

## **Specificity of Cognitive Impairment in Neurological Disease: a Methodological Critique of Parkinson's Disease**

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Multiple cognitive deficits have been recognized in many neurological disorders but the specificity of the findings and the relationship to the underlying neuropathology remain obscure. Definitions of dementia have been proposed based on symptom profiles of the cognitive disorder and qualitative differences have been claimed between dementias of different aetiology. Some conditions have been claimed to show patterns of cognitive deficit that are distinguished from dementia and related to specific neuropathology or psychological processes, e.g. frontal lobe deficits in Parkinson's disease. Sometimes, a relationship has been established between certain cognitive deficits and particular neurochemical deficits which has led to the notion of specific drug treatment, e.g. cholinergic deficits and memory failure in Alzheimer's disease. However, these conclusions are often potentially flawed by methodological inadequacies. This critique presents some methodological issues relevant to the study of brain-behaviour and drug-behaviour relationships in syndromes of multiple cognitive deficit, using Parkinson's disease as the model. The following recommendations are made: rigid diagnostic criteria; representative patient groups; avoidance of arbitrary quantitative criteria to limit definitions of dementia; matching of groups for overall level of cognitive impairment in the search for qualitative cognitive differences related to neuropathology or effects of particular drugs; the use of suitable controls in patient groups, neuropsychological tests and treatment regimes; the use of specific quantitative tests of cognition, affect and motor disability; and longitudinal, compared with cross-sectional, study design.

### **Introduction**

Dementia is recognized in Parkinson's disease (PD) but the reported prevalence varies widely (reviewed Mortimer *et al.*, 1985) and frontal-lobe deficits are described as specific changes, even in early cases (reviewed Sagar and Sullivan, 1988; Brown and Marsden, 1988, 1990). The neuropathological basis of the cognitive changes is unclear; however, interest has centered on the role of co-existent Alzheimer's disease or diffuse cortical Lewy body disease in the pathogenesis of the dementia, and of both dopaminergic and nondopaminergic neurochemical lesions in early cognitive change and possibly also dementia (Agid *et al.*, 1987). Chronic levodopa therapy has been thought to induce greater cognitive impairment in PD (Rajput *et al.*, 1984) and anticholinergic therapy may exacerbate memory loss and confusion in demented patients with PD (de Smet *et al.*, 1982). Observations such as these have led to numerous hypotheses concerning the psychological and pathological processes underlying the cognitive impairment in PD. However, results often conflict and no unitary theory appears adequate to

explain all the observations. The reasons for these difficulties almost certainly include the heterogeneous nature of the populations under study, the nature of the experimental task or tasks employed and the failure to include suitable controls for subject and method. No study has undertaken a detailed, comprehensive evaluation of cognitive dysfunction in PD and related it to motor deficits, effects of pharmacologically specific drugs, duration of disease and underlying neuropathology. Such studies are required but precautions must be taken in the methods that are used to evaluate the cognitive dysfunction and the factors that may be responsible for it. The purpose of this paper is to outline these methodological difficulties and to develop specific proposals to deal with them. The issues also have relevance to analysis of brain-behaviour relationships in other conditions that produce global cognitive impairment. The problems to be discussed include the population under study, confounding clinical variables and quantitative and qualitative cognitive test methods (Table 1).

### The Population under Study

Differences among populations of patients selected for study may lead to wide variability in the reported prevalence of cognitive impairment in PD. Thus, Patrick and Levy (1922) observed clinical dementia in 2% of patients with PD, using analysis of the records of private physicians; by contrast, a prevalence of 77% (Lewy, 1923) was based on a study of institutionalized patients and probably included many conditions other than PD (analyzed by Mortimer *et al.*, 1985). Patients drawn from institutions, long-term hospital follow-up, tertiary centres, specialist clinics and general practice may show widely different prevalence of cognitive dysfunction depending upon the intractability of the clinical condition and the interests of the clinical personnel. Epidemiological studies of cognitive impairment in PD must examine a large community-based sample. Similar remarks apply to other cognitive disorders.

