. Simultagnosia, refers to a syndrome in which patients often have full visual fields and are able to recognize most objects, but are unable to see more than one object, or part of an object, at a time (Farah, 1990). The underlying deficit in simultagnosia appears to be attentional. Experimental evidence suggests the attentional limitations associated with simultagnosia are both spatially- and object-based. Patients with simultagnosia following damage to dorsal regions of the visual system show limitations both in the region of visual space and the number of objects that can be attended to at the same time (Farah, 1990; Humphreys and Riddoch, 1993). The results of the Egly study would suggest that the right and left parietal lesions associated with simultagnosia may contribute to the respective spatially- and object-based attentional restrictions associated with this syndrome.

Deficits in orienting visual attention have also been reported in Alzheimer's disease (Parasuraman and Haxby, 1993). Parasuraman *et al.* (1992) investigated the effects of attentional shifting using a letter-discrimination task; stimulus onset asynchrony varied between 200 and 2000 ms and central and peripheral cues were used. They found that reaction time costs were elevated in the Alzheimer's disease group compared with the age-matched normal control group, which suggests that Alzheimer's disease subjects are impaired at shifting visual attention away from invalidly cued locations. Additionally, right–left asymmetries in reaction time costs were correlated specifically with left–right asymmetries in resting levels of cerebral glucose metabolism in the superior parietal lobe, as measured using PET. The study by Parasuraman *et al.* (1992) indicates that Alzheimer's disease subjects show deficits in shifting selective visual attention and that these deficits are related to parietal dysfunction.

Experiment 1

From previous studies of attentional functioning in Alzheimer's disease, two main points seem to be emerge. The first is that Alzheimer's disease patients are impaired at shifting visual attention from previously attended locations. Secondly, this attentional deficit is related to parietal dysfunction, and more specifically asymmetries in parietal dysfunction. The purpose of the present study was to distinguish between the spatial and object components of the deficit in attentional orienting reported in previous studies of Alzheimer's disease and to examine whether these deficits are differentially related to right and left parietal dysfunction. Alzheimer's disease subjects were tested on an attentional task adapted from Egly *et al.* (1994). The results of the Egly study together with the attentional deficit seen in patients with simultagnosia provided the motivation for the main hypothesis that the bilateral parietal damage associated with Alzheimer's disease would result in both spatially- and object-based attentional deficits. This hypothesis was examined by comparing the performance of Alzheimer's disease and age-matched normal control subjects (herafter referred to as

control subjects) on a version of the Egly task. It was predicted that the predominantly bilateral parietal damage associated with Alzheimer's disease would result in impaired shifting of attention both between- and within-objects.

Methods

Subjects

Two groups of subjects participated in this experiment, a group with mild to moderate Alzheimer's disease (15 males, 14 females) and a group of healthy age-, sex- and education-matched control subjects (eight males, nine females). All subjects had normal or corrected vision of at least 20/40. Alzheimer's disease subjects had standard neurological and biochemical tests in addition to MRI to rule out secondary causes of dementia. Subjects in the Alzheimer's disease group met the NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Work Group) diagnostic criteria for 'probable' Alzheimer's disease (McKhann *et al.*, 1984). To reduce the possibility of concomitant vascular disease, all Alzheimer's disease subjects had a modified Hachinski score of $\leqslant 4$ (Hachinski *et al.*, 1975). Except for two Alzheimer's disease subjects (one male, one female), all subjects were right-handed. The demographic characteristics of the Alzheimer's disease and control subjects are shown on Table 1. In addition to mental status testing, Alzheimer's disease subjects also received a more detailed battery of neuropsychological tests, the results of which are summarized in Table 1.

For the control group, standard neurological and psychological exclusion criteria were applied in selecting subjects for participation in the study. There were no significant differences in the age [$t(42) = 1.53$, $P = 0.1327$] and education [$t(38) = 1.70$, $P = 0.0955$] of the two groups; however, as expected, the Alzheimer's disease group scored lower on the Mini-Mental State Examination (MMS) (Folstein *et al.*, 1975) [$t(37) = 9.52$, $P = 0.0000$] (Table 1). Of the 29 Alzheimer's disease subjects, 12 subjects had mild deficits [MMS 20–28, Mattis Dementia Rating Scale (DRS) (Mattis, 1976), 115–132], and the remaining 17 subjects were moderately demented (MMS 10–19, DRS 74–114). All procedures were approved by the institutional ethics review board at Sunnybrook Health Science Centre and informed consent was obtained from all subjects and/or their guardians following appropriate ethical procedures.

Stimuli

The fixation display consisted of two coloured rectangles (one blue and one green) positioned either above and below, or to the left and right of, a fixation point measuring $0.5° \times 0.5°$ (when viewed at a distance of 60 cm) (Fig. 1). Each rectangle measured $9.5° \times 1.9°$ and was formed from lines that were six pixels thick and 50% grey in colour. The centres of the rectangles were $3.8°$ from the centre of fixation. The rectangles were oriented parallel to each other, so that the distance between the ends of the two rectangles was $7.6°$. Cueing was accomplished by superimposing three $1.9°$ white lines over one end of a rectangle, which had the effect of brightening the rectangle end. The target was a solid white square measuring $1.8° \times 1.9°$. All stimuli were presented on a black background.

Apparatus

Stimulus presentation and recording of response time were controlled using SuperLab software on a Macintosh IIci with a 14-in colour monitor (70-Hz refresh rate). Subjects made responses to the target using their dominant hand to press a key interfaced to the computer.

Procedure

Subjects were tested in a quiet room, with subdued lighting. Trials began with the presentation of a fixation display for 1000 ms. Following the fixation display, one of the ends of the two rectangles was cued by brightening the rectangle. The cue lasted for 200 ms, after which time the cued end returned to its original colour (grey). Then, the fixation display was immediately presented for another 200 ms, after which time the target square appeared (i.e. the inter-stimulus interval was 200 ms). The target square remained visible until the subject responded, or for 2000 ms if there was no response. Once the subject responded, or 2000 ms lapsed, the screen was blank (black) for 500 ms and then the next trial began. On 'catch' trials, the fixation display was presented for 2000 ms following the cue, and no target was presented.

Both key-response accuracy and reaction time were measured. Subjects were told to maintain fixation on the fixation point throughout each trial, and that, although reaction time was being recorded, it was equally important to respond only when the target was detected. Trials on which the subjects were distracted or required re-instruction were marked by the experimenter and excluded from analysis. All subjects included in this analysis had at least 15 trials in each condition analysed. Additionally, response times of <250 ms were considered as anticipation and were not analysed.

Before starting the experiment, subjects were given a practice session consisting of 20 trials. The task was explained during the practice trials. If subjects made more than five errors ($\geqslant 25\%$) on the practice trials, the practice trials were repeated until the error rate dropped below 25%. Of the 31 Alzheimer's disease subjects who attempted the experiment, two were unable to achieve this level of performance and were excluded from the study, leaving 29 subjects in the Alzheimer's disease group. All control subjects were able to complete the experiment.

