

Attentional Networks in Normal Aging and Alzheimer's Disease

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By combining a flanker task and a cuing task into a single paradigm, the authors assessed the effects of orienting and alerting on conflict resolution and explored how normal aging and Alzheimer's disease (AD) modulate these attentional functions. Orienting failed to enhance conflict resolution; alerting was most beneficial for trials without conflict, as if acting on response criterion rather than on information processing. Alerting cues were most effective in the older groups—healthy aging and AD. Conflict resolution was impaired only in AD. Orienting remained unchanged across groups. These findings provide evidence of different life span developmental and clinical trajectories for each attentional network.

Keywords: Alzheimer's disease, executive processing, orienting, conflict resolution, alerting

Early stages of Alzheimer's disease (AD) are characterized by deficits in episodic memory caused by medial-temporal lobe atrophy and neuronal loss in the basal forebrain cholinergic system (Köhler et al., 1998; Whitehouse et al., 1982). Although memory impairments are at the core of AD, over the past 10 years, evidence has accumulated for early deficits in attention (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Rizzo, Anderson, Dawson, Myers, & Ball, 2000; for reviews, see Fernandez-Duque & Posner, 2001; Parasuraman, Greenwood, & Sunderland, 2002). Some of the brain areas most important for attention are hypometabolic in early AD, and attention is influenced by acetylcholine—which is decreased in AD (Davidson & Marocco, 2000; Parasuraman, Greenwood, Haxby, & Grady, 1992). This has led some researchers to propose that memory problems in AD may stem in part from a cholinergic disruption of attention (Voytko, 1996).

The term *attention* refers to many different cognitive abilities, such as orienting to sensory stimuli, maintaining the alert state, and orchestrating the computations needed to perform the complex

tasks of daily life (Fernandez-Duque & Posner, 1997). Falling under this last category are the abilities to switch between tasks and to inhibit prepotent responses, as well as other skills sometimes referred to as *executive functions* (Baddeley et al., 2001; Fernandez-Duque, Baird, & Posner, 2000). After reviewing the anatomical literature, Posner and Petersen (1990) proposed dividing the attentional system into three discrete anatomical networks: orienting, alerting, and executive. By emphasizing anatomical networks with specific computational functions, this model has encouraged the development of neuroimaging and neuropsychological studies exploring dissociation and interactions among attentional processes. The model has also shifted the emphasis from etiology to brain localization, arguing that different pathologies would lead to the same cognitive deficit if they affected the same brain area. This emphasis on anatomy has further allowed for predictions on the role of different neuromodulators based on their unique patterns of cortical projections. These features of the model have converged with evidence from AD research on cholinergic dysregulation and regional atrophy. As efforts for early treatment of AD move closer to reality, it becomes all the more important to fully understand the attentional deficits in AD, the interactions among the attentional networks, and the neurochemical substrates underlying them. The current study is a step in this direction.

Several studies have looked at the ways in which different components of attention are disrupted by AD. Most of the research has been devoted to the orienting network after early reports revealed an orienting deficit in AD (Buck, Black, Behrmann, Caldwell, & Bronskill, 1997; Danckert, Maruff, Crowe, & Currie, 1998; Faust & Balota, 1997; Festa-Martino, Ott, & Heindel, 2004; Maruff & Currie, 1995; Oken, Kishiyama, Kaye, & Howieson, 1994; Parasuraman et al., 1992; Tales, Muir, Bayer, & Snowden, 2002). Some studies have further reported an orienting deficit in the rescaling of the attentional focus (i.e., zoom-in function; Coslett, Stark, Rajaram, & Saffran, 1995; Greenwood, Sunderland, Friz, & Parasuraman, 2000; Parasuraman, Greenwood, & Alexander, 2000). Other studies have explored executive functions such as inhibitory control and dual-task performance (Baddeley et al.,

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2001; Spieler, Balota, & Faust, 1996), partly motivated by the finding that healthy older adults are impaired in these functions (Hasher & Zacks, 1988; Mayr, 2001). Finally, other studies have investigated whether vigilance decrements and alerting effects are spared in AD and healthy aging (Baddeley, Cocchini, Della Sala, Logie, & Spinnler, 1999; Berardi, Parasuraman, & Haxby, 2001; Festa-Martino et al., 2004; Nebes & Brady, 1993; Tales, Muir, Bayer, Jones, & Snowden, 2002).

In contrast to the wealth of research probing individual attentional networks, there have been no assessments of the three networks within a single experimental paradigm. In some studies, separate tasks have been tested in the same group of patients and patterns of correlations taken as evidence for interactions among networks (Levinoff, 2002). This approach should be commended for its inclusiveness, but it requires a large number of participants, and superficial differences across tasks may obscure the interpretation of the findings. A different approach is to design a task in which all three components can be assessed simultaneously. Recently, Posner and collaborators have developed such a paradigm, which they labeled the Attentional Network Test (ANT) and tested in normal young adults (Fan, McCandliss, Sommer, Raz, & Posner, 2002).

The ANT is a combination of Posner's covert orienting task and Eriksen's flanker task (Eriksen & Eriksen, 1974; Posner, 1980). In the covert orienting task, attention is cued to one side or another before the target appears. The reaction time (RT) difference between valid and invalid cued locations constitutes a measure of orienting. Other trials include a warning cue that provides temporal information about the target onset but no spatial information (neutral cue). These trials are compared with trials in which the target occurs without any warning (no cue). The difference in RT is a measure of alerting. Eriksen's flanker task displays a target flanked by distractors with information congruent or incongruent to the target. For example, in an incongruent trial, the target arrow may point to the left, with the flanking arrows pointing to the right. The difference in RT between congruent and incongruent trials provides a measure of conflict resolution, one of the functions of the executive network.

By combining the four types of cue (valid, invalid, neutral, no cue) with the two types of distractor (congruent, incongruent), our modified version of the ANT explored how alerting and orienting influence conflict resolution (see Figure 1).¹ We explored whether and how normal aging and AD would modulate these effects and whether the patterns previously observed in young adults would generalize to healthy aging and AD.

Method

Participants

Patients with AD were recruited through the Cognitive Neurology Unit at Sunnybrook and Women's Health Science Centre in Toronto, Ontario, Canada, where the project received approval from the Research Ethics Board. Age-matched normal controls were recruited from a pool of healthy community older volunteers at the same Cognitive Neurology Unit and at Baycrest Centre for Geriatric Care. The group of young adults consisted of 13 undergraduate students at the University of Toronto who participated in the task for course credit. Consent for participation in the study was obtained from all participants, as well as from the patients' caregivers. All participants had normal or corrected-to-normal vision. Demographic information about the participants is given in Table 1.

All patients met criteria for probable AD, as established by the workgroup of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). As part of the standard work-up of AD, brain imaging was obtained in all the patients. This included a measure of regional cerebral blood flow using single photon emission computed tomography, as well as an MRI ($n = 11$) or computerized tomography whenever MRI was contraindicated ($n = 1$). Only patients with mild dementia were selected (Mini-Mental State Examination [MMSE; Folstein, Folstein, & McHugh, 1975] score ≥ 20). Nine of the 13 patients were treated with cholinergic agents for at least 80 days before testing.

