Computerized assessment in neuropsychiatry using CANTAB: discussion paper

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This paper illustrates how recent developments in computing technology can be exploited for the neuropsychological assessment of neurodegenerative diseases. Computerized tests have many advantages over traditional paper and pencil tests, including precision, speed and reliability. For example, it is possible to measure response latencies to millisecond accuracy, necessary for reaction time studies. Furthermore, the computer can be used to give feedback to the subject in a systematic and objective fashion. These general design features have now been utilized extensively in a set of tests known as the Cambridge Neuropsychological Test Automated Battery (CANTAB). Other important design features of these tests are:

(1) They are designed to test different aspects of mental functioning so that a profile of performance can be constructed for a particular patient group.
(2) Where appropriate they are graded in difficulty in order to assess a broad range of cognitive ability.
(3) They employ non-verbal stimuli and require non-verbal responses. This, of course, is essential for patients with language impairment, but is also an important advantage for cross-national studies.
(4) They are designed to be visually attractive and interesting, using positive feedback which has a 'game-like' quality and maintains motivation.

CANTAB consists of three separate batteries of tests measuring visual memory, attention and planning. They are designed to run on an Acorn BBC Master Microcomputer and more recently on IBM PC and compatible machines. In both cases the programs employ high resolution graphics and responses are made using a touch sensitive screen.

The theoretical rationale of the tests is based on two main themes: (i) adapting those tests of animal neuropsychology that have proved useful in establishing the neural substrates of certain types of cognitive function and; (ii) undertaking a componential analysis of the processes comprising particular forms of cognitive function; for example spatial planning may involve the ability to store and sequence particular spatial representations, as well as manipulate them in working memory. A patient could fail a planning test because of impairments in any one of these constituent functions.

The tests are comprehensive in terms of the range of functions they assess, and have been shown to be sensitive to deficits, as well as progressive decline, in patients early in the course of dementia of the Alzheimer type (DAT)[1,2] and Parkinson's disease (PD)[3,4]. Importantly, some of the deficits show patterns of double dissociations across these groups which indicate the possibility of contrasting types of cognitive deficit, perhaps dependent on different types of neural substrate. In addition, many of these tests have recently been used to assess performance in neurosurgical patients with localized excisions of the frontal and temporal lobes[5,6]. By direct comparison with DAT and PD patient groups these neuropsychological studies are proving useful in establishing precisely which neural substrates are responsible for the pattern of cognitive deficits observed in patients with these neurodegenerative diseases.

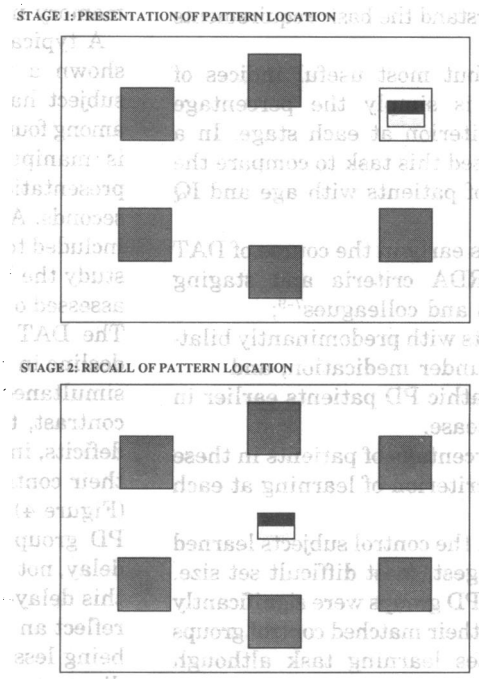

Figure 1. The CANTAB paired associates task. Following the initial presentation stage, the pattern location is identified by touching the appropriate box

One of the tests we have found to be especially sensitive in the testing of DAT patients is a paired associates learning task in which the subjects have to learn the locations of visual patterns on the screen. The arrangement of six locations (or boxes) is shown in Figure 1.

In the initial (presentation) stage the six boxes open up, one at a time to reveal a different pattern inside. The patterns then appear again singly in the middle of the screen (recall stage) and the subject responds

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by touching the appropriate box in the periphery. If the subject makes any mistakes the position of each pattern is shown again and the subject has another opportunity or trial to indicate the correct locations. Subjects have up to 10 trials in which to learn correctly the locations of all stimuli. If the subject still has not attained criterion at this point then the computer terminates the session automatically and thanks the patient for taking part. It is important that the test begins at a very easy level with a single pattern in one of the boxes and then gradually becomes more difficult with two and three pattern sets before tests with six and finally eight items (in eight boxes on the screen) are finally reached. This ensures that the tests are suitable for severely impaired demented patients and also that the less severely affected patients do understand the basic requirements of the task.

