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Utility of CANTAB in functional neuroimaging

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Introduction

The design, theoretical rationale, and validation of the Cambridge Neuropsychological Test Automated Battery (CANTAB) are described in this chapter. The utility of the battery for functional neuroimaging studies is examined, based on its links with animal neuropsychological research, its decomposition of complex tests of cognition into their constituent parts, and its validation in patient groups with defined brain lesions. The use of selected tests from the battery is then surveyed, including the Tower of London test of planning, tests of spatial span and self-ordered working memory, a rapid visual information processing test of sustained attention, a delayed-matching-to-sample test of visual recognition, and a test of attentional set shifting. Each paradigm is shown to be associated with distinct neural networks of elevated regional cerebral blood flow (rCBF) using positron emission tomography (PET) based on $H_2{}^{15}O$. The use of these paradigms to delineate impaired neural networks in depression and other neuropsychiatric disorders is described. The final discussion assesses the prospects of future applications, including the use of other neuroimaging paradigms, such as functional magnetic resonance imaging (fMRI) and the PET ligand-displacement method.

The CANTAB was originally devised to assess cognitive function in elderly and dementing subjects (Robbins et al., 1994a). However, in the 1990s, it has also been used in the analysis of cognitive function in a range of adult neuropsychiatric syndromes, following drug treatments in healthy adult volunteers, and also in a neurodevelopmental context. The CANTAB comprises a set of computerized tests administered with the aid of a touch-sensitive screen. The two main guiding principles have been to use some tests that can be related to the extensive neuropsychologic literature in animals and to employ tests that can be broken down into their discrete cognitive components in order to define more readily which functions are impaired and which are spared, and thus the overall specificity of any deficits. Some examples of these principles can be gleaned from a brief survey of the main tests contained within the battery, which itself is divided into smaller batteries of tests of "visual memory", "spatial working memory and planning" and "attention" (Table 21.1). For example, the delayed-matching-to-sample (DMTS) test of visual recognition memory is derived from an analogous paradigm used with monkeys (Mishkin, 1982) and the test of attentional-set shifting is in fact a simplified and decomposed version of the Wisconsin Card Sorting Test (WCST), which is frequently used to assess frontal lobe function (Milner, 1964). The CANTAB version of the attentional set-shifting task is based on tests of visual discrimination learning and reversal, as well as specific transfer tests termed "intra" and "extra"-dimensional shifts, the latter capturing the essential qualities of the WCST. Moreover, the self-ordered test of spatial working memory is based on similar procedures used in experimental animals that derive from foraging paradigms (Olton, 1982; Passingham, 1985; Owen et al., 1990). These tests are further described in Chapter 22.

However, it is worth emphasizing that the CANTAB is not solely preoccupied with extrapolation from animals to humans and vice versa. One of the most prominent tests from the working memory and planning battery is an adaptation of the Tower of London test of planning, which derives from cognitive psychology more than from the animal literature (Shallice, 1982). This test, however, does exemplify the decomponential principle: as measures of thinking time are derived from a yoked control procedure in which the sequence of moves actually used by the subjects is played back to them, move by move, in order to quantify the time taken in visuomotor execution, thus

Table 21.1. Main sub-batteries of CANTAB and constituent tests

Test battery	Constituent tests[a]
Visual memory	Pattern and spatial recognition memory
	Simultaneous and delayed matching-to-sample
	Paired visuospatial associates learning
Spatial working memory and planning	Spatial span
	Self-ordered spatial working memory (spatial search)
	Tower of London (Stockings of Cambridge)
Attention	Serial choice reaction time
	Visual search, matching-to-sample
	Attentional set-formation and shifting
	Rapid visual information processing

Note:

[a] The motor screening test is common to all three batteries. These batteries are identical for use in children or adults.

assessing sensorimotor components of the latency measures. This sensorimotor component is then subtracted from the overall response latency to estimate the residual "thinking time", this being done both for the initial latency before the subject implements the solution and also for the subsequent "thinking time" during problem completion (see Owen et al., 1990).