TABLE 1. *Methodological difficulties in assessing cognitive dysfunction in PD*

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1. Study population:
Unrepresentative samples
Incorrect diagnosis
2. Confounding clinical variables
Age and age-related disease
Drug effects
Depression
Motor disability
3. Test measures: quantitative criteria for the diagnosis of dementia
Clinical (e.g. DSM-III)
Minimal state examinations
Specific neuropsychological tests
4. Test measures: qualitative differences among dementias of different aetiology

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TABLE 2. *Some causes of Parkinsonism and dementia*


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1	Parkinson's disease
2	Diffuse cortical Lewy body disease
3	Progressive supranuclear palsy
4	Multi-system atrophy
5	Alzheimer's disease
6	Cerebrovascular disease
7	Head trauma
8	Wilson's disease
9	Creutzfeldt-Jakob disease
10	Intermittent pressure hydrocephalus
11	Guam complex
12	Toxins, e.g. carbon monoxide

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TABLE 3. *United Kingdom Parkinson's Disease Society's Brain Bank diagnostic criteria for the diagnosis of Parkinson's Disease*

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1. Bradykinesia, i.e. slowness of initiation of movement with progressive decrease of amplitude of movement.
  2. At least one of the following:
    - a. 4-6 cycles per second rest tremor
    - b. Rigidity
    - c. Postural instability not due to primary visual, vestibular, cerebellar or proprioceptive deficits.
  3. None of the following:
    - a. Exposure to neuroleptic medication within last 12 months
    - b. Past history of encephalitis or oculogyric crises.
    - c. Past history of stroke or stepwise course.
    - d. Toxin or designer drug exposure.
    - e. Cerebellar or pyramidal signs.
    - f. Early severe autonomic failure.
    - g. Supranuclear downgaze palsy.
    - h. Frontal tumour or communicating hydrocephalus.
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Parkinson's disease is not, of course, the only cause of Parkinsonism plus dementia (Table 2). Indeed, many causes of Parkinsonism, such as progressive supranuclear palsy, show a far higher prevalence of clinical dementia than does idiopathic PD. Erroneous inclusion of these cases into a study of idiopathic PD may lead to falsely high estimates of the prevalence of dementia in PD (Quinn *et al.*, 1986). Problems of incorrect diagnosis and consequent errors of commission apply to all epidemiological studies but are particularly relevant to PD because there is no specific diagnostic test and the main differential diagnoses tend to occur at a similar age. Thus until *in vivo* diagnostic methods are freely available, research studies of PD should employ strict clinical criteria for the diagnosis of PD, such as those of the PD Society (Table 3), and preferably should seek autopsy confirmation of the diagnosis after death. Many other cognitive disorders, such as Alzheimer's disease and Huntington's disease, rely upon clinical diagnosis for information implicating specific cerebral pathology.

### Confounding Clinical Variables

#### *Ageing*

In normal subjects, *ageing* is associated with declining performance on neuropsychological tests (Birren and Schaie, 1985). Ageing is also associated with a rising incidence of conditions known to be associated with cognitive decline, including Alzheimer's disease and diffuse cerebrovascular disease. In PD, the natural history of the condition may differ between young and old patients and it has been postulated that the pathology of PD interacts with subclinical AD pathology to increase the prevalence of cognitive impairment in elderly patients with PD (Quinn *et al.*, 1986). Studies of cognition in PD must therefore take account of the age of the study population, particularly in comparison with other studies, and must exclude or account for co-existent age-related neurological disease as far as possible.

#### *Drugs*

Drugs used for treatment of the motor symptoms of PD have powerful effects on cognition. Although the long-term effects of levodopa on the prevalence of dementia remain controversial (Rajput *et al.*, 1984; Portin and Rinne, 1986), short-term confusional effects are well-recognized and specific cognitive functions may be affected (Gotham *et al.*, 1988). Anticholinergic drugs produce memory loss and confusional states in demented PD patients (de Smet *et al.*, 1982) and sub-threshold doses of anticholinergics impair visual memory of non-demented PD patients but do not affect normal subjects (Dubois *et al.*, 1987). Clearly, it is essential to take account of current drug therapy in evaluation of the prevalence of dementia in PD and in investigation of the specific effects of additional drugs on cognitive function. Caution is required, however; although errors of wrong diagnosis (commission) require exclusion, it is equally important to avoid errors of omission: since cognitively impaired subjects are more prone to drug-induced confusion (de Smet *et al.*, 1982), ascribing cognitive dysfunction solely to drug side-effects, even when these are contributory, will lead to an artificial under-estimate of the prevalence of cognitive dysfunction in untreated PD.

