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Visual attention deficits in Alzheimer's disease: Relationship to HMPAO SPECT cortical hypoperfusion

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ABSTRACT

Patients with Alzheimer's disease (AD) display a multiplicity of cognitive deficits in domains such as memory, language, and attention, all of which can be clearly linked to the underlying neuropathological alterations. The typical degenerative changes occur early on in the disease in the temporal–parietal lobes, with other brain regions, such as the frontal cortex, becoming more affected as the disease progresses. In light of the importance of the parietal cortex in mediating visuospatial attentional processing, in the present study, we investigated a deficit in covert orienting of visual attention and its relationship to cortical hypoperfusion in AD. We characterized the visual attentional profile of 21 AD patients, relative to that of 26 matched normal individuals, and then assessed the correspondence between behavior and hypoperfusion, as measured by regional cerebral blood flow using SPECT. Relative to controls, the AD group demonstrated a unilateral attentional deficit, with disproportionate slowing in reorienting attention to targets in the left compared to the right hemispace, especially following an invalid peripheral cue. Furthermore, even in the presence of bilateral pathology typical of AD, there was a positive correlation between this unilateral attentional disorder and the magnitude of the right superior parietal lobe hypoperfusion. The association of the altered attentional processing profile (i.e., greater difficulty disengaging attention from right-sided stimuli) with right-hemisphere-predominant hypoperfusion not only confirms the critical role of the right parietal lobe in covert attentional orienting but, more importantly, identifies a potential locus of the behavioral alterations in visuospatial processing in AD.

1. Introduction

In Alzheimer's disease (AD), deficits in cognitive processes result from regionally selective neuropathological changes, including marked loss of synapses (Terry, Masliah, & Hansen, 1994) and the emergence of neurofibrillary tangles (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992). Early in the disease process, there is a distinct topography to the distribution of pathology, with the damage typically accentuated in the hippocampal, mediolateral temporal, posterior parietal and the posterior cingulate regions, and, later, affecting the prefrontal region (Brun, 1983). Recent developments in neuroimaging have provided unprecedented opportunities to index brain dysfunction in AD. For example, on PET and SPECT, AD has been associated with the following features: (1) reduced perfusion in the parietotemporal association cortices, even early in the disease process (Kumar et al., 1991); (2) the reduced perfusion is bilateral, although an asymmetry in the degree of hypoperfusion is often observed (Haxby, Duara, Grady, Cutler, & Rapoport, 1985); (3) in more advanced cases, perfusion in the frontal association cortex is also reduced (Waldemar et al., 1994); and (4) perfusion in primary sensory and motor cortical regions remains relatively unaffected (Jagust, Reed, Ellis, Eberling, & Budinger, 1993; Kumar et al., 1991).

Of interest to the current investigation of AD is the reduced perfusion in the posterior parietal and prefrontal regions. These cortical areas form part of a cortical network involved in the

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maintenance and shifting of attention (Corbetta, Miezin, Shulman, & Petersen, 1993; Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002; Turkington et al., 1993; Yantis, 2008). Given that these regions are implicated in AD, one would predict that deficits in visual attention would be frequently encountered in these patients. Moreover, the deficit is expected to have a particular profile, with a prominent feature being impaired attentional switching, as this process is contingent on parietal lobe integrity (Yantis, 2008). Despite the fact that key parietal and prefrontal regions of the visual attention network are damaged early in AD, only a handful of studies have systematically investigated visual attention in this population (Buck, Black, Behrmann, Caldwell, & Bronskill, 1997; Caffarra, Riggio, Malvezzi, Scaglioni, & Freedman, 1997; Foster, Behrmann, & Stuss, 1999; Gorus, De Raedt, Lambert, Lemper, & Mets, 2006; Hao et al., 2005; Maruff, Malone, & Currie, 1995; Rizzo, Anderson, Dawson, Myers, & Ball, 2000; Rosler, Mapstone, Hays-Wicklund, Gitelman, & Weintraub, 2005; Tales, Muir, Bayer, & Snowden, 2002) and even fewer have attempted to relate observed deficits in attentional performance directly to brain dysfunction (but see, Buck et al., 1997; Hao et al., 2005; Parasuraman, Greenwood, Haxby, & Grady, 1992). Better characterization of these attentional deficits is crucial both to differentiate performance decrements associated with normal aging from early AD and other forms of dementia, but also potentially to provide a useful performance measure for monitoring the disease progression (Ballesteros, Reales, Mayas, & Heller, 2008; Mapstone, Dickerson, & Duffy, 2008).

Of course, the definition of 'attention' has proven thorny and has been used in reference to a plethora of processes: AD deficits have been documented based on generalized measures of attention derived from tests such as the Mini Mental State Exam (MMSE) and Digit Span (Engel, Cummings, Villanueva-Meyer, & Mena, 1993; Weintraub et al., 2009), from visual search tasks (Parasuraman, Greenwood, & Alexander, 1995; Rosler et al., 2005), from selectivity in memory encoding (Castel, Balota, & McCabe, 2009) and from measures of sustained attention/vigilance (Berardi, Parasuraman, & Haxby, 2005) or orienting (Fernandez-Duque & Black, 2006), to name but a few. Here, we focus specifically on the covert orienting of attention (Klein, 2009; Posner, 1980), a process whose neural correlate is well characterized and involves a network of cortical regions, including the posterior parietal lobe (for review, see Yantis, 2008).

To examine alterations in attentional switching in AD and its underlying neural correlate, we adopted a well-established covert attentional task, based on the paradigm of Posner (1980), in which subjects respond manually when a target (asterisk) appears at a peripheral location on a computer display (Fig. 1). The target is preceded by a cue that summons attention to a location at which the target may (valid cue) or may not appear (invalid cue). A cue can be either an abrupt visual onset at the cued location (i.e., a reflexive or exogenous cue) or a centrally presented arrow pointing to or away from the valid location (i.e., a volitional or endogenous cue). The standard response profile is that observers respond faster to targets presented at validly cued than invalidly cued locations (Posner, 1980). The reaction time (RT) difference between these two target types, also referred to as the validity effect or RT cost, is assumed to arise from the additional time required to redirect or switch attention from the invalidly cued location to the correct target location (Eriksen & St James, 1986; Posner, 1980). As such, the magnitude of the validity effect serves as a robust indicator of switching efficiency. At a neural level, the validity effect has been shown to modulate scalp electrical activity in humans (Mangun & Hillyard, 1987) as well as the excitability of neurons in non-human primates (Cavada & Goldman-Rakic, 1993), to be sensitive to posterior parietal damage (Posner, Walker, Friedrich, & Rafal, 1984), and to elicit strong parietal activation in normal individuals as revealed in functional MRI investigations (Yantis, 2008). Furthermore, both exogenous and endogenous forms of cueing appear to engage the same large-scale fronto-parietal network (Peelen, Heslenfeld, & Theeuwes, 2004), with perhaps enhanced activation in right dorsolateral prefrontal cortex (BA 46) in the latter condition (Rosen et al., 1999). As such, this paradigm provides a window into the integrity of the covert attentional switching mechanism, and permits us to map the behavioral profile in AD patients and to explore its underlying neural correlate.