The CANTAB has now been used quite extensively in the testing of patients with Alzheimer's disease and other forms of dementia (Sahakian et al., 1988, 1990; Sahgal et al., 1991, 1992; Fowler et al., 1997), patients with basal ganglia disorders such as Parkinson's (Downes et al., 1989; Owen et al., 1992, 1993) and Huntington's diseases (Lange et al., 1995; Lawrence et al., 1996), and those with Korsakoff's syndrome (Joyce and Robbins, 1991), depression (Abas et al., 1990; Beats et al., 1996; Elliott et al., 1996) and schizophrenia (Pantelis et al., 1997; Elliott et al., 1998; Hutton et al., 1998).

Like most cognitive test batteries initially designed for use in adult subjects, the CANTAB has not yet been employed often in developmental neuropsychology, although the ability of the battery to draw parallels with the animal neuropsychologic literature and its limited dependence on language abilities makes it attractive as a means of testing hypotheses about the neural substrates of cognition in children. One of our studies did use some of the tests from CANTAB to assess children with either learning disabilities or autism (Hughes et al., 1994). This study was successful in showing that autistic children had selective difficulties with two of the main CANTAB tests sensitive to frontal lobe dysfunction: extradimensional set-shifting and Tower of London planning performance. This study has been theoretically significant in recent debates about the "theory of mind" and "executive" hypotheses of the core cognitive deficit in autism. Many of the CANTAB tests have been used recently in a large cross-sectional study that has made inferences about cognitive development in the context of cortical maturation (Luciana and Nelson, 1998; see Chapter 22).

Two main issues in the use of CANTAB in a clinical neuropsychologic context relate to its standardization and validation. These issues have been dealt with in other publications and will not be discussed in great detail here, except to point out that the tests have been standardized on large populations of healthy normal subjects across a wide age span (Robbins et al., 1994a, 1996, 1998). Questions such as test–retest reliability are currently being addressed. The validation of the tests depends, in part, on their sensitivity relative to other clinical instruments and their ability to discriminate deficits in marginal cases of brain dysfunction or in early stages of disease processes, for example in asymptomatic HIV (Sahakian et al., 1995), gene-positive Huntington's disease (Lawrence et al., 1998a), or early in the course of dementia of the Alzheimer type (Fowler et al., 1997). The precise clinical utility of computerized tests is still under debate, although advantages in terms of the standardized presentation of tests and objective and accurate recording of the data are obvious. The automatized nature of the tests makes them suitable for adaptation to functional neuroimaging designs. Their componential nature, which allows complex performance to be broken down into constituent parts, also lends itself well to the functional imaging approach, as will be made clear later in this chapter. The goal of functional neuroimaging is to elucidate neural networks that underlie different cognitive processes, as well as the effects of defined brain lesions on performance on the different tests. Such information can be extrapolated in part from the effects of lesions in experimental animals, particularly nonhuman primates. For example, we now have extensive knowledge of the neural substrates of delayed nonmatching-to-sample (DNMTS) task in macaque monkeys, which bears on the design of the human analog DNMTS task that is included in the CANTAB. These include deleterious effects of lesions to different regions of the temporal lobes, the midline thalamic nuclei, and the ventromedial prefrontal cortex (see Murray (1992) for review). Similar analyses might be applied to the CANTAB tests of self-ordered working memory and attentional set-shifting, which depend on different regions of the prefrontal cortex (Petrides et al., 1993a; Petrides, 1996; Dias et al., 1996).

The validation process is strengthened by the study of patients with defined brain lesions, such as neurosurgical excisions of the frontal or temporal lobes (e.g., Owen et al., 1995a; Robbins et al., 1997). Some of the CANTAB tests are sensitive to frontal lobe and others to temporal lobe damage or to amygdalo-hippocampectomy (Owen et al., 1991, 1995a). However, this approach is limited in determining the nature of the neural networks engaged by the various cognitive processes because of the arbitrary and essentially ill-defined nature of brain lesions in humans. An appropriate paradigm for determining neural activity, therefore, is that of functional neuroimaging, whether using PET or fMRI. The knowledge to be gained from the combination of studies of brain lesions and functional imaging in normal subjects is attractive, because the evidence from the lesion studies helps to establish the causal (direct and indirect) nature of any apparent involvement of a particular structure. The logic involved here is quite clear. If an activation is detected in a particular structure from a neuroimaging study and yet performance of the task remains normal when that area is absent or damaged, questions can be asked about whether the structure in question is, in fact, necessary for efficient task performance. If, however, there is a deficit following a lesion to a structure that is activated in the normal brain during task performance, this provides quite strong evidence for the causal involvement of that structure in performance. If there is no activation in the structure, then a deficit following a lesion could conceivably reflect an indirect impairment caused by a compensatory change in other brain regions. Alternatively, the lack of activation in the normal brain might reflect inadequacies or insensitivity in the neuroimaging technique employed.

