

A Neural Systems Approach to the Cognitive Psychology of Ageing Using the CANTAB Battery

*T.W. Robbins, M. James, A.M. Owen, B.J. Sahakian,
L. McInnes, Patrick Rabbitt**

INTRODUCTION

Considerable data are now available which bear on cognitive theories of ageing (Rabbitt, 1993; Salthouse, 1985, 1991). However, these data and theories are not well integrated with accumulating neurobiological information about the ageing brain. While ageing often leads to generalised atrophy of the brain (Petit, 1982), specific regions and systems have from time to time been implicated (Flood & Coleman, 1988). For example, there is now accumulating evidence of major effects in structures such as the hippocampus (e.g. Nagahara, Nicolle, & Gallagher, 1993), and regions of the association cortex (e.g. parietal, prefrontal, certain regions of the temporal cortex; Brody, 1994; Mann, Yates & Marcyniuk, 1984; Parashos & Coffey, 1994) as well as in certain of the chemically defined systems of the isodendritic reticular core of the brain (Whitehouse, 1994), such as the noradrenergic locus coeruleus (Vijayshankar & Brody, 1979), the dopamine-containing cells of the substantia nigra, pars compacta (Hirai, 1968; Marshall, Drew, & Neve, 1983), and the cholinergic cells of the basal forebrain

* T.W. Robbins, Department of Experimental Psychology, University of Cambridge, Cambridge, U.K.; M. James, Department of Psychology, National Hospital, London, U.K.; A.M. Owen and B.J. Sahakian, Department of Psychiatry, University of Cambridge, Cambridge, U.K.; L. McInnes, North-East Age Research Panel, Department of Psychology, Newcastle University, U.K.; Patrick Rabbitt, Age and Cognitive Performance Research Centre, Manchester University, U.K.

(Fischer, Chen, Gage, & Bjorklund, 1991; Smith, Deadwyler, & Booze, 1993; Stroesner-Johnson, Rapp, & Amaral, 1992). Evidence of disproportionate atrophy of the frontal cortex in ageing (Petit, 1982) and selective reductions in regional cerebral blood flow in this region (Shaw et al., 1984) have encouraged some to focus on neuropsychological changes in "frontal" function in ageing (Whelihan & Leshner, 1985; see West, 1996, for a recent review). This chapter considers the use of neuropsychological tests in the healthy ageing population with proven utility in the assessment of brain-damaged patients, where it is possible to infer the relationship between performance deficits and the anatomical localisation of the brain damage or dysfunction. Such an approach may even enable the development of novel hypotheses at the purely cognitive level. We will focus particularly on tests sensitive to frontal lobe dysfunction that are suggested to tap aspects of "executive" function, those control processes by which an individual optimises his or her cognitive performance.

This neuropsychological approach is facilitated by several developments: first the growing use of structural imaging techniques (such as MRI) for gaining precise information about the locus of brain damage; second, the use of functional imaging (using PET or MRI) to provide information from healthy controls about the likely neural substrates of complex cognitive operations; third, growing knowledge about the interconnectivity and organisation of neural structures into discrete systems; and finally the use of experimentally discrete lesions and manipulations to make inferences concerning localisation of function in experiments with animals.

As much of our knowledge about ageing in the CNS depends on the interpretation of neuroanatomical and neurochemical evidence from experiments with animals, parallel information concerning the functional correlates of these changes is important when attempting to relate the findings to humans. Consequently, this has required the development of sophisticated neuropsychological tests for animals in several cognitive domains. In some cases, such test development has been based on understanding how cognitive capacities in animals have been shaped by environmental and evolutionary constraints, for example, in foraging. In other cases, the test development depended upon advances in animal learning theory. Applying this information to the problem of human ageing, however, has been limited by the degree to which the experimental paradigms can be extrapolated to humans. This important issue has been addressed so far by only a few other investigators (e.g. Bartus, Dean, & Beer, 1980; Flicker, Bartus, Crook, & Ferris 1984; Solomon, Beal, & Pendlebury, 1988), mainly stimulated by research into Alzheimer's disease.

This connection between work on experimental animals and human neurological disease has formed a major focus of our own research effort in the design of the Cambridge Neuropsychological Test Automated Battery

(CANTAB), the theoretical impetus for which was to adapt paradigms developed for testing animal models of dementia, in order to relate the findings to man. This battery thus comprises a set of computerised neuropsychological tests, some of which are based on neuropsychological tests for animals, and some of which are versions of established clinical neuropsychological tests, modified so that they can also be used in experiments with animals.

The battery, which operates on a standard IBM-type PC, capitalises on novel technological developments which include the use of a touch-sensitive screen, so that immediate feedback for responding to the test stimuli can be provided most effectively and the participant is thus not faced with the problems of divided attention provided by the conjoint requirement to attend to a video display unit but respond via a keyboard. The tests are graduated in level of difficulty, and so boost motivation in the elderly participant. The use of such computerised tests, after initial screening and training to overcome possible problems posed by the unfamiliar test setting has the advantage of avoiding the distress sometimes associated with pencil and paper tests and formal interviews. The stimuli and contingencies of the tests are presented in a standard way, and objective and accurate measures of responding, particularly in terms of latency, are ensured. Finally, the computerised collection of data should simplify the collation and analysis of results from large-scale longitudinal and cross-sectional studies of ageing.

CANTAB BATTERIES

Currently, the CANTAB tests are divided into three main batteries, "visual memory and learning," "working memory and planning," and "attention." In each battery, the principle is that there are one or more complex tests (i.e. having several cognitive components) that can be fractionated into their constituent parts. Thus, the visual memory battery has separate tests of visual pattern recognition and spatial recognition memory, as well as a difficult visual delayed matching to sample task. There is also a visuospatial paired associates task which requires the participant to remember and learn the location of up to eight different visual patterns. Thus, the pattern and spatial recognition tasks are likely to tap components of the paired associate learning task (as confirmed by factor analysis, see below, Table 10.2; see Robbins et al., 1994 for full test descriptions).

