HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol. Clin. Exp. **14**, 483–489 (1999)

A Psychophysiological Investigation of Fluctuating Consciousness in Neurodegenerative Dementias

M. P. WALKER[1]*, G. A. AYRE[2], C. H. ASHTON[3], V. R. MARSH[3], K. WESNES[2], E. K. PERRY[1], J. T. O'BRIEN[1], I. G. McKEITH[1] and C. G. BALLARD[1]
[1]*Medical Research Council Neurochemical Pathology Unit, Institute for the Health of the Elderly, Newcastle General Hospital, Newcastle, UK*
[2]*Cognitive Drug Research Ltd, Reading, UK*
[3]*University Department of Psychiatry, Newcastle upon Tyne University, Royal Victoria Infirmary, Newcastle, UK*

Fluctuating levels of consciousness (FC) are a key feature in neurodegenerative dementias, yet clinical identification is poor, hindering accurate diagnosis. One hundred and nineteen patients (32 Dementia with Lewy Bodies (DLB), 57 Alzheimer's disease (AD) and 30 controls) with clinical scores of FC were assessed using an attentional task. Cortical arousal was assessed in 25 of these patients using electroencephalography. Over 90 s both variability in attention ($p < 0{\cdot}0001$) and fluctuations in electrocortical activity ($p < 0{\cdot}0001$) correlated with clinical FC scores, and with each other ($p < 0{\cdot}0001$). Variability in attention and electrocortical arousal are accurate FC markers and can assist differential diagnosis of AD and DLB. Previous work has underestimated the intensity and hence impact of FC in dementia. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — fluctuating levels of consciousness; Dementia with Lewy Bodies; Alzheimer's disease; Choice Reaction Time; electrocortical arousal

INTRODUCTION

Fluctuating levels of consciousness (FC) are common and important in all major neurodegenerative dementias. They are characterised by periodic shifts in the level of arousal from episodes of lucidity to reduced awareness and even stupor. These alterations in consciousness are reported in 80–90 per cent of patients suffering from Dementia with Lewy Bodies (DLB) (Byrne *et al.*, 1989; McKeith *et al.*, 1992), the second most common neurodegenerative dementia (Gomez-Tortosa *et al.*, 1998; Kosaka, 1995), and 20 per cent of patients with Alzheimer's disease (AD) (Kolbeinsson and Jonsson, 1993; Robertson *et al.*, 1998).

Current assessment methods of FC rely on expert clinical judgement. Although symptom recognition has been achieved in some specialist centres, inter-rater reliability is poor (Litvan *et al.*, 1998; McKeith *et al.*, 1996b; Mega *et al.*, 1996), precluding symptom characterisation and evaluation of the impact upon the patient. Improved precision with simple, descriptive screening tests for FC would not only elucidate further the clinical profile but also reveal the consequence of these dramatic fluctuations on daily activities. Moreover, accurate markers of FC could enhance the diagnostic accuracy between degenerative dementia subtypes (Ballard, 1998; McKeith *et al.*, 1996b), a key issue given the severe neuroleptic sensitivity reactions in DLB sufferers (Ballard *et al.*, 1998; McKeith *et al.*, 1995).

Existing theoretical models suggest a severely compromised ascending cholinergic system as the prime candidate in the genesis of FC (Perry *et al.*, 1998; Walker and Ballard, 1998). The reduction in afferent cholinergic projections are believed to result in an unstable level of cortical activation, with corresponding fluctuations in consciousness and cognitive performance, particularly attention (Ayre *et al.*, 1998; McKeith *et al.*, 1995). Investigations using serial measures of electroencephalography EEG and cognitive examinations may therefore prove accurate markers of FC.

*Correspondence to: M. P. Walker, Medical Research Council Neurochemical Pathology Unit, Institute for the Health of the Elderly, Newcastle General Hospital, Newcastle, UK. Tel: +44-191-273-5251. Fax: +44-191-272-5291. E-mail: m.p.walker@ncl.ac.uk

CCC 0885–6222/99/070483–07$17·50

We evaluated attentional performance and electrocortical activity across 90 s, 1 h, and 1 week, in patients clinically diagnosed as AD or DLB and in healthy elderly volunteers. Our hypothesis was that variability in these measures over time would significantly correlate with clinical FC scores.