The CANTAB tasks used clinically often have to be modified for the purposes of neuroimaging, not only because of the intrinsic requirements of the PET or fMRI protocols but more particularly to avoid ceiling effects that can occur in younger and more intelligent normal adult volunteers. The following review examines, in turn, results from some of the main CANTAB tests employed in functional imaging, usually PET studies with $H_2{}^{15}O$. Defining appropriate neural networks for particular tasks is not an end in itself, but it may be an essential preliminary step in investigating the neural substrates of altered performance in neuropsychiatric disorders with no obvious structural damage (e.g., depression or schizophrenia). Therefore, several studies have examined the neural substrates of impaired task performance in patients with neuropsychiatric disorders such as depression or schizophrenia having previously focused on normal subjects, who can then serve as a suitable control group.

Use of CANTAB in functional imaging paradigms

To date, of the CANTAB tests, variants of the Tower of London task have been the most frequently employed in functional neuroimaging studies, although more recently, several other tasks from the battery have also been investigated, mainly in PET studies of rCBF using $H_2{}^{15}O$.

Planning ability (Tower of London/Stockings of Cambridge)

Planning is the ability to think ahead and is necessary in situations where a goal must be reached through a series of intermediate steps, each of which does not necessarily lead directly toward that goal (Owen, 1997a). Research into the fundamental neural mechanisms of planning has been carried out in studies of lesions in nonhuman primates (e.g., Petrides, 1994), and in neuropsychologic studies of human patients (e.g., Klosowska, 1976; Shallice, 1982, Owen et al., 1990). Both types of study have implicated the frontal lobe as being essential in planning behavior (for review see Owen, 1997a). However, it is only with the emergence of functional neuroimaging techniques such as single photon emission computed tomography (SPECT), PET and fMRI during the 1990s that the precise anatomic substrates of planning have been investigated in healthy human subjects. Typically, changes in rCBF measured by these techniques while subjects are engaged in specific tasks serve as an indirect index of neuronal activity during cognitive, motor, and/or sensory processing.

Using a three-dimensional computerized version of the Tower of London task presented on a touch-sensitive screen, Morris et al. (1993) employed SPECT to investigate the neural correlates of planning in normal adults. In comparison with a control task that did not require planning but was matched for motor movements and visual stimulation, a significant increase in rCBF was observed in the left prefrontal cortex during the Tower of London task. This result had some similarities to those reported by Rezai et al. (1993) and supports the general role of the frontal lobe in planning behavior. However, given the relatively low spatial resolution of SPECT, this technique is inadequate for investigating the precise functional specialization of the distinct cytoarchitectonic areas within the prefrontal cortex.

In comparison with SPECT, and depending on the particular scanner used, PET possesses greater spatial resolution, which when combined with structural MRI can provide more precise localization of function. Several more recent studies have used PET to measure rCBF during the Tower of London task. Using this technique, 6–12 scans are

conducted and for each, a radioactive tracer is introduced into the vascular system, usually ^{15}O in the form of $H_2{}^{15}O$. The PET scanner measures the spatial distribution of the tracer over a 60–120 s period, during which the subject carries out an experimental or control task. The experimental task involves the cognitive, motor, or sensory process of interest while the control task is designed to require many, but not all, of the same processes. A common approach to statistical analysis is via subtraction whereby scans from different conditions are "subtracted" from one another (e.g., experimental task – control task) to isolate regions activated by the processes of interest involved in the experimental task but not in the control task. A basic comparison is of the task with a "rest" condition (e.g., "eyes closed") in which there are no specific task requirements. From our perspective, the closer the cognitive requirements of the experimental and control tasks, the greater is the chance of isolating activations specific to a particular cognitive function. The subtractions can then be coregistered with a normalized structural MRI scan, enabling the precise location of significant regions of activation. Local maxima of activation are usually reported in terms of stereotaxic coordinates (x, y, z; Talairach and Tournoux, 1988) and/or the cytoarchitectonic region in which they lie (e.g., Brodmann area (BA)).