The working memory and planning battery has three main tests (see Owen, Downes, Sahakian, Polkey, & Robbins, 1990): the Tower of London test of single contingency planning, devised by Shallice and McCarthy (Shallice, 1982); a self-ordered spatial working memory task; and a test of spatial span, modelled after that of Corsi (Milner, 1971). The reasoning behind this set of tests is that the two tests of spatial memory provide

controls for some aspects of performance on the test of planning, for example, the ability to retain and execute a sequence of five moves, the longest number of moves required in the planning test. The form of the Tower of London test employed requires the participant to consider two arrangements of a set of three differently coloured balls resting in three suspended "socks" or "stockings" of different lengths. The top arrangement is the goal position which the participant has to reach by manipulating the balls in the initial position, below. Merely touching the appropriate ball and then the position to which it is to be moved is all that is required. The participants are instructed on the number of moves in which each problem can most efficiently be completed. The accuracy of solving the problem (in terms of both the number of "excess moves" and "perfect" solutions, which use the minimum number of moves) provides measures of accuracy of problem solving, whereas the latencies to think either prior to the initiation of the problem solution ("initial thinking time"), or during it ("subsequent thinking time") are also measured. These latencies are corrected by subtracting "movement time" measures; the problem solutions are played back to the participant move-by-move on the upper display, and the times taken to copy the computer-generated moves on the lower display are subtracted from the total latencies. It is important to realise that this test was designed to measure "look ahead", planning function, rather than the trial and error sequencing that mainly characterises the Tower of Hanoi variant, which has recently been criticised as a test sensitive to frontal lobe dysfunction (Goel & Grafman, 1995). Furthermore, certain measures in the test (e.g. thinking times for perfect solutions) provide measures of planning that are *not* contaminated by move retracing elements that are claimed to confound pure measures of planning (see Goel & Grafman, 1995).

Finally, the "attentional" battery consists not only of easy one-choice and five-choice reaction time tasks, similar to those employed by Leonard, and in experimental analogues in rats (see Robbins, Muir, Killcross, & Pretsell, 1993), but also a visual search paradigm, and a set of visual discrimination tasks which decompose the Wisconsin Card-Sorting Test (WCST). The latter is often used as a clinical test for impaired frontal lobe function. The visual search procedure requires the participants to match complex visual stimuli which are similar to those used in the delayed matching to sample test of the visual memory battery. They must match a centrally displayed stimulus to a peripheral stimulus placed in one of eight locations around the screen by releasing a keypad (reaction time) and touching the appropriate stimulus on the screen (movement time). Sets of two, four or eight stimuli are displayed, so that the participant has to conduct a serial search, according to a Sternberg-like procedure (see Downes et al., 1989).

The WCST analogue is based on a set of visual discriminations, initially using simple stimuli (e.g. shapes or lines) and then stimuli compounded from

these two perceptual dimensions. The participant has to respond selectively to an exemplar from one dimension during discrimination learning and reversal procedures, on the basis of computer feedback, and then receives transfer tests of intra- or extradimensional shifts, with novel exemplars to assess the capacity to maintain selective attention to the entrained dimension, or to shift to a previously irrelevant one. The extradimensional shift, as defined in animal and human learning paradigms, is in fact the core requirement of the WCST (see Downes et al., 1989 for full description).

The battery thus contains at least three tests that might be expected to be sensitive to frontal lobe dysfunction, on the basis of clinical and experimental evidence (see Table 10.1): the Tower of London test of planning, the spatial working memory task, and the WCST analogue (see Fig. 10.1). However, it is an important methodological feature of the battery that each of these tests is not only graded in difficulty, but also generally decomposed into a number of cognitive components. It is an unusual feature of our approach in assessing cognitive performance during ageing that we consider several different aspects of executive and non-executive function in tests that have been carefully studied using patients with neurosurgical excisions of different regions of the cortex, including the prefrontal cortex.

TABLE 10.1
Summary of Neuropsychological Findings Using the CANTAB Battery

	<i>Temporal/ Hippocampal Lesions</i>	<i>Frontal Lesions</i>	<i>DAT</i>	<i>Parkinson's Disease*</i>
<i>Tests of Visual Memory</i>				
Pattern Recognition	✗	✓	✗	✓
Spatial Recognition	✓	✗	✗	✗
Delayed matching to sample	✗	✓	✗	✗
<i>Tests Sensitive to Frontal Lobe Dysfunction</i>				
<i>Spatial working memory</i>				
Between error score	✗	✗	✗	✗
Strategy score	✓	✗	✓	✓
<i>Tower of London</i>				
Minimum moves	✓	✗	✗	✓
Initial thinking time	✓	✓	—	✗
Subsequent thinking time	✓	✗	—	✓
Attentional shift task	✓	✗	✓ (early) ✗ (late)	✗

NOTE: ✗ = impairment; ✓ = no impairment; DAT = dementia of the Alzheimer type.

* The exact effects of Parkinson's disease depend on disease severity.

SOURCE: Taken from Downes et al., 1989; Owen et al., 1990, 1991, 1992, 1993a, 1995; Sahakian et al., 1988, 1991; Sahgal et al., 1991, 1992.

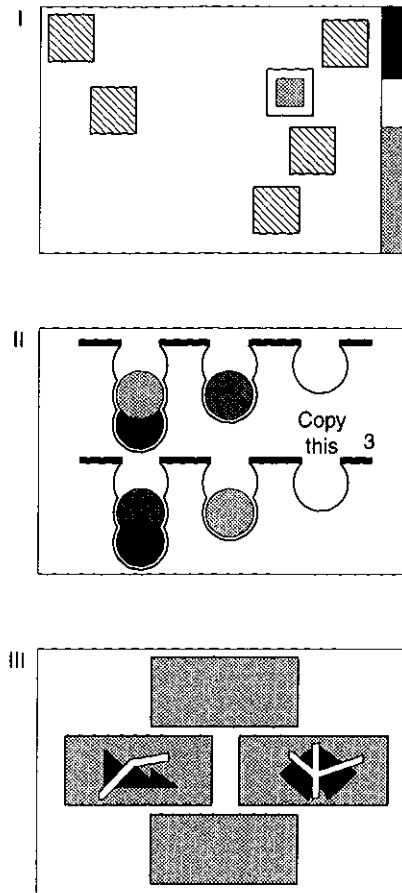


FIG. 10.1. Schematic drawings of three tests sensitive to frontal lobe dysfunction: I. spatial working memory; II. the Tower of London test of planning; and III. the attentional set-shifting task (intra/extradimensional shifting). Source: Robbins et al. (1992). Reproduced by kind permission of Oxford University Press. See Downes et al., 1989 and Owen et al., 1990 for further explanation.

