

# Attention Network Functioning in Patients with Dementia with Lewy Bodies and Alzheimer's Disease

Luis J. Fuentes<sup>a</sup> Pedro J. Fernández<sup>a</sup> Guillermo Campoy<sup>a</sup>  
Martirio M. Antequera<sup>b</sup> Julia García-Sevilla<sup>a</sup> Carmen Antúñez<sup>b</sup>

<sup>a</sup>University of Murcia and <sup>b</sup>University Hospital Virgen de la Arrixaca, Murcia, Spain

## Key Words

Alzheimer's disease · Dementia with Lewy bodies ·  
Cognitive neuropsychology, dementia

## Abstract

**Background:** Attention deficits are at the core of the defects in neuropsychological performance which define both dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). Most studies have used separate tasks to test different attention abilities in patients with these diagnoses, precluding the assessment of any interaction among the different attention components. **Methods:** We used a version of the Attention Network Test in which the alerting, orienting and executive attention networks, along with their interactions, could be assessed with a single task. Three groups of participants were tested: DLB patients (n = 13), AD patients (n = 18) and healthy controls (n = 18). **Results:** The alerting signal improved orienting attention and increased the conflict effect in the healthy controls, but they had no effect on these networks in the AD patients. The DLB patients only showed preserved orienting and conflict effects when the alerting signal was present, indicating that there was regulation of the orienting and executive attention networks by the alerting signal. **Conclusions:** The most important differences among the 3 groups were observed in the attention network inter-

actions, where alerting played a more relevant role in the DLB than in the AD patients. Under alerting states, the DLB patients showed evidence of certain regulation in the orienting and executive attention networks.

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## Introduction

It is now well accepted that dementia with Lewy bodies (DLB) is a clinical entity distinct from Alzheimer's disease (AD) [1, 2]. These patients' brains are characterized by the presence of Lewy bodies in the cerebral cortex, substantia nigra, locus ceruleus and components of the basal forebrain cholinergic system. Fluctuation in cognition, visual hallucinations and parkinsonism are the core clinical manifestations of the disease. However, it remains challenging to differentiate DLB from other dementias, such as AD, given the overlapping neuropathology that both clinical entities present. For instance, several studies of hospital-based autopsies have suggested that DLB accounts for 10–15% of the dementia cases [3], but as many as 12–27% of the patients diagnosed as having AD also meet the pathological criteria for a diagnosis of DLB [2, 4].

Recent studies have relied on neuropsychological and cognitive testing as a way of finding a more reliable procedure to distinguish DLB from AD [5–9]. Some authors have shown that attention fluctuations play a fundamental role in these pathologies [10, 11], and both attentional and perceptual processing might underlie the visual hallucinations that are experienced by most DLB patients. For instance, Calderon et al. [6] showed that DLB patients performed poorly and below AD patients in most visuo-perceptual tasks that required both the ventral and the dorsal processing pathways, and in all attentional tasks that needed sustained, selective and divided attention. In contrast, AD patients were impaired in tasks that required the ventral processing pathway, but showed uncompromised sustained attention compared with the matched control group. Ballard et al. [10] assessed attention performance through the use of a standardized battery of computerized tasks that required both rapid and accurate responses. DLB patients were impaired in both cognitive reaction time (RT) and the vigilance tasks compared with AD patients, and likewise exhibited greater variability in RTs. These results support the hypothesis that fluctuation in attention is a critical feature of DLB. These attention deficits in DLB patients might reflect an important deficiency in the cholinergic system, which plays a relevant role in the orientation of visual attention [12]. However, as Ballard et al. [10] point out, deficits in attention become more pronounced in both DLB and AD patients as the severity of dementia increases, and hence a more detailed evaluation of attention functioning would be useful to aid in the diagnostic assessment.

