Research report

Exogenous phasic alerting and spatial orienting in mild cognitive impairment compared to healthy ageing: Study outcome is related to target response

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ABSTRACT

Whether or not attentional mechanisms such as phasic alerting, spatial cueing and inhibition of return (IOR) remain intact in adults with Alzheimer’s disease (AD) and mild cognitive impairment (MCI) remains a matter of debate. This is possibly the result of inter-study outcome variation caused by the adoption of different methodological components by different research groups. Here we investigated the influence of methodological factors upon study outcome, using a Posner-type exogenous cueing paradigm with amnestic MCI patients and healthy older controls. Specifically, we compared results when the required response involved target discrimination with results for a simple target detection response, using cue-to-target intervals (CTIs) of 200 msec and 800 msec in each case and with the same participants completing all conditions.

For both groups, the presence or absence of both alerting and spatial cue-related effects depended upon the combination of target response requirement and CTI. Moreover, differences between the groups were specific to certain task conditions. The MCI group showed the same alerting effects as healthy people with a discrimination response, but the alerting effect shown by controls with a 200 msec CTI and target detection was absent in MCI. Patients and controls showed similar spatial cue validity effects at 200 msec CTI, but group differences emerged at 800 msec CTI: target discrimination evoked a validity effect in the MCI group only, while target detection evoked an IOR effect in the healthy group only. These data indicate that detection and discrimination responses may each activate different attentional mechanisms, which are themselves differentially vulnerable in MCI.
1. Introduction

Alzheimer’s disease (AD) is often preceded by a prodromal phase characterised by a varying period of mild cognitive impairment (MCI) (Morris et al., 2001; Petersen et al., 2001). However, not all individuals with symptoms of MCI develop AD as it can represent also the outer limits for function in healthy ageing and occur transitorily or permanently as the result of a variety of clinical conditions. The challenge is therefore to find specific abnormalities in MCI that occur only in those individuals for whom it represents the very earliest stages of AD. As AD is traditionally characterised and diagnosed in relation to abnormalities in memory, MCI has also tended to be studied primarily in relation to the integrity of such function (so-called amnesic MCI, Petersen et al., 1999). It appears however that tests of such function may lack the sensitivity and specificity necessary to differentiate MCI from healthy ageing and to determine for whom MCI represents the early stages of AD on an individual patient basis. Furthermore, multiple subtypes of MCI are now recognized with presentations featuring symptoms in cognitive domains other than solely memory (Petersen and Negash, 2008). Thus it is necessary to search for additional and specific MCI and AD-related functional abnormalities.

An aspect of brain function of potential importance in this respect is that of visual attention (Fernandez-Duque and Black, 2006; Parasuraman and Greenwood, 2004). This is mediated by a widespread network of neuroanatomical structures including regions of the parietal and frontal lobes commonly affected by AD-related pathology (e.g., Fan et al., 2007; Fernandez-Duque and Black, 2006; Braak and Braak, 1991; Perry and Hodges, 1999; Posner and Petersen, 1990). Furthermore, as acetylcholine (ACh), which is related to the control of visuospatial attention in some of these regions, is depleted in AD, one would expect to observe AD-related deficits in such function (e.g., Bentley et al., 2008, 2003; Nobili and Sannita, 1997). Indeed this prediction was initially made several years ago by various research groups and examined using a range of Posner-based exogenous and endogenous cueing paradigms (Posner, 1980). The results of early studies were encouraging in that they revealed significant AD-related deficits compared to healthy ageing, but study proliferation revealed variation in study outcome, with visuospatial attention reported to be abnormal in some and spared in others; for example, see Parasuraman et al. (1992), Parasuraman and Haxby (1993), Danckert et al. (1998), Tales et al. (2002a, 2005, 2006); Festa-Martino et al. (2004), Perry and Hodges (1999), Parasuraman and Greenwood (2004), Festa et al. (2006), Tales and Snowdon (2006) and Fernandez-Duque and Black (2006).

The equivocal nature of the outcome of such studies may appear to render useless the clinical application of such findings in relation to understanding the disease process and its signs and symptoms and in the search for early disease markers. However, in interpreting the results from such studies one must consider the possibility that although purporting to measure a particular aspect of visuospatial attention, their methodological variability makes it likely that they evoke slightly or even significantly different aspects of this function, each of which may be differentially sensitive to the presence of AD. For example, in relation to the early studies, Perry and Hodges (1999) suggested that outcome variability may be the result of whether attention was cued exogenously (automatically) or endogenously (at will). In a subsequent study, in which exogenous and endogenous effects were carefully separated, the data suggested significant AD-related abnormality in exogenous but not endogenous cueing (Tales et al., 2002a), namely preservation of the voluntary (strategic) but not the involuntary orientation mechanism respectively (Prinzmetal et al., 2005, 2009; Esterman et al., 2008).