One of the simplest but most useful indices of learning in this task is simply the percentage of patients attaining criterion at each stage. In a recent study[1] we have used this task to compare the following three groups of patients with age and IQ matched control groups:

(1) patients diagnosed as early in the course of DAT using NINCDS-ADRDA criteria and staging according to Hughes and colleagues[7-9];
(2) idiopathic PD patients with predominantly bilateral symptoms and under medication; and
(3) non-medicated idiopathic PD patients earlier in the course of the disease.

Figure 2 shows the percentage of patients in these three groups attaining criterion of learning at each stage of this test.

With one exception, all the control subjects learned the task even at the largest, most difficult set size.

In contrast, both of the PD groups were significantly impaired compared with their matched control groups on this paired associates learning task although neither group were as impaired as the patients with DAT.

A second computerized task that has been extensively used in both PD and DAT patient groups is a test of short term visual memory based on the delayed

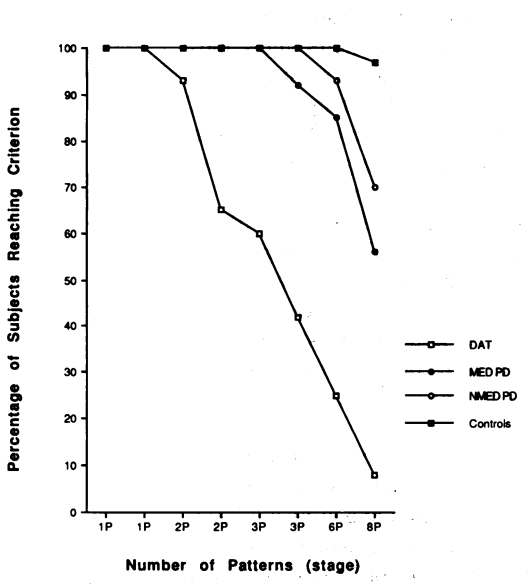

Figure 2. The percentage of DAT patients, non-medicated PD patients (NMED PD) and medicated PD patients (MED PD) reaching criterion at each stage of the paired associates learning test. The combined (mean) control performance is also shown

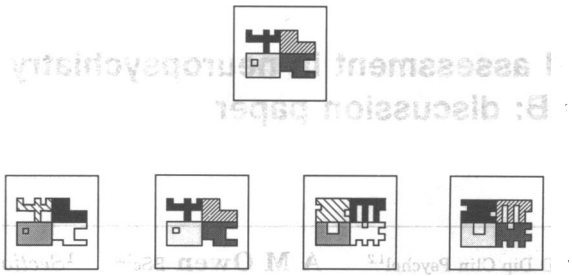

Figure 3. The CANTAB delayed matching to sample procedure. The target stimulus (top) must be identified from among three distractors (below)

matching to sample paradigm used by Mishkin and others to define the neural substrates of visual memory in primates[10,11].

A typical trial is shown in Figure 3. After being shown a target stimulus for several seconds the subject has to pick out the identical pattern from among four possible alternatives below. Task difficulty is manipulated by varying the delay before the presentation of the four response stimuli from 0 to 16 seconds. A simultaneous matching condition is also included to control for perceptual deficits. In a recent study the DAT and PD groups described above were assessed on this test of delayed matching to sample[1]. The DAT group showed a sharp delay dependent decline in choice accuracy, with no impairment with simultaneous stimuli or 0 sec delay (Figure 4). By contrast, the PD groups showed delay-independent deficits, in other words they were less accurate than their controls at all delays to an equivalent degree (Figure 4). Thus, in this test we see a deficit in the PD group at simultaneous presentation and 0 sec delay, not shown in the DAT group. It is possible that this delay-independent deficit in the PD group may reflect an attentional dysfunction, with the patients being less able to switch between the two stimulus dimensions (ie *shape* and *colour*) when encoding the sample stimuli as an integrated percept. This hypothesis is supported by the impaired performance of PD patients on the Wisconsin Card Sort Test[12,13]