Many attention studies in dementia, however, lack a theoretical framework that takes into consideration both how the different components of attention might work independently and how they might interact. The cognitive neuroscience model of attention by Posner and Petersen [13] might constitute such a theoretical background. The model distinguishes 3 attention-related neural networks. The alerting network is involved in achieving and maintaining an alert state, which is defined as an internal condition that prepares the individual to perceive or respond to a target. Pharmacological studies have revealed a relationship between this network and the norepinephrine system rooted in the locus ceruleus [12], and it has been shown that the right parietal and frontal areas are activated when people maintain an alert state [14]. The orienting network is involved in aligning attention with a source of sensory input. Pharmacological studies conducted with animals have shown that cholinergic systems arising in the basal forebrain seem to

modulate covert orienting responses [12]. The parietal lobe, pulvinar, superior colliculus and frontal eye fields form part of the anatomical framework of the orienting network. Finally, the executive network is required for activities that involve planning, novelty, target detection, error detection, monitoring and resolving conflict, and the inhibition of automatic responses. The anterior cingulate and lateral prefrontal areas comprise part of the neural circuitry involved in different forms of conflict tasks [15], and some portions of the basal ganglia supply dopamine to the network.

The Attention Network Test (ANT) has been designed to assess the function of the 3 attention networks in a single experiment [1, 16, 17]. Response to conflict, a function of the executive network, is assessed by means of a flanker task. In this paradigm, a central arrow (the target) points to the left or the right. The target is flanked by 4 distracting arrows that can be either congruent (pointing in the same direction as the target) or incongruent (pointing in the opposite direction to the target). Subjects are told to respond to the direction of the target arrow and ignore the distracters. The orienting network is assessed by using peripheral cues (asterisks) to summon attention to a location. In cued trials, the target is presented at the location of the previous peripheral cue, while in uncued trials, it is presented at the opposite location of the peripheral cue. The alerting network is assessed observing the effects of playing a tone prior to the cue presentation. The ANT has proved to be a useful approach in decomposing the attention system into the 3 different attention networks proposed by Posner and Petersen [13].

In this study, we assessed attention functioning in people diagnosed as having either DLB or AD, as well as a group of healthy matched controls (HC). The ANT version used here allowed us to assess dementia-related deficits not only in the function of the individual attention networks but also in the interactions among them [1, 17].

## Methods

### *Participants*

Eighteen HC, 13 patients diagnosed as having DLB and 18 patients with AD participated in the experiment. The HC participants were recruited from the community and were free from serious medical conditions (i.e. heart disease, cancer, stroke, dementia, or drug and alcohol abuse). The AD and DLB participants were patients from the Dementia Unit at the University Hospital Virgen de la Arrixaca (Murcia, Spain). The probable AD and DLB diagnoses were made by a neurologist according to NINCDS-ADRDA criteria and the 3rd report of the DLB consortium [18].

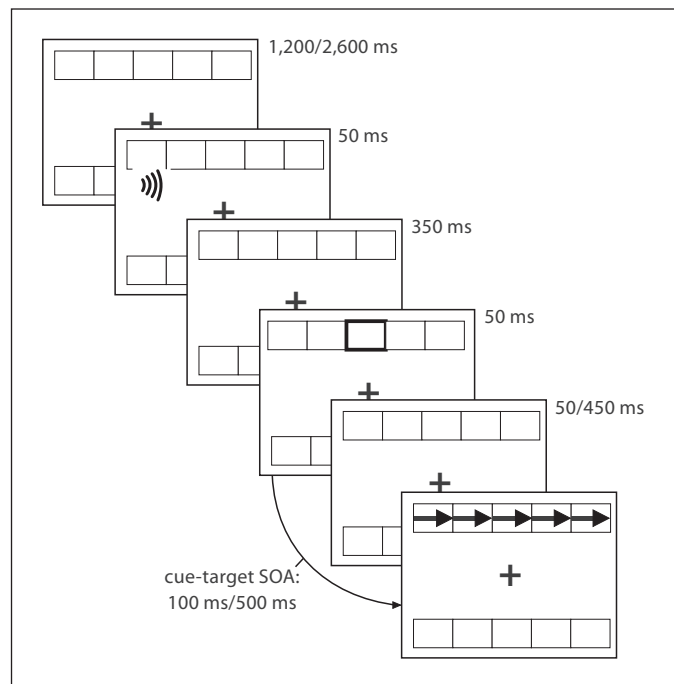
MRI, CT or SPECT were used in the patients' diagnosis. The 3 groups were equated in age and education. We obtained written informed consent to participate in the study from the participants and patients' caregivers. The ethics committees of both the Virgen de la Arrixaca Hospital and the University of Murcia approved this study.