A key issue to be addressed is whether AD individuals evince a behavioral asymmetry in the validity effect, i.e., a differential RT cost for switching from left to right or vice versa, and whether this asymmetry is associated with a neuropathological asymmetry. Interestingly, whereas a unilateral right parietal focal lesion typically gives rise to a unilateral (contralesional) attentional deficit with the patient slowed at shifting attention from a rightward cue to a left target, the relationship between bilateral parietal damage in AD and the ensuing visual attention profile is less transparent. One prediction is that, if each parietal lobe is involved in shifting attention contralaterally away from previously attended ipsilateral locations, then bilateral parietal damage will be associated with greater RT switching costs for invalid trials where the cue is directed to either hemispace. Another prediction stems from the claim that the right parietal lobe is specialized for spatial attention and can mediate attentional shifts to both the right and left sides of space, while the left parietal lobe is involved primarily in attentional shifts to the right side of space (Heilman & Van Den Abell, 1980; Shulman et al., 2010). In this case, bilateral parietal damage in AD might result in an asymmetrical attentional deficit that is more pronounced when subjects shift attention from a right-sided cue to left-sided targets. The final, perhaps most counterintuitive prediction is that there will be minimal, if any, attentional deficit following bilateral parietal involvement in AD. This prediction comes from a theoretical account in which attentional selectivity emerges from the interaction and competition between the hemispheres (Desimone & Duncan, 1995; Robinson, Bowman, & Kertzman, 1995). On this account, hemispatial neglect results from unilateral damage to the parietal region because stimuli in the affected portion of the contralesional visual field ineffectively compete with ipsilesional stimuli for visual processing (Kinsbourne, 1977). With bilateral damage, however, the attentional deficit should be minimal, since the loss of competitive weights is more or less symmetrical and consequently neither hemifield has a competitive advantage over the other. This latter prediction is supported by reports of patients with bilateral parietal damage who show no evidence of a bilateral disengage deficit (Coslett & Saffran, 1991; Verfaellie, Rapcsak, & Heilman, 1990).

Although various studies have explored attentional processing in AD, there has not been a clear consensus on whether the behavioral alterations are unilateral or bilateral in nature. For example, in one study, AD individuals did not show any attentional asymmetry in covert attention, relative to controls (Maruff et al., 1995). A closer analysis of the data, however, revealed that there were three subgroups of patients each with qualitatively different performance deficits: relative to controls, one subgroup showed significant elevations in RT cost in both visual fields (as in Parasuraman et al., 1995) and the other two groups showed elevated RT costs in only the left or the right visual field. The absence of a main effect of group (AD versus matched controls) was replicated in a later study by Caffarra et al. (1997) but because this study did not examine variation among the AD individuals, we do not know whether similar subgroup patterns were evident.

We also do not fully understand the relationship between the attentional dysfunction and its underlying neural correlate in AD. For example, in an attentional task using letter discrimination, AD subjects showed elevated RT costs in both hemifields, relative

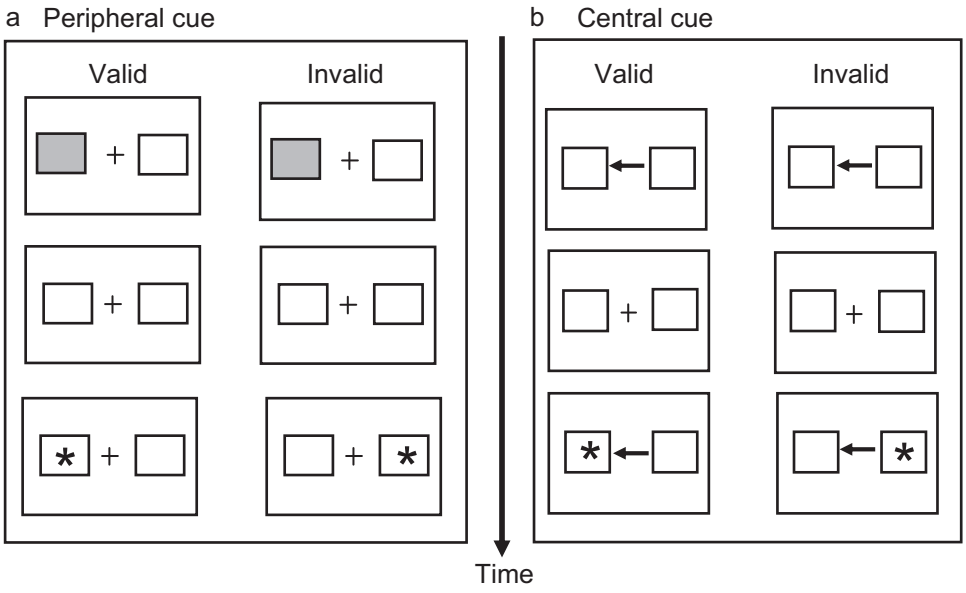

Fig. 1. Stimulus display in spatial-precueing paradigm for peripheral and central cueing conditions.

to controls (Parasuraman et al., 1992), and this impairment was related to the degree of asymmetry in superior parietal damage visible on PET scanning. Unfortunately, because there was no analysis of how the target location (right versus left) interacted with the attentional deficit, it remains unclear whether the AD group also displayed asymmetries in the validity effect, and whether spatial asymmetry interacted with the metabolic measures.

Given the uncertainty in both the behavioral and neural data, here we probe the relationship between deficits in shifting visual attention in AD, in relation to both the asymmetry and severity of parietal dysfunction. Furthermore, to provide a comprehensive account of the attentional alteration in AD, we document the RT cost in attentional shifting in each visual field under both peripheral and central orienting conditions. Some researchers suggest attentional switching can be differentially impacted by these different types of cueing (Klein, 2009): the much studied cost in switching attention contralaterally following an ipsilateral target in neglect patients, is consistently documented under exogenous orienting conditions, but substantially reduced or non-existent under endogenous conditions (Losier & Klein, 2001). Whether this is also the case in AD is unknown and so we examine AD performance under both types of cueing and explore the relationship of this performance to the underlying neural substrate.