During test sessions, eye movements were monitored visually by the experimenter. Trials on which eye movements

Table 1 *Demographic and neuropsychological characteristics of Alzheimer's disease patients and age-matched controls*

Subject	Preferred hand	Age (years)	Sex	Education (years)	MMSE	Mattis DRS	Rey copy	FAS fluency	Semantic fluency	Boston naming	Line orientation
1	L	70.5	F	14	16	94	–	9	5	18	0
2	R	75.6	M	20	28	119	29	26	10	27	28
3	R	75.5	M	14	22	131	33	29	8	26	28
4	R	58.9	F	9	16	84	0	10	2	12	0
5	R	74.4	F	8	21	118	7	21	8	25	8
6	R	70.3	F	8	26	125	36	33	10	27	22
7	R	69.2	M	16	17	109	4.5	14	5	20	0
8	R	75.8	M	20	26	104	32	27	10	15	30
9	L	78.8	M	12	17	95	33	10	8	8	27
10	R	70.3	M	6	17	99	2.5	10	4	14	14
11	R	82.9	F	13	25	107	2	15	3	16	13
12	R	67.8	M	11	19	97	23	19	6	13	–
13	R	72.1	M	18	17	105	23.5	6	5	17	13
14	R	75.6	F	8	20	120	26	30	11	16	16
15	R	63.7	M	8	15	87	21.5	11	6	12	21
16	R	50.3	F	16	21	117	4.5	27	10	22	2
17	R	81.4	F	11	18	114	27	33	8	19	13
18	R	60.1	M	13	22	131	20	11	10	27	21
19	R	58.3	F	15	10	74	2	27	1	6	–
20	R	82.3	F	13	22	113	33	16	14	14	20
21	R	73.4	F	16	22	118	28	45	11	24	21
22	R	83.3	M	16	23	109	36	1	8	19	25
23	R	78.0	M	12	21	103	34	18	9	15	–
24	R	71.9	F	10	28	125	31	22	11	20	18
25	R	72.8	M	14	28	144	32.5	18	39	19	28
26	R	77.1	M	18	18	111	31	26	9	25	20
27	R	73.6	F	8	20	125	20.5	33	8	21	11
28	R	85.7	M	12	21	122	35	31	9	27	26
29	R	70.5	F	12	21	119	3	30	6	22	8
Alzheimer's disease patients											
Mean ± SD		72.4 ± 8.18	15M/14F	12.8 ± 3.78	20.6 ± 4.27	111 ± 15.5	21.8 ± 12.8	21.0 ± 10.3	8.76 ± 6.53	18.8 ± 5.84	16.7 ± 9.41
Age-matched controls											
Mean ± SD		69.2 ± 5.95	8M/9F	14.53 ± 2.94	28.91 ± 1.22						
P-value*		> 0.05	> 0.05	> 0.05	< 0.0001						

L/R = left hand/right hand; M/F = male/female; MMSE = Mini-Mental State Examination; Mattis DRS = Mattis Dementia Rating Scale; *see* Lezak (1995) for detailed test descriptions and normative scores. *P*-value based on independent samples *t* test (except test of sex which was based on the χ^2 test).

occurred were marked and later excluded from analysis. There were no group differences in the ability to maintain fixation.
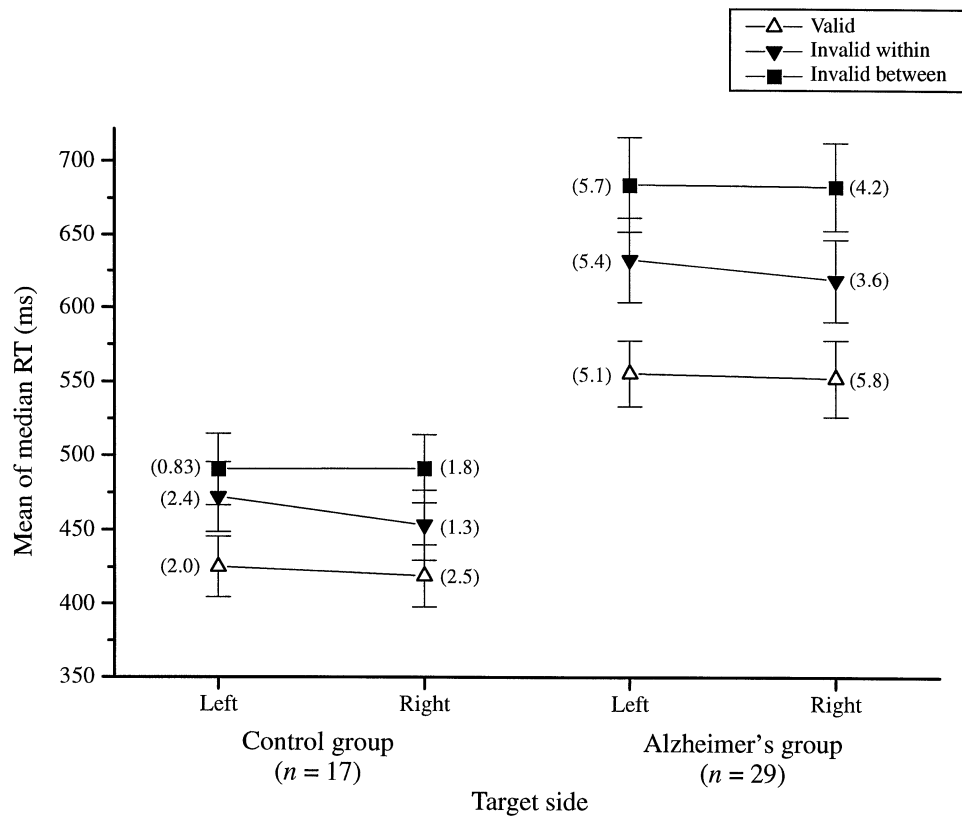
Design

The experiment consisted of six blocks of 80 trials, three blocks with the horizontal and three with the vertical displays. The blocks alternated between all horizontal and all vertical displays, and the order of the blocks was counterbalanced between subjects. Each block of trials consisted of 48 valid trials, 16 invalid trials and 16 catch trials. Trials within a block were randomized by the computer. Blocks lasted ~5 min each, and subjects were allowed a break between blocks, which typically lasted ~1–2 min.

Statistical analyses

To examine whether there were differences in reaction times to targets eliciting horizontal versus vertical shifts of attention, a preliminary analysis of the data was conducted. Some

studies have found slower vertical shifts of attention in the contra-lesional field for neglect patients (Baynes *et al.*, 1986) suggesting that neglect affects spatial attention in both the horizontal and vertical meridians. Analysis of variance (ANOVA) was used to examine whether the orientation of the rectangles in the fixation display influenced the reaction time. The between-subject factor was group (Alzheimer's disease, control) and the within-subject factors were target side (left, right), cue conditions (valid, invalid within, invalid between) and rectangle orientation (horizontal, vertical). Consistent with previous investigations (Egly *et al.*, 1994; Vecera, 1994), this analysis revealed no main effect of rectangle orientation ($P > 0.50$), and no significant inter-action between rectangle orientation and any of the other effects ($P > 0.25$). Therefore, to simplify the interpretation of the results and to increase the power of the analysis, the rectangle orientation term was dropped from all subsequent analyses.

To examine the group differences in error rates and the median reaction time, mixed-factorial ANOVA was used.

Fig. 2 Mean (±SE) of the median reaction time (RT) as a function of cue condition, target side and group. Percentage errors for each condition are shown in parenthesis.

The degrees of freedom for within-subject *F*-ratios were corrected using the Greenhouse–Geisser Epsilon (Stevens, 1986). Cue effects were compared between groups using planned single degree of freedom interaction-contrasts (Keppel and Zedeck, 1989). All tests were evaluated using two-tailed probabilities, with the significance level set to 0.05.

Results

Accuracy

The mean hit-rate (±SD) was 93.5 ± 5.2% for the Alzheimer's disease group and 97.7 ± 2.7% for the control group. On catch trials, the Alzheimer's disease subjects made a significantly greater number of responses than the control subjects [$t(44) = -3.64$, $P = 0.001$]. The mean (±SD) false-alarm rates for the Alzheimer's disease and control group was 7.01 ± 6.39% and 1.34 ± 1.95%, respectively. Figure 2 shows the percentage errors and the mean of the median reaction time for the two groups, as a function of cue condition and target side. Three-way repeated measures ANOVA was performed on the error rate for target present trials with group (Alzheimer's disease, control) as the between-subject factor, and target side (left, right) and cue condition (valid, invalid within, invalid between) as within-subject factors. The only significant source of variance was the main effect of group [$F(1,44) = 8.56$, $P = 0.005$], which

shows that Alzheimer's disease subjects made more errors across all experimental conditions.