A full neuropsychological battery was used to characterize the deficits of the AD patients. All 13 patients and 8 age-matched control participants completed general neuropsychological testing. The other 5 age-matched control participants completed a subset of tests (MMSE, the digit span task, the Verbal Fluency tasks), performing within normal levels. Table 2 shows the results of the neuropsychological tests. As expected, the AD group was impaired relative to the normal controls in most domains.

Participant Selection

Data from 13 participants in each group were included in the analyses. Data from 4 patients were excluded from the analyses because they did not meet some of the following criteria: overall accuracy better than 75%, less than 20% of trials with eye movements, and at least 10 trials per cell from which to compute the median RT. Two other patients were unable to reach criterion in the practice trials and therefore did not participate in the actual test.

Equipment

Stimuli were displayed on a 19-in. monitor set to a screen resolution of $1,024 \times 768$ pixels. Data were collected via the keyboard of a Dell computer equipped with a Pentium III processor and Windows 98. Timing of stimulus display and data collection were managed using E-prime, a commercial experiment application.

Stimulus and Design

The stimulus display is illustrated in Figure 1. The basic display was visible at all times and consisted of two black rectangular boxes and a black fixation cross against a gray background. The boxes were centered horizontally on the monitor and displayed 3.5 cm (4° visual angle [VA]) above and below fixation, measured from the fixation cross to the center of the box. Each box was 12 cm wide and 2.2 cm high ($13.7^\circ \times 2.7^\circ$ VA), and the lines that formed the box were 3 pixels wide.

In any given trial, a set of five black arrows was displayed inside one of the rectangular boxes. Each arrow measured 1.4 cm in length, with the arrowhead measuring 1 cm in height ($1.6^\circ \times 1.1^\circ$ VA). Arrows were separated from each other by 1 mm. The central arrow constituted the target, and the flanking arrows constituted the distractors. Target and distractors could point in the same direction (congruent trials) or in different directions (incongruent trials).

The attentional cue consisted of the brightening from black to white of one or two of the boxes. Depending on its relation to the five-arrow display, the cue provided information that was spatially valid (same location),

¹ The ANT, in its original version, does not include invalid trials, and the validity effect has to be estimated by comparing valid trials with trials with neutral cues. That design reduces the number of required trials but does not assess the cost of disengaging attention from an invalid location. Previous studies have suggested deficits in disengaging attention in AD. Thus, we modified the original design to include invalid trials a third of the time that the cue provided spatial information.

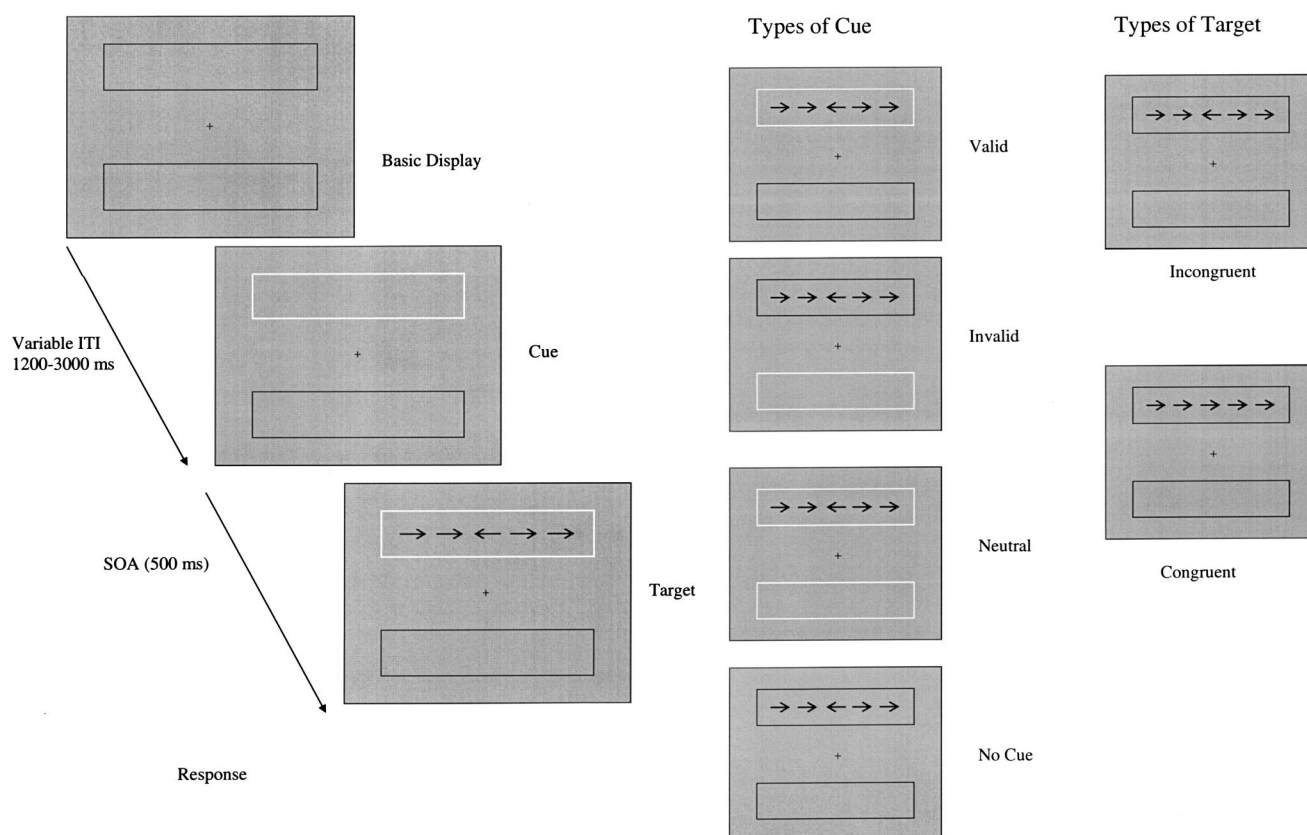


Figure 1. The experimental design: Five hundred ms after the onset of the peripheral cue, target and distractors were displayed at the cued location (valid trials) or at the uncued location (invalid trials). Target and distractors pointed in the same direction (congruent trials) or in different directions (incongruent trials) for an equal number of trials. Spatial cues were predictive at a ratio of 3 to 1 (valid to invalid). There were also neutral trials, in which both locations were cued, and no-cue trials. ITI = intertrial interval; SOA = stimulus onset asynchrony.

invalid (different location), or neutral (brightening of both boxes). There were also no-cue trials, in which neither box brightened. Valid cues occurred in 50.0% of trials, and each of the other cue conditions (invalid, neutral, no cue) occurred in 16.7% of trials. The proportion of valid to invalid trials was 3 to 1, meaning that for trials in which spatial information was given, the validity of the cue was 75.0%.

Besides the congruency factor and the cue factor, we counterbalanced whether the target pointed left or right and whether the arrows were displayed in the top or the bottom box. All possible combinations of this $2 \times 4 \times 2 \times 2$ design were represented in each block of 48 trials. There were five blocks, for a total of 240 trials.