Further variation in methodological factors such as whether the required target response is one of detection or discrimination (Perry and Hodges, 1999; Brawn and Snowdon, 2000; Prinzmetal et al., 2009), the magnitude of the cue-to-target interval (Cti) (Maruff et al., 1999), the number of trials and the nature of the stimuli themselves (Fernandez-Duque and Black, 2006), may also contribute to the equivocal outcomes of such studies. Arguably, outcome variability in response to the controlled manipulation of methodological variables should be exploited as it may reveal not only specific disease-related abnormality but the particular attention-related environmental conditions under which the detrimental effects of MCI or AD are exacerbated. This would be expected to augment current knowledge about the potential underlying cause of some of the signs, symptoms and behavioural abnormalities of the AD process. Such information is an important factor in the design of appropriate care environments for individuals with AD (Jones and van der Eerden, 2008). Furthermore, such studies may inform the design of future clinically-related research by revealing the experimental conditions under which maximum differentiation between healthy ageing and AD or MCI occurs. Adopting this approach we have examined visuospatial attention-related function, namely attentional disengagement and inhibition of return (IOR), in AD, MCI and healthy ageing, using various adaptations of the Posner-based exogenous cueing technique.

1.1. Exogenous cueing

Combined with a simple target detection task, exogenous cueing permits the study of two important components of visuospatial function: attentional disengagement and IOR. In a typical task the participant is asked to respond as fast as and as accurately as possible to a target which can appear on either side of a central fixation point. Prior to the appearance of the target,
a ‘spatial cue’, designed to attract attention, is presented at one of the two potential target locations. The cue can either be valid, in which it correctly informs the location of the subsequent target, or invalid, in which it directs attention to the location opposite to that of the subsequent target. In general, at short CTIs of around 200 msec, invalid cueing results in an increased target reaction time (RT) compared to that in response to valid cueing, as attention has to be disengaged and shifted from the incorrect to the correct target location. The difference in RT between invalidly and validly cued targets \((\text{IVRT} - \text{VRT})\) is known as the validity or spatial cueing effect. Increasing the CTI to around 800 msec results in a reversal of this cueing effect, namely response to invalidly is more rapid than that to validly cued targets. This IOR effect represents the operation of a mechanism to bias attention towards potentially important novel locations and away from a recently attended region (Posner and Cohen, 1984; Klein, 2000).

Our combination of exogenous cueing and simple target detection has revealed both significantly abnormal validity and IOR effects in AD compared to healthy ageing (Tales et al., 2002a, 2005) with the older adult group displaying no validity effect but a significant IOR effect while the AD group display a significant validity effect but no IOR effect. Furthermore, although IOR was found to be preserved in MCI (Tales et al., 2005) patients with MCI differed from controls in showing a significant validity effect at a level similar to that found in AD. This study outcome indicated that at least some proportion of the MCI group exhibited attentional disengagement-related deficits closely resembling those evident in well-established AD (Tales et al., 2005, 2002a). This provided evidence indicative of the possibility that amnestic MCI is not simply a ‘memory-related disorder (see Perry and Hodges, 2003) and also highlighted the possibility that other brain abnormalities could contribute to its signs and symptoms.

Compared to simple target detection, target discrimination demands additional and more complex processing and response strategies. It has been suggested that if such complex processing is detrimentally affected by AD, the use of a discrimination task should elicit a disproportionate decrement of visual attention-related performance in relation to healthy ageing, compared to that revealed by a simple detection task (e.g., Prozzolo et al., 1981; Parasuraman et al., 1992; Pate et al., 1994; Maruff et al., 1999; Perry and Hodges, 1999; Foldi et al., 2002; Parasuraman and Greenwood, 2004; Tales et al., 2002a, see also Pate et al., 1994). On the basis of such supposition it would seem sensible to employ discrimination tasks in our exogenous cueing studies in order to increase the differentiation between healthy ageing and AD, thus increasing their potential clinical utility.

A paucity of robust experimental evidence exists in relation to the effects of target detection and discrimination in relation to exogenous cueing study outcome. This is because previous studies have tended to measure either target detection or discrimination and inter-study variation in a variety of methodological factors and participant group characteristics renders direct outcome comparison inappropriate. In a previous study, although we attempted to examine performance in relation to both target detection and discrimination, the inability of some individuals with AD to perform discriminatory responses precluded direct statistical comparison between the two conditions (Tales et al., 2002a). This highlighted a potential problem with the use of target discrimination tasks in the measurement of attention-related function in AD. Although the discriminatory response was expected in theory to produce a disproportionately greater spatial attention deficit in AD compared to simple target detection, in practice any such effects can be obscured simply by an inability to perform the more complex task.