Group differences in reaction time

The mean of the median reaction time for the correct responses was analysed using a mixed three-factor ANOVA. For the ANOVA, the between-subject factor was group (Alzheimer's disease, control), and the within-subject factors were target side (left, right) and cue condition (valid, invalid within, invalid between). The mean of the median reaction time as a function of group, target side and cue condition is shown in Fig. 2. ANOVA showed a significant two-way interaction between group and cue condition [$F(1,88) = 9.48$, $P = 0.001$]. To identify the source of the interaction, the 2 × 3 interaction was decomposed into three separate planned comparisons, each comparison consisting of a 2 × 2 (group by cue condition) interaction contrast (Keppel and Zedeck, 1989).

The purpose of the first contrast was to compare the difference between the valid and combined invalid conditions (i.e. the effect of cue validity) between the groups. Since the perceptual–motor processing demands of the invalid and valid conditions were matched, it was assumed that generalized slowing would equally affect responses on valid and invalid trials. The contrast was significant [$F(1,88) =$

Fig. 3 The mean (±SE) cue effect sizes shown for the Alzheimer's disease and control groups. Validity effect = invalid – valid; spatial effect = invalid within – valid; object effect = invalid between – invalid within. *Mean group differences significant at $P < 0.05$, based on planned contrasts.

10.05, $P = 0.003$]. indicating that while both groups showed validity effects, the reaction time cost or difference between invalid and valid trials (although strictly speaking without a neutral cue this is a combined reaction time cost plus reaction time benefit) was significantly greater in the Alzheimer's disease group (mean = 101 ms) than in the control group (mean = 55 ms) (Fig. 3). This finding is consistent with other studies that showed Alzheimer's disease subjects have deficits disengaging selective attention (Parasuraman *et al.*, 1992; Maruff *et al.*, 1995); however, it does not address the central issue of whether the attentional deficits seen in Alzheimer's disease subjects were object- or spatial-based.

To examine the relative contributions of the object and spatial components to the deficit observed in the Alzheimer's disease group, the invalid conditions were separated according to whether they elicited attentional shifting (i.e. from the cue to the target) between rectangles (invalid-between) or within rectangles (invalid-within). Two more planned interaction contrasts were performed. The first of these compared, between the groups, the difference between the invalid-within and valid conditions (i.e. the spatial reaction time cost). The contrast was significant [$F(1,44) = 5.78$, $P = 0.020$] indicating that the reaction time cost of shifting attention between spatial locations was greater in the Alzheimer's disease group (mean = 72 ms) compared with the control group (mean = 41 ms) (Fig. 3).

The purpose of the final contrast was to examine whether the Alzheimer's disease group also showed an object-based attentional deficit. This was tested by comparing the mean reaction time difference between the invalid-between and invalid-within conditions (i.e. the reaction time cost of shifting attention between objects) as a function of group. Since the invalid-within condition elicited a spatial shift of attention and the invalid-between condition involved an equivalent spatial shift of attention plus a shift between rectangles, the

difference between the two conditions measures the reaction time cost of shifting attention between objects. This final contrast was also significant [$F(1,44) = 5.47$, $P = 0.024$], indicating that the object reaction time cost was elevated in the Alzheimer's disease group (mean = 58 ms versus 28 ms the control group) (Fig. 3). Thus, based on the three planned comparisons it appears that Alzheimer's disease subjects, showed both spatially- and object-based deficits in attentional shifting.

The elevated effects of cue validity in the Alzheimer's disease group did not, however, depend on target side as indicated by the non-significant three-way interaction between group, cue condition and target side [$F(2,88) = 0.18$, $P = 0.96$]. The two-way interactions between target side and group, and target side and cue condition, as well as the main effect of target side were also not significant ($P > 0.10$). There was a significant main effect of group [$F(1,44) = 10.29$, $P = 0.002$], reflecting generalized reaction time differences between the Alzheimer's disease and control subjects across cue conditions (Fig. 2). Finally, the main effect of cue condition [$F(1,88) = 100.52$, $P = 0.000$] was significant, which simply suggests that both groups benefited from valid over invalid cues (Fig. 2).

Discussion

These results are consistent with previous investigations of attention in Alzheimer's disease (Parasuraman *et al.*, 1992; Maruff *et al.*, 1995) in showing that Alzheimer's disease subjects are impaired in shifting selective attention away from invalidly cued locations. This experiment also examined the spatially- and object-based components of this deficit. Compared with age-matched control subjects, Alzheimer's disease subjects showed elevated reaction time costs for shifting attention between both spatial locations and objects. This supports the hypothesis that the predominantly bilateral parietal damage in typical Alzheimer's disease would produce both spatially- and object-based attentional impairments. However, without indices of parietal dysfunction the proposal of a relationship between the observed attentional deficit and brain dysfunction is speculative. The next experiment addresses whether the same relationship between the spatially- and object-based attentional deficits and parietal damage, as reported by Egly *et al.* (1994) in unilateral stroke patients, similarly exists in patients with Alzheimer's disease. We predict that the deficit in shifting attention within-objects will be correlated with right parietal dysfunction and the between-object deficit will be correlated with left parietal dysfunction.

Experiment 2

In the previous experiment, Alzheimer's disease subjects showed both spatially- and object-based deficits in shifting selective attention. The question that remained was how these attentional deficits relate to the brain dysfunction associated

with Alzheimer's disease. Recent PET (Corbetta *et al.*, 1993, 1995) and focal lesion (Egly *et al.*, 1994) studies provide some clues. These studies are consistent with the view that each hemisphere controls attentional shifting bilaterally, based on the representation for which it is specialized (i.e. spatially- or object-based). The other hemisphere may be involved to a much lesser extent, perhaps only in generating contralateral shifts. For example, if the left parietal region controls shifting of attention between objects, then following unilateral left parietal damage, ipsilesional between-object shifts of attention could still be initiated by the right parietal lobe, while contra-lesional between-object shifts would be disrupted due to the damaged left hemisphere. Similar reasoning could be applied to explain the finding that right parietal damage affects spatial shifting of attention in the left hemispace.

Given the results of the above PET and focal lesion literature, it may have been expected that, in the first experiment, the deficit in shifting attention seen in the Alzheimer's disease subjects would interact with target side. The prediction would be that the impairment in shifting attention between locations would be greatest for right-sided targets whereas the shifts of attention between objects would be most impaired for left-sided targets. This interaction was not found in the first experiment but given that, unlike that in stroke patients, the damage in Alzheimer's disease is predominantly bilateral, this is perhaps not surprising. The bilateral nature of the brain damage in Alzheimer's disease may reduce the asymmetry of any deficits in shifting attention. The lack of any group asymmetries in the attentional deficit does not preclude the possibility of hemispheric asymmetries in the control of spatial and object-based orienting processes, or that parietal damage asymmetrically affects attentional functioning. In the next experiment this issue was further addressed.

The purpose of the second experiment was to examine, in the same group of Alzheimer's disease subjects described in Experiment 1, the relationship between the observed attentional deficit and parietal dysfunction as indexed by SPECT imaging. The main hypothesis tested was that right parietal hypoperfusion would be associated with increased spatial reaction time costs, while left parietal hypoperfusion would be associated with increased object reaction time costs. Specifically, since parietal damage is thought to affect attentional shifting asymmetrically, it was hypothesized that the strongest relationships would be seen between right parietal hypoperfusion on SPECT and the left spatial reaction time cost, and left parietal hypoperfusion and the right object reaction time cost.