Table 1
Demographic Information

Characteristic	Young adults	Healthy older adults	Patients with AD
No. of participants	13	13	13
Male/female	6/7	6/7	6/7
Age in years	19.8 (1.3)	72.5 (5.7)	74.7 (6.7)
Years of education	13.8 (0.6)	14.3 (3.6)	14.1 (3.9)

Note. Numbers in parentheses are standard deviations. AD = Alzheimer's disease.

Procedure

Participants sat approximately 50 cm away from the screen and used their left and right index fingers to press keys *S* and *L* on the keyboard. Eye movements were videotaped, and whenever an eye movement was detected online, participants were reminded to keep fixation.

Each trial began with a cue and was followed by a target 500 ms later (for no-cue trials, the cue event was invisible). Cue and target remained on display until response or for a maximum of 5 s. Trials in which participants were slower than 2,000 ms were followed by visual feedback that read "too slow" for the first 1,000 ms of the intertrial interval. Intertrial interval was randomized between 1,200 and 3,000 ms. Each of the five blocks of 48 trials lasted approximately 3 min, and participants were encouraged to take short breaks between blocks.

Instructions

Task instructions were read out loud and illustrated with computer displays. Participants were told that it was "very important that you keep your eyes looking at the center cross and that you try to see the whole display without moving your eyes."

To illustrate the congruency component, a five-arrow display was presented in the top box with the target arrow pointed to the right and the distractors pointing to the left (i.e., an incongruent trial). Participants were instructed that "the central arrow will indicate which key to press. In this

Table 2
Neuropsychological Information

Test	Maximum score	Age-matched	Patients with AD
MMSE	30	29.0 (0.5)	24.3 (2.5)**
DRS			
Total	144	141.4 (2.1)	122.9 (11.2)**
Attention	37	36.0 (0.7)	34.3 (2.0)*
Initiation	37	36.4 (1.4)	31.3 (4.7)**
Praxis	6	5.7 (0.5)	5.3 (0.7)
Conceptualization	39	38.5 (1.0)	34.7 (3.7)**
Memory	25	25.0 (0.0)	17.3 (4.2)**
NART-R FS-IQ		117.5 (3.4)	107.3 (9.8)*
Boston Naming Test	30	29.0 (1.2)	21.0 (5.8)**
Western Aphasia Battery			
Total	100	99.3 (0.6)	92.5 (4.2)**
Apraxia	60	59.4 (1.1)	59.7 (0.6)
Rey-Osterrieth Complex			
Figure Test	36	33.6 (1.5)	26.2 (6.1)**
Line Orientation Task	30	25.7 (3.7)	23.9 (3.4)
Visual Memory Immediate	41	32.6 (6.6)	19.9 (6.6)**
Visual Memory Delayed	41	24.7 (7.5)	3.7 (5.7)**
Semantic Fluency		17.7 (2.0)	10.9 (4.5)**
Verbal Fluency (FAS)		45.5 (6.5)	30.3 (13.5)**
CVLT			
Acquisition (Trial 5)	16	10.6 (1.8)	5.8 (2.3)**
Short Delay Free Recall	16	8.9 (3.3)	1.8 (2.2)**
Short Delay Cued Recall	16	10.0 (2.5)	4.2 (2.6)**
Long Delay Free Recall	16	8.3 (3.3)	1.5 (2.0)**
Long Delay Cued Recall	16	9.4 (3.2)	3.4 (2.7)**
Forward digit span	12	9.6 (1.2)	8.3 (1.6)
Backward digit span	12	7.8 (1.9)	6.1 (2.4)
Trail Making Test			
Part A		37.2 (9.6)	43.2 (12.7)
Part B		78.7 (17.9)	180.0 (66.4)**
WCST			
Categories	6	3.5 (1.7)	2.3 (1.2)
Correct	64	44.0 (6.5)	44.3 (6.5)
Raven's Progressive Matrices	36	34.1 (1.5)	25.9 (4.3)**

Note. Numbers in parentheses are standard deviations. AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; DRS = Dementia Rating Scale; NART-R = National Adult Reading Scale—Revised; FS-IQ = full-scale IQ; FAS = the letters F, A, and S; CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Task.

* $p < .05$. ** $p < .01$.

example you should press right, because the central arrow points to the right." The next three examples illustrated the remaining possible combinations between target direction (left, right) and distractor type (congruent, incongruent). Following the illustration, participants completed four practice trials, one for each possible combination of target direction and distractor type. If any errors were made, the illustration and practice trials were repeated until the performance was flawless.

Next, the spatial component of the task was explained. A five-arrow display was illustrated in the bottom box, and participants were told that "in half of the trials, the arrows will appear in the bottom box. One of the boxes will light up, indicating where the arrows will most likely occur. For example, . . ." Four examples of valid trials followed.

Next, the alerting component of the task was explained by telling participants that "sometimes the outline of both boxes will turn white, indicating no favorite location. The whitening of the outline will also inform you that the arrows will occur immediately." These instructions were followed by two trials in which the spatially neutral cue was displayed.

Participants were reminded once again not to move their eyes and started 10 trials of practice. For practice trials, no speed feedback was given, and participants were encouraged to take as much time as they

needed to answer correctly. Participants repeated practice blocks until they reached a criterion of 90% accuracy in a 10-trial block.

After practice, participants completed five blocks of actual testing. For the actual test, participants were instructed to respond as fast and accurately as possible and were warned that speed feedback would follow abnormally slow responses. At the beginning of each block, participants were reminded to respond to the central arrow (i.e., the target) of the five-arrow display.

Results

Consistent with previous findings (Faust & Balota, 1997), patients with AD had increased difficulties maintaining fixation and made eye movements in a larger percentage of trials than age-matched controls, $t(24) = 3.3$, $p < .001$, (patients with AD: $M = 9.6\%$, $SD = 7.0\%$, range: 1.8–23.0%; healthy older participants: $M = 2.9\%$, $SD = 2.0\%$, range: 0.0–5.4%). Trials with eye movements were excluded from the analyses. Error trials and trials immediately following an error were further excluded from the RT analyses.

From the remaining trials, median RTs were calculated for each group (young, healthy older, AD), cue type (valid, invalid, neutral, no cue), and distractor type (congruent, incongruent; see Table 3). To control for the possibility that differences in overall speed among groups influenced the absolute size of the effects, we also computed proportional scores. For each participant, the median RT in each condition was divided by the participant's overall RT (Faust & Balota, 1997). These transformed data yielded the same pattern of results, unless otherwise specified.

Error data were analyzed following the same approach as RT data. We analyzed the raw error data and also the arcsine-transformed error rates, which reduced the skewness of the distribution and minimized the effect of outliers (Winer, 1971). We report the analysis on the raw error data, but the transformed data yielded a similar pattern of results, unless otherwise noted.

First, we assessed the effects of aging by comparing young and healthy older participants. Later, we assessed the effects of AD by comparing patients with AD and healthy older participants.

Effects of Normal Aging

Congruency Effect and Aging

To assess the effect of normal aging on the congruency effect, we ran a mixed analysis of variance with age (young, healthy older) as a between-subjects factor and distractor type (congruent, incongruent) and cue type (valid, invalid, neutral, no cue) as within-subject factors. We ran this analysis on the median RTs, the proportional scores (to control for differences in overall speed among groups), and the error rates.