NEURAL VALIDATION

The CANTAB tests have been quite widely used, on a variety of clinical populations, as well as in functional imaging studies and for the testing of effects of psychoactive drugs, in normal volunteers. In the clinical application of CANTAB, adequate comparisons have to be made with the performance of normal volunteers who are matched with the patients on the basis of age, gender, and IQ measures. This requirement to standardise the

CANTAB tests in large populations of elderly volunteers has provided some of the impetus for the data reported in this chapter. It is clear that the various tests provide dissociations of deficits across different clinical populations, sometimes on a basis that can be related to the dysfunctioning of quite specific brain regions. For example, the tests of pattern recognition memory and delayed matching to sample are indeed sensitive to neurosurgical damage of the temporal lobes, including the amygdala and hippocampus (Owen, Sahakian, Semple, Polkey, & Robbins, 1995; see Table 10.1), as would have been expected on the basis of certain animal studies (Mishkin, 1982). On the other hand, performance on such tests is relatively insensitive to neurosurgical excisions of the frontal lobe (Owen et al., 1995; Table 10.1). In contrast, general performance on tests sensitive to frontal lobe dysfunction, such as the extradimensional shift paradigm and the Tower of London, is not impaired by temporal lobe damage (Owen et al., 1990, 1991, 1995). Furthermore, on certain tests, for example, spatial working memory, there are impairments in some aspects of test performance following frontal lobe damage that are not present following damage to the temporal lobe, and vice versa (see Owen et al., 1995, 1996c). Thus, the use of an effective strategy for conducting this self-ordered spatial working memory task is impaired by frontal lesions in humans, whereas this is not the case for lesions of the temporal lobe, which nevertheless still impair performance at the more difficult levels. The visuospatial paired associate learning test is another that is affected by damage to both regions, although probably for different reasons (Owen et al., 1995).

There is less evidence available to differentiate the possible role of the parietal cortex in performance of these tests, but recent evidence using PET (Baker et al., 1996; Owen et al., 1996a, 1996b) makes it clear that the parietal cortex is heavily implicated, probably bilaterally, in the Tower of London test. In the latter functional imaging study, the left dorsolateral prefrontal cortex, as well as the left caudate nucleus also exhibited increases in regional cerebral blood flow (rCBF). Thus, it is important to realise that the Tower of London task activates a network of neural structures with related functions.

Activation using PET has also illuminated the neural substrates of three tests of different aspects of spatial memory. For example, tasks similar to the CANTAB spatial recognition memory test are known to activate the right dorsolateral prefrontal cortex in man, in keeping with its similarity to the delayed response task that is prototypically associated with this region in work with monkeys (Jonides et al., 1993; Owen et al., 1996a). Moreover, a test similar to spatial span activates the right midventrolateral regions, whereas the spatial working memory task activates both of these zones (Owen et al., 1996a). These data are also consistent with the rationale of the CANTAB working memory and planning battery: the separate tests of spatial function help to decompose the components of the planning task.

Experiments with monkeys performing the extradimensional shift test have recently shown that lesions of the dorsolateral prefrontal cortex selectively impair the extradimensional shifting component while leaving reversal learning unaffected, whereas orbitofrontal lesions have the opposite patterns of effects (Dias et al., 1996). These data are consistent with the view that the prefrontal cortex is heterogeneous with respect to function in primates (Petrides, 1994), and suggest that "executive functions" may themselves comprise a loose collection of control processes, at least some of which are mediated by different regions of the prefrontal cortex.

Results from patients with Alzheimer's and Parkinson's diseases also help to define neural and neurochemical substrates of some of the CANTAB tests (see Table 10.1). For example, the anticholinesterase tacrine has been shown to improve the accuracy and speed of performance of patients with Alzheimer's disease (Sahakian et al., 1993), data consistent with results from animal studies suggesting that accuracy of detection of visual signals in a similar Continuous Performance test depends on the integrity of the cholinergic projections from the basal forebrain to the frontal cortex (Muir, Everitt, & Robbins, 1995). Moreover, initial thinking time is slowed in Parkinson's disease patients, but remediated partly through treatment with L-Dopa (Lange et al., 1992), suggesting that the slowing of movement caused by nigro-striatal dopamine degeneration is paralleled by a slowing of thinking ("bradyphrenia") which may similarly depend on dopamine loss from the striatum. This critical structure is quite possibly the caudate nucleus, on the basis of the functional imaging studies of normal volunteers described above. Both serotonergic and noradrenergic influences on cognitive function are suggested by recent studies of the effects of low tryptophan drinks (Park et al., 1994) or the alpha-2 receptor agents clonidine and idazoxan (Coull, Middleton, Robbins, & Sahakian, 1995 a, b), on different aspects of performance on the CANTAB tests. Some of these data are consistent with the hypothesis that alpha-2 receptors in the frontal cortex are implicated in spatial working memory performance, especially in aged monkeys (Arnsten & Goldman-Rakic, 1984).

Overall, it should be realised that it is naive to assume that there is necessarily a one-to-one relationship between a deficit on a given neuropsychological test and brain damage to an anatomically defined region. Many brain regions are interconnected in neural networks which mean that performance on a particular test may be impaired by lesions to widely distributed brain structures. This is particularly true of the prefrontal cortex which has major reciprocal projections to posterior cortical areas, as well as to subcortical areas such as the hypothalamus, the striatum, and the chemically defined systems of the reticular core of the brain (see Goldman-Rakic, 1987). The challenge posed by this anatomical circuitry is to understand which distinct types of information processing are subserved by

each component of the neural system or network. However, it is clear that the way in which the prefrontal cortex is anatomically interconnected with different brain regions makes it an ideal candidate for coordinating processing between many different regions and thus mediating many aspects of executive function.