In subsequent studies an abnormal validity effect in AD has been demonstrated under both target detection and discrimination conditions (Tales et al., 2002a, 2005, 2006; Festa-Martino et al., 2004; Tales and Snowden, 2006; Festa et al., 2006). However in contrast, a study by Fernandez-Duque and Black (2006) using a modified version of the Attentional Network Test (ANT, which allows the concurrent assessment of orienting, alerting and executive function) (Fan et al., 2002) using target discrimination, revealed a validity effect that was mostly unaffected by AD. In response to this outcome, Fernandez-Duque and Black (2006) also suggested that other factors such as their type of cueing (peripheral as opposed to central) may account for the discrepancy with previous studies, although further evidence also indicates that significant abnormality in the validity effect can be revealed in AD using exogenous/peripheral cueing (Tales et al., 2002a, 2002b, 2005). Fernandez-Duque and Black (2006) also highlight other potential sources of study outcome variability such as whether horizontal or vertical shifts of attention are required and the size of the stimuli employed. Here is further evidence therefore in support of the idea that study methodology can impact significantly upon the outcome of studies examining visual attention-related processing in AD.

In subsequent application of our simple target detection task to the measure of visual attention-related function in MCI revealed a large and statistically significant validity effect (Tales et al., 2005) compared to the negligible validity effect seen in healthy ageing; an effect mirroring that observed in probable AD (Tales et al., 2002a, 2005). As a result of the problems encountered in the use of a discrimination task in individuals with AD (Tales et al., 2002a) we decided not to use such a task in our MCI study. In retrospect we consider the possibility that, unlike the individuals with AD, those with MCI retain the ability to perform a discrimination task at a level necessary for inclusion in statistical analysis. Memory and cognitive deficits are not as severe in this disorder as in AD and neither do these individuals have dementia. We thus question whether the use of a discrimination task would have influenced the outcome of such a study. Furthermore, different aspects of spatial attention appear to be variably contingent upon whether a target detection or discrimination task is used. This is highlighted in spatial cueing where the change from the validity to an IOR effect emerges at longer CTIs for discrimination compared to detection tasks (Van Der Lubbe et al., 2005; Lupiánez et al., 2001; Chica et al., 2006) and
where IOR can show differential age and AD-related vulnerabilities depending upon task and timing characteristics (Langley et al., 2001; Faust and Balota, 1997). The relationship between task (detection and discrimination) and CTI is therefore likely to be complex and it is possible that varying combinations of such factors affect the outcome and thus clinical utility of studies measuring spatial cueing in healthy ageing and MCI.

In the present study we administer both target detection and discrimination versions of the exogenous cueing paradigm to a single group of older adult controls and a single group of patients with MCI in order to determine the impact of this factor upon study outcome, namely the pattern of the response to spatial cues for both groups and whether significant group differentiation is achieved.

1.2. Phasic alerting

In studies examining exogenous attentional deployment, the cue not only denotes the possible location of the target but evokes also a non-spatial reaction which signals that the target is imminent. This reaction enhances the processing of the target stimulus via an increase in the brain’s sensitivity to potentially important events (e.g., the appearance of the target) (Oberlin et al., 2005). This so-called ‘phasic alerting effect’ (Fernandez-Duque and Posner, 1997) is typically observed as a speeded RT to the target when it is preceded by a spatially neutral cue compared to when the target is presented in the absence of a cue.

Although phasic alerting is closely associated with cholinergic-associated attentional shifting-related operations it appears to be highly dependent upon the action of noradrenaline. Experimental evidence indicates that reduced levels of brain noradrenaline result in a lowering of the magnitude of the alerting effect to non-spatial cues (Oberlin et al., 2005; Coull et al., 2001; Witte and Marrocco, 1997). It is now widely acknowledged that the degeneration of the locus coeruleus (LC, the nucleus necessary for noradrenaline production) and decreased cortical levels of noradrenaline are common findings in AD. Indeed, noradrenergic deficits may exceed those of ACh in this disorder (Haglund et al., 2006). One would therefore predict abnormal phasic alerting in AD and hence possibly in MCI and indeed, using a simple target detection version of our exogenous cueing task, we found that whereas healthy older adults exhibited a significant phasic alerting response, this effect was absent in AD and MCI (Tales et al., 2002b, 2005).

As in visuospatial cueing, there is paucity of information regarding any potential influence of whether target detection or discrimination is employed upon the outcome of studies examining phasic alerting in AD using the Posner cueing technique. Evidence is equally unclear in relation to the outcome of studies examining this effect in relation to other techniques (e.g., Pate et al., 1994; Nebes and Brady, 1993). Thus in a subsequent study we examined the phasic alerting effect in AD under target discrimination conditions (Tales et al., 2006). The results were at odds with the outcome of our two previous target detection studies (Tales et al., 2002a, 2002b, 2005) in that both the AD and healthy older adult groups displayed large and significant phasic alerting effects of similar magnitude. However, the results for our discrimination task were in agreement to those of Fernandez-Duque and Black (2006) who found a significant and similar phasic alerting effect in both healthy older adults and patients with AD, namely preserved phasic alerting in AD in response to a target discrimination task.