Owen et al. (1996a) used PET to investigate the role of distinct frontal cortical areas in planning behavior using the computerized Tower of London (or Stockings of Cambridge) task from the CANTAB in healthy adult male volunteers. The subjects were scanned during easy (two or three move) and difficult (four or five move) Tower of London problems of the task and also during a control condition. By subtracting the control condition from the easy and difficult planning conditions and also the easy and difficult planning conditions from each other, the network of cortical and subcortical areas involved in the planning aspect of the Tower of London task can be isolated.

Subtraction of the control condition from the difficult planning condition yielded a significant increase in rCBF in the left mid-dorsolateral frontal cortex, which comprises mainly BA 9 and BA 46 and lies within the superior and middle frontal gyri. There was also a trend for increase in rCBF in slightly more anterior regions of the same area in the opposite hemisphere, but this failed to reach statistical significance. That only the left prefrontal activation reached significance does not necessarily indicate that the process of planning is strongly lateralized to the left hemisphere. In fact, this observation is more likely to have been an artifact of the subtraction technique employed (Owen, 1997a). Since both the planning and control conditions involve visuospatial processes that are believed to be mediated largely by the right hemisphere (Milner, 1971, 1974), subtracting the control condition from the planning condition would inevitably remove or, at least reduce, any right hemisphere activation in the comparison. This interpretation is supported by Owen et al. (1996a), who observed significant right dorsolateral prefrontal cortex activation compared with a resting condition in the difficult planning condition prior to the subtraction of the specific task control condition. Furthermore, planning deficits are evident in patients with either right or left prefrontal cortical damage (Shallice, 1982; Owen et al., 1990, 1995b).

Subtractions of the control condition from the easy planning condition did not, however, yield a significant increase in rCBF in the prefrontal cortex, although a significant increase in rCBF was observed in the right premotor cortex and in bilateral regions of the parietal and occipital lobes. This probably reflects the fact that the easier two/three move problems can be solved simply by matching each ball in the sample configuration with its corresponding ball in the target configuration, with little need for thinking ahead (i.e., comparable with a visual matching-to-sample). Consequently, the need for planning is minimized or even absent, resulting in a decreased involvement of the prefrontal cortex. In contrast, a visual matching-to-sample strategy may place a greater load on posterior visual and attentional systems, while activation of the premotor cortex may reflect more basic processes of motor planning (Owen, 1997a).

The difference in activation observed between difficult and easy Tower of London problems in the study by Owen et al. (1996a) could conceivably reflect the difference in movement demands; while difficult problems require over four movements, simple problems can be solved within three moves. To account for this, a modified version of the task developed previously (Owen et al., 1995b) was used during PET by Baker et al. (1996). This version, known as the "one-touch" Tower of London (Fig. 21.1), requires the subjects to indicate their answers to problems at all levels of difficulty by executing a single movement. In brief, for each problem the subjects are required to plan the minimum number of moves that are required to reach the goal position from the initial position without actually physically making any of the moves. They indicate their answer instead by touching the appropriate number (standing for the number of moves required to solve the problem) on a response panel at the bottom of the touch-screen monitor. As a control condition, the subjects are presented with identical upper and lower arrays. Following a delay matched to the latency of their response in the corresponding test trial, one of the balls "blinks" and the subject responds by touching the number 3.