#### The ANT

A computer controlled the task, with stimuli being displayed on a 17" monitor set to a screen resolution of 640 × 480 pixels. Responses were collected through a PST Serial Response Box (Psychology Software Tools, Inc.) connected to the computer. External speakers were used to present the alerting tones. The basic display, which was visible throughout the experiment, consisted of a black fixation cross between 2 rows of 5 horizontally arranged rectangular boxes (fig. 1). The boxes were 40 pixels wide and 30 pixels high, while the fixation cross was 18 pixels wide and 18 pixels high. The distance between the fixation cross and the central box of each row was 60 pixels from center to center. For the visual cue, the outline around the central box of the relevant row was briefly increased from 1 to 4 pixels wide. In each trial, 5 black arrows were presented inside each of the 5 boxes in the row. The arrow presented in the central box was the target, whereas the arrows in the other 4 boxes were the flankers. The arrows were 36 pixels in length. The alerting tone was a 50-ms beep of 2,000 Hz.

Each trial began with the basic configuration being presented for a variable duration between 1,200 and 2,600 ms (the duration was determined randomly with the constraint that the entire range was homogeneously represented within every block of trials). The alerting tone was presented for 50 ms in half of the trials (tone condition), whereas an equivalent empty audio file was run in the other half of the trials (no-tone condition). The orienting visual cue appeared 350 ms after the tone and was presented for 50 ms in the central box of either the upper or the lower box row. The cue could appear in the same box as the target (cued condition) or in the other row (uncued condition). In trials without a visual cue, the basic configuration remained unchanged during the corresponding interval (no-cue condition). Finally, after an interval of 50 ms (stimulus onset asynchrony, SOA = 100) or 450 ms (SOA = 500), the target and flankers were presented until the participants indicated the direction of the target arrow by pressing the right or left key of the response box. The target arrows pointed to the right in half of the trials and to the left in the other half. The flanker arrows pointed in the same direction as the target (congruent condition) in half of the trials or in the opposite direction (incongruent condition) in the other half. The participants were instructed to respond as quickly and accurately as possible.

The test comprised 288 trials divided into 3 blocks of 96 trials that combined alerting (tone, no-tone), cueing (cued, uncued, no-cue), cue-target SOA (100 and 500 ms), flanker congruency (congruent, incongruent), target locus (upper row, lower row) and target orientation (right, left). Target locus and orientation were not experimental factors. There were a total of 12 trials per experimental condition. The participants ran 10 practice trials, with additional blocks of 10 new trials until there were at least 9 correct responses with no RTs >2.5 s in the last practice block. Rest periods were established every 48 trials.



**Fig. 1.** Outlined representation of the experimental procedure.

#### Statistical Analysis

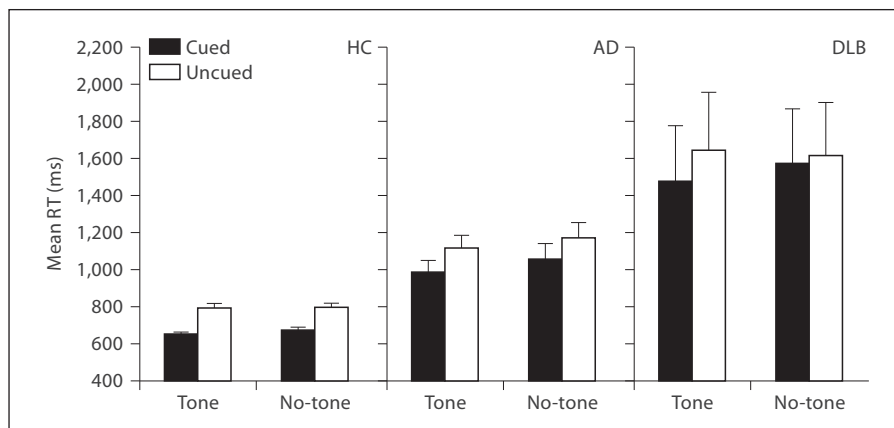
Sociodemographic data and participants' performance in neuropsychological tests were analyzed by simple analysis of variance (ANOVA) with group (HC, AD, DLB) serving as the between-subjects factor. Post hoc t tests were performed when appropriate to compare mean scores across groups.