In our previous target detection studies, the lack of a significant effect lead us to conclude that phasic alerting was abnormal in both AD and MCI per se. However, the outcome of our target discrimination study and that of the study by Fernandez-Duque and Black (2006) forced us to reconsider this suggestion and to examine the possibility that in AD, and potentially in MCI, abnormality in phasic alerting is revealed only under certain experimental conditions, particularly those related to whether target detection or discrimination is required. In relation to potential clinical application, any variability in phasic alerting in MCI and AD induced by methodological manipulation may indicate its functional integrity in relation to specific environmental situations and also how such variation may increase group differentiation and thus the clinical potential of such tests.

1.3. Study aims

In the present study we examine exogenously mediated visuospatial attention (attentional disengagement and IOR) and phasic alerting in MCI compared to healthy ageing, in relation to both target detection and discrimination. Our use of the same older adult and MCI groups for both target conditions eliminates potential confounding factors related to potential inter-group variation in factors such as diagnosis, disease stage and demographics which may have obscured previous target-related effects.

We hope to reveal whether, for a given CTI, the choice of target detection or target discrimination can influence the outcome of studies examining both spatial and phasic alerting cueing effects in healthy older adults and patients with MCI. Furthermore we hope to determine whether such relatively unexplored combinations of target response and CTI can reveal new information of potential importance in relation to the characterization of MCI. The design of the present study also enables us to examine whether the heterogeneity of outcome in previous cueing studies may be the result, at least in part, of the experimenter’s choice of target response.

2. Methods

2.1. Stimuli

We presented an exogenous, covert Posner-style cueing paradigm and compared the time taken to respond to the target when it was preceded by invalid, valid, spatially neutral cues or no cue at CTIs of 200 and 800 msec, for separate target detection and target discrimination conditions. All stimuli were presented on a Toshiba 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. Target stimuli were horizontal or vertical lines 10 mm in length and
1 mm in width which were presented at 60 mm either side of a small central fixation cross. The exogenous, non-predictive visual cues consisted of four small squares that defined a larger square. The small square had 3 mm sides and defined a larger square with 26 mm sides; the width of the lines was .25 mm. The larger square was centred 60 mm horizontally from the fixation cross (see Tales et al., 2002b for figures of similar stimuli).

Each trial commenced with a 1000 msec presentation of the central fixation cross upon which the participants were asked to focus. The non-predictive (50–50) cue was then presented and remained on screen for the rest of the trial. The target stimulus was presented 200 or 800 msec after the onset of the cue, a range chosen to span the duration over which an exogenous cue could be expected to produce spatial orienting, namely a validity and IOR effect respectively and phasic alerting. The target remained on screen until a response was made. For target detection blocks, the participant was required to respond to both vertical and horizontal target orientations with a single response-pad button press. For the target discrimination condition the participant was required to respond to the vertical and horizontal target orientations using different keys on the response-pad. Participants were instructed on the importance of keeping their eyes fixed upon the central cross. The experimenter monitored the participant’s eyes to ensure compliance with this instruction and marked any trials in which the eyes failed to return to the fixation point in advance of the next trial. Each type of trial (valid, invalid, neutral and no cue) was presented 20 times at each CTI for both the detection and discrimination tasks. In addition, the detection task contained a total of 21 catch trials in which no target appeared. Trial order was randomised for both the detection and discrimination task and the order of the detection and discrimination task blocks was counter-balanced (within the limits of unequal participant numbers).

Participants were instructed on the task requirements and asked to respond as quickly and as accurately as possible to the target. All participants were asked to explain the task to the experimenter to demonstrate their comprehension of the task requirements and to ensure that they could clearly see all the stimuli and respond accordingly. Instructions were repeated at intervals throughout testing to ensure that full task understanding was maintained.

2.2. Participants

All individuals with MCI had presented to their general practitioner (GP) with a subjective memory problem (corroborated by an informant) and subsequently been referred to the Memory Clinic at University Hospital Llandough, Penarth. Following detailed clinical assessment, including history and physical examination, neuropsychological testing with Addenbrooke’s Cognitive Examination (ACE; Mathuranath et al., 2000), Mini Mental State Examination (MMSE; Folstein et al., 1975), Kendrick Object Learning Test (KOLT; Kendrick and Watts, 1999) and immediate and delayed Story Recall from the Arizona Battery for Communication Disorders of Dementia (ABCD; Bayles and Tomoeda, 1993), laboratory testing and neuroimaging, patients were recruited for this study on a consecutive incident basis if they fulfilled the consensus criteria for amnestic MCI (Petersen, 2003; Tales et al., 2005). Thus all had a subjective decrease in short or long term memory and objective memory decline at a level of >1 standard deviation (SD) (and usually >1.5 SD) from the age-appropriate mean, but preserved general intellect (ACE score ≥ 83; MMSE ≥ 24) and daily functioning (Clinical Dementia Rating – CDR score ≤ 5). None met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) criteria for possible or probable AD.