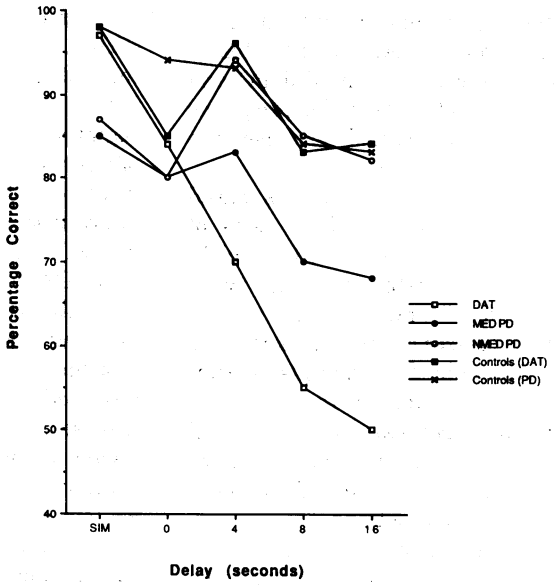

Figure 4. The performance of DAT patients, non-medicated PD patients (NMED PD) and medicated PD patients (MED PD) on the delayed matching to sample paradigm. The DAT controls and the mean values for the PD control groups are also shown

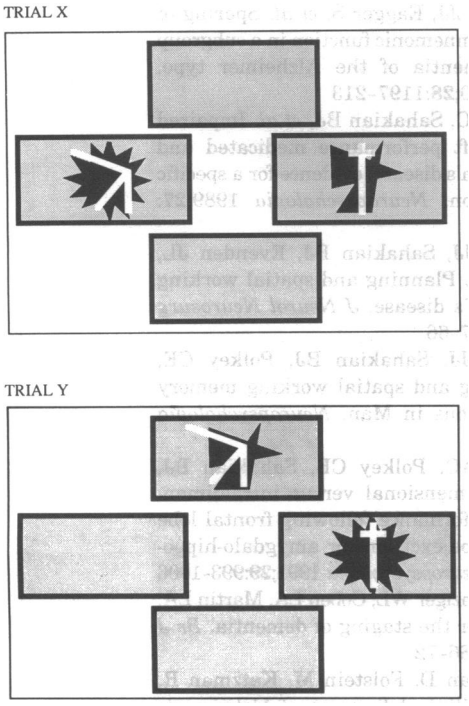

Figure 5. Example stimuli from several stages of the CANTAB attentional set shifting task. The 'white line' and 'purple shape' stimuli are shown exactly as they appear on the screen

which is known to be sensitive to frontal lobe dysfunction[14].

We have recently investigated attentional set shifting mechanisms in DAT and PD patients using a third computerized test of visual discrimination learning culminating in an intra-dimensional and an extra-dimensional shift. An intra-dimensional shift occurs when a subject, trained to respond to a particular stimulus dimension (such as 'shape') is required to transfer that rule to a novel set of exemplars of that same stimulus dimension (eg a new 'shape'). An extra-dimensional shift occurs when a subject is required to shift response set to an alternative, previously irrelevant stimulus dimension (eg 'line'). In this paradigm, two dimensions are used, purple filled shapes and white line figures (see Figure 5). Initially, subjects are presented with two simple stimuli on the screen and are requested to guess which is correct by touching one of the two stimuli. The computer automatically responds by indicating to the subject that they are right or wrong and the subject must then use this feedback to develop and learn the rule such that they respond correctly on every presentation of the stimuli. Once the subject has learnt the rule, they continue to follow it on each new presentation until it is automatically changed by the computer. This occurs when a criterion of six correct responses in a row has been attained. First simple discrimination and reversal learning are tested to stimuli varying in one of the two dimensions only (eg purple shapes or white lines). A second irrelevant dimension is then introduced, and compound stimulus and reversal learning are tested. At this stage, the intra-dimensional shift occurs and the subject is required to continue using the same rule with novel exemplars of the two dimensions. Finally an extra-dimensional shift occurs and the subject is required to shift response set to one exemplar from the alternative, previously irrelevant dimension (Figure 5).