Two main analyses were conducted regarding the ANT.

- (1) Mean RTs for correct responses were submitted to a mixed ANOVA with alerting (tone, no-tone), cueing (cued, uncued), cue-target SOA (100, 500 ms) and congruency (congruent, incongruent) as the within-subject factors and group (HC, AD, DLB) as the between-subjects factor. We did not include no-cue trials in this first analysis to appreciate better the possible interactions between alerting and orienting and between orienting and congruency (note that no-cue trials were irrelevant to those purposes). When necessary, interactions were analyzed by additional F tests.
- (2) A mixed ANOVA was performed on no-cue trials only. This allowed us to study the potential interaction between alerting and congruency without the additional alerting effect generated by the visual cue [1, 12]. Again, interactions were analyzed by additional F tests.

Equivalent analyses in terms of number of errors were also performed. They did not reveal additional effects and did not show evidence of trade-off between speed and accuracy, so they are not reported. All statistical analyses were conducted with SPSS 14 for Windows (SPSS Inc., USA). The criterion for statistical significance was set at 5%. RTs above or below 3 standard deviations from the participant's mean were not included in the analyses.

**Fig. 2.** Mean RTs as a function of cueing (cued, uncued), alerting (tone, no-tone) and group. Only cued and uncued trials are considered. Errors bars represent mean standard errors.



**Table 1.** Demographic information, means of neuropsychological testing and GDS scores for each group

Sociodemographic data and tests	Maxi- HC mum	DLB	AD
N	18	13	18
Sex (F/M)	9/9	4/9	10/8
Age, years	70 (9)	76 (9)	72 (9)
Education, years	6 (3)	6 (5)	5 (3)
MMSE <sup>a, b</sup>	30	29 (1)	22 (3)
GDS <sup>a, b</sup>	7	1 (0)	4 (0)
<i>CERAD battery</i>			
Semantic fluency <sup>a, b</sup>	16 (2)	9 (2)	11 (4)
Boston Naming Test <sup>b</sup>	15	13 (1)	12 (2)
Word list memory <sup>a, b</sup>	10	7 (1)	5 (1)
Word list recall <sup>a, b</sup>	10	5 (2)	2 (2)
Word list recognition <sup>a, b</sup>	20	19 (1)	16 (3)
Constructional praxis	11	10 (1)	9 (2)
Recall of constructional praxis <sup>a-c</sup>	11	8 (2)	4 (3)
Trail Making Test (part A) <sup>a, b</sup>	78 (34)	257 (120)	186 (76)
Trail Making Test (errors)	1 (2)	2 (2)	2 (3)
<i>Barcelona Test (subtests)</i>			
Imitation of postures (praxis) <sup>a, c</sup>	8	8 (0)	6 (2)
Forward digit span	9	4 (1)	4 (1)
Backward digit span <sup>a</sup>	8	3 (0)	2 (1)
Abstraction <sup>a, b</sup>	12	7 (2)	5 (3)
Random Letters Test (errors)	1 (1)	4 (4)	2 (5)
Phonological fluency (P) <sup>b</sup>	8 (4)	5 (3)	5 (4)

Figures in parentheses are SD. Trail Making Test part B was not included due to the small number of records in this condition as a consequence of the low academic level of the patients and controls. The MMSE was corrected by age and education [19]. MMSE = Mini-Mental State Examination; GDS = Global Deterioration Scale; CERAD = the Consortium to Establish a Registry for Alzheimer's Disease.

<sup>a</sup> Significant difference between HC and DLB.

<sup>b</sup> Significant difference between HC and AD.

<sup>c</sup> Significant difference between DLB and AD.