MATERIALS AND METHODS

One hundred and nineteen subjects were assessed in two cohorts from a dementia case register of consecutive referrals to old age psychiatry services in Tyneside, UK, with an informant in close contact. DLB patients from the register with Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975) scores of over 5, together with AD patients matched for age, gender and dementia severity were recruited, as well as age and gender matched controls. Patients were examined using structured psychiatric and physical assessment (for full methodology see Ballard *et al*., 1998). Identification of FC relied upon the expert clinical judgement of two old age psychiatrists, using a semi-standardised instrument, quantifying the *frequency* and *duration* of FC episodes on a 0–4 scale, based upon an informant interview. Frequency and duration scores were multiplied together to produce an overall severity score from 0 to 12 (by definition a score of 16 is not possible as this would reflect continuous stupor). Operationalised clinical diagnoses were made using the NINCDS ADRDA AD criteria for AD (McKhann *et al*., 1984) and the consensus criteria for DLB (McKeith *et al*., 1996a).

Cohort 1. A pilot group of 25 subjects exhibiting a range of FC scores (11 DLB, 10 AD and 4 healthy elderly volunteers) were assessed. Mean ages for the study groups were: DLB $78{\cdot}7 \pm 6{\cdot}6$, AD $78{\cdot}8 \pm 3{\cdot}9$, healthy elderly volunteers $77{\cdot}5 \pm 4{\cdot}5$. The mean MMSE score was $19 \pm 5{\cdot}7$ for the DLB cohort and $16{\cdot}9 \pm 4{\cdot}2$ for the AD cohort. FC scores ranged from 0 to 12, with a mean FC score of 9 for DLB patients (range 0–12), 2 for AD patients (range 0–4) and 0 for the healthy volunteer group. All subjects underwent neuropsychological and neurophysiological assessment.

Neuropsychological tests

Attentional ability was assessed using a validated, well-tolerated computerised Choice Reaction Time task (CRT) (Simpson *et al*., 1991). The CRT task requires sustained attentional responses across a 90-s period, producing a *within* trial standard deviation (SD) value as a measure of performance variability. The CRT trial was repeated three times in 1 h and a further three times over 1 week, again using SD *across* each time frame as a measure of fluctuation. The coefficient of variation (CV) was applied to account for any differences in mean length of reaction time.

Neurophysiological tests

Electroencephalography was recorded from 17 primary channel electrodes, placed according to the international 10–20 system. The power frequency spectra were calculated on the average of 45×2 s epochs of resting eyes open (REO) and resting eyes closed (REC) in three separate trials across 1 h. The total averaged power values ($\mu V^2/Hz$) for all electrodes were calculated in the delta (0–3·9 Hz), theta (4–7·9 Hz), alpha (8–14 Hz) and beta (14·1–26 Hz) frequency bands. For each frequency band, the SDs *across* the three repeat trials in 1 h were used as a measure of fluctuating electrocortical activity.

Visual evoked potentials (VEPs) were elicited using an 'oddball paradigm'. The averaged amplitude (μV) and latency (ms) of the P_{300} waveform for each of the three trials *across* 1 h were measured; peak to peak N_2P_{300} for amplitude and time of P_{300} peak after stimulus presentation for latency. Standard deviations in both P_{300} amplitude and latency *across* all three trials were calculated as correlates of fluctuating cortical cognitive ability.

Cohort 2. A second larger cohort of 94 subjects (22 DLB, 46 AD and 26 healthy elderly volunteers) exhibiting a range of FC scores were assessed using the same standardised clinical protocol (except for cognitive impairment), which was evaluated using the Cambridge Assessment for mental disorders in the elderly, section B-CAMCOG (Roth *et al*., 1986).

There were 55 (58 per cent) female subjects, and their mean ages were: DLB $77 \pm 7{\cdot}7$, AD $80 \pm 7{\cdot}2$ and healthy elderly volunteers $74 \pm 7{\cdot}7$. Mean CAMCOG scores were $61{\cdot}5 \pm 17{\cdot}5$ for DLB patients and $63 \pm 16{\cdot}1$ for those with AD. FC scores in this cohort ranged from 0 to 12, with a mean FC score of 6 for DLB patients, 1 for AD patients and 0 for the healthy volunteer group.