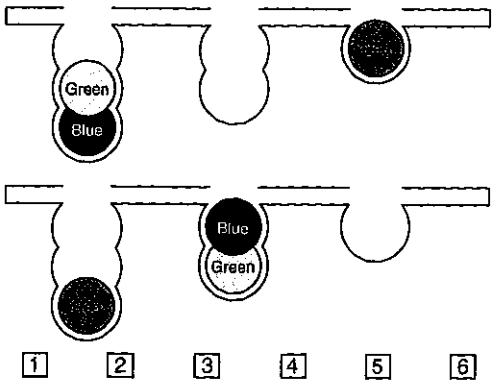

Fig. 21.1. The display on the touch-screen monitor for the "one-touch" Tower of London test of planning, as it appears to the subject. The subject is required to select (by simply touching it) one of the numbered boxes at the bottom of the display according to the number of moves the subject estimates for the solution to the problem of mentally matching or converting the bottom arrangement of "balls" to the top "goal" arrangement (three for the problem shown above). The instruction is that this should be done in the minimum number of mental "moves", as constrained by the hanging arrangement of the "pool balls" lodged in "pockets" or "socks". Illegal moves, such as trying to remove a ball when there was another ball sitting above it in the same pocket, were carefully explained to the subject; if attempted, such moves evoked no response from the computer. Only when subjects were entirely familiar with these "rules" were they allowed to proceed to test problems. Further details are provided in Owen et al. (1995b).

Baker et al. (1996) scanned subjects while they solved easy and difficult "one touch" Tower of London problems as well as during the corresponding yoked control task. It was found that both easy and difficult planning problems activated the premotor cortex bilaterally as well as the more posterior occipitoparietal cortical areas. In contrast to the results described by Owen et al. (1996a), the prefrontal cortex was significantly activated in *both* the easy and difficult conditions. However, the distribution of this activation differed between these two conditions: both conditions activated the dorsolateral prefrontal cortex bilaterally but, in addition, the difficult planning condition activated an extensive region of the right rostrolateral prefrontal cortex (notably BA 10 and BA 9/46). The predominant right hemisphere activation relative to the study by Owen et al. (1996a) may reflect the greater demands placed by the "one touch" Tower of London on visual imagery (Owen, 1997a).

A more recent study has used PET with a modified "one-touch" Tower of London task to investigate differences in the neural response to negative and positive feedback in healthy subjects during planning (Elliott et al., 1997a). Slight modifications were made to the task in that the subjects were required to respond within 10 s of the problem being presented. Furthermore, there were three feedback conditions, namely, *no feedback*, *positive feedback*, and *negative feedback*. In the positive condition, 100% of trials were followed by a "YOU ARE RIGHT" message regardless of whether the responses made were actually correct. In contrast, in the negative condition, only 20% of trials were followed by this positive message; the other 80% were followed by a "YOU ARE WRONG" message regardless of whether the responses were actually wrong. The same feedback conditions were presented for a guessing task that also acted as a control task for the planning task. In that task, the subjects were presented with two identical arrays of colored balls that would disappear after a short delay. The subjects were required to "guess" by touching one of six response buttons. Prior to the task, they were informed that three of these buttons were randomly assigned as correct on each trial.

On comparing the planning task with the guessing task without regard to the use of feedback or its absence, it was found that similar, though less extensive, regions were activated relative to those reported by Baker et al. (1996). It is possible that the guessing task was a more demanding control than that employed by Baker et al. (1996) and, therefore, led to a significant proportion of the activations being "subtracted out" in the comparison. In the presence of feedback relative to the no-feedback condition, a significant increase in rCBF was observed in the medial caudate nucleus and the ventromedial orbitofrontal cortex. Examining negative and positive feedback separately showed an increase in rCBF in the same areas during the guessing task, although there was no such increase for the planning task. This may reflect the possibility that neural processing of feedback is greater in tasks in which the outcome is unpredictable and beyond control.

Planning, as measured by the Tower of London task, has been shown to be impaired in depressed patients (e.g. Elliott et al., 1996), as well as in patients with Parkinson's disease (Morris et al., 1988; Owen et al., 1992, 1995b) and other neurodegenerative conditions (Robbins et al., 1994b; Lange et al., 1995). In an attempt to understand the relation between cognitive dysfunction in these conditions and the underlying neurophysiologic abnormalities, several patient groups have been studied using the Tower of London task. Using the $H_2{}^{15}O$ PET technique, Elliott et al. (1997b) scanned a group of unipolar depressed patients on the "one touch" Tower of London task and compared the results with those of the normal subjects reported in Baker et al. (1996). Relative to controls, the depressed patients exhibited a significant attenuation of bilateral rCBF activation of the cortical and subcortical regions that are

involved in the Tower of London task. Those regions included the anterior cingulate cortex, caudate nucleus, thalamus, and cerebellum, as well as the more posterior cortical areas. In addition, there were significant attenuations in the right dorsolateral and rostrolateral prefrontal cortex of the depressed patients.

