Qualitative performance characteristics differentiate dementia with Lewy bodies and Alzheimer’s disease

E K Doubleday, J S Snowden, A R Varma, D Neary

J Neurol Neurosurg Psychiatry 2002;72:602–607

Objective: To determine whether dementia with Lewy bodies (DLB) and Alzheimer’s disease (AD) can be differentiated on the basis of qualitative performance characteristics during neuropsychological evaluation.

Methods: Forty one patients with clinically defined DLB were matched with 26 patients with AD for age, illness duration, nature and severity of cognitive deficits, and regional blood flow distribution on SPECT. The presence or absence of a set of qualitative performance characteristics, observed and recorded during the patients’ initial cognitive evaluation, was identified by retrospective analysis of patients’ records and the groups compared.

Results: Inattention, visual distractibility, impairments in establishing and shifting mental set, incoherence, confabulatory responses, perseveration, and intrusions were significantly more common in DLB than AD. Intrusions were particularly common in DLB, occurring in 78% of the group. They included externally cued intrusions arising from the visual environment, a feature never seen in AD. In a stepwise logistic regression analysis impaired mental set shifting, perseveration, and the presence of intrusions correctly classified 79% of patients.

Conclusion: It is possible to differentiate DLB and AD on the basis of qualitative features of performance. As many features are amenable to detection at clinical interview, they ought to contribute to clinicians’ diagnostic armoury, leading to improved clinical recognition of DLB.

The current diagnostic criteria for “probable” dementia with Lewy bodies (DLB) require the presence of cognitive impairment, together with two of the following: hallucinations, fluctuations in mental state, and extrapyramidal signs. Cognitive impairment may be the most prominent feature. Comparative studies of DLB and Alzheimer’s disease (AD) have suggested that memory impairment is less severe in DLB than AD, whereas visuo-perceptual, visuospatial, and constructional abilities are more impaired. Nevertheless, impairments in perception, spatial function, constructional abilities, and memory occur in both DLB and AD, so that consideration of the severity of dysfunction may have limited value in the diagnosis of an individual patient in a clinical setting. As yet, no unique neuropsychological pattern has been identified in DLB that clearly differentiates it from AD. Neuroimaging also has limited differentiating value. Although some studies have found that patients with DLB more commonly have reduced perfusion in the occipital lobes than patients with AD, others have failed to find any significant differences between the patterns of regional cerebral blood flow distribution.

In view of the combination of cortical and prominent subcortical pathology in DLB and the characteristic fluctuating mental state, patients with DLB might be expected to share neuropsychological characteristics of other confusional states—for example, those caused by metabolic encephalopathies—in which there is both cortical and subcortical dysfunction. Patients in confusional states typically show poor sustained and selective attention, they are easily distracted from the task at hand, and they have difficulties in establishing, maintaining, and shifting mental set. Responses are perseverative and may include intrusions from irrelevant stimuli. Additionally, there is marked fluctuation in the severity of deficits from moment to moment and from day to day.

There is evidence that patients with DLB perform worse than patients with AD on formal tests of sustained, selective, and divided attention. It might be anticipated that impairments in attention and fluctuations in mental state ought to be reflected in different qualitative patterns of behaviour and test performance in DLB compared with AD. The purpose of the present study was to test the prediction that patients with DLB and those with AD, matched for overall severity and nature of cognitive deficits, will exhibit qualitative differences in their pattern of performance and that patients with DLB will show performance characteristics akin to those of metabolic confusional states. The identification of such qualitative characteristics ought to be of value in the clinical differentiation of DLB and AD.