Methods
Subjects
Twenty-four of the 29 subjects tested on the Egly task had SPECT imaging performed as part of their routine clinical work-up. For these 24 subjects, the mean time ($\pm$SD)

between the SPECT scan and reaction time testing was 3.3 ± 2.6 months (range 0–9 months). For the remaining five subjects (numbers 1, 4, 13, 24 and 25; *see* Table 1), SPECT imaging had not been completed within 9 months of the test session and consequently these subjects were excluded from further analyses.

SPECT imaging protocol
The SPECT imaging was obtained as part of the clinical workup for the Alzheimer's disease subjects. SPECT imaging was performed using a rotating dual-headed gamma camera (Picker Model 2000), a minimum of 15 min and a maximum of 120 min after intravenous injection of 740 MBq (20 mCi) of [^{99m}Tc]-HMPAO. Images were acquired using 120 planar views, over 360°. Each view consisted of a 128×128 pixel image with a reconstructed image resolution of ~10.5 mm full width at half maximum. Each view took 20 s, with the entire scan session lasting 20 min. Reconstruction was performed using a ramp-filtered back-projection algorithm followed by the application of a 3D low pass post-filter.

During reconstruction, the sets of SPECT images were corrected for head-tilt in the sagittal, coronal and transverse planes. This correction served to standardize the slice orientation of the sets of SPECT data between subjects. The procedure involved the identification of three coordinate baselines used in the Tailarach and Tournoux (1988) stereotaxic brain atlas: the anterior commissure/posterior commissure (AC/PC) line, the midline and the anterior–posterior (AP) centre-line. Since the AC/PC line cannot be visualized on SPECT, the orbitomeatal (OM) line was identified on a sagittal view instead. The OM line has been shown to approximate the AC/PC line within 5° (Vanier *et al.*, 1985). The midline and AP centre-line were selected by visually identifying the axis of symmetry in the coronal and transverse planes, respectively. Rotation of the data sets was performed in each plane to align the matrix of the image data sets with the three coordinate baselines. Inter- and intra-rater standard deviations (four operators, three repetitions per operator) in the angles of reorientation was previously determined as 1.5° for the coronal plane and 1.6° for the transverse plane (Stapleton *et al.*, 1992).

SPECT semiquantification: cortical rim method
The reconstruction procedure yielded ~20 transverse slices aligned parallel to the OM line. From these slices, semiquantitative measurements of standardized regional cerebral blood flow (srCBF) were obtained using a cortical rim method (Hellman *et al.*, 1989). Images were processed on a SUN SPARCstation2 (SUN Microsystems, Mountain View, Calif., USA). The first step was to define a cortical rim (annulus) on the transverse SPECT images. The outer boundary of the cortical rim was defined using the image editing procedure included with the ANALYZE© 7.5 software package (Biomedical Imaging Resource, Mayo Foundation,

USA) (Robb, 1994). This boundary was delimited semi-automatically using a threshold value of 40% of the mean cerebellar counts. The procedure for determining mean cerebellar perfusion is described below. Placement of the outer boundary was inspected on all slices to ensure that it was correctly positioned on the surface of the cortex, at the interface between grey matter and cerebrospinal fluid. The inner boundary was defined by moving seven pixels radially inwards from the outer boundary, using a morphological filter (i.e. an 'erosion' operation). Then the eroded images were subtracted from the original image, resulting in the 'cortical rim' image alone.

Next, for each slice, six individual regions of interest per hemisphere were created by subdividing the cortical rim into 12 equal 15°-sectors. Within each region of interest, mean counts per pixel were calculated. The cortical rim procedure was applied to the 10 slices that encompassed the superior and inferior limits of the cortex, yielding srCBF values for 120 regions of interest per patient. Standardization of region-of-interest data was performed by dividing mean counts per pixel in the region under analysis by mean counts per pixel in both lobes of the cerebellum. The cerebellum was selected as a reference region because it is largely unaffected in Alzheimer's disease; perfusion remains relatively intact and constant with progression of the disease (Minoshima *et al.*, 1995).

Mean cerebellar perfusion was determined in a standardized manner by tracing the cerebellum using a semi-automatic threshold technique. The first step was to locate the slice that included the maximum counts for the cerebellum. The cerebellar region was then defined using a threshold set to 50% of the maximum counts. The average counts per pixel were determined within this region of interest and used as the standardization factor.

Regions of interest: definition using co-registered MRI

Inter-subject registration was performed to permit the srCBF within the cortical rim segments to be compared between subjects. Due to the limited anatomical resolution of SPECT, it was decided that the inter-subject registration of SPECT scans and the localization of regions of interest should be improved by the co-registration of T_1-weighted MRIs (the scan parameters are described in the next section). MR-SPECT co-registration was performed on five subjects. For these five subjects, the absolute mean time (±SD) between the MRI and SPECT scans was 6.7 ± 4.3 months.

The five co-registered MRI-SPECT scans were used to generate 10 SPECT images that closely matched the following transverse slices from the Talairach atlas (Tailarach and Tournoux, 1988): 10–11, 9–10, 8–9a, 7–8, 6–7b, 6, 4–5, 3–4, 2–3 and 1–2. For the remaining 19 subjects, without co-registered MRI scans, SPECT slices at the same level as the template SPECT slices were selected by two raters (both

blind to subject identity) based on visual identification of anatomical landmarks. Raters were given hardcopies of each subject's SPECT scan and were instructed to select the 10 transverse slices that most closely matched (i.e. contained the same brain structures) the 10 template slices. There was agreement between raters on 296 out of 380 (78%) of the total slices. For the slices on which the two raters disagreed (which never differed by more than one slice), the best slice was selected based on a consensus of the two raters.

Once the SPECT slices were registered across subjects into a standardized stereotaxic space, the cortical rim segments could be localized with reference to the Talairach atlas. For this experiment, the primary region of interest was the posterior parietal region (Brodmann areas 5, 7, 39 and 40). Based on Talairach's atlas, six cortical rim segments were located (unilaterally) within the posterior parietal region (Fig. 4). These cortical rim segments were located on the SPECT slices that corresponded to the transverse Talairach slices located +55 mm, +45 mm and +35 mm above the AC/PC line (i.e. slices 2–3, 3–4, 4–5).
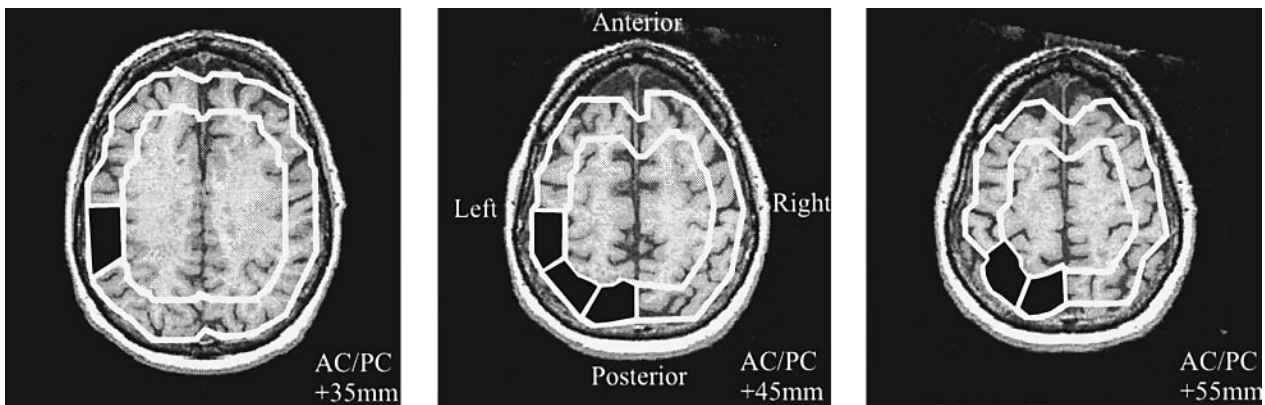
MRI protocol

MRI was conducted with a 1.5 Tesla MRI system (Signa, Version 4.7; General Electric Medical Systems, Milwaukee, USA). A volumetric three-dimensional sequence covering the whole brain was performed in the sagittal plane. One hundred and twenty-four contiguous 1.3 mm thick slices were obtained using a T_1-weighted sequence, 192 phase-encoding steps, with a TR/TE of 35/5 ms, a flip angle of 35° and a field of view of 20 cm in an imaging time of 14.4 min.

