

# Attention and Fluctuating Attention in Patients With Dementia With Lewy Bodies and Alzheimer Disease

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**Background:** Attentional deficits are described in the consensus clinical criteria for the operationalized diagnosis of dementia with Lewy bodies (DLB) as characteristic of the condition. In addition, preliminary studies have indicated that both attentional impairments and fluctuation of attentional impairments are more marked in patients with DLB than in patients with Alzheimer disease (AD), although neuropsychological function has not previously been examined in a large prospective cohort with confirmed diagnostic accuracy against postmortem diagnosis.

**Methods:** A detailed evaluation of attention and fluctuating attention was undertaken in 155 patients with dementia (85 with DLB and 80 with AD) from a representative hospital dementia case register and 35 elderly controls using the Cognitive Drug Research Computerized Assessment System for Dementia Patients computerized neuropsychological battery. Operationalized clinical diagnosis was made using the consensus criteria for DLB and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for AD. High levels of sensitivity and specificity have been achieved for the first 50 cases undergoing postmortem examination.

**Results:** The groups were well matched for severity of cognitive impairments, but the AD patients were older

(mean age, 80 vs 78 years) and more likely to be female (55% vs 40%). Patients with DLB were significantly more impaired than patients with AD on all measures of attention and fluctuating attention (for all comparisons,  $t \geq 2.5$ ,  $P < .001$ ), and patients from both dementia groups were significantly more impaired than elderly controls for all comparisons other than cognitive reaction time, which was significantly more impaired in DLB patients than controls but was comparable in controls and AD patients. There were, however, significant associations between the severity of cognitive impairment and the severity of both attentional deficits and fluctuations in attention.

**Conclusions:** This large prospective study confirms that slowing of cognitive processing, attention, and fluctuations of attention are significantly more pronounced in DLB and AD patients, although fluctuating attention is common in patients with moderate-to-severe AD. Deficits of cognitive reaction time appear to be specific to DLB, except in severe dementia. A detailed evaluation of attentional performance could make an important contribution to differential diagnosis, although the results need to be interpreted within the context of the overall severity of cognitive deficits.

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**L**EWY BODIES are intraneuronal eosinophilic inclusion bodies that are seen in the brainstem and cortex of patients with Parkinson disease and some patients with dementia. Studies<sup>1-6</sup> have suggested that dementia with Lewy bodies (DLB) accounts for 10% to 25% of dementia cases in clinical populations. An international meeting in 1996 developed operationalized clinical diagnostic criteria<sup>7</sup>; key features included fluctuating cognition associated with disturbances of consciousness, persistent or recurrent visual hallucinations, and parkinsonism. Early and pronounced impair-

ments were described as characteristic and thought to underpin fluctuating cognition, although there have been few empirical studies in this area. The complex array of neuropsychiatric, motor, and cognitive deficits and the extreme sensitivity reactions to neuroleptic drugs experienced by DLB patients raise a number of vital treatment issues that can only be managed optimally with accurate diagnostic assignment.<sup>7</sup> In most studies examining the clinical criteria for the operationalized diagnosis of DLB, the specificity of diagnosis has been high, but sensitivity has been poor.<sup>8</sup> There have been a paucity of studies examining the neuropsychological pro-

## SUBJECTS AND METHODS

The study sample consists of 155 dementia subjects (85 with DLB, 80 with AD) and 35 elderly controls. Patients were recruited from a dementia case register of consecutive referrals to old age psychiatry services in Tyneside, England, with spouses of patients recruited as healthy elderly volunteers. Good diagnostic accuracy has been achieved for the first 50 patients undergoing postmortem examination from the sample of 338 individuals within the overall case register (DLB: sensitivity, 0.83; specificity, 0.91; AD: sensitivity, 0.87; specificity, 0.83<sup>20</sup>). Patients with dementia were matched for the severity of cognitive impairment using the Mini-Mental State Examination (MMSE).<sup>21</sup> All patients were assessed with a structured psychiatric history (history and etiology schedule<sup>22</sup>), a standardized physical examination that incorporated the modified Unified Parkinson's Disease Rating Scale (M-UPDRS),<sup>23</sup> and a validated instrument to evaluate symptoms of depression (Cornell Depression Scale,<sup>24</sup> which in conjunction with questions regarding impact and duration of symptoms was used to diagnose major depression according to *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*<sup>25</sup> criteria). Dementia with Lewy bodies was diagnosed according to the internationally agreed consensus criteria<sup>7</sup> and AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.<sup>26</sup>

The Joint Ethics Committee of Newcastle and North Tyneside Health Authority University of Newcastle Upon Tyne granted ethical approval. Following full explanation and discussion of the study, patients and healthy volunteers gave their consent to the test, with additional assent from the next of kin for all cognitively impaired patients.