2. Methods

2.1. Subjects

Two groups of participants completed this study: a group of individuals with mild to moderate AD ($n = 21$) and a group of normal control (NC) subjects ($n = 26$). All participants had normal or corrected vision of at least 20/40 and were right-handed. All AD individuals (11 males, 10 females), drawn from the Cognitive Neurology Clinic at Sunnybrook Health Sciences Centre as part of the Sunnybrook Dementia Study, met the NINCDS – ADRDA diagnostic criteria for 'probable' Alzheimer's disease (McKhann et al., 1984). AD subjects 3 and 20 presented as language impaired variants, which negatively impacted their MMSE scores, but did not impact their ability to complete the attentional switching paradigm used here. The MR/CT scans of the individuals were either normal or showed atrophy, and their EEGs were either normal or showed generalized slowing. To reduce the possibility of concomitant vascular disease, all AD individuals had a modified Hachinski score of 4 or less (Hachinski et al., 1975) and the degree of any hyperintensities seen in the periventricular white matter was considered age-appropriate. The demographic characteristics of all individuals are presented in Table 1. About half the AD subjects ($n = 12$) had mild deficits (MMSE scores 20–25), while the remaining 9 subjects were moderately demented (MMSE 6–19) (Table 1). AD subjects 1 and 4 were taking Tacrine at the time of testing. They had been on this cognitive enhancer for approximately 3 and 2 years, respectively, prior to participating.

Standard neurological and psychological exclusion criteria were applied in selecting subjects for the NC group (9 males, 17 females). The two groups did not differ in age [$t(45) = -1.135$, $p = 0.098$], but the AD group had 2.5 years less education than the NC group [$t(45) = 2.891$, $p = 0.006$] (Table 1). All procedures were approved by the Institutional Review Board of Sunnybrook Health Sciences Center and informed consent was obtained from all subjects and/or their guardians.

All subjects were tested, in two separate sessions, on two computerized tests. Of the 21 AD subjects, 20 had ^{99m}Tc-HMPAO SPECT imaging performed as part of their clinical workup. The mean duration between the SPECT scan and RT testing was 52.1 days (range 0–128).

2.2. Stimuli

The experiment was modeled on the covert visual attention paradigm described by Posner et al. (1984) (Fig. 1). For both peripheral and central cueing tasks, the display consisted of two peripheral boxes located 3.8° to the left and right of a central fixation point when viewed from 60 cm. The boxes were drawn from lines 0.23° thick, and measured 1.4° by 1.4°. For the peripheral cue task, the boxes were cued by shading the interior of one of the two boxes. The shading was accomplished by superimposing over the box, a 50% grey square identical in size. For the central cue task, the cue consisted of a centrally presented arrow, drawn in 72 point (approximately 1°) Symbol font. The target (asterisk) was drawn in 72 point Helvetica font.

2.3. Procedure

Stimulus presentation and recording of responses was controlled with PsychLab software (Bub & Gum, 1988) on a MacIntosh computer. The peripheral and central cueing versions of the experiment were run in two different sessions (counterbalanced). Trials started with the presentation of a 1000 ms display containing the central fixation point and the two peripheral boxes. Thereafter, one of the two boxes was cued, depending on the task, either by shading the box interior or with a centrally presented arrow. Cues lasted for 200 ms. Following the offset of the cue, the fixation display was presented for another 150 ms or 500 ms (SOA) after which time the target appeared in one of the two boxes. The target remained visible until response or for 2000 ms if there was no response. After this, the screen was blank for 500 ms and then the next trial began.

Subjects were instructed to maintain fixation on the central fixation point, and to respond as quickly and accurately as possible to the target. Subjects used the index finger of their dominant (i.e., right) hand to press the key, as quickly as possible, when the target was detected. Both accuracy and reaction time were recorded.

Subjects were given a practice session of 40 trials during which time the task was carefully explained. Subjects who were unable to complete the practice trials ($n = 3$) were not included as part of the group of 21 AD subjects reported here. In piloting this experiment, subjects were videotaped, and eye movements monitored. Importantly, the AD subjects were able to maintain fixation as instructed. During subsequent test sessions, eye movements were monitored visually by the experimenter and, if an eye movement occurred, subjects were re-instructed to maintain fixation.

Table 1
Demographic and neuropsychological characteristics of Alzheimer's subjects (AD) and means of age-matched controls (NC).

Subject	Hand preference	Age (years)	Sex	Education (years)	Duration of disease (months)	MMSE	Mattis DRS
1	R	74	M	13	45	25	129
2	R	54	F	14	31	18	
3	R	59	F	5	60	6	82
4	R	58	M	9	72	20	102
5	R	84	M	15	31	15	
6	R	61	M	12	47	14	87
7	R	68	F	9	57	23	120
8	R	67	M	16	58	22	108
9	R	76	M	12	40	26	112
10	R	69	F	15	24	19	107
11	R	62	M	17	32	14	106
12	R	69	M	6	51	12	94
13	R	84	F	13	109	20	119
14	R	51	F	16	74	21	71
15	R	68	F	15	46	21	115
16	R	74	F	12	37	21	106
17	R	57	F	15	38	22	118
18	R	75	M	10	42	25	127
19	R	78	M	15	44	18	109
20	R	66	F	14	55	8	79
21	R	84	M	11	55	21	120
AD group ($n=21$)	Mean	68.5	11M/10F	12.6	49.9	18.6	105.8
	S.D.	9.82		3.26	18.83	5.37	16.43
NC group ($n=26$)	Mean	63.4	9M/17F	15.0			
	S.D.	18.4		2.63			
	p-value*	n.s.	n.s.	0.006			

n.s.: not significant at the alpha = 0.05 level; L/R: left hand/right hand; M/F: male/female; MMSE: mini mental state exam; Mattis DRS: Mattis Dementia Rating Scale.
* p-value based on independent samples t-test (except test of sex which was based on Chi-square test.

2.4. Design

Both tasks consisted of 160 trials, divided into two conditions: (1) 120 (75%) valid trials in which the target appeared in the peripheral box that was cued; (2) 40 (25%) invalid trials in which the target appeared in the uncued box. The ratio of valid to invalid trials was selected based on previous experiments that showed maximal effects of cueing probability when approximately 75% of the trials are valid (Posner, Cohen, & Rafal, 1982). Note that the peripheral cueing version of this task is generally considered to elicit exogenous forms of attentional orienting whereas the central cueing version is associated with endogenous or volitional cueing. Because we have opted to bias attention strongly in the valid condition to assess the ability of the AD individuals to exploit the cues, 75% of the trials are valid. This high level of predictability alters the peripheral cueing task from being purely exogenous to have an endogenous component, too. Therefore, for clarity in our experiments, we refer to the two types of orienting tasks as peripheral and central cueing, rather than as exogenous and endogenous per se.