The older adult control group was recruited from volunteers at the Bristol Memory Disorders Clinic. Each control participant displayed normal function in relation to their age and educational attainment in the following tests: MMSE (Folstein et al., 1975), immediate, delayed and verbal recognition memory (Hopkins Verbal Learning Test-Revised) (Benedict et al., 1998), WAIS-III sub-tests of digit span forwards and backwards, similarities and picture completion (Wechsler, 1998), face recognition (Wilson et al., 1998), the Boston Naming test (Fastenau et al., 1998), S-word fluency and animal fluency (Spreen and Strauss, 1998), Weigl’s color-form sorting test (Byrne et al., 1998), the CLOX test [executive function] (Royall et al., 1998), the Visual Form Discrimination Test (VFDT) (Benton et al., 1994), and digit copying (Kendrick, 1985), cognitive speed (trails making test Reitan, 1958) and premorbid intelligence quotient [IQ; National adult reading test (NART)] (Nelson and Willison, 1991).

The demographics of the two groups are displayed in Table 1.

Exclusion criteria included poor general health, a history of stroke or transient ischaemic attack, significant head injury, any other psychiatric disorder or neurological disease. All had normal or corrected-to-normal vision. Although medication could not be controlled in either group, none of the participants were receiving medication deemed likely to affect cognitive function and none of the patients were receiving drug treatment of any kind for their cognitive problems. None of the participants in the present study had taken part in our previous studies of Posner cueing in ageing, MCI or AD. All

<table>
<thead>
<tr>
<th>Table 1 – Group demographics.</th>
<th>Gender</th>
<th>Age in years</th>
<th>Years of education</th>
<th>NART</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>Mean, Range, SD</td>
<td>Mean, SD</td>
<td>Mean, SD</td>
</tr>
<tr>
<td>Older adult group</td>
<td>8</td>
<td>8</td>
<td>71.9, 65–82, 4.98</td>
<td>15.3, 2.9</td>
<td>117.7, 8.3</td>
</tr>
<tr>
<td>MCI group</td>
<td>10</td>
<td>7</td>
<td>74, 65–85, 6.4</td>
<td>14.5, 2.6</td>
<td>113.4, 6.9</td>
</tr>
</tbody>
</table>

1.5 SD) from the age-appropriate mean, but preserved general intellect (ACE score ≥ 83; MMSE ≥ 24) and daily functioning (Clinical Dementia Rating – CDR score ≤ 5). None met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) criteria for possible or probable AD.

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participants gave written informed consent and the research protocol was approved by the local research ethics committee.

2.3. Data analysis

Trials were excluded from analysis if the RT was below 150 msec (i.e., anticipatory responses) or above 1500 msec (i.e., as a result of a lack of concentration) and if they were associated with an obvious distraction or if they represented trials in which the eyes were not initially focused centrally (see Table 2). From the remaining RTs the median RT for each condition was determined and any catch trials (from the detection task) and errors (from the discrimination task) were recorded for each individual. Group means were then determined and are displayed in Graphs 1 and 2.

3. Results

3.1. Phasic alerting

In order to examine the phasic alerting effect, we analysed RTs to targets following a spatially neutral cue, relative to targets preceded by no cue. Analysis of variance (ANOVA) on median RT, comparing CTI (200 and 800 msec), task (detection, discrimination), cue (cue, no cue) and group (old, MCI) revealed a significant main effect of task, namely a greater overall RT in response to the discrimination compared to the detection task \(F(1,31) = 345.02, p < .001\], a significant main effect for cue with longer RTs to un-cued than cued targets, namely a phasic alerting effect \(F(1,31) = 32.25, p < .001\], but no significant main effect of CTI \(F(1,31) = .13, p = .72\] or group \(F(1,31) = .006, p = .94\]. Significant interactions existed between CTI and task \(F(1,31) = 8.42, p = .007\], CTI and cue \(F(1,31) = 4.62, p = .039\], task by cue \(F(1,31) = 13.66, p = .001\] and CTI by task by cue by group \(F(1,31) = 4.83, p = .036\]; hence we explored these complex patterns further with planned comparisons separating out the task types for each CTI.

3.2. 200 msec CTI

At this short CTI, ANOVA on target detection data revealed a significant main effect for cue, namely a significant phasic alerting effect \(F(1,31) = 14.2, p = .001\], but no significant main effect of group \(F(1,31) = .036, p = .85\]. There was however a significant cue by group interaction \(F(1,31) = 10.91, p = .002\] accounted for by the elicitation of a significant phasic alerting effect for the older adult group \([df 15] = 5.05, p < .001\], but not for the MCI group \([df 16] = .33, p = .75\].

ANOVA on target discrimination data revealed a significant main effect of cue, i.e., a significant phasic alerting effect \(F(1,31) = 16.3, p < .001\] but no significant main effect of group \(F(1,31) = .036, p = .85\] and no significant cue by group interaction \(F(1,31) = 1.47, p = .23\] thus indicating a phasic alerting effect of similar magnitude for both groups.