### NEUROPSYCHOLOGICAL EVALUATIONS OF ATTENTION AND FLUCTUATING ATTENTION

Subjects were assessed using the COGDRAS-D.<sup>12</sup> Attentional tasks included the following: SRT (20 trials), each

time "yes" was presented in the center of the screen, the participant was required to press the "yes" button as quickly as possible; CRT (30 trials), each time "yes" or "no" was presented in the center of the screen, the participant was required to press the corresponding "yes" or "no" button as quickly as possible (accuracy and reaction time measures were derived); cognitive reaction time (CogRT), calculated by subtracting the SRT from the CRT; VIG (90 trials), a digit was displayed constantly on the right-hand side of the screen (VIGRT) and 90 digits were serially presented (80 min<sup>-1</sup>) in the middle of the screen; participants were required to press "yes" every time that digit matched the digit constantly displayed on the right side of the screen.

Within-trial variability (SD in the attentional measures of CRT) and an overall measure of attentional variability (CRT SD × VIGRT SD) were assessed in single trials, all lasting approximately 90 seconds.

### STATISTICAL ANALYSIS

The mean scores and the measures of variability on the attentional tasks were compared between DLB and AD patients and between both dementia groups and controls using the independent sample *t* test. The same evaluation was completed separately to compare DLB and AD patients with MMSE scores greater than 20 to provide additional information regarding differences in attentional performance and processing speed in patients with mild dementia. The pattern of change in attentional performance with increasing cognitive impairment is described and evaluated with pairwise correlations using the Pearson multivariate correlation coefficient (*R*). All of these evaluations were completed for the overall group and separately, excluding patients who did not attain 50% accuracy on the respective CRT or VIG tasks. Both parkinsonism and depression were considered to be potentially important confounders. The correlation between the M-UPDRS score and each of the attentional measures was evaluated using Pearson multivariate correlation coefficient, and patients with and without major depression were compared using the 2-sample *t* test. Data were analyzed using the SPSS computer software program.<sup>27</sup>

file of DLB and the contribution of neuropsychological evaluation to the diagnostic workup. Expert opinion has highlighted attentional deficits as a key area in DLB,<sup>7</sup> although the empirical evidence base is small.

Hansen et al<sup>1</sup> compared 9 patients with DLB with 9 patients with AD. More severe deficits of attentional function (digit span subtest from the Wechsler Adult Intelligence Scale–Revised) were seen in DLB. Sahgal et al<sup>9</sup> reported that DLB patients had significantly greater impairment on a computerized delayed matching-to-sample task. Ayre et al<sup>10,11</sup> used the Cognitive Drug Research Computerized Assessment System for Dementia Patients (COGDRAS-D) computerized test battery<sup>12</sup> to compare attention in 46 patients with AD and 24 patients with DLB. The DLB group performed significantly worse on simple reaction time (SRT) and choice reaction time (CRT) tasks and digit vigilance (VIG) compared with the AD group.

The overall pattern is consistent, with DLB patients showing significantly greater impairment on a range of attentional tasks. However, each of these studies is mod-

est in size, none including more than 24 patients with DLB, and few had verified accuracy of clinical diagnosis. A larger study, from a cohort with confirmed diagnostic accuracy, is required to confirm the pattern of attentional deficits in DLB.