Recently, PET has been used by Owen et al. (1998) to investigate striatal and prefrontal cortical blood flow in patients with Parkinson's disease during planning and spatial working memory tasks. For the planning aspect, patients with moderate disease were scanned while performing easy and difficult CANTAB Tower of London problems and rCBF changes were compared with those of age-matched control subjects performing the same task. During a control condition, subjects were required to carry out a visuomotor task in which they attended to the lower half of the Tower of London test display and touched a series of locations that were highlighted with yellow rings. The moves that were required corresponded to the moves produced by the same subject during the difficult planning condition; furthermore, the subjects' responses were paced according to their own response latencies in the previous condition.

When the visuomotor control condition was subtracted from the difficult planning condition, a significant increase in rCBF was observed in the age-matched control subjects in the dorsolateral, ventrolateral, and premotor areas of the left frontal lobe: in the ventral frontal, premotor, posterior, parietal, and prestriate cortices of the right hemisphere; and in the striate cortex at the midline. The same subtraction for the patients with Parkinson's disease patients yielded a significant increase in rCBF in the ventrolateral and premotor regions of the right frontal lobe and in the left prestriate cortex. An increase in rCBF was also observed in the right dorsolateral frontal cortex and in the left mid-dorsolateral frontal region, but both of these failed to reach statistical significance according to conventional statistical criteria.

However, a highly significant difference was observed between the two subject groups in the region of the right globus pallidus. Specifically, the planning task was associated with an increase in rCBF in the internal segment of the globus pallidus in the control subjects, whereas in the patients with Parkinson's disease, the tasks were associated with a decrease in rCBF in the same region. In the same study, very similar findings were observed when the subjects were scanned during a spatial working memory condition, also known to place significant demands on frontal lobe systems. From these results, it was suggested that striatal dopamine depletion in patients with Parkinson's disease disrupts the normal pattern of basal ganglia outflow, which, in turn, disrupts the various cognitive functions of the frontal lobe by interrupting normal transmission of information through frontostriatal circuitry. One such circuit is the fronto-cortico–striatal loop, which consists of efferent projections from the internal segment of the globus pallidus to discrete frontal regions and afferent projections from the same frontal regions to the neostriatum of the basal ganglia.

Spatial working memory

Whereas the Tower of London task is primarily conceptualized as a planning task, it undoubtedly involves many other discrete cognitive components that combine to produce an efficient plan of action. One of these is working memory, which is recognized to be closely related to planning behavior in both neural and neurophysiologic terms (for full review see Owen, 1997a). In brief the term "working memory" was first introduced by Baddeley (1986) and refers to the temporary storage and on-line manipulation of information that may occur while carrying out a wide range of tasks.

Two CANTAB tests specifically target spatial working memory functions, the spatial span and the self-ordered spatial working memory tasks (referred to below as "spatial search"). Both have been used in the context of PET scanning to resolve a number of theoretical issues concerning the organization of working memory within the frontal lobe. Research in this area has been carried out via lesion and electrophysiologic studies in nonhuman primates (for review see Goldman-Rakic, 1987; Petrides, 1994), neuropsychologic studies of patients with frontal lobe damage or excisions (e.g. Petrides and Milner, 1982; Owen et al., 1990, 1995a,b, 1996c), and functional neuroimaging studies in humans (e.g., Jonides et al., 1993; Petrides et al., 1993a,b; Courtney et al., 1996; Owen et al., 1996a,b; for full review see Owen, 1997b). Two contrasting theories have arisen out of this research, both of which describe a functional difference between the ventrolateral prefrontal cortex, or BA 45 and BA 47, and the dorsolateral prefrontal cortex, or BA 9 and BA 46. The first theory suggests that these two areas subserve the same function of working memory storage and retrieval but differ in terms of the modality of information processed according to their connections to modality-specific posterior cortical regions. Thus, while the dorsolateral prefrontal cortex has been suggested to be specific for spatial information, the ventrolateral prefrontal cortex has been suggested to be specific for object-based information such as shape and color (Goldman-Rakic, 1996). While the delayed response task in nonhuman primates may map onto some of the