METHODS

Patients

Dementia with Lewy bodies group

The study group comprised 41 consecutive patients, referred to a regional diagnostic dementia clinic, who exhibited clinical features of DLB. Twenty six patients (63%) presented initially with cognitive and/or behavioural changes, and thus fulfilled diagnostic criteria for DLB as strictly defined. The remaining 15 patients (37%) had developed mental symptoms in the course of established and long standing parkinsonism, but were otherwise clinically similar to the 26 patients. At the time of investigation 71% of the total group had visual hallucinations and 71% were reported by relatives to fluctuate in their mental state from day to day or during the course of a day. Extrapyramidal signs were present in 93% of patients on neurological examination. Patients in whom hallucinations had coincided with an alteration in medication for parkinsonism were not included in the study. The clinical diagnosis of
DLB has subsequently been confirmed in four of the 41 patients at necropsy. The presenting cognitive symptom in 46% of patients with DLB was of memory impairment and in 5% of difficulties in language expression. The remaining 49% presented with a combination of memory, visuo-perceptual, and language disturbances. Functional imaging using single photon emission tomography (SPECT) disclosed the presence of posterior hemispheric abnormalities in 94% of patients with DLB; in 41% these were selective and in 53% they were combined with anterior hemispheric abnormalities. Only 3% of patients showed selective abnormalities in the anterior hemispheres. In 3% of patients SPECT findings were reported to be normal.

Demographic and clinical features are summarised in table 1.

Alzheimer’s disease group
Twenty-six patients with AD, attending the regional diagnostic dementia clinic, served as a comparison group. Patients exhibited impairments in memory and other domains of cognitive functioning, in the context of physical wellbeing and no impairment of consciousness, in keeping with current clinical criteria for AD. The diagnosis of AD has subsequently been confirmed in three of the 26 patients at necropsy. In no patient with AD was there a history of fluctuating mental state or of visual hallucinations.

The patients with AD were selected to be as closely matched as possible to the DLB group on a range of demographic and clinical variables (table 1). The AD group did not differ significantly from the DLB group in age, illness duration, years of education, overall severity of cognitive impairment as measured by the mini mental state examination (MMSE), and in conjunction with historical and neurological examination (table 2). The instrument, which has been previously described, carries some similarities to the CAMDEX, although it emphasises the qualitative analysis of patients’ performance, such as error type and behaviour during testing, in addition to accuracy scores. Cognitive profiles elicited by the instrument show a strong relation to findings on functional imaging, and in conjunction with historical and neurological data have yielded a 97% accuracy of clinical diagnosis in 200 pathologically verified cases of dementia in this centre.

Qualitative aspects of patients’ behaviour, found during the course of the testing session, which lasts about 1 hour, are systematically recorded by trained examiners. Features are reported only as present or absent, in view of the difficulty in determining severity.

Features include:
- General inattention: inability to maintain vigilance and attention during the test period.
- Distraction: (a) visual—that is, attending and responding to irrelevant visual stimuli in the immediate environment (for example, during the test, patient comments at an inappropriate time on an object on the shelf); (b) auditory—that is, attending and responding to irrelevant auditory stimuli in the immediate environment (for example, during the test, patient comments irrelevantly on phone ringing in adjacent room).
- Impaired mental set establishment—that is, impairment in initial engagement in test procedure.
- Impaired mental set shifting—that is, impairment in the smooth and appropriate sequential transition from one task to the next.

### Table 1
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DLB</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F:26</td>
<td>M:14</td>
</tr>
<tr>
<td>Age at onset (mean y (SD))</td>
<td>68 (5)</td>
<td>65 (7)</td>
</tr>
<tr>
<td>Duration (mean y (SD))</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Education &lt;12 years</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>12 years</td>
<td>8</td>
</tr>
<tr>
<td>MMSE/30 (mean (SD))</td>
<td>15 (8)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>CDR (mean (SD))</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Method of evaluation
At the time of their initial clinical neurological assessment all patients had undergone a neuropsychological evaluation using a locally constructed cognitive screening instrument, designed to provide a profile of performance across a wide range of cognitive functions: language, perception, spatial abilities, praxis, memory, and frontal/executive functions (table 2). The instrument, which has been previously described, bears some similarities to the CAMDEX, although it emphasises the qualitative analysis of patients’ performance, such as error type and behaviour during testing, in addition to accuracy scores. Cognitive profiles elicited by the instrument show a strong relation to findings on functional imaging, and in conjunction with historical and neurological data have yielded a 97% accuracy of clinical diagnosis in 200 pathologically verified cases of dementia in this centre.