Fluctuating cognition occurs in all the major dementias and is characterized by periodic shifts in the level of arousal, ranging from episodes of lucidity to reduced awareness and even stupor. Fluctuating cognition occurs in 80% to 90% of patients with DLB<sup>13,14</sup> and in 20% of patients with AD.<sup>15,16</sup> Prevalence rates of 30% to 50% are also reported in vascular dementia.<sup>17,18</sup> Consistent with expert opinion, Walker et al<sup>19</sup> identified a significant association between fluctuating cognition and fluctuating attention, both of which were significantly more severe in DLB than AD patients.

We investigated the hypothesis that attention and fluctuating attention are significantly more impaired in DLB than AD patients in a large representative patient sample, with confirmed diagnostic accuracy.

**Table 1. Attention and Variability in Attention: Comparison of DLB and AD\***

	DLB (n = 85) vs AD (n = 80) Overall		DLB (CRT n = 75, VIG n = 52) vs AD (CRT n = 74, VIG n = 68)†		DLB vs Controls (n = 36)		AD vs Controls (n = 36)	
	t	P	t	P	t	P	t	P
SRT	3.5	<.001	...	...	6.6	<.001	6.6	<.001
SRT variability	4.0	<.001	...	...	5.7	<.001	5.2	<.001
VIG accuracy	5.8	<.001	...	...	11.1	<.001	5.5	<.001
VIG reaction time	5.9	<.001	1.6	.10	7.5	<.001	6.7	<.001
VIG reaction time variability	3.7	<.001	3.4	<.001	8.4	<.001	7.5	<.001
CRT	4.0	<.001	3.7	<.001	6.1	<.001	6.1	<.001
CRT variability	4.0	<.001	3.8	<.001	6.0	<.001	2.6	.01
Cognitive reaction time	2.7	<.001	2.3	.02	3.1	.003	0.2	.84
CRT accuracy	4.4	<.001	...	...	4.2	<.001	2.3	.03
VIG × CRT variability	3.6	<.001	3.0	.003	4.5	<.001	3.2	.002

\*DLB indicates dementia with Lewy bodies; AD, Alzheimer disease; CRT, choice reaction time; VIG, vigilance; SRT, simple reaction time; and ellipses, not applicable.

†Excluding patients with poor accuracy.

**Table 2. Correlations Between Specific Measures of Attention and Processing Speed and Mini-Mental State Examination Score\***

	DLB Overall (n = 85)		AD Overall (n = 80)		DLB With Good Accuracy (CRT n = 75, VIG n = 52)		AD With Good Accuracy (CRT n = 74, VIG n = 68)	
	R	P	R	P	R	P	R	P
SRT	-0.42	.001	-0.22	.06	...	...	...	...
SRT variability	-0.38	.004	-0.38	.001	...	...	...	...
VIG accuracy	-0.35	.009	-0.31	.008	...	...	...	...
VIG reaction time	0.09	.52	-0.11	.35	0.12	.48	-0.22	.08
VIG reaction time variability	-0.34	.001	-0.13	.27	-0.38	.02	-0.23	.06
CRT	-0.43	.001	-0.43	<.001	-0.41	.003	-0.29	.01
CRT variability	0.36	.007	-0.39	<.001	-0.40	.004	-0.26	.03
Cognitive reaction time	-0.21	.11	-0.13	.29	-0.19	.19	-0.13	.27
CRT accuracy	-0.27	.04	-0.11	.36	-0.38	.006	...	...

\*DLB indicates dementia with Lewy bodies; AD, Alzheimer disease; CRT, choice reaction time; VIG, vigilance; SRT, simple reaction time; and ellipses, not applicable. Good accuracy is more than 50% accuracy on choice reaction time tasks.

