Alerting and Orienting in Alzheimer’s Disease

Andrea Tales
University of Bristol

Robert J. Snowden
Cardiff University

Michelle Brown and Gordon Wilcock
University of Bristol

Recently, researchers (E. Festa-Martino, B. R. Ott, & W. C. Heindel, 2004; A. Tales, J. L. Muir, A. Bayer, R. Jones, & R. J. Snowden, 2002; A. Tales, J. L. Muir, A. Bayer, & R. J. Snowden, 2002) have found significantly abnormal spatial orienting together with the abolishment of the alerting effect in Alzheimer’s disease (AD). However, these research groups differed in their interpretation of the results. A. Tales, J. L. Muir, A. Bayer, R. Jones, and R. J. Snowden (2002) and A. Tales, J. L. Muir, A. Bayer, and R. J. Snowden (2002) explained their data in terms of two independent processes, whereas E. Festa-Martino et al. (2004) interpreted their findings as indicative of an inverse association, namely that the increased spatial orienting effect in AD was the direct result of the abolition of the phasic alerting effect. In this further study examining exogenous spatial orienting and phasic alerting, the authors present evidence to suggest that the increased spatial orienting effect in AD is not the result of a decreased phasic alerting effect.

Keywords: visual attention, Alzheimer’s disease, alerting, orienting

As a result of the brain’s limited processing resources, not all of the information contained within the visual environment can be selected in parallel for priority or high-level processing (Posner, 1980). Instead, attention has to be sequentially shifted to, and focused on, specific regions of interest to select stimuli for such further processing. The focus of attention can be shifted to a region of interest at will (endogenously, with conscious intent) or automatically (exogenously) in response to properties of the stimulus itself or to a cue that signals its subsequent appearance. Importantly, exogenous attentional capture allows the brain to be apprised of potentially significant events that are not the current focus of attention (e.g., Näätänen, 1992). A popular method for assessing such processing is the spatial-cueing paradigm introduced by Posner (1980).

In the spatial-cueing task, the participant responds to a target that can occur at one of two locations on either side of a fixation mark. Prior to the appearance of the target, a visual cue appears at one of these locations so that attention may be focused at this locus in advance of the target. It is commonly found that at short intervals between the appearance of the cue and that of the target, the response to the target is speeded when it subsequently appears at the same location as the cue compared with when it appears on the opposite location. The difference in reaction time (RT) between these respectively valid and invalidly cued target responses is known as the validity effect or the spatial orienting effect and is generally regarded as representing the extra time needed to disengage and shift attention to the location of the target from its incorrectly cued position.

However, the cues not only denote the possible location of the target but also signal that the target is imminent. The results from numerous studies have indicated that even if the cue does not provide any information about the location of the target (i.e., when it is spatially neutral), it can still enhance the processing of the target stimulus via a phasic increase in alertness (Fernandez-Duque & Posner, 1997), which we shall term the phasic alerting effect.

Given the importance of spatial orienting and phasic alerting in the processing of external stimuli and their relevance for appropriate environmental interaction, it is not surprising that this paradigm has been used to investigate the functional integrity of these processes in those individuals with Alzheimer’s disease (AD). However, in the domain of spatial orienting, the outcomes of such studies have been equivocal in terms of whether individuals with AD exhibit significant deficits in such processing (e.g., see Buck, Black, Behrmann, Caldwell, & Bronski, 1997; Caffara, Riggio, Malvezzi, Scaglioni, & Freedman, 1997; Danckert, Maruff, Crowe, & Currie, 1998; Faust & Balota, 1997; Maruff & Currie, 1995; Maruff, Malone, & Currie, 1995; Oken, Kishiyama, Kaye, & Howieson, 1994; Parasuraman, Greenwood, Haxby, & Grady, 1992). A potential cause of such heterogeneity—discussed in detail by Tales, Muir, Bayer, Jones, and Snowden (2002) and Festa-Martino, Ott, and Heindel (2004)—is the blurring of the distinction in these studies between exogenous and endogenous attention. The majority of previous studies failed to obtain a “pure” measure of the exogenous system (as described by Festa-Martino et al., 2004; Tales, Muir, Bayer, Jones, & Snowden, 2002). However in a rare outbreak of agreement, two laboratories have recently reported very similar patterns of results. Tales, Muir, Bayer, Jones, and Snowden (2002) demonstrated that the spatial aspect of an exogenous cue that precedes the presentation of a target pro-
duces a much larger spatial orienting effect for patients with AD compared with either healthy older or younger controls. For endogenous cues, no such AD-related change in performance was found. Festa-Martino et al. (2004) performed a very similar experiment using only exogenous cues and reported exactly the same pattern of results for this condition. Tales, Muir, Bayer, and Snowden (2002) also tested for any changes in the phasic alerting effect in AD. They have shown that this phasic alerting effect (the faster performance in trials with both locations cued compared with those with no cue) was present in young and old controls but was abolished in patients with AD. Festa-Martino et al. (2004) also included such trials and once again provided a replication of this abolition of the phasic alerting effect in patients with AD (although they appeared to have been unaware of the previous work of Tales, Muir, Bayer, & Snowden, 2002, in this area).