#### *Depression*

Depression is common in PD (reviewed Harvey, 1986) and, indeed, more common than in other debilitating conditions (Fibiger, 1984), but the relationship between depression and cognitive impairment is unclear. In non-PD cases, depression seldom produces levels of cognitive dysfunction that could be confused with dementia on neuropsychological testing (Kopelman, 1986). In PD, however, depression has been regarded as an integral feature of subcortical dementia (Cummings and Benson, 1984) and a complex relationship between depression and cognitive function has been

proposed (Rogers *et al.*, 1987). Although tricyclic medication has been used effectively in the treatment of depression in PD, its action on cognitive function has been little explored. However, in a recent study of 60 newly diagnosed untreated patients with a mean disease duration of one year, we found significant impairment in several cognitive domains at diagnosis but the deficits did not correlate with severity of depression or motor disability (Cooper *et al.*, in press). Treatment of the motor disorder with standard anti-PD medication improved co-existent depression but had no effect on cognitive dysfunction. These observations suggest a dissociation between cognition and affect, at least in the early cases. These conclusions may not apply to chronic cases, however, because the relationship between cognitive impairment and depression may differ between early and chronic PD patients (Starkstein *et al.*, 1989). In our present incomplete state of knowledge, cognitive studies in PD must include a quantitative measure of depression, such as the Yesavage Rating Scale (Yesavage *et al.*, 1983). Depression scales that include a large number of somatically related items should, however, be avoided because pure motor symptoms of PD will artificially elevate the depression rating. Moreover, it is essential in interpretation of the nature and origin of cognitive and affective disturbance in PD to take account of disease chronicity.

#### *Motor dysfunction*

Finally, disability due to *motor dysfunction* in PD may be difficult to dissociate from cognitive dysfunction in its effects on activities of daily living. Indeed, cognitive and motor dysfunction may be correlated in some PD cases (Mortimer *et al.*, 1982) and motor disability may encompass "higher order" deficits, such as sequencing and dual task performance, that are closely linked to cognition (Marsden, 1982). In order to avoid these confounding variables, cognitive tests should be used that minimize the motor requirements of the tests; movement time should be evaluated in all tasks measuring latency of response; depression scales should be selected for low somatic bias; questionnaires that assess everyday cognitive function from ability to perform motor tasks should be avoided; and motor disability should be evaluated quantitatively and concurrently with cognitive capacity in all studies of cognitive function in PD.

#### **Test Measures: Quantitative Criteria for the Diagnosis of Dementia**

It is a common clinical impression that "dementia" signifies a recognizable, unitary entity which should therefore be open to a limiting definition. Unfortunately, no evidence exists to support this notion. Many definitions of dementia have been used in research studies but they differ almost entirely in the *quantitative* criteria required for the diagnosis and do not clearly distinguish qualitatively distinct groups of patients. Moreover, the definitions do not easily compare with each other. Broadly, three categories of definition can be recognized, differing in the quantitative level of cognitive

impairment required to satisfy the diagnosis: clinical criteria, such as DSM-III; minimal state examination results, and performance on sensitive neuropsychological tests.

#### *Clinical criteria*

Clinical criteria for the diagnosis of dementia, such as DSM-III, are derived largely from observations on patients with Alzheimer's disease. The diagnosis requires memory loss plus other cognitive impairment "of severity sufficient" to interfere with social and occupational functioning (American Psychiatric Association, 1980). When applied to PD, 10–15% patients satisfy the diagnostic criteria when strict measures are incorporated to account for age, drug toxicity and false diagnosis (Brown and Marsden, 1984). A possible inference that patients thereby deemed "non-demented" are cognitively normal is, however, incorrect and many of these patients satisfy other criteria for the diagnosis of dementia (reviewed Sagar and Sullivan, 1988). Application of DSM-III criteria to PD may also be problematic because of the particular difficulty in distinguishing the effects on everyday living of the motoric and cognitive aspects of the disease. Moreover, memory loss is a cardinal sign of AD but is less prominent in PD; although non-mnemonic cognitive dysfunction in PD may have a major effect on daily living, a diagnosis of dementia by DSM-III criteria would not be permissible in the absence of memory loss. These considerations highlight difficulties in the generalization to all diseases of definitions of dementia derived from a single disorder.

#### *Minimal state examinations*

Minimal state examinations, such as the Blessed Dementia Scale (BDS; Blessed *et al.*, 1968) and the Folstein Minimal State Examination (Folstein *et al.*, 1975) provide brief measures of orientation, memory and visuo-spatial capacity. They are more sensitive in detecting cognitive impairment than is clinical evaluation, so that definitions of dementia based upon abnormal test scores will tend to yield a higher prevalence than diagnoses based upon DSM-III criteria. In PD, 20–30% of patients scored abnormally on minimal state examinations (Growdon and Corkin, 1986) although many of these patients were not considered demented by DSM-III criteria.