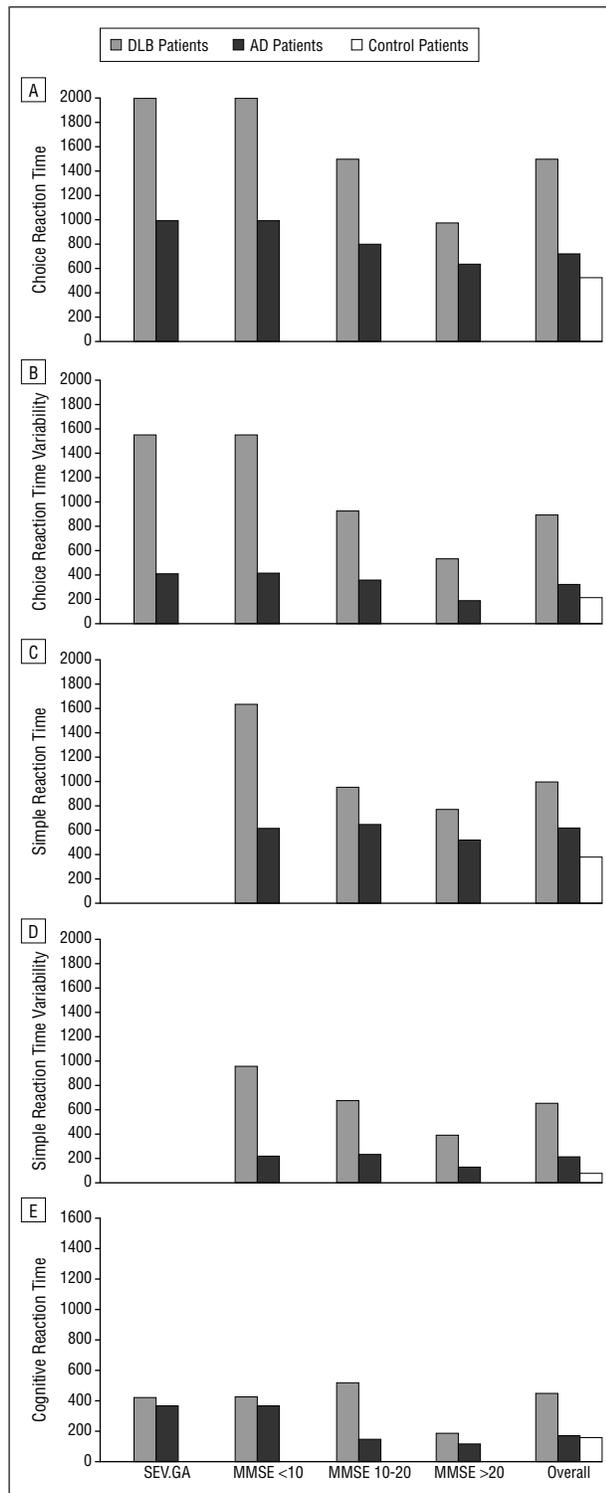
## RESULTS

One hundred fifty-five patients (85 with DLB: 40% female; mean ± SD age, 78.0 ± 6.3 years; mean ± SD MMSE score, 17.3 ± 4.6; 80 with AD: 55% female; mean ± SD age, 79.3 ± 6.8 years; mean ± SD MMSE score, 17.3 ± 4.6) and 35 elderly controls (71% female; mean ± SD age, 73.9 ± 7.4 years; mean ± SD MMSE score, 28.3 ± 1.2) were assessed.

The DLB patients were significantly more impaired than the AD patients on all tests of attention and fluctuating attention. In a repeat analysis excluding patients with less than 50% accuracy on the respective CRT or VIG tasks, differences between the VIGRT of patients with the 2 dementias disappeared, but the DLB patients were more impaired on all of the other tasks (**Table 1**). Both dementia groups were significantly more impaired on SRT, CRT, VIG, and all measures of attentional variability than the elderly controls. Cognitive reaction time was, however, significantly more impaired in DLB patients than controls, but was not significantly more impaired in those with AD than the control group (Table 1), indicating that impairment of CogRT was specific to DLB.