The T_1-weighted MRI sets of images were co-registered to the SPECT scans using an automated registration algorithm (Woods *et al.*, 1993). Prior to matching the MRI and SPECT images, non-brain structures must be segmented from brain structures and deleted from the T_1-weighted image set. MRI images were segmented and edited using the 3D morphological operations included with ANALYZE© image processing software. The procedure for editing the T_1-weighted images using morphological filtering has been detailed elsewhere (Hohne and Hanson, 1992).

Data analyses

Statistical tests on the data were performed using SPSS for Windows 6.1.2 (SPSS USA, 1995). Stepwise multiple regression was used to examine the relationship between mean perfusion in parietal cortical rim segments (the independent variable) and reaction time costs of invalid cueing within and between rectangles (the dependent variable). To account for the multiple independent variables evaluated with stepwise regression, the probability for entry into the model was set conservatively at 0.005.

Models were developed using the reaction time cost measures as the dependent variables and the twelve cortical

Fig. 4 The cortical rims extracted from a SPECT image are superimposed on co-registered MRIs oriented parallel to the AC/PC line as described in the text. The distance above the AC/PC line for each slice is indicated in the lower right-hand corner. For purpose of illustration, in the left hemisphere, the six superior and inferior parietal segments that were entered into the multiple stepwise regression are shown in black.

rim segments corresponding to left and right, posterior parietal regions as independent variables. All cortical rim segments were standardized by dividing the mean counts in each segment by the mean cerebellar counts. Although there were *a priori* hypotheses regarding hemispheric specialization for spatial and object attentional shifts, both left and right hemisphere cortical rim segments were included in each model, in order to assess the specificity of any detected relationships between srCBF and task performance.

The relatively low spatial resolution inherent to SPECT imaging means that the cortical rim segments are not fully independent. Conventional statistical methods such as multiple regression may not be ideally suited for examining the relationship between behavioural performance and the activity of multiple correlated brain regions. Therefore, this second experiment was limited to examining the specific hypothesis that attentional performance would be related to parietal hypoperfusion and did not aim to address the broader issue of which brain systems are involved in performing this task. More sophisticated data-analysis tools such as Partial Least Squares (McIntosh *et al.*, 1996) have been proposed to extract this latter type of information from imaging data, but these techniques are not yet widely available.

Results
Analysis of reaction time data
Figure 5 shows the mean of the median reaction time data and percentage errors as a function of cue validity and target side for the subset of Alzheimer's disease subjects ($n = 24$) with SPECT imaging that were used in this experiment. Prior to examining the relationship between measures of srCBF and attentional performance, ANOVA was performed on the reaction time data. The purpose of this analysis was to ensure that the subset of subjects selected for inclusion in this experiment were representative of the larger group of 29 subjects described in the previous

experiments. Specifically, it was important to establish that the Alzheimer's disease subjects selected for the SPECT analysis showed, as a group, an impaired ability to shift attention between both spatial locations and objects.

The structure of the ANOVA was identical to the analysis described in Experiment 1. ANOVA was performed on the mean of the median reaction time for the correct responses made by the 24 Alzheimer's disease subjects with SPECT imaging, and the same group of control subjects described in Experiment 1. Most important, the ANOVA revealed a significant group-by-cue condition interaction [$F(1,78) = 8.18$, $P = 0.003$], replicating the finding that the cueing effects in the Alzheimer's disease subjects were elevated relative to the control subjects. Furthermore, the reaction time cost of shifting attention between both spatial locations and objects was elevated in the Alzheimer's disease group compared with the control group ($P < 0.05$) (Table 2).

Relationship between reaction time costs and srCBF
The spatial and object reaction time cost measures were calculated separately for left- and right-sided targets (as described in Experiment 1), and were used as dependent variables in multiple stepwise regression models. For each model, 12 cortical rim segments from the left and right posterior parietal region were included as putative independent variables. Segments were included in a model when they accounted for a significant portion of the variance (i.e. if $P < 0.005$) in the dependent variable.

Results of these analyses are shown in Table 3. As hypothesized, for the right object reaction time cost, a segment located in the left inferior parietal region (Brodmann area 39, 40) entered into the model [$F(1,22) = 10.00$, $P = 0.0045$]. The negative slope (β) indicated that the relationship was in the expected direction, with reduced srCBF being associated with increased reaction time costs
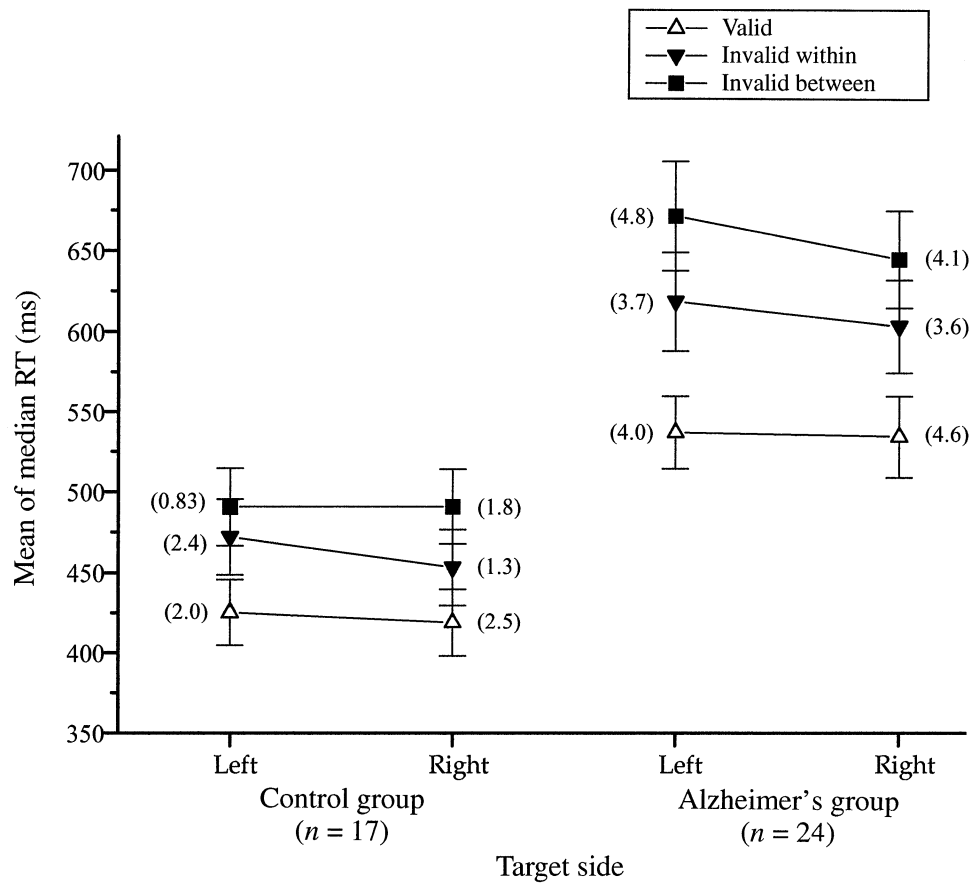
Fig. 5 Mean (±SE) of the median reaction time (RT) and as a function of target side, cue condition and group. Percentage errors for each condition are shown in parentheses.