Therefore, the two laboratories are in agreement that the spatial orienting effect elicited in response to an exogenous cue is exaggerated more in patients with AD compared with healthy controls and that the phasic alerting effects of the cue are abolished. However, they do not agree on the interpretation of the results. Tales, Muir, Bayer, Jones, and Snowden (2002) and Tales, Muir, Bayer, and Snowden (2002) interpreted their data in terms of two independent processes—a spatial orienting effect that is underpinned primarily by cholinergic function and a phasic alerting effect underpinned by primarily noradrenergic function, both of which are dysfunctional in AD. However, Festa-Martino et al. (2004) interpreted their data as indicating “relatively intact exogenous orienting” (p. 265). They posited an inverse association between the two systems. They have suggested that the enhancement of sensory processing can be mediated by phasic alerting and exogenous orienting but that under normal conditions sensory processing is maximally enhanced through phasic alerting with little or no additional benefit obtained from exogenous orienting (i.e., from the valid cue). According to this viewpoint, as the sensory enhancement from phasic alerting decreases as a result of AD, the valid cue is then able to provide a benefit in sensory processing that increases as the contribution from phasic alerting decreases (see Festa-Martino et al., 2004, p. 264). They have argued, therefore, that the increased spatial orienting effect in AD is due not to an increased deficit in disengaging attention from invalidly cued targets (as suggested by Tales, Muir, Bayer, Jones, & Snowden, 2002, for example) but to an increased benefit of validly cued targets that is the direct result of the AD-related decrease in the phasic alerting benefit provided by these cues (Festa-Martino et al., 2004, p. 265).

To make such a prediction, Festa-Martino et al. (2004) had to assume the basic tenet that changes in phasic alerting would somehow affect valid cues more than invalid cues (i.e., it selectively speeds RT to the valid but not the invalid or neutral cues). However, the same phasic alerting effect is also present on invalid trials; indeed, changes in levels of phasic alerting would be expected to alter RTs for all trials that have a cue (i.e., valid, invalid, and neutral; see Fernandez-Duque & Posner, 1997). Thus, one would not predict a change in the spatial orienting effect per se, and so this argument in itself may be invalid.

One might attempt to save the explanation of Festa-Martino et al. (2004) by appealing to the fact that the judgment of the target at the invalid location takes place a little later (50–100 ms) than at the valid location, and therefore the effect of the phasic alerting might have dissipated, but this seems to stretch probability. It is also worth noting that Tales, Muir, Bayer, Jones, and Snowden (2002) showed the same pattern of results for spatial orienting in both detection and discrimination tasks with average RTs that are quite different (see also Fernandez-Duque & Posner, 1997).

In addition, Festa-Martino et al. (2004) based their findings and theory on a cost benefit analysis of their data and have stated that failing to perform such analysis (as did Tales, Muir, Bayer, Jones, & Snowden, 2002) results in misinterpretation of the data. However, although Festa-Martino et al. (2004) are quite right in pointing out that the results of Tales, Muir, Bayer, Jones, and Snowden (2002)—namely, the increased AD-related spatial orienting effect—cannot distinguish between increased costs because of invalid trials or increased benefits on valid trials (in relation to spatially neutral trials) because no cost benefit analysis was performed, one has to question the validity of using such data partition in his or her study. The problems regarding the interpretation of costs and benefits have been previously noted (Jonides & Mack, 1984).