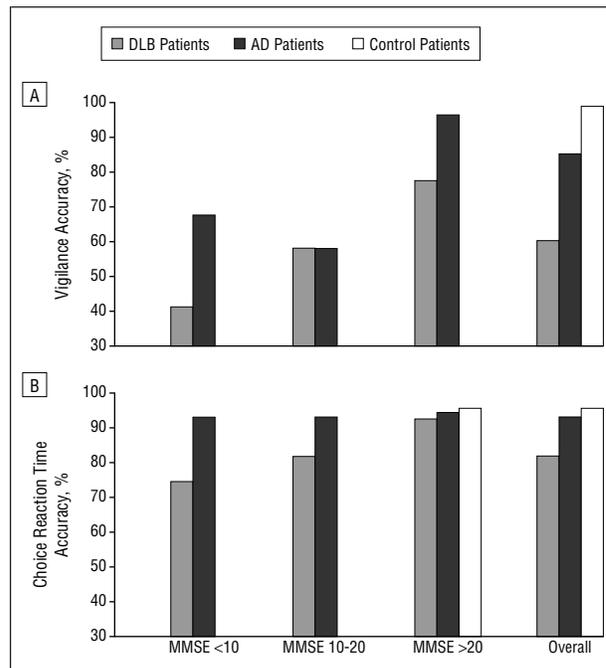
The M-UPDRS score was inversely correlated with VIG accuracy ( $R = -0.26, P = .04$ ), but there were no significant correlations with any of the other parameters (SRT  $R = 0.16, P = .22$ , SRT SD  $R = 0.16, P = .21$ , VIGRT  $R = 0.24, P = .06$ , VIG SD  $R = 0.08, P = .55$ , CRT accuracy  $R = -0.14, P = .28$ , CRT  $R = 0.19, P = .13$ , CRT SD  $R = 0.16, P = .22$ , CogRT  $R = 0.11, P = .45$ ). Major depression was not significantly associated with any of the measures (SRT  $t = 0.4, P = .70$ , SRT SD  $t = 0.6, P = .58$ , VIG accuracy  $t = 0.1, P = .92$ , VIGRT  $t = 0.3, P = .79$ , VIG SD  $t = 0.6, P = .53$ , CRT accuracy  $t = 0.7, P = .47$ , CRT  $t = 0.5, P = .64$ , CRT SD  $t = 0.5, P = 0.67$ , CogRT  $t = 0.1, P = .93$ ).

In both DLB and AD, most measures of attentional performance and most indices of fluctuating attention were significantly correlated to the MMSE score. This effect was still apparent on CRT tasks among DLB patients when excluding the group with poor accuracy (<50%), although it was attenuated to some extent for CRT variability in AD patients with good levels of accuracy (**Table 2**). In both DLB ( $R = 0.21, P = .11$ ) and AD ( $R = 0.13, P = .29$ ), however, there were no significant correlations between MMSE and CogRT.



**Figure 1.** Reaction times (in milliseconds): relationship with severity of cognitive impairment. MMSE indicates Mini-Mental State Examination; SEV.GA, severe dementia (MMSE score <10) with good accuracy (>50%); DLB, dementia with Lewy bodies; and AD, Alzheimer disease. For DLB patients, n=84 (MMSE scores <11, n=8; MMSE score of 11-20, n=61; MMSE score >20, n=15); for AD patients, n=75 (MMSE scores <11, n=6; MMSE score of 11-20, n=54; MMSE score >20, n=15); and for control patients, n=35.

The severity and fluctuation of attentional impairments are particularly pronounced in DLB patients with MMSE scores of 10 or less, even excluding patients with



**Figure 2.** Choice reaction time, accuracy, and vigilance accuracy. MMSE indicates Mini-Mental State Examination; DLB, dementia with Lewy bodies; and AD, Alzheimer disease. For DLB patients, n=84 (MMSE scores <11, n=8; MMSE score of 11-20, n=61; MMSE score >20, n=15); for AD patients, n=75 (MMSE scores <11, n=6; MMSE score of 11-20, n=54; MMSE score >20, n=15); and for control patients, n=35.

poor levels of accuracy (<50%). It should, however, be noted that the differences between DLB patients with MMSE scores greater than 20 and AD patients with MMSE scores of 10 or less were rather modest for most categories of symptoms. Cognitive reaction time was similar in AD patients with MMSE scores of more than 10 and controls, but became more comparable to DLB values in the patients with the lowest MMSE scores (**Figure 1** and **Figure 2**). Statistical comparisons between the DLB (n=15) and AD (n=15) patients with MMSE scores greater than 20 indicated significant differences in VIG accuracy ( $t=2.4, P=.02$ ), CRT ( $t=2.4, P=.02$ ), and CRT variability ( $t=2.6, P=0.01$ ) despite the small sample size.