Both groups responded slower to incongruent than to congruent trials: distractor main effect, $F(1, 24) = 121.3, p < .0001$. It is important to note that young adults were no better at resolving conflict than healthy older participants: Distractor \times Age interaction, $F(1, 24) = 0.3, ns$ (see Figure 2, right). In fact, when overall speed was taken into account by analyzing the proportional scores, older adults exhibited a smaller congruency effect than young adults (not shown in Figure 2): Age \times Distractor interaction for the proportional scores, $F(1, 24) = 5.8, p < .03$. Possibly, the general slowness with which older adults responded afforded them more time to resolve conflict information, thus decreasing the

congruency RT effect. The error data support this interpretation. Only young adults were sensitive to the congruency effect and made increased errors to incongruent trials: Distractor \times Age interaction, $F(1, 24) = 9.9, p < .001$.

Alerting Effect

To assess the effect of normal aging on alerting and the influence of alerting on conflict resolution, we ran a mixed analysis of variance with age (young, healthy older) as a between-subjects factor and distractor type (congruent, incongruent) and alerting (neutral cue, no cue) as within-subject factors.

Alerting and aging. As expected, the RT analysis revealed faster response times to targets preceded by a neutral cue than to targets occurring without a cue, $F(1, 24) = 55.4, p < .0001$. More interestingly, this alerting effect interacted with age, being most beneficial for older participants, $F(1, 24) = 10.2, p < .004$ (simple effects $p < .05$; see Figure 2, left). A possible interpretation is that older adults had difficulty sustaining attention in the absence of an external cue and therefore were disproportionately slow in no-cue trials. Alternatively, older adults might have adopted a more conservative response criterion overall, thus giving more room for the alerting cue to exercise its effect. The error data revealed no age differences in the effectiveness of the warning cue, $F(1, 24) = 0.1, ns$.

Alerting and conflict resolution. The alerting RT effect interacted with the type of distractor, $F(1, 24) = 8.6, p < .01$, being least effective for incongruent trials. In other words, participants benefited most from a cue announcing the imminent occurrence of a target when target and distractor were congruent and conflict resolution was not required (see Figure 3). This finding is consistent with previous claims that alertness acts by shifting the response criterion rather than by truly enhancing information processing (Fan et al., 2002; Posner, 1978; Prinzmetal, Hansen, & Park, 2005). Also consistent with this hypothesis, the error data revealed an interaction between alertness and congruency, $F(1, 24) = 3.8, p < .06$. More specifically, alerting cues led to an increased number of errors for incongruent trials, probably by triggering a motor response before conflict was resolved in such trials.

Table 3
Median Reaction Times and Error Rates

Group	Alert		No Cue		Valid		Invalid	
	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent
Median reaction times (ms)								
Young	455 (47)	566 (39)	493 (46)	574 (40)	429 (44)	538 (40)	495 (53)	600 (52)
Older	637 (110)	743 (87)	712 (105)	782 (101)	601 (87)	726 (88)	710 (132)	777 (79)
Patients with AD	761 (160)	948 (164)	851 (131)	947 (180)	729 (137)	889 (149)	817 (143)	982 (156)
Error rates (%)								
Young	1.9 (3.3)	8.1 (8.8)	1.2 (3.0)	5.5 (6.1)	0.4 (1.4)	7.6 (6.3)	1.5 (3.1)	6.2 (6.3)
Older	0.4 (1.4)	4.2 (5.2)	1.6 (2.5)	0.8 (1.8)	0.2 (0.6)	2.4 (2.5)	7.1 (7.2)	2.4 (3.5)
Patients with AD	3.6 (7.5)	9.3 (13.0)	2.8 (4.0)	7.2 (12.6)	2.2 (3.2)	8.3 (9.2)	2.8 (4.1)	8.5 (9.7)

Note. Numbers in parentheses are standard deviations. AD = Alzheimer's disease.

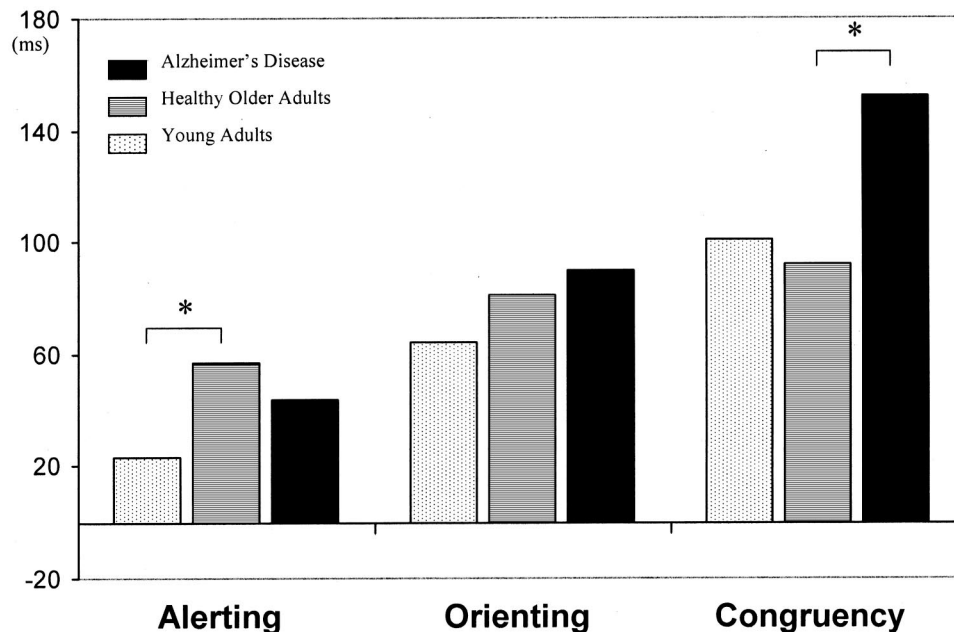


Figure 2. The adult developmental and clinical trajectory of the three attentional networks. The figure illustrates the reaction time main effects of alerting (no-cue trials minus neutral trials), orienting (invalid trials minus valid trials), and congruency (incongruent trials minus congruent trials). Asterisks indicate statistically significant differences. The alerting effect increased with age across both healthy aging and Alzheimer's disease (AD) groups, whereas the congruency effect increased with the AD group but not with the healthy aging group. There were no significant modulations of the orienting network.

Validity Effect

To assess the effect of normal aging on spatial attention and the influence of spatially valid cues on conflict resolution, we ran a mixed analysis of variance with age (young, healthy older) as a between-subjects factor and distractor type (congruent, incongruent) and spatial cue (valid, invalid) as within-subject factors.

Spatial attention and aging. As expected, RTs were faster when the target appeared at the cued location, $F(1, 24) = 50, p < .0001$. This validity effect was similar for young and older adults, with no interaction between validity and age, $F(1, 24) = 0.7, ns$ (see Figure 2, center). However, the error data did reveal an interaction, $F(1, 24) = 6.2, p < .02$, and simple effects showed a validity effect for older adults but not for young adults.