The rationale of cost benefit analysis hinges on a critical assumption, namely, that spatially neutral and spatially informative cues must be identical with respect to all their effects except that of the spatial information they contain (Jonides & Mack, 1984). Festa-Martino et al. (2004), however, performed a cost benefit analysis using spatially neutral cues in which the alerting component may not have been representative of that of the spatial cues. In Festa-Martino et al’s study, both the valid and invalid cues were in the form of a single black square outline, whereas the spatially neutral cue was represented by two such figures. In the absence of information about the relationship between the pattern and extent of retinal stimulation and the elicitation and the magnitude of the alerting response, one has to question whether the critical assumption that the spatially neutral and spatially informative cues are identical with respect to their alerting components and, thus, effects has been violated in their study. When such an assumption cannot be met, then although the magnitude of the spatial orienting effect remains the same, its interpretation—which is based on cost benefit analysis—can vary in relation to whether the alerting component of the spatial cue is under- or overestimated by the neutral cue leading therefore to the possibility of under- or overestimating the cost and benefits involved.

In addition, although Festa-Martino et al. (2004) have provided an overview of information in support of their proposed inverse relationship between phasic alerting and spatial cueing, this inverse associate notion is also challenged by experiments in which phasic alerting or spatial orienting is affected by some manipulation but the other system appears not to change. For example, pharmacological manipulation of the cholinergic system has shown changes in phasic alerting without changes in spatial orienting (Witte & Marrocco, 1997). In addition, Fernandez-Duque and Posner (1997) have shown that the spatial orienting effect remains the same despite manipulation of the state of phasic alertness of the normal human observer. More recently, the Attention Network Test has been developed to simultaneously measure spatial orienting, phasic alerting, and executive control. Using this test, Fan, McCandliss, Sommer, Raz, and Posner (2002) have shown that there are no significant correlations between spatial orienting and phasic alerting (see also Callejas, Lupiáñez, & Tudela, 2004; Fossella, Posner, Fan, Swanson, & Pfaff, 2002)—a
finding supportive of their independence. Indeed, brain activity measures while performing the Attention Network Test show quite separately brain activity related to spatial orienting (parietal lobe and frontal eye fields) compared with phasic alerting (thalamic activations and activations of posterior and anterior cortical sites). These studies are in broad agreement with previous studies that have measured orienting and alerting in isolation (Sturm & Willmes, 2001; Thiel, Zilles, & Fink, 2004).

If Festa-Martino et al.’s (2004) supposition is true, then irrespective of a cost benefit analysis, a decrease in the magnitude of the alerting effect in AD compared with older adults should be accompanied by an increase in the magnitude of the AD-related spatial orienting effect. In the current study, we further investigated the dependence or independence of the spatial orienting and the phasic alerting effects in patients with AD and in age-matched healthy controls.

The participant’s task was to indicate the orientation of the target bar (vertical or horizontal) by pressing one of two keyboard buttons. The orientation of the target was independent of the location of the cue or the location of the target. Thus, this was a discrimination task rather than the detection task that we have used in our previous alerting-related published studies (Tales, Muir, Bayer, & Snowden, 2002; Tales, Snowden, Haworth, & Wilcock, 2005). We used a discrimination task to (a) investigate whether our previous finding that used a detection task in a combined study of phasic alerting and spatial orienting would generalize across discrimination tasks; (b) repeat the conditions used by Festa-Martino et al. (2004), that is, the use of a discrimination task; (c) attempt to elicit greater spatial orienting effects with this task (Snowden, Willey, & Muir, 2001; Tales, Muir, Bayer, & Snowden, 2002), thus creating a more sensitive assay of the relationship between orienting and phasic alerting effects; and (d) maximize differences in the spatial orienting effects between old and AD patients (Perry & Hodges, 1999; Tales, Muir, Bayer, & Snowden, 2002). We note that Festa-Martino et al. (2004) used a task in which a discrimination was required (whether the target was located to the left or right); however, this task appears to confound the nature of the discrimination (left vs. right) with the location of the cue and thus is maybe more akin to the classic Simon effect (e.g., Lupiáñez, Milán, Tornay, Madrid, & Tudela, 1997) than to spatial orienting (for criticisms of this method, see Spence & Driver, 1996). The design of the current discrimination task enables the true effect of a discriminatory task requirement on spatial orienting and phasic alerting to be assessed.