On both valid and invalid trials, the target appeared with equal probability in the left and right box, yielding 60 valid and 20 invalid trials for each hemifield. The interval between the offset of the cue and target onset (i.e., the SOA) was 150 ms on 50% of the trials and 500 ms on the remaining trials. These SOAs were chosen because the attentional processes evoked by endogenous cues are thought to be more effective at longer SOAs than those evoked by peripheral cues and so we wished to sample both shorter and longer time periods. SOA was crossed orthogonally with cue validity and target hemifield to yield 30 valid and 10 invalid trials for each target hemifield (left, right), and SOA (150 ms, 500 ms). The trials were divided into two blocks of 80 trials. Trials were randomized within a block, which lasted about 8 min. A break was given between blocks.

2.5. SPECT imaging protocol

The SPECT imaging, obtained as part of the AD clinical workup, was performed using a rotating dual-headed gamma camera (Picker Model, 2000), a minimum of 15 min and a maximum of 120 min after injection of 740 MBq (20 mCi) of ^{99m}Tc-HMPAO. Images were acquired over 360° using 120 planar views. Each view consisted of a 128 × 128 pixel image with a reconstructed image resolution of approximately 10.5 mm full width at half maximum (FWHM). 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 Wiener post-filter. Additionally, images were corrected for attenuation using a calculated, Chang first order method. SPECT scans were then transferred to a SUN™ Workstation (Sun Microsystems, Mountainview, CA) for further analyses.

2.6. SPECT semiquantification: ROI methodology

Each SPECT scan was co-registered using AIR 3.07 (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998) to a SPECT template to obtain regional blood flow measures (Lobaugh, Caldwell, Black, Leibovitch, & Swartz, 2000). The SPECT template was created by aligning the SPECT scan of a normal control subject ("base SPECT") to the MRI scan ("base MRI") for the same subject. A region-of-interest (ROI) template was created by manually tracing 79 brain areas (39 ROIs per hemisphere plus 1 ROI for the pons) on the corresponding MRI scan (see Table 2 for listing of ROIs). The ROI template was then overlaid on the aligned SPECT scan to obtain perfusion ratios. Each subsequent SPECT scan (i.e., from each patient) was aligned using AIR 3.0 to the base SPECT and then to the base MRI. The SPECT template was then overlaid to obtain regional counts. Images were also viewed in ANALYZE™ (MAYO Foundation, Rochester, NY) to ensure proper alignment of all regions, including the cerebellum. This was especially important since the cerebellum was used as the reference region to obtain semiquantitative data and, thus, all other ROIs were divided by the total cerebellum value. These normalized ROI ratios were used in all subsequent analyses.

3. Results

Trials were excluded from the analysis if subjects: (1) did not respond within 2000 ms of target onset or (2) were distracted or required re-instruction during the trial.

3.1. Accuracy

An analysis of variance (ANOVA) with cue type (central, peripheral), cue validity (valid, invalid), SOA (150, 500 ms) and target side (left, right) as within-subject factors and group as a between-subjects factor, with percentage accuracy as the dependent measure, revealed a significant interaction of group × cue type × cue validity × SOA: whereas the NC group made more invalid than valid errors with the longer than shorter SOA, especially on the central task, the AD group showed more invalid than valid errors at both SOAs and to an equivalent extent on the central and peripheral tasks ($F(1,45) = 8.2$, $p < 0.01$). Of relevance too is the significant interaction of side × SOA × group ($F(1,45) = 4.2$, $p < 0.05$), reflecting the greater number of errors to left- than right-sided targets for the AD than NC group, especially at the longer SOAs. There were

Table 2
Two sample *t*-test values from comparison of rCBF in ROIs between AD patients and elderly healthy volunteers. Significantly different regions are bolded.

Region	BA	Left hemisphere *t*-test	Right hemisphere *t*-test
Cortical medial surface			
Paracental gyrus	4/5	−2.12	−1.41
Precuneus	7	**−5.84**	**−6.07**
Cuneus	17/18/19	−2.43	−2.19
Lingual gyrus	18/19	−2.69	−2.84
Retrosplenial cortex	26/39/30	**−5.28**	−4.05
Cingulate cortex: 5 ROIs			
Cingulate Ant1	25	−2.33	−1.88
Cingulate Ant2	24/32/33	−3.08	−3.81
Cingulate Ant3	24/32/33	−1.96	−2.05
Cingulate Post1	23/31	**−6.97**	**−6.15**
Cingulate Post1	23/31	−3.10	**−4.84**
Cortical lateral surface			
Frontal Pole	10	−2.49	−2.49
Orbital frontal	11	−2.37	−2.84
Inferior frontal gyrus, posterior	44	−3.67	−2.70
Inferior frontal gyrus, anterior	45	−1.99	−1.66
Middle frontal gyrus, posterior	8/9	**−4.93**	−3.65
Middle frontal gyrus, anterior	46	−3.55	−3.10
Superior frontal gyrus, posterior	6/8	−1.37	−1.28
Superior frontal gyrus, anterior	8/9	−3.83	−3.40
Precentral gyrus	4	−2.81	−3.07
Postcentral gyrus	5/1/2/3	−4.16	−3.95
Superior parietal lobe	7	**−6.01**	**−6.94**
Supramarginal gyrus	40	**−7.67**	**−6.48**
Angular gyrus	39	**−7.15**	**−7.11**
Occipital cortex	18/19	−3.34	−4.15
Occipital pole	17	−3.31	−0.62
Temporal lobe			
Temporal pole	38	**−5.22**	**−5.20**
Inferior temporal gyrus	20/37	**−5.95**	−4.76
Inferior temporal, medial	28/35/36/37	−3.41	−3.27
Middle temporal gyrus	21/37	**−7.14**	**−7.18**
Middle temporal, medial	28/35/36	−4.36	−4.94
Superior temporal gyrus	22/41/42	**−6.75**	**−6.16**
Superior temporal, medial	27/34	−4.35	−3.31
Hippocampal area	35	−3.42	−3.40
Other			
Insula		−3.55	−2.93
Caudate/putamen		−4.31	−2.94
Thalamus/hypothalamus		−2.79	−2.48
White matter		**−5.39**	**−5.06**

no other interactions involving group, but there was a significant main effect of group reflecting the overall lower accuracy for the AD (accuracy ± SE; 97.8 ± 0.4) than NC group (accuracy ± SE, 99.2 ± 0.3) ($F(1,45) = 7.15$, $p = 0.010$).