Table 2 – Mean RT (msec), SD, % errors (discrimination tasks), % catch trials (detection tasks) and % outliers for all cue and task response conditions.

<table>
<thead>
<tr>
<th>Phasic alerting</th>
<th>Spatial cueing</th>
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<tbody>
<tr>
<td>Detection</td>
<td>Discrimination</td>
</tr>
<tr>
<td>200 msec CTI</td>
<td>800 msec CTI</td>
</tr>
<tr>
<td>Cue</td>
<td>No cue</td>
</tr>
<tr>
<td>Old adult group</td>
<td></td>
</tr>
<tr>
<td>Mean RT (msec)</td>
<td>477.5</td>
</tr>
<tr>
<td>SD</td>
<td>137.9</td>
</tr>
<tr>
<td>Catch trials</td>
<td>0</td>
</tr>
<tr>
<td>Mean % errors</td>
<td>/</td>
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<tr>
<td>Mean % outliers</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>/</td>
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<tr>
<td>MCI group</td>
<td></td>
</tr>
<tr>
<td>Mean RT (msec)</td>
<td>503.6</td>
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<tr>
<td>SD</td>
<td>121.2</td>
</tr>
<tr>
<td>Catch trials</td>
<td>0</td>
</tr>
<tr>
<td>Mean % errors</td>
<td>/</td>
</tr>
<tr>
<td>Mean % outliers</td>
<td>2.0</td>
</tr>
<tr>
<td>SD</td>
<td>3.9</td>
</tr>
</tbody>
</table>
3.3. 800 msec CTI

At this long CTI, ANOVA on target detection data revealed a no significant main effect of cue, namely no significant phasic alerting effect \( F(1,31) = 2.92, p = .097 \), no significant main effect of group \( F(1,31) = .999, p = .76 \) and no significant cue by group interaction \( F(1,31) = .52, p = .82 \).

ANOVA on target discrimination data revealed a significant main effect of cue, namely a significant phasic alerting effect \( F(1,31) = 14.61, p = .001 \) but no significant main effect of group \( F(1,31) = .099, p = .76 \) and no significant cue by group interaction \( F(1,31) = .24, p = .63 \) thus indicating a phasic alerting effect of similar magnitude for both groups.

3.4. Detection versus discrimination task order effects in phasic alerting

As mentioned in the Methods section, the order of the detection and discrimination tasks was counterbalanced (within the limits of unequal participant numbers). ANOVA on Order, CTI, task and cue confirmed that there were no significant main effects of order for either the MCI \( F(1,15) = .59, p = .54 \) or the older adult group \( F(1,14) = .55, p = .47 \) with no interactions between order and other factors for either group.

3.5. Spatial cueing; the validity and IOR effects

In order to examine the validity and IOR effects, we analysed RTs to targets following spatially invalid cues relative to spatially valid cues. ANOVA on median RT for CTI (200 and 800 msec), target (detection and discrimination), cue (valid and invalid) and group (old, MCI), revealed a significant main effect of task, with longer target discrimination than detection RTs \( F(1,31) = 334.7, p < .001 \), a significant main effect of cue, with longer overall RTs to invalidly than validly cued targets \( F(1,31) = 10.03, p = .003 \), but no significant main effect of group \( F(1,31) = .052, p = .82 \) or CTI \( F(1,31) = 1.1, p = .3 \). Significant interactions were found only between CTI and cue \( F(1,31) = 27.4, p < .001 \), task by cue \( F(1,31) = 20.2, p < .001 \) and cue by group \( F(1,31) = 11.75, p = .002 \) and were explored further in planned comparisons as before.

3.6. 200 msec CTI

ANOVA on target detection data revealed a significant main effect of cue consistent with a validity effect, namely an overall greater RT to invalidly than validly cued targets \( F(1,31) = 5.4, p = .027 \), but no significant main effect of group \( F(1,31) = .08, p = .78 \) and only a marginally significant cue by group interaction \( F(1,31) = 3.79, p = .061 \).

ANOVA on target discrimination data revealed a significant main effect of cue, namely a significant validity effect \( F(1,31) = 28.2, p < .001 \) but no significant main effect of group \( F(1,31) = .18, p = .67 \) and no significant interaction cue by group interaction \( F(1,31) = 1.17, p = .29 \) thus indicating a validity effect of similar magnitude for both groups.

3.7. 800 msec CTI

ANOVA on target detection data revealed a significant main effect of cue but now consistent with an IOR effect, namely an increased RT to validly than invalidly cued targets \( F(1,31) = 14.57, p = .001 \). Although there was no significant main effect of group \( F(1,31) = .023, p = .88 \), there was a significant cue by group interaction \( F(1,31) = 7.47, p = .01 \) whereby the IOR effect was significant for the healthy group \( t(15) = 4.29, p = .001 \) but not the MCI group \( t(16) = .84, p = .41 \).

