Phasic visual alertness in Alzheimer’s disease and ageing

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An individual's ability to see and react quickly to a target stimulus is enhanced if they are alerted to the arrival of this target by a stimulus that occurs just prior in time to it. This alerting effect is thought to occur due to a phasic increase in alertness mediated by noradrenergic activity. In Alzheimer’s disease (AD) there is a dysfunction in the noradrenergic system resulting in a decrease in central levels of noradrenaline. We therefore predicted that patients with AD would not be able to benefit from the prior stimulus to the same extent as that seen in healthy older adults and thus would have a reduced or abolished alerting-effect. We measured reaction times to respond to a visual target that could be preceded (by 200 ms) by a visual alerting cue, in 17 patients with Alzheimer’s disease, 19 age-matched controls and 13 younger controls. We found that the alerting cue significantly decreased the reaction times for both the young and old controls, but that this cue had no effect upon the reaction times for those with AD. This marked inability to increase phasic alertness in AD may contribute to the everyday problems faced by these patients, and may provide a simple tool to aid diagnosis and disease progression.

INTRODUCTION

Many studies have now demonstrated deficits in attention in Alzheimer’s disease (AD), with the capacity to divide (attend to more than one thing at once), switch (move attention from one object to another) and focus (ignore objects that we are not attending to) attention, appearing to be particularly vulnerable, whereas the ability to sustain attention (keep attention at the same object for a long time) remains relatively preserved in the early stages [1–4]. It appears that, like memory, distinct features of attention-related function may be differentially sensitive to the effects of AD. Due to the brain’s limited processing resources, attention has to be sequentially shifted to, and focused upon, specific regions of interest in order to select stimuli for priority or high level processing [5]. This discriminative focusing of attention (selective attention), mediates many aspects of the mnemonic, cognitive, perceptual and sensory processing necessary for appropriate environmental interaction and subsequent behaviour. Changes in the functional integrity of the attentional systems may therefore contribute to many of the everyday problems experienced by individuals with AD.

The point in space, or object, of attention has often been manipulated by visual cues that draw attention to a particular location [5]. Targets that occur near the location of the cue are processed more efficiently, and therefore the observer is faster and more accurate at identifying the target, when compared to targets occurring far away from the cued location [5]. However, such cues not only signal the possible location of the target; they also signal that the target is imminent as the target normally quickly follows the visual cue. Many studies have shown that even if the cue does not provide any information about the location of the target, the cue can still enhance the processing of the target stimulus [6]. It is suggested that this improvement occurs due to a phasic increase in alertness [7] that lasts on the order of several hundred milliseconds.

The locus ceruleus noradrenergic system, (which provides the principle noradrenergic innervation of the cerebral cortex) plays an important role in maintaining sensory readiness to external stimuli [8–10]. Studies in healthy individuals and animals using cueing tasks in conjunction with the administration of clonidine (an α2-adrenoceptor agonist that reduces synaptic noradrenaline, though evidence to the site of action is mixed [11]) have indicated that noradrenaline status governs the magnitude of this increase in phasic alertness to the cue. Witte and Marrocco [11] found that clonidine reduces the effect of the visual cue (a reduced alerting effect) in non-human primates, and Coull et al. [12] found a similar reduced alerting effect when clonidine was...
administered to humans. Noradrenergic integrity has also been found to be disrupted in AD [13]. For example, Hoogendijk et al. [14] reported mean noradrenaline concentrations in the locus ceruleus significantly below those of controls. These findings, together with evidence from previous studies showing disrupted responses to warning stimuli in AD [15,16], led us to hypothesise that the alerting function of visual cues would be disrupted by this disease process.

MATERIALS AND METHODS

Three groups of individuals participated in the study. The AD group was recruited from the memory clinics at Llandough Hospital, Cardiff and St. Martin’s Hospital, Bath and consisted of 17 individuals (ten male, seven female), mean age 74.2 ± 6.87 years. The diagnosis of probable AD was based on neurological, physical and biochemical examination, neuropsychological testing, including the Mini-Mental State Examination [17], family interview and detailed history, neuroimaging and psychiatric interview, according to DSM III-R and NINCDS-ADRDA criteria [18]. Individuals with additional psychiatric problems were excluded. The mean MMSE score for the AD group was 22.1 ± 2.37. Three participants in the AD group were receiving a cholinesterase inhibitor (two donepezil hydrochloride, one rivastigmine hydrogen tartrate); the rest were free of medication deemed likely to affect cognitive function.

The age-matched older control group consisted of 19 healthy individuals (six male, 13 female) mean age 71.0 ± 3.9 years. The older adults were recruited from the community participant panel of the School of Psychology at Cardiff University. The younger adult control group consisted of 13 individuals (eight female, five male) mean age 27.3 ± 5.2 years recruited from the Cardiff University student population. All reported that they were free of medication deemed likely to affect cognitive function and all had taken part in previous studies that had involved neuropsychological testing. None of the participants had a detailed history, neuroimaging and psychiatric interview, according to DSM III-R and NINCDS-ADRDA criteria [18].

Individuals in all groups had normal or corrected to normal vision and, if appropriate, had visited an optician within the past 12 months. To further ensure visual capability appropriate for the task all participants were asked to read out loud the task instructions displayed on the computer screen, and given practice trials in which they were required to report what they could see on screen, i.e., to describe the fixation cross, the cues and the targets.

All participants gave informed consent obtained according to the Declaration of Helsinki and the research protocol was approved by the appropriate local research ethics committees.