3.2. Reaction time

The same ANOVA applied to accuracy, but with RT as the dependent measure, revealed a four-way interaction of cue type × cue validity × side × group ($F(1,45) = 3.8$, $p = 0.05$). This interaction is plotted in Fig. 2, where we indicate the RT for invalid and valid trials for each task and for left and right targets. Although SOA does not contribute significantly to the interaction, we still plot the data with SOA as a factor – we do this because exogenous effects are usually observed at shorter SOAs than are endogenous effects and even though SOA is not statistically significantly interacting, we do see a greater disengage deficit numerically at shorter than longer SOAs.

Post hoc testing using Tukey HSD on the significant four way interaction reported above reveals that the NC group shows an equivalent validity effect (difference between valid and invalid trials) for both left and right targets, but the magnitude of the cost is greater in the central than in the peripheral task. The AD group is obviously slower than the NC group across the board (AD 642.6 ms, NC 409.2 ms ($F(1,45) = 31.7$, $p < 0.0001$)) and shows a greater validity effect in all conditions, relative to the NC group (group × cue validity interaction ($F(1,45) = 9.9$, $p < 0.001$)). Critically, there is a greater validity effect for left than right-sided targets but while the validity cost for right-sided targets does not differ significantly between the peripheral and central cueing task (102 versus 88 ms) in the AD group, there is a disproportionately greater validity cost

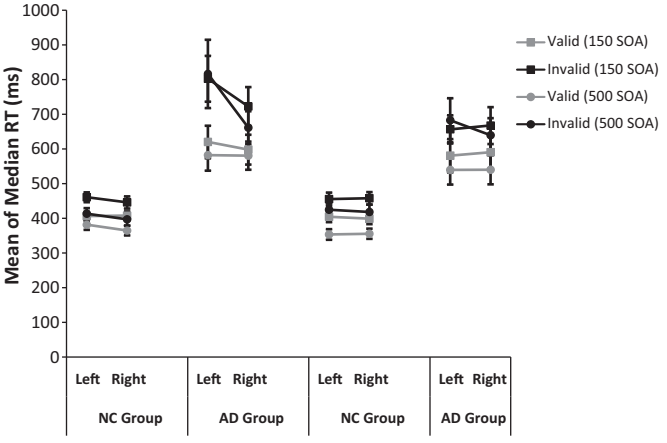

Fig. 2. Mean of the median RT (and standard error) as a function of target side, cue condition, and group for the peripheral and central cue conditions.

Table 3
Effect size (using Cohen's *d*) of validity effect in covert orienting task.

	Cohen's *d*
Peripheral cue	
Valid left	1.43
Valid right	1.49
Invalid left	1.76
Invalid right	1.62
Central cue	
Valid left	1.22
Valid right	1.27
Invalid left	1.32
Invalid right	1.33

for left targets for peripheral than for central cueing (208 versus 109 ms). These results reveal an asymmetry in switching attention in the invalid trials from the right to the left hemispace that holds in both tasks but is exaggerated in the peripheral over central cueing task.

As evident from Fig. 2, there was also a significant three-way interaction of cue type × cue validity × group ($F(1,45) = 11.6$, $p = 0.001$), reflecting the greater RT cost for invalid over valid trials for the AD than NC group to a greater degree in the case of peripheral than in the case of central cueing. There was also a significant three-way interaction of cue validity × side × group ($F(1,45) = 10.2$, $p < 0.005$), arising from the greater difference between invalid over valid trials for the AD than NC group for left versus right targets, and a side × group interaction ($F(1,45) = 4.7$, $p < 0.05$) with disproportionately slower performance for left than right targets in the AD than NC group. There were no other significant interactions with group as a factor. Furthermore, comparison of the AD and NC groups revealed respectable effect sizes ranging between 1.2 and 1.8 across all conditions (Table 3). Note that the peripheral task had slightly higher effect size values compared with the central task, and the highest effect size of all conditions was for invalid left trials.

Note that, unlike previous studies which did not find a significant group difference between AD and NC (Caffarra et al., 1997; Maruff et al., 1995), we do find such a difference (and note that some of the subgroups in Maruff et al. do show such a difference), and it is differential in magnitude as a function of side (worse for left than right targets) and task (worse on peripheral than central). As in Maruff et al. (1995), we also explored whether there were different subprofiles in the AD sample. Fig. 3 contains plots of the validity effect (invalid–valid RT) for each AD individual, along with the means for each group (and CI for controls) separately for each of the peripheral and central cueing tasks. Close examination of the figures does not reveal obvious, distinct and separable subgroups although there is variability in the individuals' pattern. As seen in Fig. 3, some individual points fall around the normal mean but these data points also appear to fall along a continuum with the remaining AD subjects. Of note too is that not every individual shows the identical profile: for example, on the central task, two individuals show no left-sided cost and three show no right-sided cost. While there are no obvious subgroups, there are clearly different individual profiles and the critical question is whether there is any relationship between these behavioral profiles and the underlying neural substrate.

Before we turn to the SPECT data, we explore one further prediction, which is that problems with central cues (more endogenous orienting) might occur later in the course of the disease when more frontal areas are implicated. To assess this, we ran the same ANOVA as above, using RT as the dependent measure, but instead of comparing NC and AD, we split the AD group based on MMSE severity (by median split). The more severe group had a mean MMSE of 15 whereas the less severe group had a MMSE mean of 23. Although this analysis revealed a main effect of group ($F(1,19) = 5.1$, $p < 0.04$) (RT severe: 729 ms, less severe: 547 ms), and there was a marginal interaction of group × side ($F(1,19) = 3.8$, $p = 0.06$) with a 60 ms and a 9 ms disadvantage for left versus right targets for the more severe and less severe groups, respectively, there were no interactions with task per se.