Spatial attention and conflict resolution. The valid cue did not reduce the cost of incongruent distractors. In fact, valid trials sometimes elicited a larger congruency effect than invalid ones, as revealed by a three-way interaction among cue type, distractor type, and group, $F(1, 24) = 6.2, p < .02$. Post hoc analyses of this three-way interaction revealed that, for young adults, cue type and distractor type did not interact, $F(1, 12) = 0.1, ns$, but for older adults, valid cues led to larger congruency effects than invalid cues, $F(1, 12) = 8.6, p < .01$ (see Figure 4). The error analysis revealed a larger congruency effect for valid than for invalid trials for both groups, $F(1, 24) = 13.9, p < .001$. These data argue against a beneficial effect of spatial cuing on conflict resolution in paradigms such as this.

Effects of Alzheimer's Disease

Congruency Effect and Alzheimer's Disease

Data from patients with AD were compared with data from healthy older participants. We used the same statistical approach as before, running a mixed analysis of variance with group (AD, healthy older) as a between-subjects factor and distractor type (congruent, incongruent) and cue type (valid, invalid, neutral, no cue) as within-subject factors.

As expected, the overall RTs were slower for the AD group than for their age-matched controls: group main effect, $F(1, 24) = 10.9, p < .003$. Also as expected, responses were slower when the distractors provided information that conflicted with the target: congruency main effect, $F(1, 24) = 128.2, p < .0001$. Most important to note is that there was an interaction between distractor type and group, $F(1, 24) = 7.7, p < .01$, so that the cost of an incongruent distractor was larger for patients with AD than for the age-matched controls (see Figure 2, right). This finding suggests that patients with AD had greater difficulty resolving conflict. The interpretation, however, is qualified by the overall group differences in RTs. When overall speed was taken into account by analyzing the proportional scores, the congruency effect for AD patients was not significantly different from that for age-matched healthy adults, although with a trend in the right direction, $F(1, 24) = 2.4, p < .13$. Consistent with a true deficit in conflict resolution in patients with AD, the error data revealed a strong trend for interaction between distractor type and group, $F(1,$

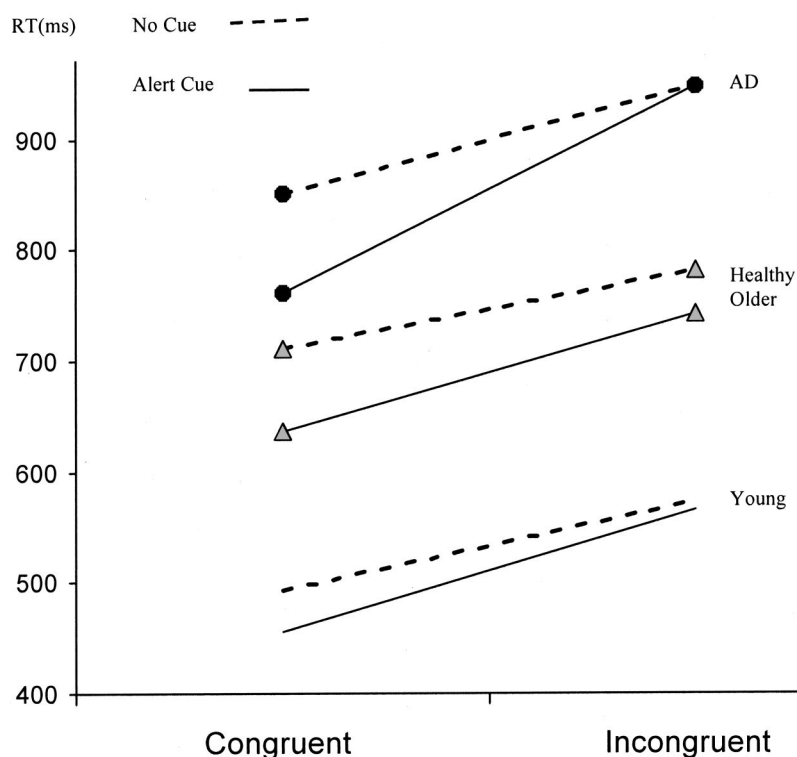


Figure 3. Interaction between alerting and conflict resolution. The alerting cue increased the congruency effect in all three groups, with warning signals being most effective in trials with no conflict (i.e., congruent trials). AD = patients with Alzheimer's disease; RT = reaction time.

24) = 3.8, $p < .06$. In other words, accuracy was disproportionately affected by incongruent trials in the AD group.

Alerting Effect

To explore whether alerting was altered in patients with AD and whether alerting interacted with conflict resolution, we ran a mixed analysis of variance with group (AD, healthy older) as a between-subjects factor and distractor type (congruent, incongruent) and alerting (neutral cue, no cue) as within-subject factors.

Alerting and Alzheimer's disease. The RT analysis revealed that neutral cues speeded up response times relative to trials with no cue, $F(1, 24) = 27.2$, $p < .0001$. The benefit provided by a warning was similar for patients and controls, with no interaction between alertness and group, $F(1, 24) = 0.4$, *ns* (see Figure 2, left). The same was true for the error data, $F(1, 24) = 0.1$, *ns*.

Alerting and conflict resolution. The RT data revealed that neutral cues were more effective for trials in which the distracting information was congruent to the target than for trials with incongruent distractors, $F(1, 24) = 10.7$, $p < .003$ (see Figure 3). This result replicates the findings from young adults and suggests that the alerting effect acted on the response criterion rather than enhancing information processing. Consistent with this view, alert trials increased the number of errors as compared with incongruent trials, $F(1, 24) = 4.2$, $p < .05$.

Validity Effect

To assess the effect of AD on spatial attention and the influence of spatially valid cues on conflict resolution, we ran a mixed

analysis of variance with group (AD, healthy older) as a between-subjects factor and distractor type (congruent, incongruent) and spatial cue (valid, invalid) as within-subject factors.

Spatial attention and Alzheimer's disease. This analysis revealed the standard validity effect, $F(1, 24) = 41.7$, $p < .0001$. The validity effect was as large in AD patients as it was in age-matched controls, and there was no interaction, $F(1, 24) = 0.1$, *ns* (see Figure 2, center). The error data revealed a main validity effect, $F(1, 24) = 5.5$, $p < .05$, and a nonsignificant trend toward interaction with pathology, $F(1, 24) = 3.5$, $p < .07$, in that healthy older participants, but not AD patients, benefited from valid cues.

Spatial attention and conflict resolution. There was no interaction between validity and type of distractor. Thus, spatial attention was ineffective in reducing the RT cost of conflict resolution, $F(1, 24) = 1.6$, *ns* (see Figure 4). Furthermore, the error data revealed a larger congruency effect for valid trials than for invalid ones, $F(1, 24) = 5.1$, $p < .04$. Similar to the data from young adults, the findings from this analysis argue against a role for spatial attention in conflict resolution when target and distractors occur inside the attentional focus.