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### Table 2
<table>
<thead>
<tr>
<th>Domain</th>
<th>Neuropsychological tasks constituting the neuropsychological profile assessing each domain of cognitive functioning</th>
<th>Median rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Immediate and delayed free recall, cued recall and recognition of a story (/12), recalling and recognising famous faces after a delay (/9), orientation for time and place (/10)</td>
<td>DLB 0 AD 1</td>
</tr>
<tr>
<td>Language</td>
<td>Conversational speech, series speech, description, word repetition, reading, writing, spelling</td>
<td>DLB 1 AD 2</td>
</tr>
<tr>
<td>Perception</td>
<td>Identification of 10 line drawings and nine famous faces</td>
<td>DLB 2 AD 2</td>
</tr>
<tr>
<td>Spatial function</td>
<td>Tracing road map, locating the centre of a circle, line bisection, copying drawings, geographical localisation</td>
<td>DLB 1 AD 1</td>
</tr>
<tr>
<td>Executive function</td>
<td>Picture sequencing, copying motor hand sequences, Weigl’s blocks (/9)</td>
<td>DLB 0 AD 1</td>
</tr>
</tbody>
</table>
• Incoherent line of thought—that is, verbal responses that are tangential, illogical, irrational departures from the designated subject or topic of conversation.

• Confabulation—that is, introduction of fictional elaborations in test responses (for example, in recalling a story, patient adds extraneous, elaborate elements).

• Perseveration—that is, repetition of the immediately preceding verbal or motor response (for example, patient correctly names picture as “scissors” but then also names next picture as “scissors”).

• Intrusions—that is, irrelevant responses which are: (a) related to previously presented test material. These within test intrusions may occur from (1) interference of earlier memory test material in memory tasks (memory interference), for example, elements from one story included in the patient’s account of a second story, (2) interference of previous tasks in non-memory verbal tasks (language interference), for example, in reciting months, the patient says “England” (patient had previously been asked to name the country), or (3) interference of previous motor actions in a later motor task (motor interference); (b) semantically associated with the test material (associative intrusions), for example, in an animal category fluency task, patient says “donkey”, followed by “Bethlehem”; (c) not related to preceding test material, but arise from stimuli in the surrounding environment (environmentally cued intrusions), for example, public sign “fire exit” interpolated irrelevance into an otherwise appropriate speech utterance.

The neuropsychological screening is carried out independently of clinical history taking, neurological examination, and neuroimaging and in patients in whom a clinical diagnosis is not yet made. These initial assessments were carried out by two of us (JS and AV) before and hence blind to clinical diagnosis, with a comparable balance between DLB and AD assessments for the two examiners.

The present study involved an analysis of recorded information, obtained from this initial neuropsychological screen and documented in written reports.

### Procedure

The evaluation of data was carried out by an independent rater ED who had not been involved in the original assessments and had no clinical contact with the patients. The rater documented each qualitative behavioural characteristic and error type as present or absent based on the examiner’s written report and the raw test data. Inattention, visual and auditory distractibility, impaired mental set establishment, and shifting were recorded as present only if those features had been explicitly reported as characterising the patients’ performance. Incoherence, perseverations, confabulations, and intrusions were recorded as present based on the examiner’s explicit report, supported by an examination of test errors.

### Results

#### Comparison of DLB and AD

Inattention, visual distractibility, impairment in establishing and shifting mental set, incoherent line of thought, confabulation, perseveration, and intrusions were all significantly more common in the DLB than the AD group (table 3), and many of the features were specific to DLB. The most marked group differences were in intrusions. Intrusions representing interference from previous tasks occurred in both groups to some degree, whereas environmentally cued intrusions were present only in patients with DLB (Fisher’s exact test \( p<0.005 \), fig 1). That is, patients with DLB incorporated irrelevently into general conversation and into their test responses, the names of extraneous objects in the immediate environment or a word or phrase from a public notice on which their glance happened