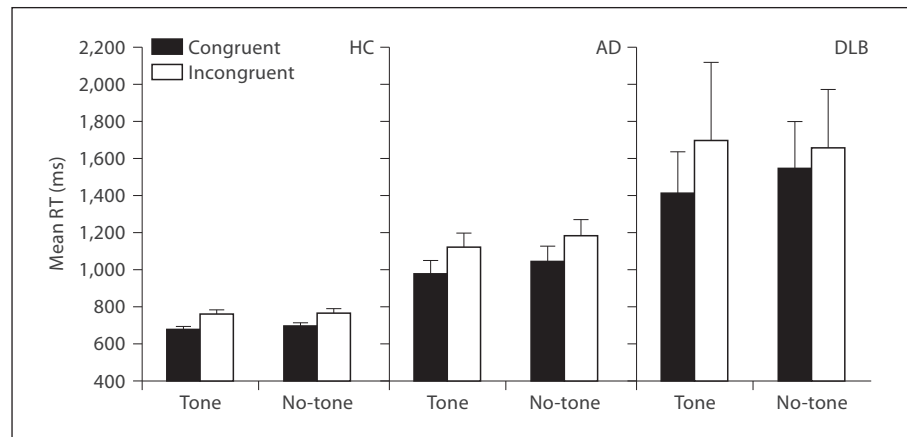
## Results

Demographic information, cognitive functioning scores and statistical differences among the 3 groups are presented in table 1.

The first analysis of participants' performance in the ANT revealed the main effects of alerting, cueing, SOA and congruency (all  $p < 0.05$ ), demonstrating that correct responses were given faster in the alerting-tone than in the no-tone trials (alerting effect = 39 ms), in cued than in uncued trials (cueing effect = 121 ms), for long-SOA than for short-SOA trials (SOA effect = 45 ms) and for congruent than for incongruent trials (congruency effect = 141 ms). The difference among the groups was also significant ( $p < 0.01$ ). The DLB patients were slower than both the AD patients ( $p < 0.05$ ) and HC participants ( $p < 0.05$ ), with the DLB group tending to be slower than the AD patients ( $p = 0.07$ ). The RT means for the HC, AD and DLB groups were 728, 1,082 and 1,581 ms, respectively.

There was an alerting  $\times$  cueing interaction ( $p < 0.05$ ), but it was qualified by the 3-way interaction involving alerting, cueing and group ( $p < 0.05$ ; fig. 2). Further analyses showed an alerting  $\times$  cueing interaction for HC ( $p < 0.01$ ) and DLB ( $p = 0.03$ ) but not for AD ( $F < 1$ ). The interaction in the HC group was due to a larger cueing effect in the alerting-tone condition than in the no-tone condition, although the cueing effect was observed in both alerting conditions ( $p$  values  $< 0.01$ ). For the AD patients, the cueing effect was also observed in both alerting conditions ( $p$  values  $< 0.01$ ), but contrary to the HC group, the size of such an effect did not differ between the 2 alerting conditions ( $F < 1$ ). The DLB patients, however, showed a cueing effect only in the alerting-tone ( $p < 0.01$ ) but not in the no-tone condition ( $F < 1$ ).

**Fig. 3.** Mean RTs as a function of flanker congruency (congruent, incongruent), alerting (tone, no-tone) and group. Only no-cue trials are considered. Errors bars represent mean standard errors.



There was an alerting  $\times$  SOA interaction ( $p < 0.03$ ) that was modulated by the marginally significant 3-way interaction among alerting, SOA and group ( $p = 0.067$ ). The alerting effect did not differ between SOAs for HC and AD ( $F < 1$ ), whereas alerting had an effect in the DLB patients with the long SOA ( $p < 0.01$ ) but not with the short SOA ( $F < 1$ ).

There was a cueing  $\times$  congruency interaction ( $p < 0.01$ ) that showed a larger congruency effect in uncued (congruency effect = 167 ms) than in cued trials (congruency effect = 117 ms).

The second main analysis revealed a 3-way interaction between group, alerting and congruency ( $p = 0.02$ ; fig. 3). The alerting  $\times$  congruency interaction was observed for HC ( $p = 0.015$ ) and DLB ( $p = 0.05$ ) but not for AD ( $F < 1$ ). The alerting  $\times$  congruency interaction in the HC group indicated a larger congruency effect with the alerting tone than without it. The DLB patients, however, showed a congruency effect with the alerting tone ( $p = 0.02$ ) but not in no-tone trials ( $F < 1$ ).