All subjects were assessed using a single 90s CRT trial (see *Neuropsychological tests*).

Statistical analysis

Correlations used Spearman's rank method, comparing the clinical FC score (0–12) against variability in CRT (separately for SD and CV). An optimal cut-off in CRT variability, derived from cohort 1, was used to calculate sensitivity, specificity, positive predictive value and negative predictive value for distinguishing DLB from AD in the combined cohort.

RESULTS

Neuropsychology

Cohort 1. Highly significant correlations were found between the FC score and both the within trial 90-s CRT variability ($r = 0{\cdot}67$, $p < 0{\cdot}0001$) and across trial 1-h variability ($r = 0{\cdot}67$, $p < 0{\cdot}0001$), but not across 1 week ($r = 0{\cdot}40$, $p < 0{\cdot}09$), with the CV producing similar results (90-s CRT: $r = 0{\cdot}41$, $p < 0{\cdot}003$; 1-h CRT: $r = 0{\cdot}56$, $p < 0{\cdot}001$; 1-week CRT: $r = 0{\cdot}36$, $p < 0{\cdot}10$). These correlations remained positive when focused within specific disease groups for the 90-s and 1-h time frames using SD (90-s: DLB $r = 0{\cdot}76$, $p < 0{\cdot}0001$, AD $r = 0{\cdot}54$, $p < 0{\cdot}001$; 1-h: DLB $r = 0{\cdot}58$, $p < 0{\cdot}0001$, AD $r = 0{\cdot}69$, $p < 0{\cdot}0001$). The level of variability in performance for individual subjects was similar across both 90-s and 1-h time frames ($r = 0{\cdot}70$, $p < 0{\cdot}0001$). Comparative CRT performance examples are shown in Figure 1.

Neurophysiology

EEG power spectrum

FC score correlations. Significant associations were apparent between the clinical FC score and the variability (SD) in the delta power spectrum across the 1-h period (REO: $r = 0{\cdot}42$, $p < 0{\cdot}03$; REC: $r = 0{\cdot}44$, $p < 0{\cdot}02$; Figures 2a,b) and also with the total averaged power in the theta band (REO: $r = 0{\cdot}35$, $p < 0{\cdot}08$; REC: $r = 0{\cdot}40$, $p < 0{\cdot}05$). All the results are shown in Tables 1 and 2.

Between group correlations. Variability in theta band power across 1 h significantly discriminated between the healthy volunteers and dementia