#### Table 3: Qualitative features of performance in patients with DLB and AD

<table>
<thead>
<tr>
<th>Feature</th>
<th>DLB (%)</th>
<th>AD (%)</th>
<th>Fisher’s exact test ( p ) value (1 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General inattention</td>
<td>17</td>
<td>0</td>
<td>0.03*</td>
</tr>
<tr>
<td>Distraction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>20</td>
<td>0</td>
<td>0.02*</td>
</tr>
<tr>
<td>Auditory</td>
<td>2</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>Impaired mental set establishment</td>
<td>22</td>
<td>0</td>
<td>0.008**</td>
</tr>
<tr>
<td>Impaired mental set shifting</td>
<td>32</td>
<td>8</td>
<td>0.03*</td>
</tr>
<tr>
<td>Incoherent line of thought</td>
<td>17</td>
<td>0</td>
<td>0.03*</td>
</tr>
<tr>
<td>Confabulation</td>
<td>17</td>
<td>0</td>
<td>0.03*</td>
</tr>
<tr>
<td>Perseveration</td>
<td>68</td>
<td>27</td>
<td>0.001**</td>
</tr>
<tr>
<td>Intrusions (total)</td>
<td>78</td>
<td>27</td>
<td>0.000***</td>
</tr>
</tbody>
</table>

\* \( p<0.05 \); \** \( p<0.01 \); \*** \( p=0.000 \).
momentarily to fall (for example, question: What programmes do you watch on television? Answer: “I watch programmes about the fire exit”). With regard to within test intrusions, both language interference (Fisher’s exact test \(p=0.005\)) and memory interference (Fisher’s exact test \(p=0.03\)) were significantly more frequent in the DLB group (fig 1), with the largest difference between DLB and AD occurring in non-memory verbal tasks, such as naming. Associative intrusions occurred only in the DLB group, although group differences did not reach formal levels of statistical significance (Fisher’s exact test \(p=0.08\)).

A stepwise logistic regression analysis identified impaired mental set shifting, perseveration, and the presence of intrusions as the combination of variables that best discriminated the groups. These three variables accurately classified 88% of the DLB group and 65% of the AD group, giving an overall accuracy of 79%.

To determine the potential discriminating value of specific types of intrusions the generic variable of “intrusions” was removed from the analysis and a further forwards stepwise logistic regression analysis was undertaken. Language interference and perseveration classified 78% of the DLB group and 62% of the AD group, giving an overall classification accuracy of 72%.

Feature frequencies had been determined on the basis of documented reports of individual patients by two of us (JS and AV). There was no difference in the frequency with which we documented any of the qualitative performance characteristics, indicating consistency of report across examiners.

**Effect of DLB presentation on performance**

Patients who develop clinical features of DLB in the context of longstanding parkinsonism do not strictly fulfil diagnostic criteria for DLB criteria as currently defined.1 When this subgroup of patients were removed from the DLB versus AD comparisons, the pattern of findings remained essentially unchanged, the only difference being that the presence of confabulation and memory interference no longer reached significance. Direct comparisons between the subgroup of patients with DLB presenting with cognitive/behavioural change and the group presenting with parkinsonism showed no differences in the frequency of qualitative features in the two subgroups.

**Interrelation between qualitative features**

Given the assumption that qualitative characteristics may relate to inattention, the interrelation in patients with DLB between inattention and each of the qualitative characteristics of performance was examined using contingency coefficients. A significant association was found between the presence of general inattention and visual distraction (contingency coefficient, \(p=0.03\)), environmentally cued intrusions (contingency coefficient, \(p=0.03\)), and impaired mental set establishment (contingency coefficient, \(p=0.01\)). No other interrelations reached significance. The association between visual distraction and environmentally cued intrusions was also examined, because both involve environmental visual stimuli. The two were not significantly related. To determine the relation between characteristics of test performance in patients with DLB and the historical report of fluctuating mental state, contingency coefficients were calculated for each variable. Fluctuating mental state was not significantly associated with the presence of any qualitative characteristics.