STUDIES WITH LARGE POPULATIONS OF NORMAL ELDERLY VOLUNTEERS

It has been possible to gain insights into the utility of the neuropsychological approach espoused here through a standardisation of the CANTAB tests on a large number of elderly volunteers (up to about 800) in collaboration with the North-East Age Research Panel under the direction of Professor P. Rabbitt. This study has made possible a detailed analysis of how cognitive functions measured by the CANTAB tests, which presumably reflect the altered functioning of some of the component neural systems, discussed above, decline with age. As the study was conducted on a panel that has been engaged in a detailed longitudinal investigation of the cognitive effects of ageing, it has also been possible to utilise information from other psychometric tests intrinsic to the longitudinal study, as well as to make useful comparisons with other neuropsychological batteries that have been used on this population. Although this study is necessarily cross-sectional at present, with all the problems of interpretation that this entails in ageing studies, it is planned to complement it by retesting the panel at a later date.

Most of the data to be described were obtained from a population aged between 55 and 79 years. A more limited data set is available from volunteers younger than 50 years. Thus, it is possible to examine age-related declines in performance over this age range, and in that sense identify which neuropsychological tests, and putatively which brain systems, are most vulnerable to the effects of ageing. This analysis, however, is limited only to this particular age range and this has certain problems of interpretation. For example, it appears that there are very large differences in performance of the extradimensional shift test between small groups of control participants relatively young (i.e. about 30 years old) and old (70 years plus) (Owen et al., 1991). This result has recently been confirmed using an independent sample of young and elderly participants (Fig. 10.2). But it appears that most of this difference must occur before 55 years, as there is little further decline in performance specifically in extradimensional shifting after that age, although the ability to form and maintain an attentional set shows a small degree of impairment (see Fig. 10.2). The problems of interpretation are thus analogous to those of identifying tests sensitive not only to cognitive decline in early Alzheimer's disease, but also to its subsequent course.

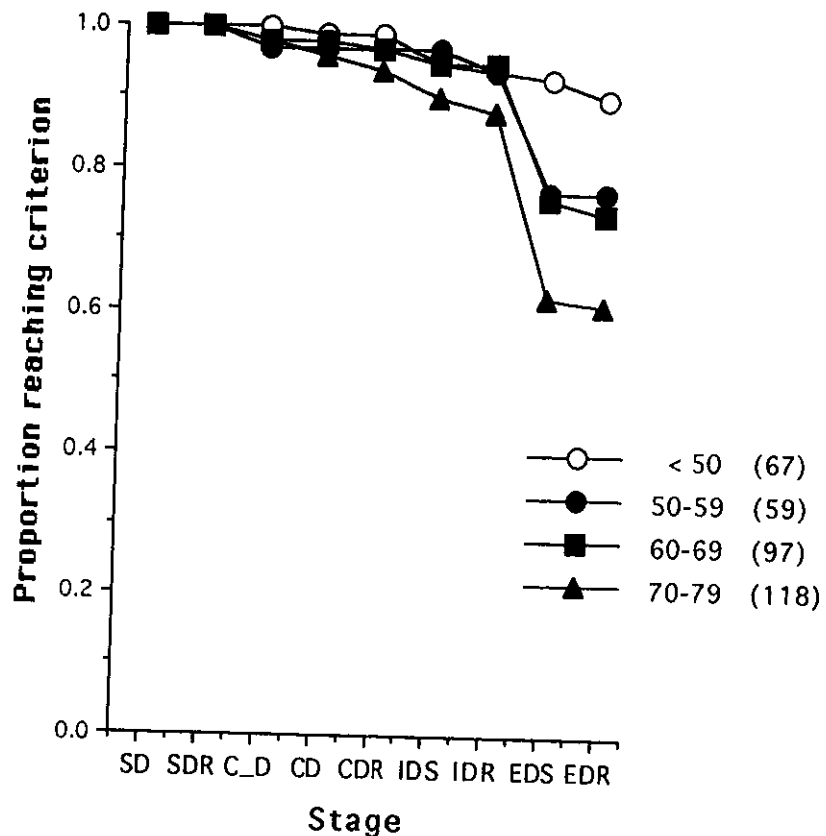


FIG. 10.2. Cumulative proportion of participants successfully reaching criterion at each stage of the attentional set-shifting paradigm. SD = simple discrimination; SR = simple reversal; C-D = compound discrimination, separated elements; CD = compound discrimination, superimposed elements; CDR = compound reversal; intradimensional shift; IDR = intradimensional reversal; ED = extradimensional shift; EDR = extradimensional reversal. *N*s refer to subjects in each age band, as defined.

Another problem in tracking performance over wide ranges of age and intellectual ability is that of avoiding tests contaminated by strong ceiling and floor effects. This problem potentially affects interpretation of results from the delayed matching to sample paradigm in the present study (Fig. 10.3). Memory retention declines mildly over delays in the youngest group (< 50 years), but is significantly inferior to performance in the perceptual control condition of simultaneous matching to sample condition, demonstrating some independence from ceiling effects at superior levels of performance. Performance of the 55-59 age group is reduced in parallel over the different delays compared with the youngest group, suggesting no