General Discussion

The pattern of interactions and dissociation among the three attentional networks replicated previous findings in young adults, generalizing them to healthy aging participants and patients with AD (Fan et al., 2002; Fernandez-Duque, in preparation). In particular, the presence of an alerting, spatially neutral cue increased the congruency effect, and the presence of a spatially valid cue was

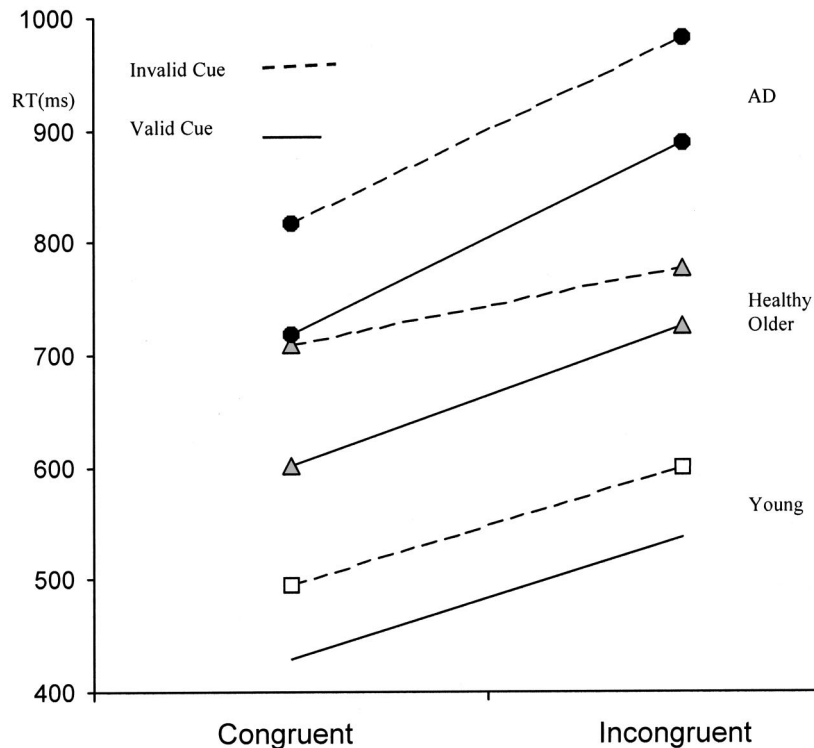


Figure 4. Orienting failed to enhance conflict resolution. For young adults and patients with Alzheimer's disease (AD), the congruency effect was as large for valid as for invalid trials; for healthy older adults, the congruency effect was larger for valid than for invalid trials. RT = reaction time.

ineffective in reducing the cost of incongruent information. We discuss these findings first. Later, we address group differences in the size of the alerting, congruency, and validity effects.

Interactions and Dissociations Among Attentional Networks Common to All Three Groups

It might be expected that a more alert state would enhance conflict resolution. If so, the increased congruency effect in alert trials could come as a surprise. However, that interaction is consistent with previous findings (Fan et al., 2002; Fernandez-Duque, 2006) and with a theory of alertness proposed by Posner (1978). That theory argues that warning signals do not enhance information processing but rather act by shifting the response criterion. As a consequence, warning signals lead to hasty decisions and fast responses with incomplete information. Thus, the theory predicts an increased number of errors following a warning cue, particularly in incongruent trials, a prediction fulfilled in our study. The claim that alerting acts by automatically shifting response criterion also receives support from event-related potential (ERP) studies. Data in such studies have shown that alertness modulates late components, such as the P300, but does not enhance earlier, perceptual components, such as the P1 and the N1 (Griffin, Minnissi, & Nobre, 2002).

The lack of interaction between validity and congruency may come as a surprise, too, as it might be expected that focused attention should help resolve conflict. However, previous studies have shown that spatial cuing does not affect congruency in the

Stroop task (Baldo, Shimamura, & Prinzmetal, 1998; Shalev & Algom, 2000), the spatial compatibility task (Ro, Machado, Kanwisher, & Rafal, 2002), or the flanker task (Fernandez-Duque, 2006). In all these tasks, target and distractor occur in the same location or in very close proximity. As a consequence, when spatial attention is focused on the target, it is also focused on the distractor, and when a target appears at an unattended location, so does the distractor. Therefore, the design of those paradigms biases spatial attention to enhance both target and distractor, leaving conflict unresolved. Consistent with this interpretation, when target and distractors are dissociated in space or when attention is focused only on the target, the congruency effect is greatly reduced by orienting (Fernandez-Duque, 2006; LaBerge, Brown, Carter, Bash, & Hartley, 1991; Van der Lubbe & Keuss, 2001). These behavioral studies converge with evidence from single neuron recording in primates, which shows that attention is most efficient when only the target is inside the neuron's receptive field (Desimone & Duncan, 1995).

Group Differences in Orienting, Alerting, and Congruency

All three groups of participants showed the same pattern of interactions and dissociations, which is evidence of continuity in the networks' trajectory through healthy aging and disease. On the other hand, the magnitude of the effects was different among groups.

The group differences in effect size cannot be fully explained by a single general factor, such as increased slowness caused by healthy aging and disease. Although overall RTs slowed down with healthy aging as well as with AD, the alerting effect became larger only with age, the congruency effect became larger only with pathology, and the validity effect remained unchanged. This pattern of results points to the existence of three distinct, albeit interactive, networks of attention: alerting, orienting, and conflict resolution.

Alerting

The alerting effect increased with age but not with AD. A possible interpretation of this finding is that older adults had difficulty sustaining attention and therefore benefited most from an external cue. However, this explanation is not supported by the literature on vigilance and aging. Under low cognitive demands, sustained attention is normal in healthy aging (Berardi et al., 2001), and a similar pattern of brain activation has been observed for older and young adults (Johansen, Jakobsen, Bruhn, & Gjedde, 1999).

A second, more likely interpretation of the increased alerting effect proposes that the older adults had normal sustained attention but adopted a more conservative criterion of response. The adoption of a more conservative response criterion by the older adults is supported by the error data, which show a congruency effect for young participants but not for healthy older participants, as if the older adults were allowing more time for resolving conflict. It is also consistent with studies on metacognition, which have demonstrated that older adults and AD patients, unlike younger adults, tend to underestimate their accuracy when predicting their performance in a conflict resolution task (Fernandez-Duque & Black, 2006b). By adopting an overall conservative criterion, older adults in both the healthy older and the AD groups stood to benefit most from a shift toward a liberal response criterion brought about by the alerting cue. In contrast, young adults with overall liberal response criteria could not afford to accelerate their responses after a warning signal because it would have entailed an increased risk of error, particularly when distractors were incongruent.

Congruency

Unlike the alerting effect, the congruency effect did not increase with age, but it did increase with AD. Although this effect might be explained by an overall slowness in response, the error data also show the same pattern. Together, these findings argue for a deficit in conflict resolution, consistent with the AD literature showing impairment in Stroop and antisaccade tasks (Currie, Ramsden, McArthur, & Maruff, 1991; Danckert et al., 1998; Spieler et al., 1996). On the other hand, the deficit observed in our study was small. Conflict resolution is only one of many components of executive attention, and it seems likely that other executive functions would be even more disrupted by AD than conflict resolution. For example, early AD patients are severely impaired in dual tasking and set switching (Baddeley et al., 2001). An important question for future research is whether the executive functions most impaired in AD are also the ones most dependent on working memory. For example, conflict resolution, which was mildly impaired in our study, seems unaffected by working memory de-

mands in young adults performing a task similar to the present one (Fernandez-Duque & Black, 2006a). In contrast, set switching and vigilance decrements are heavily dependent on memory load (Fernandez-Duque & Black, 2006a; Parasuraman, 1979), and early AD patients are particularly susceptible to those memory load modulations (Baddeley et al., 1999; Fernandez-Duque & Black, 2006a).