#### *Neuropsychological tests*

Sensitive neuropsychological tests may detect impairment in PD patients who are not demented by DSM-III or other clinical criteria and who score normally on minimal state examinations. Often, these impairments differ only in degree from those found in demented subjects, even when standard clinical neuropsychological tests are used. For example, Sullivan *et al.* (1989) evaluated memory impairment in PD from the difference between

estimated IQ and memory quotient (MQ), using standard tests. Unlike patients with AD, who showed decline in both IQ and MQ, the PD patients were disproportionately impaired in memory capacity as shown by an elevated IQ–MQ difference compared with normal subjects. Moreover, the memory deficits were evident in patients who achieved normal scores on the BDS as well as those who scored abnormally. Similar results have been shown for the capacity to date historical events (Sagar *et al.*, 1988a) and the ability to perform the Picture Arrangement sub-test of the Wechsler Adult Intelligence Scale (Sullivan *et al.*, 1989). Many other studies have demonstrated specific cognitive deficits in “non-demented” PD patients (reviewed Sagar and Sullivan 1988; Brown and Marsden, 1988, 1990), but seldom has performance been compared in relationship to other measures of global cognitive capacity. In individual cases, the relationship between these mild cognitive deficits and the risk of later development of clinically obvious global cognitive impairment is unclear. The findings in cross-sectional studies of a range of deficit from mild to severe that cuts across traditional categories of dementia and non-dementia, does, however, suggest that some cognitive dysfunction in PD may vary along a continuous spectrum of severity (Pirozzolo *et al.*, 1982). Some pathological support for this possibility stems from studies of cortical cholinergic activity in PD (Perry *et al.*, 1985): although abnormalities were most prominent in the mentally impaired group, significant cholinergic deficits were found in some brain areas of patients considered to be mentally intact (Table 4).

In conclusion, the available evidence does not clearly support a qualitative distinction in PD between “dementia” and “non-dementia”. Studies that have classified PD patients in this way have usually used quantitative measures in which the critical index of severity is arbitrarily chosen and differs among sets of criteria. Comparison of results obtained using different criteria for the diagnosis of dementia is difficult. Cognitive performance in PD must demonstrate heterogeneity among subjects before qualitatively distinct sub-groups can be meaningfully established.

TABLE 4. Mean choline acetyltransferase levels (nmol/h/mg protein) in human brain areas (modified from Perry *et al.*, 1985)

	PD			
	Normal	Non-demented	Demented	AD
Occipital	3.50	1.44 <sup>x</sup>	0.91 <sup>x</sup>	1.42 <sup>x</sup>
Parietal	6.09	2.98	1.31 <sup>x</sup>	1.08 <sup>x</sup>
Temporal	4.64	3.22	1.21 <sup>x</sup>	1.10 <sup>x</sup>
Entorhinal	8.63	7.67	2.94 <sup>x</sup>	1.91 <sup>x</sup>
Frontal	8.61	5.43	2.70 <sup>x</sup>	3.50 <sup>x</sup>

<sup>x</sup>*p* < 0.01 compared to normal

### Test Measures: Qualitative Differences among Cognitive Disorders of Different Aetiology

Diseases associated with predominant cortical pathology, such as PD, have been distinguished on behavioural grounds from those with major subcortical pathology such as PD (Albert, 1978; Cummings and Benson, 1984). Although neuropathologically inaccurate, the classification provided a pointer to brain-behaviour relationships in dementia and underlined behavioural differences among dementias of different aetiology. Many studies have examined specific cognitive functions in the cortical and subcortical dementias. In PD, deficits have been described in aspects of memory, visuospatial function, recency discrimination and attentional control (reviewed Sagar and Sullivan, 1988; Brown and Marsden 1988, 1990). Relatively few studies, however, have compared two or more disorders directly and even fewer have attempted to relate their findings to dementia criteria or measures of multiple cognitive capacities. A much more accurate appraisal of the specificity of cognitive impairment in PD can be made, however, if PD is compared with other cognitively impaired groups on a wide variety of cognitive tests. Otherwise, interpretation may be complicated by the limited number of tests administered, the sensitivity of the methods and the overall disease severity.

When several cognitive tests are administered to a homogeneous group of patients, the performance may differ among tests because of factors relating to the *pathology* and factors relating to *test sensitivity*. Thus, subjects may show impairment on one test, but not another, because the pathology disrupts one cognitive process (e.g. language) but spares another (e.g. memory) and each test is specific for one or the other process. A similar pattern of neuropsychological test performance may occur artefactually, however, simply because one test is much more sensitive than the other at detection of deficit, even though the disease is neurologically widespread. These considerations are particularly important in evaluation of test performance in dementing disorders, which typically disrupt multiple cognitive processes. Failure to take account of test sensitivity may lead to artefact in the detection of qualitative cognitive differences between diseases and in the establishment of selective cognitive impairment within a single disease.