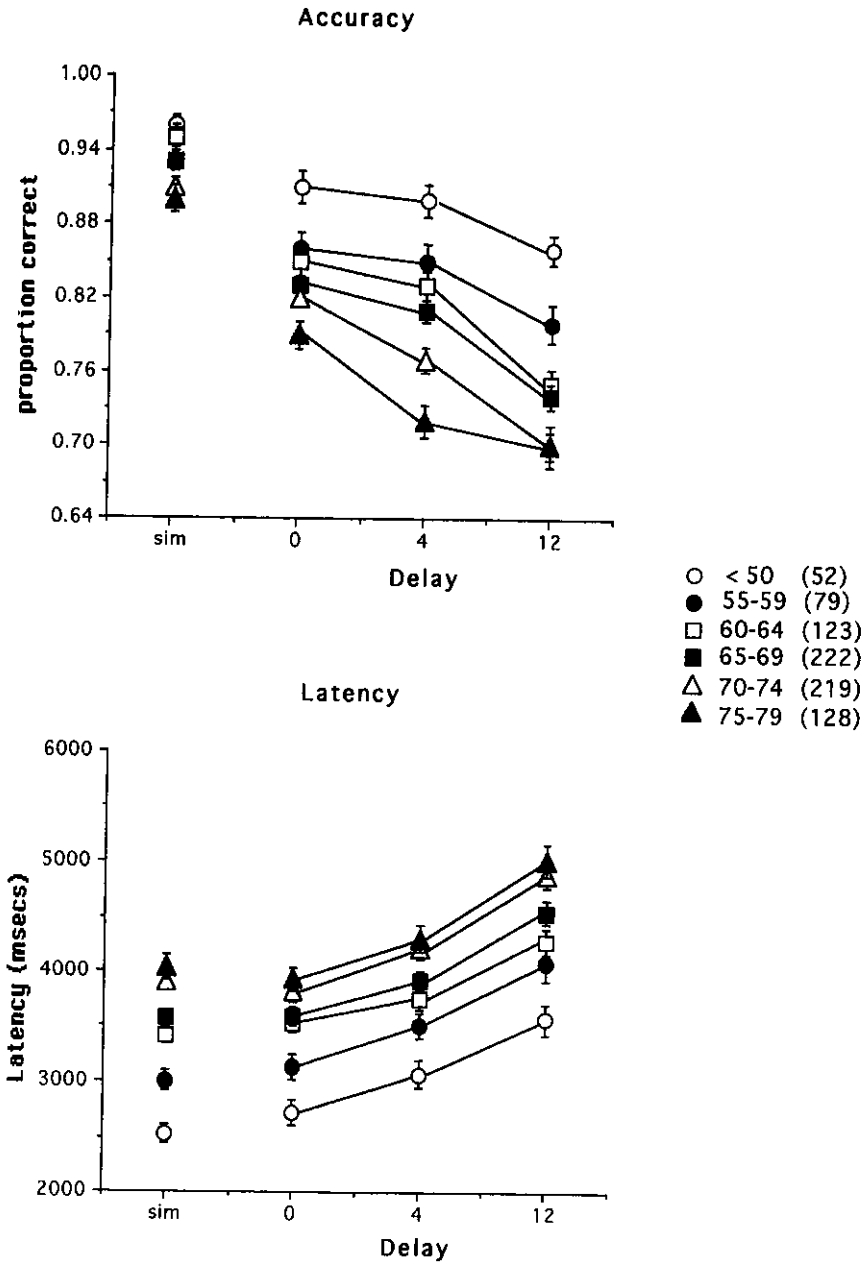


FIG. 10.3. Delayed matching to sample as a function of age in the large elderly sample studied by Robbins et al., 1994; with the addition of another group of similar NART IQ, < 50 years. Mean + SEM of measures of both accuracy and latency of performance are depicted.

specific effect of ageing on this form of recognition memory in these middle-aged groups, but a general, delay-independent decline in recognition memory accuracy that might be attributable to a perceptual factor. However, some of the subsequent declines in performance appear to be delay-dependent, as shown by the significant reductions in accuracy observed in individuals from the 55–59 year age group compared with those from the 60–64 year age group, evident at the longest delay (12s). These data suggest that the neural system in control of visual recognition memory, which presumably incorporates several components of the temporal neocortex (Murray, 1992), is susceptible to the effects of ageing. There are further, age-dependent declines in accuracy of performance for older groups, but these are limited to relatively short (4s) delays. At the longer delays, performance accuracy appears to reach floor levels in this population of about 70% correct, probably constrained by verbal encoding strategies based on colour. It is significant that patients with Alzheimer's disease at similar ages may exhibit more pronounced delay-dependent deficits in percentage correct scores that reflect the failure of encoding strategies (see Sahakian et al., 1988; Sahgal et al., 1991). The complexity of the effects is shown by consideration of the latency for correct responses measure, which shows a rather different pattern, in which there appears to be a general slowing over age, not always in concert with the percentage correct measure.

These results are complemented by performance on the CANTAB visual pattern recognition test, which is related to delayed matching to sample in its dependence on intact temporal lobe function (Owen et al., 1995), but is perceptually less complex. This may account for the similar performances in the young (< 50) and 55–59 year age groups. There is then a smooth, though gentle, decline in performance, with no statistical difference between the three eldest quincades, which is consistent with mild temporal lobe dysfunction (see Fig. 10.4), and with the apparent relative preservation of the inferior temporal gyrus in ageing (Brody, 1994). This smooth decline is to be contrasted with the discontinuities evident in spatial recognition memory performance in the same group. This form of recognition memory (unlike pattern recognition) has been shown to be impaired in patients with frontal lobe excisions (Owen et al., 1995). When different visual and spatial requirements are combined, as in the case of the visuospatial paired associate task, major differences are shown for the youngest group versus the rest, especially on the errors-to-criterion index (Fig. 10.5), suggesting that ageing differences arise when there is a need to coordinate different stimulus attributes (encoding in this case, "what" and "where"). Discontinuities in performance decline are again exhibited, as in the case for spatial recognition memory.

Spatial working memory performance is also especially sensitive to differences between the young (< 50 years) and the rest, but also to decline in