**DISCUSSION**

The study examined the hypothesis that patients with DLB would be more likely than patients with AD to exhibit qualitative performance characteristics akin to those found in metabolic confusional states. The DLB and AD groups in the present study were well matched on a range of demographic and clinical variables. They were relatively youthful, reflecting the pattern of referral to a neurological dementia clinic. They had a similar overall level of severity of cognitive impairment, a similar profile of deficits across cognitive domains, and consistent with previous reports,16-17 a similar pattern of functional imaging abnormalities on SPECT. Nevertheless, in keeping with prediction, there were significant qualitative differences in test performance between the two groups. Patients with DLB were more likely to show overall inattention and overt distractibility from the visual environment. Despite similar levels of language impairment between groups, the DLB group had more difficulty grasping and adhering to task demands (impaired mental set establishment) and more difficulty switching from one set of test demands to another (impaired mental set shifting). They were more likely to deviate from the point in conversation (incoherence) and to produce confabulatory responses. They were also more likely to exhibit intrusion errors.

Intrusions, in the present study, significantly increased the likelihood of a patient having DLB rather than AD and contributed to the discrimination between the two groups. Other studies, however, have drawn attention to intrusions as a feature of AD.28-36 Several factors may contribute to this apparent disparity. Firstly, currently accepted diagnostic criteria for AD are known to have low specificity, despite high sensitivity,28-29 so that presumed AD groups may in fact include patients with DLB. This is particularly plausible in early studies published before DLB achieved widespread clinical recognition. Secondly, reports of intrusions in AD are typically based on comparisons with controls, rather than other degenerative disorders. Even a few intrusions, as in the present AD groups, would be likely to exceed those of the normal population. It is instructive that a study that compared language function in AD and acute confusional states reported fewer intrusion errors in AD than in acute confusion.37 Thirdly, studies of AD have typically not differentiated types of intrusion.28-36 Typically, reported intrusions in AD arise from earlier test material, conforming to the within test interference categories of the present study38-40 or occur in tasks specifically designed to measure inhibitory control,28 31 41 such as the Stroop task42 or Hayling inhibition task.43 Intrusions of the associative type28 31 34 have usually arisen in list learning tasks, which are likely to be particularly vulnerable to intrusion errors. To our knowledge, environmentally cued intrusions, found in a quarter of our patients with DLB, have never been reported in AD, which is consistent with our own finding of their absence in AD.

Environmentally cued intrusions seem to have a high specificity for DLB. Although not invariable, their presence is striking. A patient whose glance falls momentarily on a spoon lying on an adjacent table may instantly incorporate the object name into an ongoing conversation (for instance, “Yesterday we went to the spoon”). Printed words on notice boards in the patients’ visual field may be similarly incorporated. In the present study, environmentally cued intrusions were reported only in the visual domain. All interviews were undertaken in a quiet test setting, so that the absence of reports of auditory intrusions might simply reflect the relative paucity of auditory compared with visual potentially distracting stimuli. Alternatively, patients with DLB might indeed be particularly susceptible to visual distraction. The issue requires prospective study.

It would be reasonable to suppose that patients who fail to maintain vigilance and attention to the testing stimuli during the assessment period, would be distractible and show intrusion errors from environmental stimuli. In support of this view, there was a strong association between reports of general inattentiveness and the presence of environmentally cued intrusions. General inattentiveness was unsurprisingly also significantly associated with reports of visual distraction. More unexpectedly though, there was no association between visual distractibility itself and the presence of intrusion errors.
from the visual environment. That is, patients whose attention was drawn to irrelevant environmental stimuli (visual distraction) did not necessarily interpolate those stimuli inappropriately into their verbal utterances.

The clinical presentation of the patients with DLB did not influence significantly qualitative performance characteristics. Patients who develop the characteristic features of DLB in the context of longstanding parkinsonism do not fulfill current diagnostic criteria for DLB as strictly defined. Nevertheless, the qualitative similarities in findings in the present study between patients presenting with cognitive change and those presenting with parkinsonism suggest that the two should be considered as a range of the same underlying disorder, as suggested by the neuropathological overlap between DLB and PD.16

Some methodological issues warrant consideration. The qualitative features documented in the present study were derived from reports of neuropsychological performance at the time of patients’ initial medical referral. The issue of logical circularity would arise if those same qualitative features contributed to the patients’ clinical diagnosis. It is worth emphasising, however, that patients with DLB fulfill current diagnostic criteria for DLB, and patients with AD fulfill criteria for AD but not for DLB, independently of the performance measures documented here. Indeed the lack of correlation between relatives’ historical reports of fluctuations in mental state and the measures reported here suggest that they are independent markers of the disorder.