Table 2 *Reaction-times for valid and invalid cue conditions, and cue effects, in Alzheimer's disease patients and control subjects*

	Mean median reaction times (ms)			Cue effect (ms)*	
	Valid cue	Invalid cue		Spatial cost	Object cost
	(1)	Within (2)	Between (3)	(2–1)	(3–2)
Patients (*n* = 24)	536 ± 23.8	611 ± 28.7	658 ± 31.4	75.1 ± 10.2	47.2 ± 7.75
Controls (*n* = 17)	422 ± 21.6	462 ± 23.2	490 ± 23.0	40.6 ± 7.41	28.2 ± 4.53
P-value[†]				0.0094	0.0415

The values given are means ± SE. *The spatial cost was calculated by subtracting column 2 minus column 1, and the object cost was calculated by subtracting column 3 minus column 2. [†]Probability based on single degree of freedom planned comparisons.

when shifting attention between objects located in the right hemispace (Fig. 6A). The analogous reaction time cost of detecting left-sided targets was not significant. Also consistent with the hypotheses was that a right superior parietal segment (Brodmann area 5, 7) entered into the model for the left spatial reaction time cost. Again the slope was negative, suggesting that hypoperfusion in this region of the right superior parietal lobe was associated with an impairment in shifting attention between spatial locations, specifically in the left-hemispace [(F1,22) = 15.81, *P* = 0.0006] (Fig. 6B). No other cortical rim

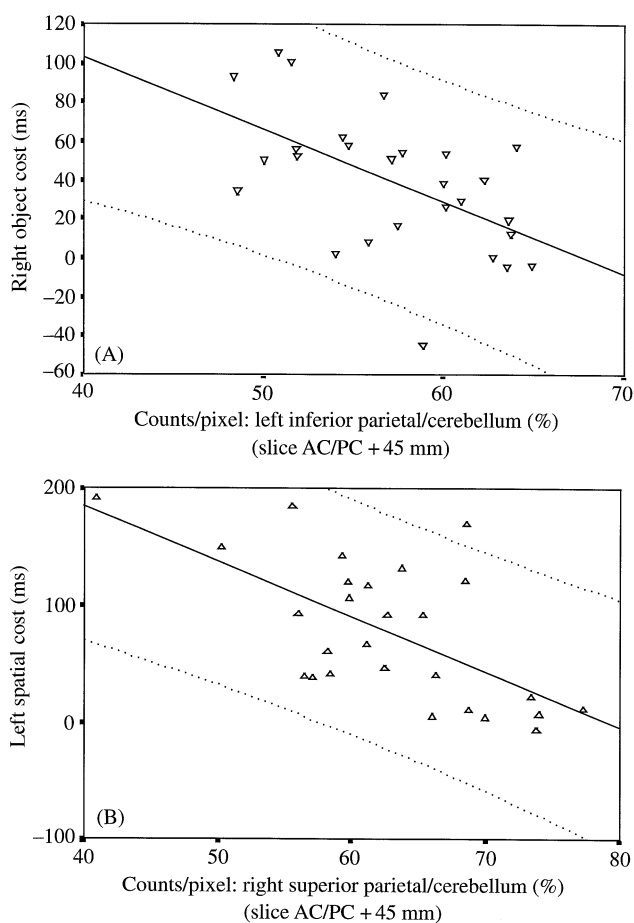segments entered into the model for the left spatial reaction time cost.

Specificity of relationship between reaction time costs and srCBF

It is possible that the reaction time costs and srCBF ratios were related to each other only indirectly, due to the fact that attentional deficits and parieto-temporal hypoperfusion were both related to dementia severity. To investigate the

Table 3 *Stepwise multiple regressions for four models examining the relationship between reaction time cost and semiquantitative SPECT measures of parietal perfusion in Alzheimer's disease patients* (n = 24)

Dependent variable (cost in ms)	Independent variable entered			*R*	*β*	*F*	*P*
	Slice (mm) (AC/PC)	Rim segment	Brodmann area				
Right object	+45	5	Left 39, 40	0.559	−3.87	10.00	0.0045
Left object	None						
Right spatial	None						
Left spatial	+45	7	Right 5, 7	0.647	−4.82	15.81	0.0006

In the column beside each dependent variable, the independent variables (if any) that entered into the regression model are listed. The *R*-value expresses the correlation coefficient between the independent and dependent variables incorporated into the regression equation. *β* represents the coefficient for the independent variable in the final regression equation.

Fig. 6 Scatterplot and regression line (continuous line) showing the relationship between the mean counts per pixel (expressed as a percentage of cerebellar counts in (**A**) left inferior parietal segment (Brodmann area 39, 40) and the cost of shifting attention between objects and (**B**) right superior parietal segment (Brodmann area 5, 7) and the cost of shifting attention between spatial locations. The dotted lines represent the 95% confidence interval for the prediction of single observations.

specificity of the observed relationship between the spatial and object reaction time costs and parietal hypoperfusion, the multiple regression analysis was repeated with the DRS score forced into the models prior to the selection

of srCBF measures. By forcing the DRS score into the models, dementia severity was controlled statistically, allowing srCBF measures to enter into the models only if they accounted for a significant portion of the variance in the reaction time cost measure, after accounting for DRS score. The results of this regression analysis were identical to the first pass. After accounting for dementia severity, srCBF in the left and right parietal segments was still significantly associated with object and spatial reaction time costs respectively (*P* < 0.005).

Another possibility explored was that the relationship between reaction time costs and parietal hypoperfusion was non-specific. That is, reaction time costs could have been related to globally decreased perfusion across all SPECT segments and not specifically to hypoperfusion in the posterior parietal segments. To examine this possibility, the multiple regression analysis was repeated using 12 cortical rim segments that were not hypothesized to be related to attentional performance. These 12 cortical rim segments (six left and six right hemisphere) were located approximately in Brodmann areas 6, 8, 9, 22, 39 (Talairach regions: GFs, GFm, GTs and GTm). The criterion for entry into the models was again set at *P* < 0.005. None of these cortical rim segments entered into the models, with right and left, object and spatial reaction time costs as dependent variables. Thus, it does not appear that reaction time costs were related non-specifically to hypoperfusion in the cortical rim segments.

General discussion

The purpose of this study was to determine the extent to which spatially- and object-based deficits in attentional shifting were present in Alzheimer's disease subjects, and whether these deficits were differentially associated with left and right parietal damage. It was hoped that the answers to these questions would provide further insight into the complex cognitive profile associated with Alzheimer's disease and enhance our understanding of how spatial and object attentional processes are organized in the human brain.

To examine these issues, covert attentional orienting was studied in Alzheimer's disease patients and control subjects, using an experimental task, involving the cueing of visual attention prior to the presentation of a target stimulus. Unlike previous experimental investigations of attentional shifting in Alzheimer's disease, the paradigm used in this study allowed for the separate examination of the spatially- and object-based components of attentional shifting. It was hypothesized that the bilateral parietal dysfunction associated with Alzheimer's disease would result in both spatially- and object-based attentional deficits. This hypothesis was based on two converging streams of evidence. First, Egly *et al.* (1994) found that unilateral right parietal damage was associated with deficits in shifting attention to contra-lesional spatial locations contained within an object, while left parietal damage was associated with an impairment in shifting attention between objects (Egly *et al.*, 1994). Also, simultagnosia, a complex disorder of visual perception that includes both spatially- and object-based attentional limitations, is typically found in patients with bilateral parietal lesions. Consistent with the hypothesis, in the first experiment, Alzheimer's disease subjects showed elevated reaction time costs for invalid cues eliciting shifts of attention both between- and within-objects, which suggests combined spatially- and object-based attentional deficits.