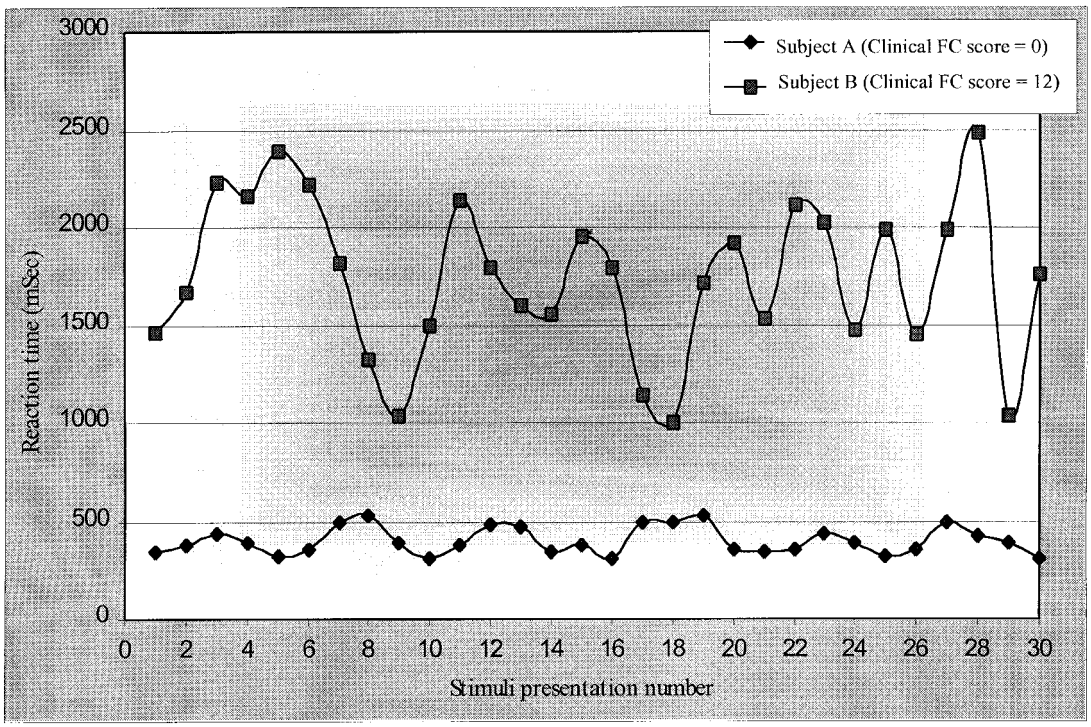

Figure 1. Fluctuating profiles in CRT across a single 90-s trial for two individual subjects of different clinical FC scores. Subject A does not suffer from FC (0), demonstrating a relatively consistent and fast CRT attentional performance. Subject B suffers severely from FC (12), demonstrating a slower, continuously variable pattern of CRT attentional performance