Validity

The validity effect was mostly unaffected in healthy older participants, consistent with previous findings showing that healthy aging spares automatic orienting and produces only modest effects in voluntary attention (Greenwood, Parasuraman, & Haxby, 1993; Hartley, Kieley, & Slabach, 1990). This result is also consistent with ERP studies showing, in older adults, a normal enhancement of P1/N1 components, an electrophysiological marker of attention (Curran, Hills, Patterson, & Strauss, 2001).

The validity effect also was mostly unaffected by AD. This was a departure from previous studies, which have shown impaired orienting in AD (Buck et al., 1997; Festa-Martino et al., 2004; Parasuraman et al., 1992). However, the orienting deficit in AD is not a universal finding and, when found, has been qualified by many factors, including the type of cue (central, peripheral), the type of task (detection, discrimination), the cue-target delay, and the severity of the disease. In fact, much of the research in AD and attention over the past 10 years has been devoted to disentangling the pattern of interactions among these variables.

Our study tested patients at a very early stage of the disease, unlike most of the other clinical studies, in which patients at more advanced stages were included (Buck et al., 1997; Oken et al., 1994; Parasuraman et al., 1992; but see Festa-Martino et al., 2004). Thus, disease severity may explain in part why our study yielded nonsignificant differences in orienting. However, disease severity alone is an unlikely explanation as significant orienting deficits have been reported in asymptomatic participants at genetic risk for AD (Greenwood et al., 2000). These were participants who performed normally in standard neuropsychological tests but carried the E4 allele of the apolipoprotein E, a genetic risk factor for AD. The validity effect in carriers of the E4 allele was 20 ms larger than in participants carrying alleles unrelated to AD. This finding suggests that mild deficits in orienting can be observed at very early stages of the disease.

There are several other candidate reasons why validity was normal for AD patients in the present study. One possibility is that our patients had an orienting deficit that was masked by our choice of peripheral cuing. We chose peripheral cuing rather than central cuing in an attempt to reduce cognitive load, minimize eye movements, and effectively manipulate the orienting system.² Although orienting deficits in AD have sometimes been reported for peripheral cuing (Buck et al., 1997; Festa-Martino et al., 2004), the AD deficit is most evident with central cues for the voluntary allocation of attention. When automatic orienting and voluntary orient-

² In a pilot study, we found that AD patients made many more eye movements to central cues than to peripheral cues. We were also concerned that the cognitive demands would increase disproportionately in AD patients when they were asked to hold in mind further instructions about how to use the central cue.

ing are pitted against each other in a task in which the target usually appears opposite to the cue, AD patients have trouble overriding the automatic cuing to take advantage of the probability information (Danckert et al., 1998; Maruff & Currie, 1995). Also, the automatic reorienting of attention is preserved at early stages of the disease, as revealed by normal inhibition of return (Danckert et al., 1998; Faust & Balota, 1997). Thus, it is possible that the absence of abnormal validity effects in the current study is due to the use of peripheral cuing.

Unlike most studies of covert orienting, the current study required vertical shifts of attention rather than horizontal ones. There are well-known hemispheric asymmetries in the orienting system of healthy adults (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000), stroke patients (Rafal, 1998), and AD patients (Buck et al., 1997; Maruff, Malone, & Currie, 1995; Parasuraman et al., 1992). Thus, it is conceivable that vertical shifts of attention exhibit a different profile in normal development and pathology than horizontal shifts (but see Buck et al., 1997). Also, stimuli in our task were larger than in most tasks in which a cuing or a flanker paradigm is used. Larger stimuli were necessary for minimizing eye movements and maximizing discrimination in peripheral vision, but they had the unintended consequence of easing perceptual discrimination, thus reducing the need for attention. It is possible that a more difficult discrimination task would have revealed group differences in orienting.

References

- Baddeley, A. D., Baddeley, H. A., Bucks, R. S., & Wilcock, G. K. (2001). Attentional control in Alzheimer's disease. *Brain*, *124*, 1492–1508.
- Baddeley, A. D., Cocchini, G., Della Sala, S., Logie, R. H., & Spinnler, H. (1999). Working memory and vigilance: Evidence from normal aging and Alzheimer's disease. *Brain & Cognition*, *41*, 87–108.
- Baldo, J. V., Shimamura, A. P., & Prinzmetal, W. (1998). Mapping symbols to response modalities: Interference effects on Stroop-like tasks. *Perception & Psychophysics*, *60*, 427–437.
- Berardi, A., Parasuraman, R., & Haxby, J. V. (2001). Overall vigilance and sustained attention decrements in healthy aging. *Experimental Aging Research*, *27*, 19–39.
- Buck, B. H., Black, S. E., Behrmann, M., Caldwell, C., & Bronskill, M. J. (1997). Spatial- and object-based attentional deficits in Alzheimer's disease: Relationship to HMPAO-SPECT measures of parietal perfusion. *Brain*, *120*, 1229–1244.
- Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary attention is dissociated from target detection in the human posterior parietal cortex. *Nature Neuroscience*, *3*, 292–297.
- Coslett, H. B., Stark, M., Rajaram, S., & Saffran, E. (1995). Narrowing the spotlight: A visual attentional disorder in presumed Alzheimer's disease. *Neurocase*, *1*, 305–318.
- Curran, T., Hills, A., Patterson, M. B., & Strauss, M. E. (2001). Effects of aging and visuospatial attention: An ERP study. *Neuropsychologia*, *39*, 288–301.
- Currie, J. N., Ramsden, B., McArthur, C., & Maruff, P. (1991). Validation of a clinical antisaccade eye movement test in the assessment of dementia. *Archives of Neurology*, *48*, 644–648.
- Danckert, J., Maruff, P., Crowe, S., & Currie, J. (1998). Inhibitory processes in covert orienting in patients with Alzheimer's disease. *Neuropsychology*, *12*, 225–241.
- Davidson, M. C., & Marrocco, R. T. (2000). Local infusion of scopolamine into intraparietal cortex alters covert orienting in rhesus monkeys. *Journal of Neurophysiology*, *83*, 1536–1549.
- Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, *18*, 193–222.
- Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*, 143–149.
- Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*, 340–347.
- Faust, M. E., & Balota, D. A. (1997). Inhibition of return and visuospatial attention in healthy older adults and individuals with dementia of the Alzheimer type. *Neuropsychology*, *11*, 13–29.
- Fernandez-Duque, D. (2006). *Attentional networks: How alerting, orienting, and zooming influence conflict resolution*. Manuscript in preparation.
- Fernandez-Duque, D., Baird, J. A., & Posner, M. I. (2000). Executive attention and metacognition. *Consciousness & Cognition*, *9*, 288–307.
- Fernandez-Duque, D., & Black, S. E. (2006a). *Dual task performance and working memory in mild cognitive impairment*. Manuscript in preparation.
- Fernandez-Duque, D., & Black, S. E. (2006b). *Metacognitive knowledge and feedback sensitivity in fronto-temporal dementia and dementia of the Alzheimer type*. Manuscript in preparation.
- Fernandez-Duque, D., & Posner, M. I. (1997). Relating the mechanisms of orienting and alerting. *Neuropsychologia*, *35*, 477–486.
- Fernandez-Duque, D., & Posner, M. I. (2001). Brain imaging of attentional networks in normal and pathological states. *Journal of Clinical and Experimental Neuropsychology*, *23*, 74–93.
- Festa-Martino, E., Ott, B. R., & Heindel, W. C. (2004). Interactions between phasic alerting and spatial orienting: Effects of normal aging and Alzheimer's disease. *Neuropsychologia*, *18*, 258–268.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 185–198.
- Greenwood, P. M., Parasuraman, R., & Haxby, J. V. (1993). Visuospatial attention across the adult lifespan. *Neuropsychologia*, *31*, 471–485.
- Greenwood, P. M., Sunderland, T., Friz, J., & Parasuraman, R. (2000). Genetics and visual attention: Selective deficits in healthy adult carriers of the E4 allele of the apolipoprotein E gene. *Proceedings of the National Academy of Science*, *97*, 11661–11666.
- Griffin, I. C., Miniussi, C., & Nobre, A. C. (2002). Multiple mechanisms of selective attention: Differential modulation of stimulus processing by attention to space or time. *Neuropsychologia*, *40*, 2325–2340.
- Hartley, A. A., Kieley, J. M., & Slabach, E. H. (1990). Age differences and similarities in the effects of cues and prompts. *Journal of Experimental Psychology: Human Perception and Performance*, *16*, 523–537.
- Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. G. Bower (Ed.), *The psychology of learning and motivation* (Vol. 22, pp. 193–225). San Diego, CA: Academic Press.
- Johansen, P., Jakobsen, J., Bruhn, P., & Gjedde, A. (1999). Cortical responses to sustained and divided attention in Alzheimer's disease. *NeuroImage*, *10*, 269–281.
- Köhler, S., Black, S. E., Sinden, M., Szekeley, C., Kidron, D., Parker, J. L., et al. (1998). Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: An MR volumetry study in Alzheimer's disease. *Neuropsychologia*, *36*, 901–914.
- LaBerge, D., Brown, V., Carter, M., Bash, D., & Hartley, A. (1991). Reducing the effects of adjacent distractors by narrowing attention. *Journal of Experimental Psychology: Human Perception and Performance*, *17*, 65–76.
- Levinoff, E. J. (2002). *Investigating the nature of selective attention impairments in patients with Alzheimer's disease: Relating structure to function*. Unpublished doctoral dissertation, McGill University, Montreal, Quebec, Canada.
- Maruff, P., & Currie, J. (1995). An attentional grasp reflex in patients with Alzheimer's disease. *Neuropsychologia*, *33*, 303–311.