Method

All stimuli were presented on a Toshiba (Weybridge, Surrey, England) SatellitePro laptop computer that was viewed from a distance of 57 cm. The presentation of the stimuli and recording of the responses were achieved via the SuperLab (Cedrus Corporation, San Pedro, CA) software. The target stimuli were horizontal or vertical lines 10 mm in length and 1 mm in width. The target stimuli were presented for 60 mm on either side of a small fixation cross, located at the center of the screen. The visual cues consisted of four small squares that defined a larger square. The small squares had a 3-mm side and defined a larger square of a 26-mm side: the width of the lines was 0.25 mm. The larger square was centered 60 mm horizontally from the fixation cross (two lines that were 7 mm long with a width of 0.5 mm).

Each trial commenced with the presentation of the fixation mark (the central cross) that was 1,000 ms in duration. The cue was then presented and remained on screen for the rest of the duration of the trial. The target stimulus was presented either 200 ms or 400 ms after the onset of the cue. We used this range of cue–target onset asynchronies (CTOAs) to span the duration over which an exogenous cue could be expected to produce a spatial orienting effect (greater CTOAs produce inhibition of return; see Klein, 2000). The target remained on screen until a response was made. The participant was required to respond to the vertical and horizontal target orientations using different keys on the response pad and was instructed to return his or her eyes to the center cross in preparation for the next stimulus. The experimenter monitored the participant’s eyes to ensure that they returned to the center cross, that is, that the eyes started in this position for each trial. This was achieved by an experimenter sitting opposite the participant and marking any trials in which the eyes failed to return to the center cross. Each type of trial (valid, invalid, neutral, and no cue) was presented 20 times at each of the CTOAs for a total of 160 trials. Trial order was randomized.

Participants

The diagnosis of AD was based on neurological, physical, and biochemical examination, including the integrity of daily living skills, neuropsychological testing, family interview and detailed history, psychiatric interview, and neuropsychological testing according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994) and to the National Institute of Neurological and Communicable Disease and Stroke–Alzheimer’s Disease and Related Disorders Association’s guidelines (McKhann et al., 1984). The individuals with AD were recruited on a consecutive incident patient basis from the Bristol Memory Disorders Clinic (Bristol, England). A total of 15 patients with AD were recruited; 7 were men, and 8 were women, with a mean age of 72.9 years (SD = 7.7) and a mean Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) score of 23.5 (SD = 3.0).

The healthy older adult control group consisted of 15 individuals (6 men, 9 women), with a mean age of 74.6 years (SD = 7.5). The participants were recruited from the healthy volunteer participant panel at the Bristol Memory Disorders Clinic (Bristol, England). They scored well within the normal range on the same neuropsychological battery used in the clinic to diagnose AD and had no significant medical or physical disorder (as assessed by the clinic physician) likely to affect the study outcome. Although medication could not be controlled in any of the groups, none of the participants were receiving medication deemed likely to affect cognitive function, and none of the AD patients were receiving medical treatment for the disorder. All participants had normal or corrected-to-normal vision. All those recruited took part, and all those taking part successfully completed all the tasks to a level that enabled their inclusion within the statistical analysis. There was no difference in the mean age of the AD and older adult control groups, t(28) = 0.6, p ≥ .05, and there was equality of variance of age for each group (Levene’s test p = .8). There was no difference in the mean years of educational attainment between the two groups, t(28) = 1.7, p > .05, and there was equality of variance of education for each group (Levene’s test p = .6). All participants gave written informed consent, and the research protocol was approved by the local research ethics committee.

Data Analysis

After initial visual inspection of the RT data, scores less than 150 ms were eliminated as anticipatory, and scores greater than 1,500 were elim-
inated because they were attributed to lapses of concentration. Trials in which obvious distraction and in which the eyes were not focused on the central cross at the beginning of a trial were also excluded from analysis. From the remaining RTs, the median score for each condition for each group was determined, and any errors were recorded. All had to have a minimum of 75% correct scores to be included in the data analysis.