In the second experiment, the SPECT scans of 24 Alzheimer's disease subjects who completed the Egly task were analysed to derive semi-quantitative indices of parietal dysfunction. In particular, perfusion in superior (Brodmann areas 5, 7) and inferior (Brodmann area 39, 40) parietal regions was the focus of this study because previous human and non-human primate studies (Posner *et al.*, 1984; Corbetta *et al.*, 1993; Corbetta *et al.*, 1995; Robinson *et al.*, 1995) have shown these regions to be involved in the shifting of visual attention. If the right and left parietal regions were differentially specialized for spatially- and object-based attentional orienting then, in Alzheimer's disease subjects, it was predicted that right parietal hypoperfusion would be significantly correlated with reaction time costs for left-sided targets in the spatial condition, and left parietal hypoperfusion would be correlated with reaction time costs for right-sided targets in the object condition. The results were consistent with these predictions. Multiple regression analyses revealed significant relationships between left spatial reaction time costs and right superior parietal hypoperfusion (area 5, 7) and right object reaction time costs and left inferior parietal hypoperfusion (area 39, 40). Both relationships were specific to targets contralateral to the damaged hemisphere and to the parietal regions, and persisted even when dementia severity was controlled. Together, the findings support the view that regions of the right and left posterior parietal lobes are specialized for shifting attention away from previously selected spatial locations and objects, respectively.

The SPECT findings are also consistent with two previous studies that examined attentional shifting using PET (Corbetta *et al.*, 1993; Corbetta *et al.*, 1995). Corbetta *et al.* (1993) found that Brodmann area 7 was activated when attention was shifted between spatial locations. The right superior parietal lobe showed two distinct foci of activation that were differentially related to attentional shifting in the left and right visual fields, while the left superior parietal lobe showed only a single focus of activation related to shifting of attention in the right visual field. On this basis, Corbetta *et al.* (1993) concluded that while both parietal lobes are involved in shifting attention in the contralateral visual field, the right superior parietal region may be specialized for shifting attention across spatial locations in both visual fields. In this study, it was shown that 'deactivation' or hypoperfusion in the right superior parietal lobe is correlated with performance deficits in attentional shifting between spatial locations. In this respect, the SPECT imaging study reported in this study can be viewed as a negative activation paradigm, and provides converging evidence to support the view that the right superior parietal lobe is specialized for the spatial orienting of attention. Together with the PET studies of attention, the present results demonstrate how functional imaging studies using similar paradigms in normal and brain-damaged subjects can provide converging evidence for the models relating human brain and cognitive function.

To date, there have been no functional imaging studies showing hemispheric specialization for object-based attentional processes. The findings of a recent study of working memory for spatial locations and objects, however, provide further support for the hemispheric specialization hypothesis advanced by Egly *et al.* (1994). Smith *et al.* (1995) investigated whether there were separate memory systems for spatial and object information. They found a double dissociation in the regions activated by the spatial and object working memory tasks. The spatial task activated only right hemisphere regions (occipital, inferior parietal and prefrontal areas), whereas the object task activated primarily left hemisphere regions (inferotemporal and inferior parietal areas). Our results suggest that this principle of left and right hemisphere specialization for spatial and object working-memory buffers may also apply to the networks of brain areas involved in selective attention.

Relationship of findings to current models of selective attention

Humphreys and Riddoch (1993) have proposed that attentional selection results from the interaction of orienting and maintenance mechanisms that are respectively spatially- and object-based. Orienting is a spatial operation that directs attention to locations of potential significance, while the maintenance mechanism is object-based and selects

whole objects rather than regions of space for enhanced processing. Humphreys and Riddoch (1993) further suggest that deficits in detecting invalidly cued targets result from disruptions in the balance between the orienting and maintenance systems. Problems in disengaging attention could stem from two types of deficits: (i) damage to the orienting system could reduce the ability of targets appearing at uncued locations to attract attention normally resulting in a spatial-based deficit, or (ii) the orienting system could be abnormally inhibited by the maintenance system resulting in the hypermaintenance of attention on cued objects.

The results reported in this study support the view of Humphreys and Riddoch (1993) that separate spatially- and object-based deficits may underlie impairments in disengaging attention. Right parietal damage in Alzheimer's disease subjects was significantly correlated with the impairment in detecting invalidly cued targets in both the cued and uncued rectangle. In terms of the Humphreys and Riddoch model, damage to the right parietal lobe could have disrupted the spatial-based orienting mechanism so that invalidly cued targets were unable to elicit attentional orienting to new (uncued) locations, regardless of the object properties associated with the target location. In contrast, left parietal damage was found to be correlated with the impaired detection of invalidly cued targets, specifically those appearing in the uncued rectangle. Unlike the right parietal deficit, the deficit associated with left parietal damage was sensitive to the object properties of the visual display. With respect to the Humphreys and Riddoch model, this object-based attentional deficit could arise from damage to the maintenance mechanism, leading to the hypermaintenance of attention on cued objects. The results of the present study, when interpreted in the Humphreys and Riddoch framework, suggest that the right superior parietal lobe may be involved in the spatial orienting of attention while the left inferior parietal lobe may be involved in the maintenance of attentional selection on objects of current interest.

Finally, in the present study the terms spatially- and object-based have been applied to the right and left parietal attentional mechanisms and the corresponding deficits. Recent studies suggest that this terminology may be somewhat inaccurate, as the representation accessed by both attentional mechanisms may be spatially structured (Vecera, 1994; Humphreys and Riddoch, 1995). For example, in a single-case study of a patient with bilateral parietal lesions, Humphreys and Riddoch (1995) demonstrated neglect on the left or right side depending on whether the visual stimuli were encoded as parts of a single perceptual object or as separate perceptual objects. This finding led the authors to suggest that right and left parietal lobes construct separate parallel representations of the relations between parts of single objects (within-object) and between separate objects (between-object). The results of this study support Humphreys and Riddoch's (1995)

proposal of two types of spatially structured representations and further suggest that these representations are coded in parallel by the left and right parietal region. Thus, in Alzheimer's disease patients, deficits in shifting attention within a rectangle may have correlated with right parietal damage because this brain region is involved in coding within-object representations. Furthermore, deficits in shifting attention between rectangles may have correlated with left parietal dysfunction due to deficient coding of the between-object representations.

Conclusions

These results suggest that performance on computerized tests of attentional orienting can be related to the location and severity of brain dysfunction in Alzheimer's disease. Locasio *et al.* (1995) recently studied cognitive deficits in Alzheimer's disease to determine which cognitive tests were best for detecting Alzheimer's disease, staging Alzheimer's disease and tracking disease progression. They found that tests of explicit memory were best suited for detecting Alzheimer's disease due to the early mediotemporal lobe pathology in the majority of cases. All cognitive tests were, however, much less effective at staging illness. The lack of effectiveness of cognitive tests for staging dementia reflects the individual variability in the anatomical distribution of pathology. The spread of lesions to the parietal and frontal lobes is variable and often asymmetric between subjects. Consequently, Locasio *et al.* (1995) recommended that the progression of disease be monitored with a range of cognitive tests that reflect the underlying spread of neuronal dysfunction associated with Alzheimer's disease. Accordingly, tests of visual attention, like the experimental tasks used in this study, could be combined with other tests of visuospatial and language functions to chart the course of the disease, and may also be useful for monitoring the outcome of therapeutic trials that claim to slow the progression of the disease.

Another implication of this study is that Alzheimer's disease combined with functional imaging methodologies can provide cognitive neuroscience with a useful model for exploring brain–behaviour relationships. The brain damage, especially in early Alzheimer's disease, is topographically selective, but still shows tremendous individual variability. This topographical variability may be indexed with brain imaging techniques such as SPECT. The variability in pathology will result in selective cognitive deficits. By combining brain-imaging techniques with tests of cognitive performance it is possible to relate deficits in cognitive performance to regional brain dysfunction. The results of this and other recent studies (Penniello *et al.*, 1995) suggest that imaging studies of Alzheimer's disease can complement both neuropsychological investigations and PET-activation studies of healthy individuals, in the investigation of brain–behaviour relationships.