3.3. Group differences in regional hypoperfusion

Before we examined brain–behavior correspondences per se, we first explored any differences in cortical perfusion ratio across the two groups. Semiquantitative regional cerebral blood flow (rCBF) was calculated on SPECT for 79 ROIs, including key regions of the fronto-parietal attentional network, for each individual in each hemisphere normalized by mean cerebellar counts. These regions were explored as they had been used previously in a comprehensive study examining rCBF changes throughout the cortex as a function of age, and therefore, reflect widespread consideration of different brain regions. rCBF differences in each of these ROIs for the AD patients and a group of previously characterized elderly healthy volunteers (Lobaugh et al., 2000) were calculated using *t*-tests (*Bonferroni* corrected for multiple comparisons). The twenty-two regions that were significantly different between the two groups are highlighted in Table 2. Of interest for the current investigation, among those regions that showed hypoperfusion in the AD group are many regions known to be involved in spatial attention, including the supramarginal gyrus, superior parietal lobe, precuneus and superior temporal gyrus (Corbetta et al., 2008; Corbetta & Shulman, 2002; Gitelman et al., 1999). This raises the possibility that, in the AD subjects, decreased perfusion in some of these ROIs might be related to the observed attentional impairment.

3.4. Individual differences in regional hypoperfusion

In AD, PET and SPECT studies have shown that the typical parietal–temporal dysfunction is usually symmetric and bilateral, although there is also considerable variability in the relative degree of right and left hemisphere hypometabolism/hypoperfusion particularly early on in the disease (Haxby et al., 1985). However, in some patients hypoperfusion can be quite asymmetric, mimicking a focal lesion; so it was important for the interpretation of this study to determine how many subjects had predominant parietal deficits on the right or left side. To assess the distribution of asymmetry in parietal dysfunction, we compared left and right superior parietal perfusion in each individual subject, and as displayed in Fig. 4, subjects to the left of the line have greater left than right superior parietal perfusion, and subjects to the right of the line vice versa. As shown, AD patients were roughly clustered around the line of symmetry, and the numbers of asymmetric participants on the left were balanced with those on the right. The perfusion ratios are approximately bilaterally equivalent, indicating that behavioral results were not driven by predominant damage on the left or on the right. We next investigated the nature of the relationship between the attentional deficit and the pattern of regional hypoperfusion.

3.5. Relationship between attentional deficit and regional hypoperfusion

The correspondences between the attentional deficit in AD and alterations in regional hypoperfusion were explored using the behavioral data from the peripheral cueing trials, as the AD abnormalities were similar across tasks but exaggerated in this version of the task. To explore the brain–behavior relations, we a priori selected those ROIs in both the left and right hemisphere that have been previously reported to be associated with covert visual attention, including the anterior and posterior cingulate, the dorsolateral frontal gyrus (middle, superior and inferior), orbitofrontal gyrus,

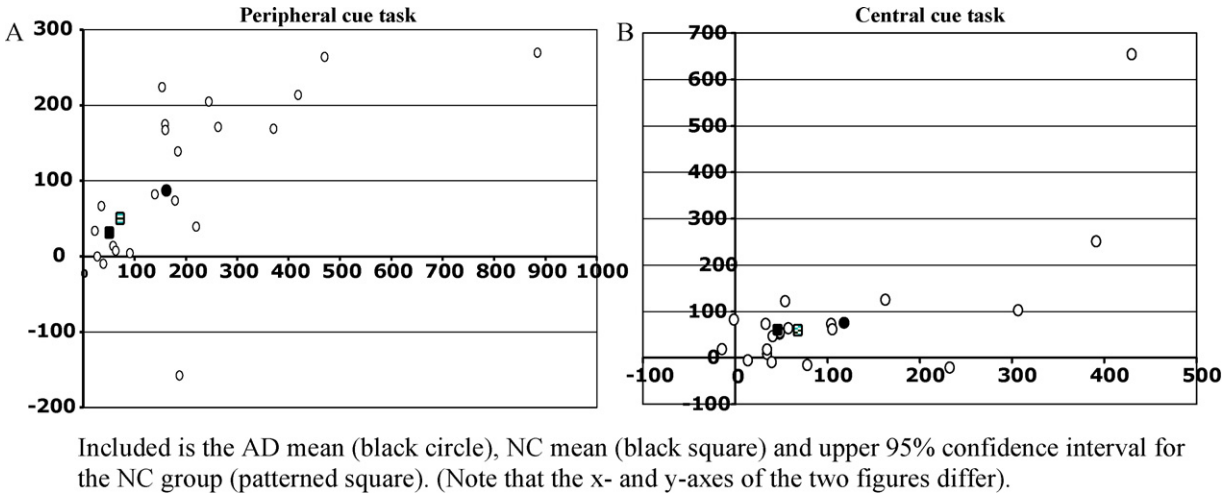

Fig. 3. Scatterplot of RT cost (invalid-valid RT) for each AD participant plotted for left (*x*-axis) and right (*y*-axis) targets.

superior parietal lobe, precuneus and supramarginal gyrus. A correlation matrix was then generated between the rCBF in these ROIs and the difference between valid trials in left and right hemispace and the invalid trials in left and right hemispace. Note that we are looking specifically for a neural correlate reflecting the relatively greater cost for invalid trials in the left than right hemispace.

Correlation coefficients were calculated using the Spearman rank algorithm, which is more conservative than many other measures and hence, less susceptible to the spurious influence of outliers. Only those correlation coefficients which reached significance at $p < 0.05$ and $p < 0.01$ are shown in Table 4 but because of the multiple comparisons, only those alpha values at <0.01 are considered significant and are bolded. Note that there is no significant correlation between rCBF in any ROI and the RT difference for valid targets on the left and right side. Importantly, however, the left and right superior (and to some extent inferior) parietal cortex as well as the right precuneus evince a negative correlation between rCBF values and the asymmetric increase in RT for invalid trials. Thus, decreased perfusion in these regions is associated with greater difficulty detecting invalidly cued left than right-sided targets. These regions have been shown previously in normal subjects to be important components of a cortical network for directing covert visual attention (Corbetta & Shulman, 2002; Shomstein & Behrmann, 2006; Yantis, 2008). However, all of these regions are correlated with the behavioral profile, making it difficult to examine the relative contribution of each area to the behavioral profile. We therefore performed a stepwise regression analysis using the left–right difference on invalid trials as the dependent measure and entering each region successively. The key result is that the right superior parietal lobule accounted for roughly 50% of the variance ($r = 0.498$; $p = 0.026$) and that, after this initial entry, no other region reached significance. Thus, while multiple regions may show some behavior–brain correlation, it is the right superior parietal cortex that dominates the regression analysis, and the other regions may be correlated with the right superior parietal cortex itself.