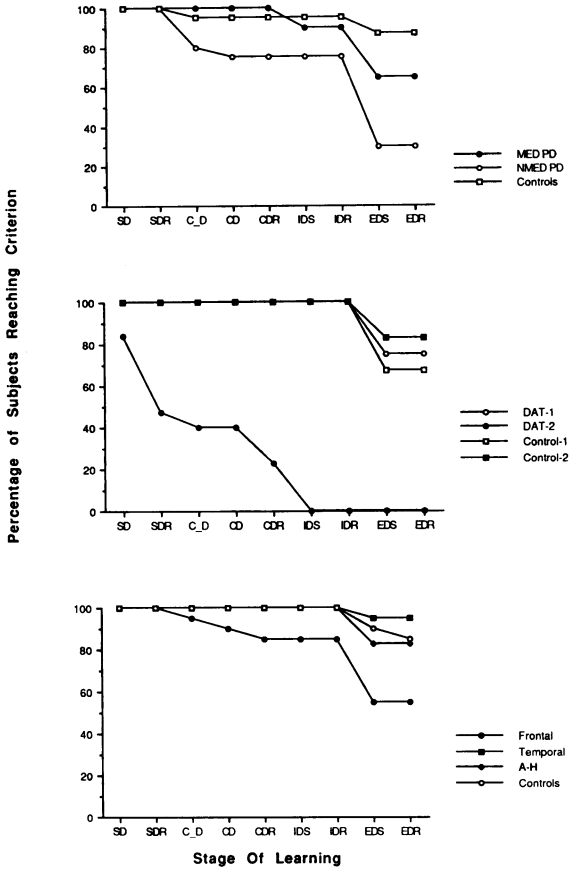

Figure 6. The percentage of subjects reaching criterion at each of the nine stages of the discrimination learning paradigm. The relative performance of MED PD and NMED PD (Downes et al., *1989), mild and moderate DAT groups (Sahakian* et al., *1990) and frontal, temporal and amygdalo-hippocampal groups (Owen* et al., *1991) are shown*

In a recent study[3] the performance of medicated and non-medicated patients with PD was compared on this test of visual discrimination learning. Both the medicated and particularly the non-medicated patients with PD were impaired in their ability to perform an extra-dimensional shift but not an intra-dimensional shift and this pattern has recently been replicated in an unrelated group of non-medicated patients (Owen *et al.*, in preparation). These data are shown in detail in Figure 6. The neural specificity of this effect has been confirmed by a parallel study in which patients in the mild stages of DAT were compared with DAT patients with more severe clinical symptoms[2]. Patients predominantly at Clinical Dementia Rating (CDR) 1 or mild dementia[6] exhibited absolutely no deficit in this attentional set shifting task even at the extra-dimensional shift (EDS) stage. The remainder of the DAT patients, which included many patients further in the course of Alzheimer's disease and at CDR 2 on the Hughes Scale (which is moderate dementia) performed very badly even at the simplest stages of the test (see Figure 6). It is important to emphasize that the patients early in the course of DAT actually performed better in this test of visual discrimination learning than the patients with PD, and consequently, that early in the course, DAT is not necessarily associated with a generalized cognitive decline. The deficits in memory and learning seen earlier in these DAT patients can also be quite specific and compared with this task, are probably related to rather different neural substrates.

This issue is currently being formally addressed in comparative studies of neurosurgical populations with localized excisions of the frontal and temporal lobes on these same computerized tests of learning, memory and attentional set shifting[5]. In a recent study, 20 such patients with discrete frontal lobe lesions were compared with a group of 20 patients with excisions of the temporal lobes and a group of 11 patients who had undergone unilateral amygdalo-hippocampectomy (A-H). The frontal lobe group were selectively impaired in their ability to shift response set to the irrelevant stimulus dimension (extra-dimensional shift), but not to shift attention to new exemplars of a previously relevant dimension (intra-dimensional shift[6]). In this respect, their performance was most similar to the groups of medicated and particularly non-medicated patients with PD, and may suggest a disruption of frontostriatal mechanisms in this neuro-degenerative group. By comparison with the frontal lobe group both the temporal lobe patients and the amygdalohippocampectomy patients were unimpaired in their ability to perform either an intra-dimensional or an extra-dimensional shift (see Figure 6). This study has demonstrated that in humans, cortical damage specific to the frontal lobes is sufficient, although may not be necessary, to produce the selective deficit in extra-dimensional set shifting ability seen in patients with PD but not in patients with mild DAT.

In summary, this paper has shown that the CANTAB battery of computerized neuropsychological tests is sensitive to, and can distinguish between these neurodegenerative diseases even early in the course of the disease process. Furthermore, the neural substrates responsible for the associated cognitive impairments can be investigated by direct comparison with patients with localized neurosurgical damage.

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