When cognitive performance is assessed by the administration of multiple tests, the resulting patterns of cognitive deficit can be defined as multiple, restricted or specific (Fig. 1). *Multiple* deficits typically occur in dementia but detection of impairment is critically linked to test sensitivity. *Restricted* deficits (impairment on some tests but not others) may represent an early stage in a more widespread spectrum of impairment or result from insensitivity of some of the test methods. *Selective* deficits, however, are evident from a *disproportionate* impairment in one cognitive domain, when judged by performance on other tests that produce a spectrum of deficit. Selective deficits can be shown if one patient group differs from another in showing disproportionate impairment within one cognitive area, *when performance of the two groups is equated on a second, equally sensitive measure*. In this



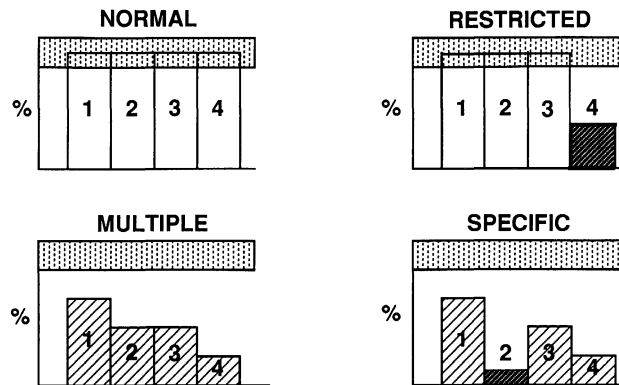


FIG. 1. Performance on four cognitive tests, numbered 1–4, to show significance of different cognitive profiles in four conditions (e.g. disease or drug effects), A–D. A. Normal: normal and possibly equal performance on all tests. B. Multiple cognitive impairments (“dementia”): impaired on several tests. Performance on some tests (e.g. 4) more impaired because of (a) different test sensitivities *or* (b) differences between cognitive processes in the extent of involvement by disease or drug. C. Restricted: impairment on some tests (e.g. 4) but not others because of (a) different sensitivity of the tests used *or* (b) selectivity of the disease to certain cognitive processes. D. Specific: as with Condition B, impaired on all tests. However, Condition D shows similar performance to Condition B for tests 1, 3 and 4 but is worse on test 2. Selective impairment on process 2 compared with Condition B indicates specific cognitive deficit despite impairment on multiple cognitive tests.

case the disproportionate nature of the impairment is likely to be related specifically to the pathology of the first condition. Sometimes, however, one disease differs from another in an impairment restricted to one or two cognitive area(s) only because the condition is overall less advanced. In this case, the two conditions cannot be equated on a second equally sensitive measure; the deficit is restricted and not necessarily specific to the pathology of the first condition. By this analysis, test sensitivity would be judged by the performance of normal control subjects; excluding floor and ceiling effects (near maximal or minimal possible scores), two tests of equal sensitivity would generate identical scores on scales of identical range when administered to normal subjects. When two groups of patients achieve identical scores on one of these measures but not the other, then the disproportionate impairment of one patient group on the second task can be related specifically to the pathology of that condition.

Without this kind of detailed information it is not possible to judge the significance of cognitive differences between disorders of different aetiology. When, in addition, the comparisons do not take account of traditional dementia criteria, it is impossible to judge the relationship between early, specific cognitive deficits and the later development of dementia, however that may be defined. When two homogeneous disorders can be equated on one sensitive measure, however, and found to differ consistently on a second measure, useful information may be obtained concerning brain-behaviour relationships in the two conditions.

Of course, this approach is an ideal which can seldom be achieved in practice. Moreover, it is often difficult to define equivalent control performance, to establish equal test scales and to remove confounding variables such as the presence of other cognitive deficits. Nevertheless, the ideal is seldom even approached and differences between cognitive disorders of different aetiology are often inferred from differing test performance between groups when the groups are clearly not matched for the level of global cognitive impairment. It may be necessary to give multiple tests and to match patients as closely as possible on some aggregate of their test performance or to rely on the findings of double dissociation of deficit across groups and tests (in absolute terms, one group performs more poorly than a second group on one test but better on another test, even though the groups are not matched). Using this approach in a comparison of PD and AD, disproportionate deficits have been found in PD in dating of remote events (Sagar *et al.*, 1988a), recency discrimination and short-term memory (Sagar *et al.*, 1988b), matching-to-sample (Sahakian *et al.*, 1988), planning, execution and sequencing (Sullivan *et al.*, 1989) and set-shifting (Pillon *et al.*, 1986; Sullivan *et al.*, 1989) (Fig. 2). Most of these deficits can be related to frontal-lobe dysfunction and imply selective frontal-lobe pathology in PD that cannot be due solely to co-existent AD. In many of these studies, the deficits were present in non-demented as well as demented sub-groups of PD patients, defined by clinical criteria or score on the BDS (Sagar *et al.*, 1988, a, b; Sullivan *et al.*, 1989). An alternative approach is to follow the groups in longitudinal study and examine for differences in the rates of progression of deficit within different cognitive domains. In this case, however, it is also