References

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 1992; 42: 631–9.

Baynes K, Holtzman JD, Volpe BT. Components of visual attention. Alterations in response pattern to visual stimuli following parietal lobe infarction. Brain 1986; 109: 99–114.

Corbetta M, Miezin FM, Shulman GL, Petersen SE. A PET study of visuospatial attention. J Neurosci 1993; 13: 1202–26.

Corbetta M, Shulman GL, Miezin FM, Petersen SE. Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. Science 1995; 270: 802–5.

Egly R, Driver J, Rafal RD. Shifting visual attention between objects and locations: evidence from normal and parietal lesion subjects. J Exp Psychol Gen 1994; 123: 161–77.

Eriksen CW, St James JD. Visual attention within and around the field of focal attention: a zoom lens model. Percept Psychophys 1986; 40: 225–40.

Farah MJ. Visual agnosia: disorders of object recognition and what they tell us about normal vision. Cambridge (MA): MIT Press, 1990.

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Hachinski VC, Iliff LD, Zilkha E, du Boulay GH, McAllister VL, Marshall J, et al. Cerebral blood flow in dementia. Arch Neurol 1975; 32: 632–7.

Haxby JV, Duara R, Grady CL, Cutler NR, Rapoport SI. Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. J Cereb Blood Flow Metab 1985; 5: 193–200.

Hellman RS, Tikofsky RS, Collier BD, Hoffmann RG, Palmer DW, Glatt SL, et al. Alzheimer disease: quantitative analysis of [^{123}I]iodoamphetamine SPECT brain imaging. Radiology 1989; 172: 183–8.

Hohne KH, Hanson WA. Interactive 3D segmentation of MRI and CT volumes using morphological operations. J Comput Assist Tomogr 1992; 16: 285–94.

Humphreys GW, Riddoch MJ. Interactions between object and space systems revealed through neuropsychology. In: Meyer DE, Kornblum S, editors. Attention and performance XIV. Cambridge (MA): MIT Press, 1993: 143–62.

Humphreys GW, Riddoch MJ. Separate coding of space within and between perceptual objects: evidence from unilateral visual neglect. Cogn Neuropsychol 1995; 12: 283–311.

Jagust WJ, Reed BR, Ellis WG, Eberling JL, Budinger TF. Single-photon emission computed tomographic perfusion imaging in autopsy-diagnosed dementia. J Neuroimaging 1993; 3: 93–9.

Keppel G, Zedeck S. Data analysis for research designs. New York: W.H. Freeman, 1989.

Kumar A, Schapiro MB, Grady C, Haxby JV, Wagner E, Salerno JA, et al. High-resolution PET studies in Alzheimer's disease. Neuropsychopharmacology 1991; 4: 35–46.

Lezak MD. Neuropsychological assessment. 3rd ed. New York: Oxford University Press, 1995.

Locascio JJ, Growdon JH, Corkin S. Cognitive test performance in detecting, staging, and tracking Alzheimer's disease. Arch Neurol 1995; 52: 1087–99.

Mangun GR, Hillyard SA. The spatial allocation of visual attention as indexed by event-related brain potentials. Hum Factors 1987; 29: 195–211.

Maruff P, Malone V, Currie J. Asymmetries in the covert orienting of visual spatial attention to spatial and non-spatial cues in Alzheimer's disease. Brain 1995; 118: 1421–35.

Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karasu TB, editors. Geriatric psychiatry: a handbook for psychiatrists and primary care physicians. New York: Grune and Stratton, 1976: 77–121.

McIntosh AR, Bookstein FL, Haxby JV, Grady CL. Spatial pattern analysis of functional brain images using partial least squares. Neuroimage 1996; 3: 143–57.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–44.

Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. [Review]. Ann Neurol 1990; 28: 597–613.

Minoshima S, Frey KA, Foster NL, Kuhl DE. Preserved pontine glucose metabolism in Alzheimer disease: a reference region for functional brain image (PET) analysis. J Comput Assist Tomogr 1995; 19: 541–7.

Morecraft RJ, Geula C, Mesulam MM. Architecture of connectivity within a cingulo-fronto-parietal neurocognitive network for directed attention. Arch Neurol 1993; 50: 279–84.

Morrow LA, Ratcliff G. The disengagement of covert attention and the neglect syndrome. Psychobiology 1988; 16: 261–9.

Mountcastle VB, Motter BC, Steinmetz MA, Sestokas AK. Common and differential effects of attentive fixation on the excitability of parietal and prestriate (V4) cortical visual neurons in the macaque monkey. J Neurosci 1987; 7: 2239–55.

Parasuraman R, Greenwood PM, Haxby JV, Grady CL. Visuospatial attention in dementia of the Alzheimer type. Brain 1992; 115: 711–33.

Parasuraman R, Haxby JV. Attention and brain function in Alzheimer's disease: a review. Neuropsychology 1993; 7: 242–72.

Penniello MJ, Lambert J, Eustache F, Petit-Taboue MC, Barre L, Viader F, et al. A PET study of the functional neuroanatomy of writing impairment in Alzheimer's disease: the role of the left supramarginal and left angular gyri. Brain 1995; 118: 697–706.

Posner MI. Orienting of attention. Q J Exp Psychol 1980; 32: 2–25.

Posner MI, Dehaene S. Attentional networks. [Review]. Trends Neurosci 1994; 17: 75–9.

Posner MI, Walker JA, Friedrich FJ, Rafal RD. Effects of parietal injury on covert orienting of attention. J Neurosci 1984; 4: 1863–74.

Rafal RD, Posner MI. Deficits in human visual spatial attention following thalamic lesions. Proc Natl Acad Sci USA 1987; 84: 7349–53.

Robb RA. Visualization methods for analysis of multimodality images. In: Thatcher RW, Hallett M, Zeffiro T, Roy John E, Huerta M, editors. Functional neuroimaging. Technical foundations. San Diego: Academic Press, 1994: 181–90.

Robinson DL, Bowman EM, Kertzman C. Covert orienting of attention in macaques. II. Contributions of parietal cortex. J Neurophysiol 1995; 74: 698–712.

Smith ES, Jonides J, Koeppe RA, Awh E, Schumacher EH, Minoshima S. Spatial versus object working memory: PET investigations. J Cogn Neurosci 1995; 7: 337–56.

Stapleton SJ, Caldwell CB, Ehrlich LE, Leonhardt C, Black SE, Yaffe MJ. A quantitative method of analyzing ^{99m}Tc-HMPAO [abstract]. Med Phys 1992; 19: 780.

Stevens J. Applied multivariate statistics for the social sciences. Hillsdale (NJ): Lawrence Erlbaum, 1986.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart: Thieme, 1988.

Terry RD, Masliah E, Hansen LA. Structural basis of the cognitive alterations in Alzheimer disease. In: Terry RD, Katzman R, Bick KL, editors. Alzheimer disease. New York: Raven Press, 1994: 179–96.

Vanier M, Lecours AR, Ethier R, Habib M, Poncet M, Milette PC, et al. Proportional localization system for anatomical interpretation of cerebral computed tomograms. J Comput Assist Tomogr 1985; 9: 715–24.

Vecera SP. Grouped locations and object-based attention: comment on Egly, Driver, & Rafal (1994). J Exp Psychol Gen 1994; 123: 316–20.

Waldemar G, Bruhn P, Kristensen M, Johnsen A, Paulson OB, Lassen NA. Heterogeneity of neocortical cerebral blood flow deficits in dementia of the Alzheimer type: a [^{99m}Tc]-*d,l*-HMPAO SPECT study. J Neurol Neurosurg Psychiatry 1994; 57: 285–95.

Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. J Comput Assist Tomogr 1993; 17: 536–46.