It remains possible, however, that the asymmetric effects of left versus right invalid trials and the correlated rCBF are related to each other only indirectly: it is possible that the attentional deficits and the parietal hypoperfusion are both related to a third variable, such as dementia severity. To investigate this possibility, a multiple regression analysis was completed with the MMSE score forced into the model prior to the entry of the significant rCBF right parietal ROI measures. Doing so ensures that dementia severity was controlled statistically, allowing the rCBF measure to enter into the model only if it accounted for a significant portion of the variance in the asymmetric validity effect measure, after accounting for MMSE score. The results of this regression analysis indicated that even after accounting for dementia severity, rCBF in the right superior parietal region was still significantly associated with the disproportionate left validity effect ($p = 0.032$), indicating that the brain–behavior relationship is not fully accounted for by dementia severity.

As with the behavioral data, we explored the prediction that the disengage deficit might be more evident in the central/endogenous

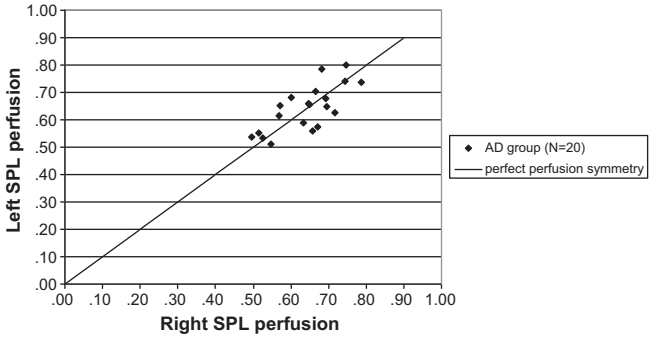

Fig. 4. Scatterplot of left versus right superior parietal perfusion for each AD subject. Line indicates hypothetical perfect perfusion symmetry between left and right superior parietal lobes. Asymmetry in hypoperfusion can be seen by comparing data points to the line. Subjects that appear on the left side of the line have greater right hypoperfusion and those on the right side of the line have greater left hypoperfusion. Distribution of the data points also indicates variability in severity of superior parietal hypoperfusion. Note that we did not have SPECT data on 1 of the 21 subjects, and data points were superimposed for two subjects who had the same perfusion ratios.

Table 4
Spearman correlation between attentional asymmetry score and regional SPECT perfusion.

	Invalid asymmetry (left minus right)	Valid asymmetry (left minus right)
Left hemisphere		
Precuneus	−0.433*	−0.441*
Inf. parietal	−0.529*	−0.038
Sup. parietal	−0.688**	−0.302
Right hemisphere		
Precuneus	−0.586**	−0.254
Inf. parietal	−0.498*	−0.149
Sup. parietal	−0.692**	−0.303

* $p < 0.05$.
** $p < 0.01$.

task as the extent of the frontal involvement increased. Using a median split on the extent of frontal hypoperfusion (averaged across left and right hemisphere), there were significant effects of group ($F(1,18) = 14.1$, $p < 0.001$) with the more affected subgroup performing more slowly (mean 783 ms) than the less affected group (mean 509.9 ms). There was also a significant interaction between group × validity ($F(1,18) = 6.4$, $p < 0.02$) with the more affected group evincing a validity cost of 158 ms and the less affected group showing a 93 ms cost. Finally, there was a significant interaction of group with side ($F(1,18 = 4.6$, $p < 0.05$) with the more affected group responding 63 ms slower to the left than right compared with the less affected group responding 7 ms slower to the left than right. Note, however, that there were no interactions with task in this analysis.

4. Discussion

The purpose of this study was to investigate the relationship between the visuospatial attentional processing abilities of individuals with Alzheimer's disease and the underlying neural correlate of this behavior, as measured by cortical perfusion indices on SPECT. Using a covert spatial attention cueing task (after Posner, 1980), we demonstrated a greater cost in the AD group in switching attention from a cued to an uncued location, relative to matched controls. This group difference was evident in both central and peripheral cueing forms of the task, albeit to a greater extent in the latter case. The group difference was also noted for both left and right target locations, but the validity effect was asymmetric and disproportionately more costly for invalid left than right targets. It seems unlikely that cognitive enhancers had significant effects on task performance in the two patients that were on them since symptomatic effectiveness tends to diminish over time, and the drugs are not disease-modifying. Furthermore, any residual drug effects would be expected to improve rather than hinder performance and to have symmetric effects, which would not have changed the main results.

The slowed reorienting attentional response is consistent with previous studies of visual attention in AD (Maruff et al., 1995; Parasuraman et al., 1992; Tales et al., 2002; Tales, Snowden, Haworth, & Wilcock, 2005) and with the research on central orienting in AD that show a reduced, or even a lack of a validity effect for reorienting following central cues (Caffarra et al., 1997; Tales et al., 2002). A plausible explanation for this common finding could be related to the neurodegenerative progression of AD. Typically, neuropathological changes begin to occur in the hippocampus and then progress to temporal–parietal lobes (Braak, Braak, & Bohl, 1993). It is only later on in the disease that the frontal cortex becomes affected. If the automatic exogenous orienting system is mediated by the parietal lobes, this system would frequently be disrupted in AD patients and indeed, we see disproportionate slowing in reorienting to left targets following exogenous or peripheral cueing, too. On the other hand, since endogenous orienting is at least partially mediated by frontal networks (Ladavas, Carletti, & Gori, 1994; Riddoch & Humphreys, 1983), difficulties with this form of attentional switching may only be observed in severe AD cases once the pathology has expanded to more frontal areas.

To investigate this last point, we subdivided the AD group first on the basis of the severity as determined by the MMSE and then on the basis of the extent of the frontal hypoperfusion. In neither of these analyses did we see a difference between the subgroups as a function of tasks (central versus peripheral), as might have been predicted. There are a number of possible explanations for this. Of course, insufficient statistical power is an obvious and probably most likely explanation. However, it may also be the case that the variance in MMSE and especially in the frontal hypoperfusion was not very large, and this might have obscured any task-related effects. In light of this, increased involvement of the frontal cortex in AD as a predictor of a greater disengage deficit in the more exogenous form of attentional orienting remains to be investigated further.

Original accounts of the difficulty in disengaging attention from its current focus in order to reorient attention, as documented here, date back to Posner's covert orienting study on patients with parietal lobe damage (Posner et al., 1984). The disengage deficit has been implicated as a major component of spatial neglect, contributing to the lack of awareness for contralesional stimuli in these patients. Although our findings reveal a similar deficit in our sample, the magnitude of this deficit is far less than that observed in patients with hemispatial neglect: whereas the cost in reorienting to the invalidly cued location was 187.8 ms for left- and 101 ms for right-sided targets, respectively, in the AD group, the same values are 454 ms and 173 ms, respectively, for contralateral and ipsilateral targets in patients with unilateral right and left focal parietal damage (Posner et al., 1984). Together, the research suggests that AD patients have qualitatively, but not quantitatively, similar deficits in attentional orienting compared to patients with parietal damage. Consistent with the similarity in patterns in stroke and AD, there have been some reports of atypical cases of AD patients demonstrating neglect, who, with right parietal disruption evince mild attention deficits (see Ishia et al., 2000; Venneri, Pentore, Coticelli, & Della Sala, 1998). One obvious explanation for the magnitude differences is that the neuronal damage following a sudden focal parietal infarct might have a greater adverse impact on cortical function than the slow neuropathological changes (for example, plaques, neurofibrillary tangles) associated with AD.