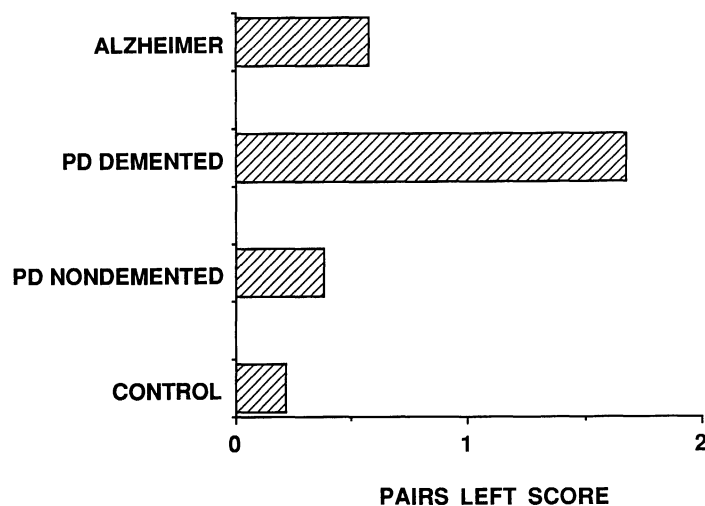


FIG. 2. The "pairs left" score (McFie and Thompson, 1972) in the Picture Arrangement sub-test of the Wechsler Adult Intelligence Scale, as a measure of set-formation or set-shifting incapacity. The deficit is greater in PD than AD or normal control subjects (Sullivan *et al.*, 1989).

necessary to match the groups on initial level of deficit because rate of cognitive decline may be non-linear and therefore differ according to the absolute level of performance on the test.

A similar approach is necessary to identify specific cognitive effects of drugs in PD. A drug may be deemed to have a specific enhancing effect upon certain cognitive processes if other cognitive functions are examined and found to be unaffected (or inhibited); if the effects in PD are disproportionately great compared with the effects in other conditions; if there is a dose-response relationship confined to one cognitive area; and if one drug has a disproportionately greater effect in one cognitive area compared with a second drug which has similar effects to the first drug in other cognitive areas.

The qualitative differences in patterns of cognitive performance between dementias of different aetiology raise serious difficulties in applying a single set of criteria for the diagnosis of dementia to all conditions, regardless of aetiology. Examination methods formulated to assess AD-type dementia, for example, may be appropriate for PD only to measure those aspects of impaired function common to the two diseases; more specific tests may be necessary to monitor changes in cognition in PD. Performance on the BDS, for example, correlates with the extent of histological and neurochemical pathology of AD. When used to monitor cognitive function across time in PD, no evidence of deterioration was found (Growdon and Corkin, 1986). Although interpreted as a lack of progression of dementia in PD, the results could equally demonstrate the inapplicability of the BDS to PD and certainly merit further study.

I have discussed that restricted deficits may occur in the early stages of a progressive globally dementing process without necessarily reflecting a pattern of impairment that is specific to the pathology of that condition. Clearly, therefore, not only should the index group be matched for disease severity to another dementia group but the neuropsychological test battery should sample several different cognitive domains. In PD, the pattern of cognitive impairment is usually regarded as reflecting dysfunction in the frontal lobes or their functional connections (reviewed Brown and Marsden, 1988, 1990). However, it is only possible to reach that conclusion if PD patients perform normally on tasks sensitive to non-frontal pathology; even poor performance on tasks entirely specific to frontal pathology does not exclude the possibility that the patients also show non-frontal dysfunction as part of a more global deficit. Similar remarks apply to the study of the effects of drugs on cognitive processes: an effect of drug A on process A does not provide definitive information on the neurochemical basis of cognitive process A until it has been shown that drug A does not also affect an independent process B or that a pharmacologically dissimilar drug B does not have the same cognitive effects as drug A. One way to deal with these issues of specificity is to include suitable controls, for subject group, for cognitive test and for pharmacological manipulation. For example, the PD group can be compared with another group of cognitively impaired patients; the test battery should sample several cognitive domains and