CANTAB tests of spatial memory (e.g., spatial recognition memory, or spatial span), it is less clear how the object-based tasks map directly onto tests sensitive to frontal lobe dysfunction in humans, whether from the CANTAB or from the wider neuropsychologic literature. In contrast, the second theory does not suggest that the dorsolateral and ventrolateral prefrontal cortices differ in terms of information modality per se, but rather that they are involved in different working memory processing systems. At a lower level, the ventrolateral prefrontal cortex has been suggested to be concerned primarily with working memory storage and retrieval while at a higher level, the dorsolateral prefrontal cortex has been suggested to be concerned primarily with the implementation of executive functions on information in working memory, for example the use of strategies needed to carry out a task and the manipulation and monitoring of information (Petrides, 1996).

A recent PET study has used the spatial span and the self-ordered spatial search tasks to provide evidence for two working memory processing systems within the lateral prefrontal cortex (Owen et al., 1996b). In this study, normal subjects were scanned while performing five different spatial working memory tasks on a touch-sensitive monitor, including variants of the CANTAB spatial search and spatial span tasks. On subtracting a matched visual control task from the two versions of the search tasks (involving eight or ten search boxes), a significant increase in rCBF was observed in the right mid-dorsolateral prefrontal cortex. A significant increase in rCBF was also observed in the ventrolateral prefrontal cortex during these tasks relative to the visuomotor control task. In contrast, when the control task was subtracted from the spatial span task, there was a similarly significant increase in rCBF in the right midventrolateral prefrontal cortex but no change in the dorsolateral prefrontal region. From these findings, it was suggested that the mid-dorsolateral frontal cortex is only recruited when spatial working memory tasks, such as the CANTAB self-ordered spatial search task, require the active monitoring and manipulation of information within working memory. However, in less complex tasks, such as the CANTAB spatial span task, which simply requires the explicit retrieval of information from working memory, only the ventrolateral prefrontal cortex is required. Further support for this position has been obtained in a recent study using forward and backward spatial span and digit span tasks. Recalling spatial/digit sequences backwards requires the manipulation of information in working memory. Therefore, relative to forward spatial and digit span, backward spatial and digit span tasks require the dorsolateral prefrontal cortex (see Owen, 1997b).

Rapid visual information processing

Sustained attention, or vigilance, is the ability to maintain attention on a series of stimuli over a period of time and is closely related to working memory. The CANTAB rapid visual information processing task (RVIP) is a test of sustained attention that also requires working memory; it has been used in neuropsychologic studies of different patient groups, for example those with dementia implicating the frontal lobe rather than typical Alzheimer's disease (e.g., Coull et al., 1996a).

To investigate the neural network underlying the RVIP task and, thus, sustained attention and working memory, Coull et al. (1996b) used PET to scan a group of four left- and four right-handed healthy male adult subjects during performance of variations of the RVIP task and a control task. For the RVIP task, the subjects were required to monitor a sequence of pseudo-random digits presented on a computer screen at a standard or fast rate and were required to detect prespecified consecutive sequences of two (e.g., 2–4, 6–8) or three digits (e.g., 4–6–8, 3–5–7) by using a simple computer mouse-press response. For the control task, the subjects were similarly presented with pseudo-random digits but were simply required to respond to the occurrence of 0. A rest condition was also used in which the subjects were scanned while keeping their eyes closed. In comparison with the rest condition, the RVIP task caused significant increases in rCBF bilaterally in the inferior frontal gyrus, parietal cortex, and fusiform gyrus, and also in the right rostral superior frontal gyrus. By subtracting the control condition from the RVIP, a similar pattern of activation was observed, except that the increase in rCBF in the right rostral superior frontal gyrus was less significant. Increasing the digit presentation speed was found to increase rCBF bilaterally in the more posterior occipital cortex and fusiform gyrus, whereas changing the working memory load of the task (two sequence versus three sequence detection) had no significant effect on rCBF in any region. No significant effects of handedness were seen.