Despite the fact that we show significant differences at a group level for the AD versus control group, closer scrutiny of the data reveals that some AD individuals show minimal slowing of RT on invalid trials, that others exhibit slowed RT in directing spatial attention to both the left and right visual field, and that some show a right or a left field disadvantage. This heterogeneity within our sample may help explain the host of different behavioral patterns reported previously, with some studies finding no difference relative to controls (Caffarra et al., 1997; Maruff et al., 1995), some revealing subgroups with different patterns (Maruff et al., 1995) and some even reporting a profile akin to right-sided neglect in a single patient (Bartolomeo et al., 1998; Bublak, Redel, & Finke, 2006). Thus, depending on the balance of these different profiles within a particular study sample, the group outcome, relative to controls, may differ. Having a relatively large subject sample is beneficial not only because we can observe the full distribution of deficits in AD, but also because this within-group heterogeneity allows us to explore the underlying neural correlates of the AD behavioral profiles. We also recognize that even though a group of 21 AD participants is a relatively large group, in comparison with some other studies, our findings might reflect some peculiar characteristics of our own sample and might not necessarily be representative of the AD population at large. Indeed, other studies report slightly different attentional profiles in their AD groups; for example, one study showed that their AD patients had essentially normal attentional orienting with non-predictive as well as with predictive peripheral cues, but had defective inhibition of orienting towards counter-predictive cues, i.e., they tended to orient towards these cues as if they were predictive (Danckert, Maruff, Crowe, & Currie, 1998). There is a clear need for further investigation of individual and group differences in AD in larger samples or across many more such studies.

To investigate the neural signature of the AD attentional profiles, we first documented the 22 regions (out of 79 ROIs) that reveal greater hypoperfusion than in the controls. An analysis of the correlation between behavior and regional hypoperfusion reveals that

the magnitude of the RT cost for left over right invalid peripherally cued targets was correlated with hypoperfusion in the right superior parietal lobe, as well as in the cuneus and inferior parietal lobe in both hemispheres. The right superior parietal hypoperfusion, however, accounted for a significant amount of the variance in the behavioral data and once this region was entered into the regression, no other regions were significant. Previous studies have implicated focal damage to the superior parietal lobe (Posner et al., 1984), and the inferior parietal area (Friedrich, Egly, Rafal, & Beck, 1998) to be critical anatomical correlates of this increased validity effect, and the general consensus is that the process by which attention is shifted from one location to another is mediated primarily, if not exclusively, by parietal cortex (Yantis, 2008). Several recent studies on attentional orienting have begun to focus more specifically on the neural correlates of the attentional operations implicated in the type of task we adopted here and have begun to fragment the parietal cortex into subregions, including the dorsal (superior parietal lobule) and more ventral (temporo-occipital junction) portions of parietal cortex (for example, Shomstein, Lee, & Behrmann, 2010), as well as the precuneus on the medial surface. Although we were able to show the correlation between brain and behavior in the right superior parietal region and the attentional deficit, we did not investigate the contribution of the precuneus per se and thus, future investigations should explore the relative contribution of this region too.

Our behavior-SPECT measures are also consistent with the data from Parasuraman et al. (1992) who correlated PET measures with performance on a covert visual attention paradigm. They found that RT costs were related to hypometabolism in the superior parietal lobe, much like the localization of hypoperfusion seen in the present study. They also found that AD patients with more right hemisphere hypometabolism had higher RT costs, consistent with the findings we have obtained in our sample. Furthermore, Buck et al. (1997) found that shifting attention between spatial locations, using a different paradigm, also lead to RT costs that were correlated with SPECT hypoperfusion especially in the right superior parietal lobe. Unlike these studies, however, we go further and confirm a hemispatial difference (left versus right), which is correlated with the right parietal hypoperfusion. Importantly, our asymmetry analysis of rCBF indicates that it was the severity of superior parietal hypoperfusion and not merely greater right than left hypoperfusion that was responsible for the behavioral deficit. In other words, our findings suggest a right hemisphere predominance for attention, manifested as a greater validity effect for left sided targets with balanced hypoperfusion deficits in our population.

A number of possible relationships have been postulated between visuospatial attention processing and its underlying neural substrate. Our findings are consistent with the claim that the hemispheres are differentially implicated in attentional processing, with the left hemisphere mediating attention for right space only, and the right hemisphere mediating attention for both sides of space (Corbetta & Shulman, 2002; Heilman & Van Den Abell, 1979, 1980). Although we observed bilateral hypoperfusion in parietal cortex in the AD group, the asymmetric validity effect was more pronounced for covert attentional shifts to left than right space, and this effect was primarily accounted for by the hypoperfusion of the right superior parietal cortex. This pattern supports the differential involvement of the right hemisphere in visuospatial processing.

Alzheimer's disease is a multifaceted neurodegenerative disorder affecting multiple cognitive domains. Consistent with several past studies, we have demonstrated that AD patients are slower to reorient their attention to invalidly cued peripheral targets. Interestingly, we have demonstrated for the first time that this reorienting deficit was more severe when patients had to reorient attention from an invalid cue indicating a probable rightward target and then re-distribute attention to the correct left-sided target location. Our imaging analysis supports lesion correlates of the disengage deficit in patients with focal parietal lesions, and also confirms more generally the engagement of cortical networks in the service of attentional orienting. Furthermore, although there is some variability in the magnitude of this behavioral asymmetry among the individual participants, the extent of this right superior parietal hypoperfusion, and not the extent of the dementia per se, accounts for these differences. Importantly, this experiment has further characterized AD, and shown that cerebral hypoperfusion associated with AD can lead to attentional deficits that share a commonality with impairments incurred from a circumscribed lesion. But more specifically, the present study suggests that asymmetric bilateral parietal pathology leads to similar behavioral dysfunction as in the case of unilateral parietal damage, and confirms the right-hemisphere predominance in attentional disengagement.

Disclosure statement

The authors have no conflicts of interest to disclose.

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