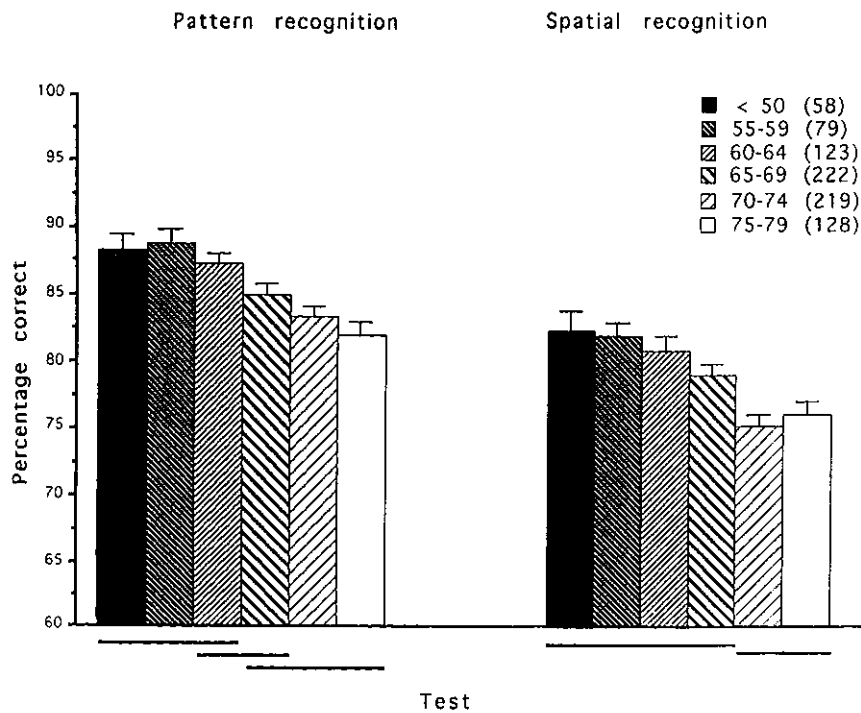


FIG. 10.4. Pattern and spatial recognition performance as a function of age (see Robbins et al., 1994). Non-overlapping horizontal lines indicate significant differences.

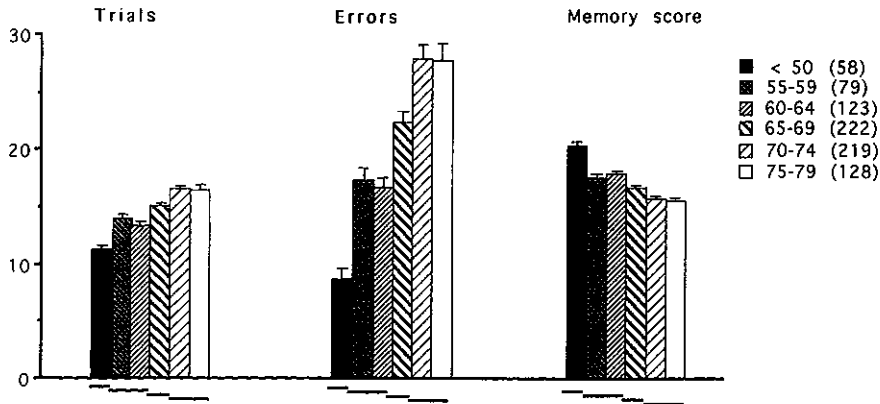


FIG. 10.5. Visuospatial paired associate learning according to three measures of number of (1) trials to criterion; (2) errors to criterion; (3) memory score on the first trial (see Robbins et al., 1994 for further details and caption to Fig. 10.4).

the most elderly quincades (Fig. 10.6). It is difficult to read too much significance into the data for these latter two tests with respect to the neural loci of the performance decrements, as they have been shown to depend on distinct neocortical regions. Both are affected by damage to the temporal and frontal lobes, although probably for different reasons in each case. For example, use of a common, effective strategy for performing the self-ordered spatial working memory task is impaired by frontal, but not temporal lobe lesions (Owen et al., 1995). This has led to the hypothesis that a major part of the frontal deficit on this task is strategic, and therefore executive in nature, whereas the temporal lobe deficits are a consequence of impaired spatial working memory capacity. The use of strategy is greater in younger (<50 years) healthy volunteers, but remains rather constant over subsequent quincades, in contrast to the precipitous decline in spatial working memory performance shown in Fig. 10.6. Further evidence for the multiple component nature of the spatial working memory task can be gleaned from the psychometric analysis of task performance described below, which is consistent with the involvement of distinct cognitive components which depend on distinct neural systems.

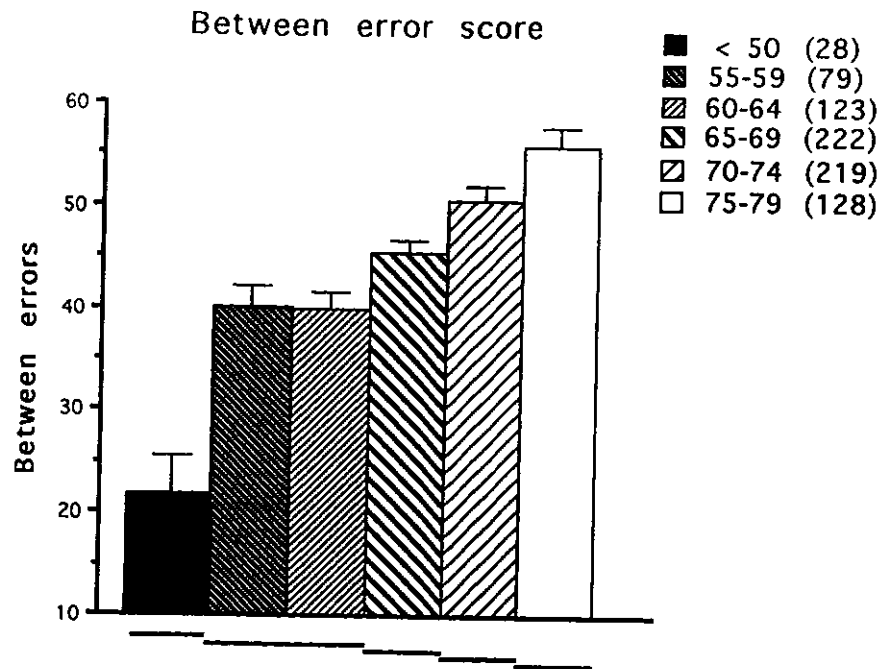


FIG. 10.6. Spatial working memory performance (mean + SEM between search errors), as a function of age (see Robbins et al., 1994 and also caption to Fig. 10.4).