Stimuli: All stimuli were presented on a MAC Powerbook 180 computer. The target stimuli were horizontal or vertical lines of 10 mm length and 1 mm width. The target stimuli were presented 60 mm either side of a small fixation cross, located at the centre of the screen. The visual cues consisted of four small squares that defined a larger square. The small squares had a side of 3 mm and defined a larger square of side 26 mm; the width of the lines was 0.25 mm. The larger square was centred 60 mm horizontally from the fixation cross (two 7 mm long lines of width 0.5 mm).

The screen’s background luminance level was 37.5 cd/m². All stimuli were black (2.0 cd/m²) and thus had a Weber contrast (dL/L) of 0.95.

Procedure: Each trial commenced with the presentation of the fixation mark (the central cross). Three different fixation durations were employed, 800, 1000 or 1200 ms, so that the timing of the target could not be inferred from the presentation of the fixation mark. The cue was then presented. Four types of cues were used: valid (the cue appeared at the location where the target would subsequently appear), invalid (cue appeared at the location contralateral to the location of the subsequent target), double (cues appeared at both locations), or no cue (no cue at any location). In this paper we are only concerned with the differences in performance between the double cue and the no-cue conditions. Results from the valid and invalid trials conformed to our previously reported results [1]. The cue remained on the screen for the rest of the duration of the trial. The target stimulus was presented 200 ms after the onset of the cue. The target remained on screen until a response was made. The participant was required to press the button when the target occurred. Rest periods were given as required (Fig. 1).

There were three blocks of trials. Within each block there were 18 catch trials (in which a cue but no target appeared); 24 valid trials, 24 invalid trials, 12 double-cue trials (in which cues appeared on both sides of the fixation cross) and 12 no-cue trials. In total, therefore, there was a maximum of 54 catch trials, 72 valid trials and 72 invalid trials, 36 double-cue trials, 36 no-cue trials.

Participants were trained to fixate and maintain fixation throughout a trial on the central cross. They were instructed on the significance and probability ratings of the cues and asked to respond as quickly and as accurately as possible to target occurrence by pressing a large hand-held button. All participants were asked to explain the task to the experimenter in order to demonstrate their understanding of the...
task requirements. All participants were asked to perform one or several practice blocks. The experimenter was positioned opposite the participant in order to monitor eye movements. Trials in which eye movements occurred were removed from analysis.

**Data analysis:** Reaction times for correct trials were measured. After initial visual inspection of the data we eliminated scores < 150 ms as anticipatory and scores > 1500 ms as due to lapses of concentration or misunderstandings of the required responses. Trials in which eye movements occurred were removed from analysis.

From the remaining reaction times, median reaction time and percentage of false responses on catch trials were calculated.

**RESULTS**

Figure 2 shows a plot of the mean reaction times (of the participants’ median reaction times) for the double cue and no-cue conditions. ANOVA showed a significant main effect of group (F(2, 46) = 8.28, *p* < 0.001) and cue type (F(1, 46) = 48.11, *p* < 0.0001). These main effects were modified by a significant interaction (F(2, 46) = 8.74, *p* < 0.001).

It was hypothesised that the alerting effect of the cue would be reduced in AD compared to young and older controls. To test this prediction an alerting effect (reaction time no-cue—reaction time double-cue) was calculated for each participant, and groups were compared using a one-tailed *t*-test. This analysis revealed that the alerting effect was significant for both the young (t(12) = 5.88, *p* < 0.0001) and old controls (t(19) = 6.80, *p* < 0.0001), but was not significant for the AD participants (t(16) = 0.53, *p* > 0.1). As predicted, a greater alerting effect than the AD group was seen in both young controls (t(28) = 3.53, *p* < 0.001) and in the older controls (t(34) = 2.82, *p* < 0.01). We did not predict any difference in alerting effect between the old and the young controls, and a two-tailed *t*-test showed no significant difference in the alerting effect in the older participants (t(30) = 1.85, *p* = 0.075). As indicated in Table 1, false alarms on catch trials were very low for all groups (<2%), providing little evidence for speed/accuracy trade-off effects.

**DISCUSSION**

Both our older and younger control participants were faster at detecting a visual target when a visual cue preceded the target stimulus by 200 ms, even though this cue provided no information about the target’s location or identity. This agrees with previous studies showing the beneficial effects of such cues [19,20]. In contrast however, the patients with AD showed no such decrease in reaction times when the cue preceded the target. Could this be the result of the inability of those with AD to process such a cue? The results from our previous study [1], which employed exactly the same visual cues to measure the validity effect (the difference in reaction times between targets occurring at the cued location compared to the not-cued location), showed that these cues produce a greater validity effect in individuals with AD, thus suggesting that these participants could process the cue appropriately. Our data indicates that at a time interval (200 ms) at which young and older people respond efficiently to warning cues, people with AD do not, possibly because the alerting effect is present in AD but takes longer to develop [15,16], producing inefficient processing of and response to, rapid changes in the environment.

The data from our AD patients resemble those found when noradrenergic function is disrupted through administration of clonidine [11,12]. The similarity of these findings therefore suggest that the reduction in the alerting effect in AD may (at least in part) be related to noradrenergic status.

As highlighted by Nebes and Brady [19] and Pate et al. [15], impairment in preparing to process external stimuli could have major consequences in situations that require a rapid and efficient processing of afferent information. Thus changes in alerting efficiency in AD may contribute to the difficulties experienced in everyday life by patients [3]. The lack of an alerting response in patients with AD, along with our previous findings of a reduced ability to switch the location of attention [1], may provide for specific tests that could have clinical use in the diagnosis and the monitoring of disease progression.

**CONCLUSION**

Alzheimer’s disease is associated with a disruption of the alerting effect of visual cues at short time intervals between the cue and target. Further work is in progress to determine
the status of the alerting effect in AD in response to various cue types and cue to target intervals.

REFERENCES

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