- Maruff, P., Malone, V., & Currie, J. (1995). Asymmetries in the covert orienting of visual spatial attention to spatial and non-spatial cues in Alzheimer's disease. *Brain, 118*, 1421–1435.
- Mayr, U. (2001). Age differences in the selection of mental sets: The role of inhibition, stimulus ambiguity, and response-set overlap. *Psychology and Aging, 16*, 96–109.
- McKhann, G., Drachman, D., Folstein, M. F., Katzman, R., Price, D., & Stadlan, E. M. (1984). 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, 34*, 939–944.
- Nebes, R. D., & Brady, C. B. (1993). Phasic and tonic alertness in Alzheimer's disease. *Cortex, 29*, 77–90.
- Oken, B. S., Kishiyama, S. S., Kaye, J. A., & Howieson, D. B. (1994). Attention deficit in Alzheimer's disease is not simulated by an anticholinergic/antihistaminergic drug and is distinct from deficits in healthy aging. *Neurology, 44*, 657–662.
- Parasuraman, R. (1979, August 31). Memory load and event rate control sensitivity decrements in sustained attention. *Science, 205*, 924–927.
- Parasuraman, R., Greenwood, P. M., & Alexander, G. E. (2000). Alzheimer disease constricts the dynamic range of spatial attention in visual search. *Neuropsychologia, 38*, 1126–1135.
- Parasuraman, R., Greenwood, P. M., Haxby, J. B., & Grady, C. L. (1992). Visuospatial attention in dementia of the Alzheimer type. *Brain, 115*, 711–733.
- Parasuraman, R., Greenwood, P. M., & Sunderland, T. (2002). The apolipoprotein E gene, attention, and brain function. *Neuropsychology, 16*, 254–274.
- Posner, M. I. (1978). *Chronometric explorations of mind: The third Paul M. Fitts lectures, delivered at the University of Michigan, September 1976*. Hillsdale, NJ: Erlbaum.
- Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology, 32*, 3–25.
- Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25–42.
- Prinzmetal, W., McCool, C., & Park, S. (2005). Attention: Reaction time and accuracy reveal different mechanisms. *Journal of Experimental Psychology: General, 134*, 73–92.
- Rafal, R. (1998). Neglect. In R. Parasuraman (Ed.), *The attentive brain* (pp. 711–733). Cambridge, MA: MIT Press.
- Rizzo, M., Anderson, S. W., Dawson, J., Myers, R., & Ball, K. (2000). Visual attention impairments in Alzheimer's disease. *Neurology, 54*, 1954–1959.
- Ro, T., Machado, L., Kanwisher, N., & Rafal, R. D. (2002). Covert orienting to the locations of targets and distractors: Effects of response channel activation in a flanker task. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 55(A)*, 917–936.
- Shalev, L., & Algom, D. (2000). Stroop and Garner effects in and out of Posner's beam: Reconciling two conceptions of selective attention. *Journal of Experimental Psychology: Human Perception and Performance, 26*, 997–1017.
- Spieler, D. H., Balota, D. A., & Faust, M. E. (1996). Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *Journal of Experimental Psychology: Human Perception and Performance, 22*, 461–479.
- Tales, A., Muir, J. L., Bayer, A., Jones, R., & Snowden, R. J. (2002). Phasic visual alertness in Alzheimer's disease and ageing. *NeuroReport, 13*, 1–4.
- Tales, A., Muir, J. L., Bayer, A., & Snowden, R. J. (2002). Spatial shifts in visual attention in normal ageing and dementia of the Alzheimer type. *Neuropsychologia, 40*, 2000–2012.
- Van der Lubbe, R. H., & Keuss, P. J. (2001). Focused attention reduces the effect of lateral interference in multi-element arrays. *Psychological Research, 65*, 107–118.
- Voytko, M. L. (1996). Cognitive function of the basal forebrain cholinergic system in monkeys: Memory or attention? *Behavioural Brain Research, 75*, 13–25.
- Whitehouse, P., Price, D., Struble, R., Clark, A., Coyle, J., & DeLong, M. (1982, March 5). Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. *Science, 215*, 1237–1239.
- Winer, B. J. (1971). *Statistical principles in experimental design* (2nd ed.). New York: McGraw-Hill.

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