PRINCIPAL COMPONENT ANALYSES

This multivariate approach may help to avoid many of the pitfalls inherent in identifying single tests with specific brain regions, and also enables relationships between various tests to be identified or checked against existing evidence from brain-damaged patients or functional imaging studies. The initial analysis utilised data from nearly 800 participants collected on tests from the visual memory battery, the test of spatial working memory, and the visual search, matching to sample task. The results were quite clear-cut. Four factors were identified after varimax rotation of the original solution. These are depicted in Table 10.2, together with the loadings for particular variables from the tests. The solution specified independent factors that could be associated with visual learning or memory, speed of responding, the spatial working memory task (perhaps including its executive features), and perceptual function. The same solution was obtained after repeated analyses of random subsets of the larger data set, and, more importantly, for each five-year age group. The latter result suggests that the structure of cognitive abilities represented by this subset of CANTAB tests remains constant over age. As this statistical structure presumably reflects the coordinated functioning of distinct regions of the cerebral cortex, as well as its interactions with subcortical structures such as the striatum and its modulation by the ascending, chemically defined systems of the reticular core of the brain, the implication is that ageing degrades these systems in

TABLE 10.2
Summary of Loadings for CANTAB Tests on Factors 1-4 Following Factor Analysis
(*N* = 787)

	<i>Factor 1</i>	<i>Factor 2</i>	<i>Factor 3</i>	<i>Factor 4</i>
Paired Associate Learning Trials	.82			
Memory score	.77			
Pattern Recognition	.73			
Spatial Recognition	.54			
DMTS (sim) Accuracy				.71
DMTS (del) Accuracy	.63			
DMTS Latency		.76		
MTS (Visual Search) Accuracy				.80
Latency		.72		
Spatial Working Memory (Between-search) errors			.88	
Spatial Working Memory (Within-search) errors			.77	

SOURCE: Robbins et al., 1994. Reproduced by kind permission of Karger Basel.

parallel. If any single cerebral region had been particularly susceptible to ageing effects, then the entire structure of interrelationships among the tests, whether probing functions mediated by the deficient structure, or alternatively not engaging it at all, would have been thrown out of balance. It is, however, possible that the diminishing influence of a single neurotransmitter system which innervates the entire cerebral cortex (e.g. the coeruleo-cortical noradrenergic system, or the basal forebrain cholinergic system) could account for such a pattern of results.

The analysis was also able to relate defining features of the population such as IQ and age to the critical cognitive factors. IQ was computed as a combined measure of five separate IQ tests (Nelson Adult Reading Test, Nelson, 1982; Mill Hill I and II, AH41 and AH42, Heim, 1968), and found to load most strongly on factor 1, visual learning and memory. (In fact, separate analyses of NART and AH4-1 and AH4-2 also show the same preferential loading on factor 1, unpublished findings.) By contrast, age loaded only on the cognitive speed factor. Such data would appear to violate hypotheses postulating that age results in progressive loss of IQ because of generalised reductions in cognitive processing speed (e.g. Salthouse, 1991). As those aspects of visual memory which load on factor 1 are particularly susceptible to deficits in early Alzheimer's disease (Sahakian et al., 1988; Sahgal, et al., 1991), the loading of age on factor 2 rather than factor 1 would also support the hypothesis that Alzheimer's disease is not simply an exaggeration of normal ageing processes.

Some caveats are necessary concerning these conclusions, however. The factor analysis pertains in the main to tests from the CANTAB battery; it would be more convincing to obtain converging evidence from an independent set of neuropsychological tests. When such analyses have been feasible in the clinic in well-studied single cases, such converging evidence has been forthcoming (e.g. Robbins et al., 1995).

It could also be argued that the CANTAB battery has not spanned a sufficient range of tests of cognitive function to be able fully to reflect integrated cortical functions. It is true, for example, that there are no verbal components to the CANTAB tests; however, such functions were reflected in some of the IQ tests administered. Another possible area of cognition covered insufficiently in the factor analysis was that tapped by tests of executive function, as performance on the spatial working memory test (the only contributor to loadings on factor 3 of Table 10.2), cannot simply be assumed to reflect its executive features. Converging evidence from other tests is required, which, it is presumed, would also be sensitive to frontal lobe dysfunction. Consequently, the final data to be described examine the structure of the CANTAB tests sensitive to frontal lobe dysfunction, the Tower of London test of planning, spatial working memory, and the extradimensional shift test (Fig. 10.2), together with their respective control

components (such as spatial span in the case of the Tower task). In addition, we also provide an analysis of data in a subset of subjects given both the CANTAB tests and a number of pencil and paper tests of executive function devised by Paul Burgess and Tim Shallice.

Table 10.3 shows the factor analysis of the tests of executive function described above, together with the participants' performance on the visual memory tasks, with a total $N=201$. There was a seven-factor solution, with eigenvalues >1.00 , which accounted for about 67% of the variance. Factor 1, as previously, was associated with tests of visual memory and learning. Factor 4 had loadings of variables related to latency measures on different tests, similar to factor 2 of the original analysis, but now incorporating the initial thinking time measure from the Tower of London test of planning (i.e. the time taken to initiate solutions). This factor presumably relates to speed of information processing. Factor 3 of the current analysis corresponds to factor 3 from the original analysis (Table 10.2, with the larger n), with the addition of loading for a measure of strategy on this self-ordered test of memory. This index has been shown to correlate significantly with good performance on the task, and, as mentioned above, is sensitive to frontal lobe, but not temporal lobe, lesions. As this index clearly relates to executive functioning in so far as it measures how well subjects utilise a strategy that can demonstrably enhance their performance, it would be reasonable to assume that factor 3 does indeed represent aspects of executive function. Factors 6 and 7 apparently reflect further aspects of executive function; the former factor has loadings from the two variables derived from Tower of London performance that are the most sensitive to frontal lobe excisions in the study of Owen et al. (1990), minimum moves, and subsequent thinking time. The former measure reflects the efficiency of problem solving, whereas the latter highlights the need for frontal patients to monitor carefully their solutions, even when these are accurate (see Owen et al., 1990). Each of the measures under factor 2 is also affected adversely by frontal lesions, including initial movement time, which forms a component of the yoked control test for the Tower of London and reflects continuous performance type functions. Overall, these functions may reflect working memory in the sense of maintaining information "online" for brief periods before responding. The loading for strategy score presumably results because the computation for this measure depends on the number of times a participant retraces a "route" at the beginning of successive searches; this then requires that the participant remember the last route employed. Overall, it is apparent that the tests of "executive function" do not all load on a single factor, as one might perhaps have anticipated. The allocation of certain tests such as the attentional shift task to a separate factor (factor 7) is also consistent with the heterogeneity of executive function, although this interpretation may be limited by the correspondence of this factor with