ANOVA on target discrimination revealed a significant main effect of cue, but in a pattern opposite that seen in target detection, namely a validity effect \( F(1,31) = 5.5, p = .025 \). Although there was no significant main effect of \( F(1,31) = .71, p = .41 \) there was a significant cue by group interaction \( F(1,31) = 4.148, p = .05 \), accounted for by the elicitation of
a significant validity effect for the MCI group \( t(16) = 3.45, p = .003 \) but not for the MCI group \( t(15) = .2, p = .84 \).

So, whereas the short CTI failed to discriminate the groups, this long 800 msec CTI condition showed significant group differentiation, but each task revealed a contrasting pattern of differences. With the detection task, the older group produced a significant IOR effect whereas the MCI failed to do so, but with target discrimination, the MCI group showed a significant validity effect that older controls did not.

### 3.8. Detection versus discrimination task order effects in spatial cueing

As mentioned in the Methods section, the order of the detection and discrimination tasks was counterbalanced (within the limits of unequal participant numbers).

ANOVA on Order, CTI, task and cue confirmed that there were no significant main effects of order for either the MCI \( F(1,15) = .325, p = .577 \) or the older group \( F(1,14) = 413, p = .53 \) with no interactions between order and other factors for either group.

### 4. Discussion

We investigated whether target detection or discrimination could influence the outcome of a study designed to examine exogenously mediated spatial cueing and phasic alerting in amnestic MCI compared to healthy ageing.

#### 4.1. Basic RT and the ability to perform tasks

As expected, for all trial types, target discrimination resulted in a significant overall increase in target RT compared to that in response to simple target detection, presumably as a result of the greater amount of time necessary for processing and responding to a more complex and demanding task. However, rather unexpectedly, the MCI group was not significantly slowed overall (compare to Tales et al., 2005). This result is possibly indicative of the heterogeneous nature of MCI groups (each potentially containing a different proportion of those in the very early stages of AD and those with other aetiologies of MCI). The MCI group also failed to reveal a disproportionate increase in target discrimination RT compared to that exhibited by the healthy older adult group. This, together with negligible errors for both groups, indicates that individuals with MCI can readily perform the discrimination task at a level highly similar to that seen in healthy ageing.

#### 4.2. Phasic alerting

With respect to the conditions of the present study it appears that, in both MCI and healthy ageing, whether or not a significant phasic alerting effect is elicited depends upon the combination of task response and CTI. Combining target discrimination with both the 200 msec and 800 msec CTIs revealed a similarly robust phasic alerting effect for both groups and thus normality of such function in MCI. Combining a target detection task with the 800 msec CTI failed to elicit any significant cueing effect for both groups, so again the MCI group appears normal in this respect. However, the combination of a detection task with the 200 msec CTI elicited a significant phasic alerting effect in the healthy older adult group but not in the MCI group for whom there was no significant cueing effect at all. Therefore, significant group differentiation in relation to phasic alerting occurred only in response to a combination of a 200 msec CTI and a target detection task.

This result confirms the findings of our previous study (Tales et al., 2005) in which a combination of a detection task and a CTI of 200 msec was employed. However, in relation to our previous study we suggested that the results were indicative of an abnormal (absent) phasic alerting mechanism in MCI. The use of both target detection and discrimination in the present study has revealed that phasic alerting is not absent in MCI per se, but rather that it emerges only under the more demanding discrimination task conditions (a result in accord with that of Fernandez-Duque and Black, 2006 in relation to AD but see Festa-Martino et al., 2004). Healthy ageing differs in that the phasic alerting effect can also emerge with a detection response, but this is additionally sensitive to CTI, disappearing as the interval lengths. Furthermore, the results from monkey neurophysiology studies (see for example Rajkowski et al., 2004) reveals that neuronal activity in the LC may correlate with task difficulty. In principle such results may represent a physiological basis for the differential task-related findings of human behavioural studies of the phasic alerting effect but we only suggest this as a hypothesis for the basis of future investigation at present.