The study was to some extent retrospective, representing an evaluation of previously acquired data. This raises the inevitable issue of reliability of data ascertained. Nevertheless, data were acquired systematically using the same testing procedure and by the same examiners. Additionally, the data were obtained independently of the clinical history, neurological examination, and neuroimaging and before a clinical diagnosis had been made thus precluding bias, based on preconceptions about clinical diagnosis. Moreover, in view of the fact that qualitative features were defined as present only when they were explicitly documented in patients’ reports, potential inaccuracies are likely to be in the direction of underestimation rather than overestimation of feature prevalence. Group differences obtained from the analyses are thus more likely to represent a conservative rather than exaggerated estimate of actual differences between DLB and AD.

The groups were closely matched for demographic variables and severity of dementia. Additional ratings of specific aspects of cognition demonstrated that the groups were broadly matched across domains as well as on the global measures. Previous studies have suggested that quantitative differences may exist between DLB and AD across cognitive domains. Memory is reported to be less impaired in DLB, whereas various studies have found visuocognitive tasks, including clock drawing, to be more impaired,6,7 and interestingly a different pattern of performance has been documented in the two diagnostic groups on the clock face task.8 Nevertheless, it was not the intention of this study to consider quantitative differences that differ in a manner similar to the previously reported9,10 may have emerged on specific tests. The severity ratings serve merely to show that the qualitative differences in performance occur despite patients being broadly matched across cognitive domains.

Qualitative analysis is inevitably subjective and prone to differences in interpretation and threshold for report. Examiners in our clinic are trained to detect and report characteristics of patients’ behaviour in a uniform and systematic fashion. Moreover, reports are based purely on the presence or absence of a characteristic, so are not dependent on subtle judgements of severity. The absence of difference in symptom frequency reported by different examiners suggests that the method of analysis is reliable. Nevertheless, it would be important to confirm the findings in prospective studies across different clinical centres. The patients were relatively youthful reflecting the pattern of referral to this specialist diagnostic centre. It remains to be seen whether comparable qualitative group differences occur in more elderly patient cohorts.

The absence of an association between relatives’ reports of mental fluctuation and the qualitative measures reported in the study is to some extent surprising. It might have been anticipated that performance characteristics such as inattention, distractibility and intrusions would cooccur with a fluctuating mental state. However, the fluctuations reported by relatives were based on observation of their relative’s mental state from one day to another or during the course of the day. By contrast, the qualitative features found in our study might be anticipated to be behavioural manifestations of momentary alterations in level of arousal, over minutes or seconds.17 The association between performance characteristics and brief attentional fluctuations warrants further investigation.

In conclusion, the study confirms that patients with DLB exhibit many of the performance characteristics that are typically associated with confusional states and that these characteristics can serve to differentiate DLB from AD. The findings are especially important in the absence of a robust diagnostic imaging or biological marker for the diagnosis of DLB. They highlight features that are largely amenable to detection at clinical interview and from patient observation, providing complementary support to the clinical history and findings on neurological examination. The identification of discriminative clinical features is also increasingly important because of improved prospects for therapeutic intervention. Patients with DLB have been found to show particular benefit from cholinergic agents such as rivastigmine,18 and patients with DLB but not patients with AD have been shown to be susceptible to neuroleptic sensitivity syndrome.19 The present study suggests that clinically observed inattention and distractibility, impairments in establishing and switching mental set, incoherence, confabulatory responses, perseverations, and intrusions are all strong differentiating features. Future prospective studies, using independent markers of fluctuation, such as encephalography, ought to shed more direct light on the precise relation between arousal and other aspects of attention and the elicitation of distinctive performance characteristics of confabulation, perseveration, and intrusions.

ACKNOWLEDGEMENTS

We thank Ms Zoë Gibbons for her help with interrater reliability.

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REFERENCES


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*J Neurol Neurosurg Psychiatry* 2002 72: 602-607
doi: 10.1136/jnnp.72.5.602

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