TABLE 5. *Proposed requirements for studies of cognition in PD*


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1.	Diagnostic clinical criteria for PD
2.	No exclusion or selection on behavioural grounds
3.	Representative population
4.	Quantitative tests of: Specific cognitive functions Depression Motor disability
5.	Cognitive and affective tests with low somatic bias
6.	Avoid global rating scales as sole cognitive measure
7.	Controlled treatment regimes
8.	Demented control group
9.	Normal control group
10.	Longitudinal, rather than cross-sectional, study design

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include measures on which the patients would be expected, on theoretical grounds, to perform normally; and pharmacological manipulations should compare the action of drugs with different pharmacological actions on several cognitive domains. Again, it may be difficult practically to achieve this ideal owing to the lack of absolute specificity of the cognitive test or the drug action. However, it is an ideal that should perhaps be pursued as closely as possible.

In conclusion, methods used to quantify cognitive impairment in one disease may be insensitive when applied to another disease owing to the qualitative differences that exist among dementias of different aetiology. Careful quantitative examination of specific cognitive processes, however, can yield valuable evidence of brain-behaviour or drug-behaviour relationships, particularly when compared across different diseases or different pharmacological manipulations. Specific recommendations are listed in Table 5.

### Conclusion

“Dementia” is a syndrome of multiple cognitive deficits but it is not homogeneous. Each deficit is specific to a psychological process and may be disrupted independently of other processes. The constellation of multiple cognitive deficits may vary in severity, or in the number and nature of processes affected. This notion of independent disruption of cognitive processes does not exclude interaction among them; thus, the severity of specific cognitive impairment may be greater with multiple cognitive impairments than with a single deficit. Nevertheless, the spectrum of dysfunction that occurs across different dementing disorders along both quantitative and qualitative lines indicated by this analysis shows that any one definition of dementia incorporates arbitrary inclusion and exclusion criteria. Moreover, a syndrome defined from observations of one disease, such as Alzheimer’s disease, need not have applicability to another, such as

Parkinson's disease. It is difficult to see, for example, why dementia defined as a syndrome of diffuse cognitive dysfunction should be necessarily any more unitary than physical disability caused by multifocal neurological pathology. A physically disabled person may differ from another in severity of functional handicap; two people disabled by multiple sclerosis may show quite different signs; and a person unable to walk because of multiple sclerosis will show different signs from someone unable to walk because of Parkinson's disease. Similarly, quantitative and qualitative heterogeneity is evident in cognitive disability.

In brain-behaviour studies, cognition needs to be assessed as specific, quantifiable sub-processes and, for research purposes, the term "dementia" should be rigidly defined or preferably abandoned altogether.

### References

- Agid, Y. *et al.* (1987) In "Cognitive Neurochemistry" (Ed. S. Stahl *et al.*) O. U. P., Oxford, pp. 248–271.
- Albert, M. L. (1978). Subcortical dementia. In "Alzheimer's Disease: Senile Dementia and Related Disorders", (Eds Katzman R, Terry R. D., Bick K. L.) (Aging vol. 7). Raven Press, New York, p. 173–180.
- American Psychiatric Association (1980). Diagnostic and Statistical Manual of Mental Disorders, 3rd edn. American Psychiatric Association, Washington, DC.
- Birren, J. E. and Schaie, K. W. (1985). "Handbook of the Psychology of Aging", 2nd edn. Van Nostrand Reinhold, New York.
- Blessed, G., Tomlinson, B. E. and Roth, M. (1968). The association between quantitative measures of dementia and of senile changes in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, **114**, 797–811.
- Brown, R. G. and Marsden, C. D. (1988). "Subcortical dementia": The neuropsychological evidence. *Neuroscience*, **25**, 363–387.
- Brown, R. G. and Marsden, C. D. (1990). Cognitive function in Parkinson's disease: from description to theory. *TINS*, **13**, 1, 21–29.
- Cummings, J. L. and Benson, D. F. (1984). Subcortical dementia. Review of an emerging concept. *Archives of Neurology*, **41**, 874–879.
- de Smet, Y., Ruberg M., Serdaru, M., Dubois, B., Lhermitte, F. and Agid, Y. (1982). Confusion, dementia and anticholinergics in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **45**, 1161–1164.
- Dubois, B., Danze, F., Pillon, B., Cusimano, G., Lhermitte, F. and Agid, Y. (1987). Cholinergic-dependent cognitive deficits in Parkinson's disease. *Annals of Neurology*, **22**, 26–30.
- Fibiger, H. C. (1984). The neurobiological substrate of depression in Parkinson's disease: a hypothesis. *Canadian Journal of Neurology*, **11**, 105–107.
- Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Minimental state". A practical method for grading the mental state of patients for the clinician. *Journal of Psychiatry Research*, **12**, 189–198.
- Gotham, A. M., Brown, R. G. and Marsden, C. D. (1988). Frontal cognitive function in patients with Parkinson's disease "on" and "off" levodopa. *Brain*, **111**, 299–321.
- Growdon, J. H. and Corkin, S. (1986). Cognitive impairment in Parkinson's disease. In "Parkinson's Disease" (Advances in Neurology series). (Ed M. D. Yahr and R. C. Duvoisin), Raven Press, New York.
- Harvey, N. S. (1986). Psychiatric disorders in Parkinsonism: 1. Functional illness and personality. *Psychosomatics*, **27**, 91–103.
- Kopelman, M. D. (1986). Clinical tests of memory. *British Journal of Psychiatry*, **148**, 517–525.