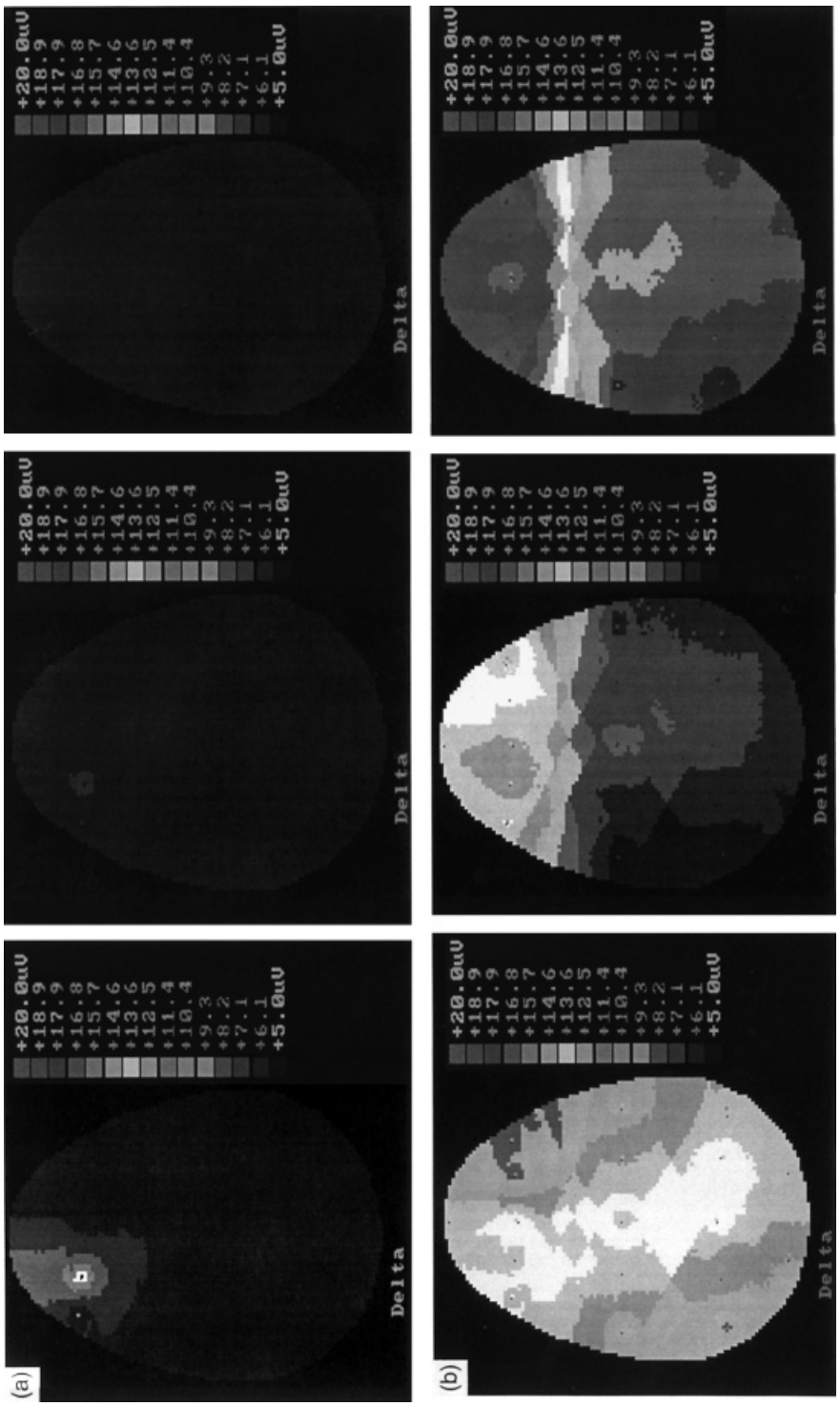

Figure 2. (a) Topographical brain maps illustrating stability in repeat trials of delta power (μV^2/Hz) across 1 h in the resting eyes closed paradigm for a subject with a clinical FC score of 0. (b) Topographical brain maps illustrating variability in repeat trials of delta power (μV^2/Hz) across 1 h in the resting eyes closed paradigm for a subject with a clinical FC score of 12

Table 1. Spearman's correlation coefficient analysis between variability (SD) in band frequency power across three repeat trials in 1 h and clinical FC scores for resting eyes open (REO) and resting eyes closed (REC) paradigms ($n = 25$). N/S indicates a non-significant result

Power band	Resting eyes open (REO) paradigm	Resting eyes closed (REC) paradigm
Delta	$r = 0{\cdot}42$ ($p = 0{\cdot}03$)	$r = 0{\cdot}44$ ($p = 0{\cdot}02$)
Theta	$r = 0{\cdot}30$ (N/S)	$r = 0{\cdot}29$ (N/S)
Alpha	$r = 0{\cdot}25$ (N/S)	$r = 0{\cdot}18$ (N/S)
Beta	$r = 0{\cdot}39$ (N/S)	$r = 0{\cdot}17$ (N/S)

Table 2. Spearman's correlation coefficient analysis between total average band frequency power ($\mu V^2/Hz$) across three repeat trials in 1 h and clinical FC scores for resting eyes open (REO) and resting eyes closed (REC) paradigms ($n = 25$). N/S indicates a non-significant result

Power band	Resting eyes open (REO) paradigm	Resting eyes closed (REC) paradigm
Delta	$r = 0{\cdot}34$ (N/S)	$r = 0{\cdot}26$ (N/S)
Theta	$r = 0{\cdot}35$ ($p = 0{\cdot}08$)	$r = 0{\cdot}40$ ($p = 0{\cdot}05$)
Alpha	$r = 0{\cdot}08$ (N/S)	$r = 0{\cdot}36$ (N/S)
Beta	$r = 0{\cdot}04$ (N/S)	$r = 0{\cdot}01$ (N/S)

cohorts (REO Mann Whitney U-test: $z = 2{\cdot}7$, $p < 0{\cdot}006$; REC Mann Whitney U-test: $z = 2{\cdot}0$, $p < 0{\cdot}03$), but did not differentiate between the dementia subtypes.

Significant correlations were evident independently between fluctuating CRT performance and delta power band variability (REO: $r = 0{\cdot}438$, $p < 0{\cdot}02$; REC: $r = 0{\cdot}447$, $p < 0{\cdot}02$) demonstrating strong internal consistency for these markers of FC.

Visual evoked potential P_{300} measures. Fifteen of the 25 subjects (8 DLB, 7 AD, and 4 healthy elderly volunteers) completed the VEP trials (mean FC scores: DLB = 8, AD = 1 and elderly volunteers = 0).

FC score correlation. Variability in the P_{300} latency demonstrated a trend towards correlating significantly with clinical FC scores at electrode sites P_z, P_3 and P_4 ($r = 0{\cdot}41$, $p < 0{\cdot}07$; $r = 0{\cdot}43$, $p < 0{\cdot}06$; $r = 0{\cdot}43$, $p < 0{\cdot}06$, respectively). Significant negative associations were evident between the total averaged amplitude and clinical FC score at P_z, P_3 and P_4 ($r = -0{\cdot}49$, $p < 0{\cdot}03$; $r = -0{\cdot}45$, $p < 0{\cdot}05$; $r = -0{\cdot}45$, $p < 0{\cdot}05$, respectively).