#### COMMENT

The present study confirms that attentional deficits and fluctuations in attention are substantially more severe in DLB patients than in those with AD, even excluding patients with poor levels of accuracy, and that both dementia groups have greater overall attentional impairments than elderly controls. A number of other factors, such as parkinsonism with slowed motor speed, depression, or general slowing of cognitive processing speed, could theoretically have contributed to these findings. The data evaluation did not, however, indicate that either motor speed or mood was a major confounder. The general slowing of reaction times could certainly imply a slowing of cognitive processing, although the broad deficits CRT and VIG accuracy and reaction times indicate a more widespread impairment of attentional processing.

Cognitive reaction time was the only attentional measure that was impaired in DLB patients compared with controls, but it did not differ significantly between controls and AD patients. Cognitive reaction time is a means of studying the information processing requirements while controlling for perceptuomotor dysfunction. Our findings indicate the possibility that slowed "central processing speed" is a specific neuropsychological feature of DLB, which is not apparent in AD patients with MMSE scores of more than 10. Between-group differences may have been underestimated, since the marked increase of SRT in DLB patients with severe dementia may have skewed the calculation of CogRT in some patients.

The pattern of change of variability in SRT and CRT tasks with increasing severity of dementia also indicated important differences between the 2 dementias. Variability in reaction time increased dramatically with increased cognitive impairment in the DLB patients, but remained fairly static at all levels of impairment in the patients with AD. This supports the hypothesis that fluctuating attention is characteristic of DLB.<sup>7</sup>

In the present study, a standardized computerized battery of attentional tasks was successfully completed by the study participants, who included a number of people with MMSE scores below 10; however, within this more impaired group care needs to be taken when interpreting the information from patients with poor levels of accuracy. This battery can be completed in 15 minutes and appears highly suitable for use in clinical practice. In addition, it clearly has sufficient sensitivity to distinguish among different dementia groups, even in mildly impaired patients. The highly significant differences in attentional performance between DLB and AD patients suggest that detailed neuropsychology could provide an important component of the diagnostic workup, although the significant correlation between attentional performance and overall MMSE score emphasize the need to interpret the results within the context of the overall severity of cognitive impairment for most attentional measures. This relationship diminished to some extent in AD patients when those with poor levels of accuracy were excluded, except for CRT, which remained significantly correlated to MMSE score. Even focusing on DLB patients with good levels of accuracy, a strong relationship to MMSE scores was evident. The exception was CogRT, which was independent of dementia severity in both dementia groups. This finding is difficult to explain and may again be an artifact of the marked increase in SRTs in patients with more severe dementia. The results are also important in emphasizing that fluctuations in attention are common among patients with moderate-to-severe AD.

Both neuropsychological and clinical observations strongly suggest that DLB patients experience great difficulty in sustaining attention. The key role of the cholinergic system in attention,<sup>28-30</sup> fluctuating cognition (particularly attention), and disturbances of consciousness<sup>19</sup> has been well documented.<sup>31</sup> The results of the present study support this hypothesis, with attentional deficits arising in mild cases of DLB, where marked cholinergic loss is an early feature,<sup>32</sup> but not occurring until a much

more advanced stage of the AD, where severe cholinergic deficits are a late feature.<sup>33</sup>

Now that sensitive and practical tests are available, further work using specific receptor ligands in vivo neuroimaging studies, detailed clinicopathological and cliniconeurochemical correlations, and pharmacological challenge can pinpoint more accurately the chemical systems of brain areas that are involved in different aspects of attentional performance. Clearly, the role of cholinesterase inhibitors will be important to investigate in this regard.

## CONCLUSIONS

Overall, slowed processing speed, attentional impairments, and fluctuation in attentional impairments are significantly more severe in DLB than AD patients. However, in both disease groups, deficits of attention become more pronounced with increasing severity of the dementia and hence need to be interpreted within the context of overall cognitive deficits. If interpreted in this way, a more detailed evaluation of attention can make an important contribution to the diagnostic assessment. Perhaps most important, however, deficits of CogRT were specific to DLB patients and were not associated with global cognitive performance and hence should form a core component of the neuropsychological evaluation of these cases. It is also evident that fluctuations in cognition are common in moderate-to-severe AD.

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