## Discussion

First, the data generated by the HC group showed some interesting results and confirmed the utility of the ANT as a means by which to test interactions among the attention networks. The interaction between cueing and congruency revealed that the visual cue helped focus attention on the target location by filtering out distracting flankers, an operation that has been attributed to the pulvinar nucleus of the thalamus [20]. The interaction between cueing and alerting showed that orienting was more effective with the alerting tone than without it in

both cue-target SOAs, supporting the hypothesis that phasic alerting enhances the functioning of the orienting network [1]. Finally, the interaction between alerting and congruency demonstrated that the tone increased the conflict score, a result that has been interpreted as a reduction in the effectiveness of the executive network to resolve conflict due to the alerting signal [14, 17]. These results obtained with HC participants replicate previous findings and therefore constitute an adequate baseline to assess dementia-related changes in attention network functioning.

The primary attention deficits observed in both AD and DLB patients are found in the network interactions. In the AD patients, for instance, the alerting tone did not improve orienting with either the short or the long SOA, in contrast to what was seen with the HC participants. Phasic alerting triggered by the tone is thought to be a transient alert state that depends on ascending thalamic projections to the right parietal and frontal lobes; this network is modulated by the neurotransmitter norepinephrine coming from the locus ceruleus. It has been shown that phasic alerting can be used to ameliorate right-hemisphere-based orienting deficits in brain-damaged patients [21–23]. Thus, the alerting network seems to coactivate the orienting network, mainly via the region of the parietal cortex involved in spatial orientation of attention [24]. The lack of improvement in orienting in the tone-cued tests in AD participants might be caused by the significant loss of locus ceruleus noradrenergic neurons that is associated with the disease [25]. Such a loss might not have a dramatic impact on the alerting effect, possibly due to top-down modulation of the noradrenergic alerting system coming from the frontal cortex [26], but might still have detrimental

consequences to produce the coactivation of the orienting network. AD patients also seem to have difficulty in maintaining an optimal level of response readiness, which is needed to deal with tasks that require rapid responses. This reduction in sustained alertness might be responsible for the longer RTs of these patients compared with HC.

DBL shared with AD the reduction in sustained alertness and was associated with even longer RTs. However, the DBL patients showed a completely different pattern of attention deficits compared with the AD patients. Alerting effects appeared later in the DBL patients than in AD (the effect was observed only with the long SOA in the former group). Importantly, without the alerting tone, the DLB patients showed neither cueing (orienting) nor congruency (conflict) effects. It seems as if the patients, on their own, were not capable of attaining the minimal activation of alertness needed for both attention and information processing to operate. The observed deficit in alerting is compatible with an important role for the deterioration that occurs in the locus ceruleus noradrenergic system. Also, the DLB patients had serious difficulties in drawing their attention to the cue location, resulting in a lack of orienting effects. Such a deficit is consistent with deterioration in the cholinergic system of the basal forebrain. Finally, these patients had problems processing the target display in both congruent and incongruent trials, resulting in long RTs in both conditions. Interestingly, when an alerting tone was provided before both the cue and the target, the DLB patients successfully regulated their orienting and

conflict effects. These results agree with previous studies that showed that alerting is a basic prerequisite for normal functioning of the other 2 attention networks [27]. The threshold of intensity to recruit the attention system seems to be seriously compromised in DLB patients.

The present study has revealed that the ANT, a task that allows us to assess the different components of attention and their interactions in a single experiment, proved to be useful in comparing and differentiating attention-related deficits in both DLB and AD patients. Concerning cognitive training, previous trials have shown that patients with left-side neglect improve their orienting deficits after an alerting training program [23]. Given that in the present study, the orienting and executive network functioning of the DLB patients was improved by simply providing an auditory warning, it is a matter of future research to assess the usefulness of such training with these patients. With training, an extrinsic alerting condition might lead to a change in intrinsic alertness, similar to what is observed in patients with brain damage undergoing such programs.

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