Cohort 2. Again, highly significant correlations were seen between 90-s variability in CRT and the clinical FC score (SD: $r = 0{\cdot}53$, $p < 0{\cdot}0001$; CV: $r = 0{\cdot}42$, $p < 0{\cdot}0001$). Correlations remained significant when focused within each disease group (DLB: $r = 0{\cdot}52$, $p < 0{\cdot}001$; AD: $r = 0{\cdot}37$, $p < 0{\cdot}01$).

When combining data from the two cohorts ($n = 119$), the 90-s CRT variability continued to correlate strongly with clinical FC score (SD: $r = 0{\cdot}54$, $p < 0{\cdot}0001$; CV: $r = 0{\cdot}48$, $p < 0{\cdot}0001$), and significantly differentiated between the two dementia types (Mann Whitney U-test: $z = 2{\cdot}7$, $p < 0{\cdot}006$). The optimal 90-s CRT SD cut-off value of >450 ms, derived from cohort 1, discriminated well between the two dementias (sensitivity 45 per cent, specificity 93 per cent, positive predictive value 79 per cent, negative predictive value 74 per cent).

DISCUSSION

One hundred and nineteen patients were investigated in two cohorts from a case register with established accuracy of clinical diagnosis against neuropathological assessment. Variability in attentional performance, measured using a CRT trial, proved to be a sensitive marker of FC both within 90 s and in repeat tests across 1 h. Furthermore, this effect held separately in both AD and DLB patients, providing compelling evidence that variability in attention is closely related to FC.

Fluctuations in electrocortical activity across 1 h, measured using EEG, also correlated with clinical scores of FC, and with the measure of variable CRT performance. The variable pattern of neural activity displayed in the EEG, particularly in the slow delta frequency band, could be key in the genesis of FC. The significant correlation between variability in the cognitive P_{300} waveform and FC score, indicate considerable variability and deficiency in cortical cognitive responses in the most severely affected patients. These results add significantly to the hypothesis that a strong relationship exists between fluctuating cortical excitation and FC.

This study clearly demonstrates a continually fluctuating symptom profile for FC, indicating past clinical observations may have seriously underestimated the prevalence and the impact which this symptom has on daily performance, making tasks of sustained attention particularly difficult. Hence, there is a need to specifically target FC in clinical

trials, which should prove feasible with the development of a reliable measurement tool.

In the combined cohort, good discrimination was seen between AD and DLB cases using the optimal CRT cut-off derived from the pilot cohort. A specificity of 93 per cent was achieved for the diagnosis of DLB cases. It is suggested that fluctuating CRT performance should be included within the framework of the existing clinical criteria for DLB (McKeith *et al*., 1996a), particularly considering its brevity and simplicity. It also avoids the problems of inter-rater reliability seen with clinical FC assessments (Litvan *et al*., 1998; McKeith *et al*., 1996b; Mega *et al*., 1996). The current data also suggest that this method will be a helpful adjunct in excluding an operationalised clinical diagnosis of AD.

It has been proposed that FC, and thus fluctuating cognitive abilities including attention (McKeith *et al*., 1996), result from an impaired ascending cholinergic activating system (Perry *et al*., 1998; Walker and Ballard, 1998). The present findings are consistent with this hypothesis. These new assessment tools will now facilitate specific correlative studies in this area.

CONCLUSION

Variability in attentional performance and electrocortical activity are closely correlated with FC, forming reliable assessment tools that identify a continually fluctuating clinical topography. Such measures highlight the likely impact of FC, which should be targeted specifically as a key symptom in treatment trials. CRT variability also significantly differentiated AD from DLB, with additional diagnostic implications.

ACKNOWLEDGEMENTS

We would like to thank the Medical Research Council for supporting this research project and CDR Ltd for the provision of the neuropsychological testing software.

REFERENCES

Ayre, G., Ballard, C., Pincock, C., McKeith, I., Sahgal, A. and Wesnes, K. (1998). Double dissociation between dementia with Lewy bodies and Alzheimer's disease on tests of attentional and mnemonic function: the role of the basal forebrain. *Journal of Psychopharmacology*, **A12**(suppl), A64.