#### 4.3. Spatial cueing; the validity and IOR effects

Our data demonstrate that the specific combination of CTI and task (detection vs discrimination) determines the overall magnitude of the validity effect, i.e., showing the expected overall greater validity effect in response to target discrimination compared to detection. Furthermore, this combination determines whether or not a significant spatial cueing effect is elicited in healthy and MCI groups. Combining the 200 msec CTI with target discrimination revealed a comparably robust and significant validity effect for both groups. Combining this CTI with target detection revealed an overall smaller validity effect which unexpectedly (compared to the findings of Tales et al., 2005) did not differ significantly (only marginally, \( p = .06 \)) between the groups. While this could be interpreted as normality of such function in MCI in both cases, it should be noted that the interaction under target detection conditions approached significance, with the validity effect more apparent in the MCI than the control group. It is not possible to determine whether the difference in outcome between our previous and present study of the validity effect in MCI is related to methodological factors, the different degrees of heterogeneity within the MCI group (i.e., the proportion of individuals that are later found to have AD in which case their MCI was due to the presence of early AD), a mixture of both factors or spurious and unknown influences. The result does however further illustrate the difficulties in trying to compare the outcome of different studies purporting to measure the same function.
In contrast, combining the 800 msec CTI with target detection revealed a significant IOR effect for the healthy older adult but not for the MCI group (note however that both groups display a tendency to reverse from a validity effect at a CTI of 200 msec to an IOR effect at 800 msec). Combining this CTI with target discrimination revealed a significant validity effect for the MCI but not the healthier older adult group. Abnormality of function in MCI is therefore suggested in both cases, although of contrasting form dependent upon the response requirements. Thus, whether or not significant group differentiation occurs, and how it is manifested, again appears dependent upon the specific combination of CTI and task response.

In a previous study examining these effects in MCI using target detection, at a CTI of 200 msec we (Tales et al., 2005) observed a similar pattern of response to that seen in the present study, namely a relatively small validity effect for the older group and a larger effect for the MCI group. While the difference in the magnitude of this effect between the groups reached significance in the previous study but not here, we nevertheless suggest that the two results are highly comparable – arguably, since this result was predictable from previous data, one-tailed testing would be appropriate in the present study and would render the interaction significant at $p = .03$. However, our previous study also examined the IOR effect using a CTI of 800 msec and found IOR to be preserved in MCI – an outcome which differs from that of the present study in which the normal IOR effect is absent in MCI. Given that methodology was relatively consistent across these two studies, these comparisons illustrate that inter-individual variability of those with an MCI diagnosis may inevitably contribute to differential outcomes between studies using different MCI patient groups.

4.4. Impact of target detection versus discrimination upon study outcome

When the same groups of individuals are used for all conditions (in order to exclude potential participant-related confounds) the differential use of combinations of CTI and task response can influence the outcome of the study and thus our perception of and understanding of the disease. For example, the use of the target detection task and 200 msec CTI alone would have led us to describe phasic alerted as abnormal in MCI. However, testing such function in relation to different CTI and task combinations reveals that in fact this effect appears abnormal in MCI only under certain conditions. Likewise, in spatial cueing, simply employing the short CTIs in relation to either task here would have suggested a marginally normally functioning validity effect in MCI, but would have overlooked the abnormal effects at 800 msec CTI, namely the presence of a validity effect with the MCI group under target discrimination conditions, and their abnormal inability to produce an IOR effect in response to a target detection task.

Importantly, this study demonstrates that the choice of target detection or discrimination is not trivial, as each may give contrasting results and seemingly demand the involvement of different attentional and other processes. We speculate that several factors may contribute to this pattern. Firstly, data using a detection response may more cleanly represent the true speed of target identification, since it requires minimal extra time and effort after the decision to translate it into a button press, unlike discrimination. The less noisy (in terms of the component processes of interest) detection data may thus be more sensitive to group and CTI differences – indeed distinctive patterns do seem to emerge more markedly with our detection than our discrimination tasks (note, for the healthy group, the clear presence of an alerting effect specific to 200 msec CTI, and an IOR effect specific to 800 msec IOR, with target detection). Secondly if, as we assume, the detection response involves lower load than the discrimination response, then the divergent patterns of response by task may genuinely reflect different attentional processes according to the activation levels maintained throughout task performance (see Pinsk et al., 2004; Muller and Eberling, 2008). It is also possible that target detection and discrimination invoke the recruitment of discrete processes in addition to those related to visual attention, or result in the differential processing of, or weighting assigned to, the warning cue. Clearly further work is required to explore these ideas.

This study has therefore highlighted the potential of what appear to be simple methodological manipulations to influence the outcome of a study designed to investigate attention-related function in MCI. In addition, it has revealed further evidence that amnestic MCI is not simply a ‘memory-related’ disorder (Tales et al., 2005). This information may be of use in improving our understanding of the signs and symptoms of MCI and indeed of AD, and in our ability to anticipate which aspects of environmental processing and response requirements may preclude normal environmental perception and thus behaviour for these individuals. Considering the contribution visual attention-related processes make to driving, such information may also be of use in helping to determine driving competence (e.g., Hodges, 2006). Such information may also be of use in guiding the design of future clinically-based studies which aim to determine whether different patterns of functional integrity in specific brain operations can help to separate the heterogeneous MCI group into homogenous sub-groups, particularly in relation to the presence or not of very early AD.

In on-going studies we are examining whether detection and/or discrimination tasks differ in relation to their ability to predict for whom the diagnosis of MCI represents the early stages of AD and whether certain patterns of experientially evoked abnormalities of attention-related function in AD and MCI translate to real-life behavioural problems.

References