- McFie, J. and Thompson, J. A. (1972). Picture arrangement: a measure of frontal lobe function? *British Journal of Psychiatry*, **121**, 547–552.
- Marsden, C. D. (1982). The mysterious motor function of the basal ganglia: The Robert Wartenburg Lecture. *Neurology (Minneapolis)* **32**, 514–539.
- Mortimer, J. A., Schuman, L. M. and French, L. R. (1981). Epidemiology of dementing illness. In "The Epidemiology of Dementia". (Eds J. A. Mortimer and L. M. Schuman). Oxford University Press, New York, p. 3–23.
- Mortimer, J. A., Pirozzolo, F. J., Hansch, E. C. and Webster, D. D. (1982). Relationship of motor symptoms to intellectual deficits in Parkinson's disease. *Neurology*, **32**, 133–137.
- Perry, E. K., Curtis, M., Dick, D. J. *et al.* (1985). Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 413–421.
- Pillon, B., Dubois, B., Lhermitte, F. and Agid, Y. (1986). Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease and Alzheimer's disease. *Neurology*, **36**, 1179–1185.
- Pirozzolo, F. J., Hansch, E. C., Mortimer, J. A., Webster, D. D. and Kukowski, M. A. (1982). Dementia in Parkinson's disease: a neuropsychological analysis. *Brain and Cognition*, **1**, 71–83.
- Portin, R. and Rinne, U. K. (1986). Predictive factors for cognitive deterioration and dementia in Parkinson's disease. In "Advances in Neurology", (Eds. M. D. Yahr and K. J. Bergmann) Vol. 45. New York, Raven Press.
- Quinn, N., Brown, R. and Marsden, C. D. (1986). Dementia and Parkinson's disease—a review of the current evidence. In "Psychiatric Disorders in the Elderly". (Eds. P. E. Bebbington and R. Jacoby) Mental Health Foundation, London.
- Rajput, A. H., Offord, K., Bear, C. M. and Kurland, L. T. (1984). Epidemiological survey of dementia in Parkinsonism and control population. In "Advances in Neurology", (Eds. R. G. Hassler and J. F. Christ) Vol. 40, pp. 229–234, Raven Press, New York.
- Rogers D., Lees A., Smith E., Trimble, M. and Stern, G. M. (1987). Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. *Brain*, **110**, 761–776.
- Sagar, H. J. and Sullivan, E. V. (1988). Patterns of cognitive impairment in dementia. In "Recent Advances in Clinical Neurology" (Ed. C. Kennard), Vol. 5, pp. 47–86, Churchill Livingstone.
- Sagar, H. J., Cohen, N. J., Sullivan, E. V., Corkin, S., Growdon, J. H. (1988a). Remote memory function in Alzheimer's disease and Parkinson's disease. *Brain*, **111**, 185–206.
- Sagar, H. J., Sullivan, E. V., Gabrieli, J. D. E., Corkin, S. and Growdon, J. H. (1988b). Temporal ordering deficits and bradyphrenia in Parkinson's disease. *Brain*, **111**, 525–539.
- Sahakian, B. J., Morris, R. G., Evenden, J. L., Heald, A., Levy, R., Philpot, M. and Robbins, T. W. (1988). A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain*, **111**, 695–718.
- Starkstein, S. E., Berthier, M. L., Bolduc, P. L., Preziosi, T. J. and Robinson, R. G. Depression in patients with early versus late onset of Parkinson's disease (1989). *Neurology*, **39**, 1441–1445.
- Sullivan, E. V., Sagar, H. J., Gabrieli, J. D. E. and Corkin, S. (1989). Different cognitive profiles on standard behavioural tests in Parkinson's disease and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, **11**, (in press).
- Yesavage, J. A. *et al.* (1983). *Journal of Psychiatric Research*, **17**, 7–49.



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