TABLE 10.3
 Summary of Main Loadings for CANTAB Tests on Factors 1-7 Following Factor Analysis (N = 201)

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Paired Associate Learning							
Trials	-.83						
Memory score	.79						
Pattern Recognition	.73						
DMTS (del) Accuracy	.65						
Tower of London							
Initial movement time		.68					
Spatial Recognition		-.63					
Tower of London							
Subsequent movement time		.52					
Spatial Working Memory							
Strategy score		.45	.43		.44		
Spatial Working Memory							
Within-search errors			.84				
Between-search errors			.74				
Tower of London							
Initial thinking time					.79		
DMTS Latency					.69		
MTS (Visual Search) Latency					.62		
Spatial Span							
DMTS (sim) accuracy						.65	
Tower of London							
Subsequent thinking time						-.82	
Minimum moves						.74	
Attentional Shift							
Stage reached							-.89
Errors							.67

performance on a single test. However, further inspection of the factor loadings for all of the variables entered revealed that errors on the matching to sample, visual search test from the Attentional battery also had a tendency to load on this factor (.39, thus below the threshold for being reported). This test also loaded in a limited way (.34) to factor 5, thus replicating the relationship between these variables shown in Table 10.2 that was identified as a possible visual perceptual factor. Introducing the data from the attentional set-shifting paradigm clearly had the effect of splitting the factor loadings between these two sources of covariance.

The third and final analysis is presented in Table 10.4. A large number of participants received some of the CANTAB tests, including the spatial working memory battery, and a battery of tests of frontal lobe function assembled by Burgess and Shallice. This analysis, conducted along the same lines as the previous ones, shows several features of interest. The first is that the Brixton test of spatial anticipation from their battery (Burgess & Shallice, 1996) loads together with performance from two of the tests of spatial memory from CANTAB that are sensitive to frontal lobe dysfunction. Therefore, this factor reflects performance from tests from different batteries that are sensitive to frontal lobe lesions, serving to cross-validate both, and again confounding the general belief that intercorrelations between tests of frontal or executive function are necessarily low. However, other well-

TABLE 10.4
Summary of Loadings on Factors 1-6 Following Factor Analysis ($N = 277$)

	<i>Factor 1</i>	<i>Factor 2</i>	<i>Factor 3</i>	<i>Factor 4</i>	<i>Factor 5</i>	<i>Factor 6</i>
AH4-1	.82					
AH4-2	.74					
NART	.78					
Digit Symbol	.63					
Similarities	.57					
Verbal Fluency (F)	.71					
Cognitive Estimates	.53					
Age		.95				
Spatial Working Memory			.60			
Spatial Recognition			.76			
Brixton			.57			
MTS Latency (8)				.90		
Pattern Recognition					.79	
Paired Associate Learning Errors					.77	
Hayling Errors						.88

known tests of frontal lobe function including verbal fluency and cognitive estimates clearly load separately from these. In fact, Table 10.4 shows that they tend to load with measures of IQ, including relatively verbal (NART, similarities and AH4-1) and non-verbal (AH 4-2 and digit symbol) components. While this reinforces in part the suspicion of Duncan (1995) that frontal lobe tests often generally reflect IQ, particularly of the "fluid" variety, the lack of loading of our main tests of executive function with these IQ measures suggests that not all tests of executive function that are sensitive to frontal lobe damage are subject to this interpretation.

EFFECTS OF AGEING ON COGNITIVE FUNCTION

The analyses presented in Tables 10.2 and 10.4 do not strongly support the hypothesis that functions sensitive to frontal lobe damage are especially sensitive to ageing effects. The extradimensional shifting test is sensitive early in the course of ageing, but not thereafter (see Fig. 10.2). However, even if a stronger relationship did exist, it would have to be determined whether the mode of failure really resembled the effects of frontal lobe damage (which are lack of control over perseverative responding) or, alternatively, of basal ganglia damage (which have more diffuse effects) (Owen et al., 1993b). The spatial working memory test does show a clear age-related deficit (Fig. 10.6), but the strategy measure does not. The Tower of London test measures (data not shown) tend to highlight initial thinking time, rather than measures more clearly related to frontal deficits, such as subsequent thinking time or minimum move solutions. In fact, if one considers the qualitative pattern of results shown in Table 10.1 across various patient groups, it is striking that it is basal ganglia disorders, as exemplified especially by Parkinson's disease, that most strongly reflect the cluster of variables most sensitive to ageing effects, rather than damage to temporal or frontal lobes, or dementia of the Alzheimer type. This interestingly mirrors the comparison that can be made between the deficits in Parkinson's disease and following frontal lobe damage; generally the same types of test are sensitive or insensitive in both cases, but the deficits are qualitatively distinct. This is certainly the case for each of the three tests of frontal lobe dysfunction considered here (see Owen et al. 1992, for further discussion). This may be consistent with the anatomical relationships that exist between the frontal cortex and the striatum, in the form of "cortico-striatal functional loops" (Alexander, Delong, & Strick, 1988). The frontal cortex and striatum may thus contribute in related, but distinct, ways to performance of presumed "executive" tasks, which may serve to refine our notions about these complex processes.

While the possible analogy of ageing with Parkinson's disease is consistent with the preserved factor structure found for the factor analysis of

the large sample (Table 10.2) as a function of age, it would be naive to suppose that the analogy is more than that. To begin with, different tiers of the substantia nigra are susceptible to ageing and Parkinson's disease (Scherman et al., 1989). Furthermore, Parkinson's disease is not associated with delay-dependent deficits in DMTS performance which clearly occurred in some of the aged quincades tested here (Fig. 10.3) and implicate impaired temporal lobe functions, which may be superimposed upon the more general picture we have described. We maintain that the development of yet more specific and sensitive tests of functioning of different neural systems will help disentangle these various forms of the cognitive sequelae of ageing.

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