Ballard, C. G. (1998). Dementia with Lewy bodies [Commentary]. *Advances in Psychiatric Treatments*, **4**, 366–368.

Ballard, C., Grace, J., McKeith, I. and Holmes, C. (1998). Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease. *Lancet*, **351**, 1032–1033.

Ballard, C. G., O'Brien, J., Lowery, K., Ayre, G. A., Harrison, R., Perry, R., Ince, P., Neill, D. and McKeith, I. G. (1998). A prospective study of dementia with Lewy bodies. *Age & Ageing*, **27**, 631–636.

Byrne, E. J., Lennox, G., Lowe, J. and Godwin-Austen, R. B. (1989). Diffuse Lewy body disease: clinical features in 15 cases. *Journal of Neurology, Neurosurgery & Psychiatry*, **52**, 709–717.

Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Mini-Mental State". A practical method for grading the cognitive state of patients for the Clinician. *Journal of Psychiatric Research*, **12**, 189–198.

Gomez-Tortosa, E., Ingraham, A. O., Irizarry, M. C. and Hyman, B. T. (1998). Dementia in Lewy bodies. *Journal of the American Geriatrics Society*, **46**, 1449–1458.

Kolbeinsson, H. and Jonsson, A. (1993). Delirium and dementia in acute medical admissions of elderly patients in Iceland. *Acta Psychiatrica Scandinavica*, **87**, 123–127.

Kosaka, K. (1995). Diffuse Lewy body disease. *Clinical Neurology*, **35**, 1455–1456.

Litvan, I., MacIntyre, A., Goetz, C. G., Wenning, G. K., Jellinger, K., Verny, M., Bartko, J. J., Jankovic, J., McKee, A., Brandel, J. P., Chaudhuri, K. R., Lai, E. C., D'Olhaberriague, L., Pearce, R. K. B. and Agid, Y. (1998). Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. *Archives of Neurology*, **55**, 969–978.

McKeith, I. G., Ballard, C. G. and Harrison, R. W. S. (1995). Neuroleptic sensitivity to risperidone in Lewy body dementia [3]. *Lancet*, **346**, 699.

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., *et al*. (1996a). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*, **47**, 1113–1124.

McKeith, I. G., Galasko, D. and Quinn, N. (1996b). Resume of clinical workshop sessions. In *Dementia with Lewy Bodies*, Perry, R. H., McKaith, I. G. and Perry, E. K. (Eds), Cambridge University Press, Cambridge, pp. 187–192.

McKeith, I. G., Perry, R. H., Fairbairn, A. F., Jabeen, S. and Perry, E. K. (1992). Operational criteria for senile dementia of Lewy body type (SDLT). *Psychological Medicine*, **22**, 911–922.

McKhann, G., Drachman, D., Folstein, M., *et al*. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*, **34**, 939–944.

Mega, M. S., Masterman, D. L., Benson, D. F., Vinters, H. V., Tomiyasu, U., Craig, A. H., Foti, D. J., Kaufer, D., Scharre, D. W., Fairbanks, L. and Cummings, J. L. (1996). Dementia with Lewy bodies: reliability and validity of clinical and pathologic criteria. *Neurology*, **47**, 1403–1409.

Perry, R., Walker, M. and Perry, E. K. (1998). Dementia with Lewy bodies: a new avenue for research into neurobiological mechanisms of consciousness? In *Progress in Alzheimer's and Parkinson's Disease*, Fisher, E. (Ed.), Plenum, New York, pp. 451–462.

Robertson, B., Blennow, K., Gottfries, C. G. and Wallin, A. (1998). Delirium in dementia. *International Journal of Geriatric Psychiatry*, **13**, 49–56.

Roth, M., Tym, E., Moutjoy, C. Q., *et al*. (1986). CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *British Journal of Psychiatry*, **149**, 698–709.

Simpson, P. M., Surmon, D. J., Wesnes, K. A. and Wilcock, G. K. (1991). The cognitive drug research computerized assessment system for demented patients: a validation study. *International Journal of Geriatric Psychiatry*, **6**, 95–102.

Walker, M. and Ballard, C. G. (1998). Dementia with Lewy bodies. *CNS*, **47**, 1113–1124.