Results

Spatial Orienting Effect

Our initial aim was to perform a 2 (cue: valid vs. invalid) × 2 (CTOA: 200 vs. 400) × 2 (group: old vs. AD) analysis of variance (ANOVA) on the data, but because of the greater variance in the data of the AD group, the conditions for ANOVA could not be achieved (nor did any transformation produce acceptable conditions). Therefore, we first established that a spatial orienting effect did occur—this was indeed the case, t(59) = 5.92, p < .001. We then calculated the spatial orienting effect (i.e., the difference between a valid and an invalid cue), which is displayed as a function of group and CTOA as the hatched bars in Figure 1. The spatial orienting effect data were suitable for ANOVA. A 2 (CTOA: 200 vs. 400) × 2 (group: old vs. AD) ANOVA showed a much greater spatial orienting effect for the AD patients than the older controls, F(1, 56) = 15.20, p < .001, d = 1.02, but no effect of CTOA (F < 1) or interaction (F < 1).

Phasic Alerting Effect

We first established that a phasic alerting effect did occur—this was indeed the case, t(59) = 2.15, p < .05. We then calculated a phasic alerting effect (i.e., the difference between a no cue and a neutral cue), and these data are displayed as the solid bars in Figure 1. A 2 (CTOA: 200 vs. 400) × 2 (group: old vs. AD) ANOVA showed no effect of group (F < 1), and there was not any effect of CTOA (F < 1) or interaction (F < 1). We therefore have shown that AD patients can show a much greater spatial orienting effect than the older control group while having a phasic alerting effect that is the same as this control group.

Discussion

We have found, using a discrimination task, that patients with AD can have far greater spatial orienting effects than age-matched controls and that this specific AD-related increase in spatial orienting effect can occur under conditions in which the phasic alerting effect is the same in both the AD and older adult control groups. This pattern of results indicates that the greatly increased magnitude of the validity effect in AD compared with normal aging appears not to be dependent simply on the greater reduction in the magnitude of the phasic alerting effect in AD as suggested by Festa-Martino et al. (2004). Our current study does not appear to uphold Festa-Martino et al’s argument for an inverse relationship between the magnitude of the phasic alerting effect and that of the spatial orienting effect. These results instead support the view that the two effects are independent or that a far more complex relationship or mediation of the phasic alerting and spatial orienting effects exists than that which can be explained by a straightforward inverse relationship between the two systems.

In our previous alerting studies that used a CTOA of 200 ms and a detection task (Tales, Muir, Bayer, & Snowden, 2002; Tales et al., 2005), there was a significant difference in the phasic alerting effect between the old and AD groups; that is, the effect was significantly greater for the old group. In the current study, which used a discrimination task, there was no significant difference in the magnitude of the phasic alerting effect between the two groups. Although there is a paucity of data in the literature on the phasic alerting effect in the normal population on which to draw, we note that differences in spatial orienting outcome have been noted between task requirements, namely, target detection and discrimination (Brawn & Snowden, 2000) and for inhibition of return (Lupiáñez et al., 1997).

In a recent study examining the effect of methodological practice on study outcome in both spatial orienting and phasic alerting in ageing and mild cognitive impairment, we have found no mild-cognitive-impairment-related reduction in the magnitude of phasic alerting at a 200-ms cue to target interval when a discrimination task was required (cf. Tales et al., 2005). This pattern of results supports the findings of a lack of a phasic alerting deficit in the current study. However, the lack of an alerting deficit in the current study is at odds with the finding of Festa-Martino et al. (2004), who obtained a significant AD-related phasic alerting deficit in response to a discrimination task. It may be the case, as pointed out previously, that their task confounded the nature of the discrimination (left vs. right) with the location of the cue and therefore that their outcome may not be a true representation of the spatial orienting effect. Alternatively, the equivocal nature of alerting study outcome may indicate that the phasic alerting effect is highly sensitive to methodological practice. Any apparent inverse relationship between spatial orienting and phasic alerting may therefore be the result of methodological, analysis, and participant-related factors; therefore, further work is needed to understand the nature of the task on the phasic alerting effect in both healthy controls and AD patients.

**Figure 1.** The cueing effect is displayed as a function of group and cue–target onset asynchrony. Error bars represent plus or minus one standard error of the mean. AD = Alzheimer’s disease.
References


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