From their observations, Coull et al. (1996b) suggested that the right rostral superior frontal gyrus may interact with specific areas of the parietal cortex in mediating sustained attention. By comparison, the left inferior frontal gyrus may be involved with specific areas of the parietal cortex in mediating certain components of auditory working memory. One such component is the phonologic loop, a common mechanism of memory rehearsal whereby presented auditory stimuli are repeated continuously in a "loop" to facilitate memory encoding. Other PET studies appear to support the notion that specific areas of the left

prefrontal cortex (notably Broca's area) are responsible for subserving the phonologic loop (e.g., Paulesu et al., 1993).

Attentional set-formation and shifting

The CANTAB suite of visual discrimination learning and shifting tests constitutes a decomposition of the WCST and has been shown to be sensitive to effects of frontal lobe excisions in humans, as well as basal ganglia disorders such as Parkinson's and Huntington's diseases and progressive supranuclear palsy (see Owen and Robbins, 1993; Lawrence et al., 1998a). Its suitability for research with nonhuman primates has meant that it has been possible to relate different aspects of visual discrimination learning, including reversal learning (where the reinforcement between two invariant stimuli is switched, e.g., between one shape that is reinforced and another shape that is not) and extradimensional shifting (from a previously relevant perceptual dimension to a previously irrelevant dimension, e.g., from "nonsense" lines to complex shapes), on the basis of shifting reinforcing feedback, as in the WCST (Downes et al., 1989) to different portions of the monkey prefrontal cortex. In the study by Dias et al. (1996), lesions of the orbitofrontal cortex in monkeys disrupted reversal learning but not extradimensional shifting, and lesions of the lateral prefrontal cortex had the reverse pattern of effects. There were no effects of either lesion on intradimensional shifting, where a subject has to shift responses to novel stimuli of the same perceptual dimension. This intradimensional shift condition acts as a control for both of the other forms of shifting. As different regions of the prefrontal cortex project to different areas within the striatum, the results obtained by Dias et al. (1996) could potentially explain the greater susceptibility of patients with Huntington's disease to difficulties with extradimensional shifting early in the course of the disease and to deficits in reversal learning late in the disease process (because of the dorsal to ventral spread of the disease throughout the striatum; Lawrence et al., 1998a).

We have recently completed a $H_2{}^{15}O$ PET imaging study with an adapted version of the CANTAB attentional set-shifting paradigm in order to test some of the predictions about the neural substrates for the task in healthy male, adult volunteers (Rogers et al., 2000). Subjects were scanned while completing discrimination learning or performance in four main conditions: (i) compound discrimination (i.e., visual discrimination between exemplars varying in at least two perceptual dimensions) where subjects continued to respond on a visual discrimination task learned prior to scanning, (ii) intradimensional shift, (iii) extradimensional shift, and (iv) reversal learning. The four conditions were repeated three times each (12 scans in all). The design of the stimuli was modified from those used in the original paradigm because of the above-average IQ levels of our volunteer sample. Specifically, stimuli could be derived from three, rather than two, perceptual dimensions. The design allowed several types of comparison: (i) all three conditions with the baseline discrimination task, (ii) comparison of each of reversal and extradimensional shifting with intradimensional shifting and, (iii) the contrast of extradimensional shifting directly with reversal.

The results are complex; some predictions were upheld and others were not. For example, the extradimensional shift did appear to activate the frontal pole (BA 10) on the left side and BA 9/46 on the right. However, no caudate activation was discernible, as might have been predicted from neuropsychologic studies of Huntington's disease. Reversal learning predictably engaged a different circuitry, which, as expected, did include subcortical structures functionally associated with the ventromedial prefrontal cortex, specifically the ventral striatum and (on the first scan only, when the task was novel) the amygdala. However, there was no strong evidence for an activation of the orbitofrontal cortex itself. It is possible that this apparent failure reflects the relatively rapid nature of shifts in reversal learning paradigms. The temporal resolution of PET is approximately 30–90 s and, therefore, PET is limited in its ability to detect instantaneous activation changes associated with shifts in response. We are investigating the above hypothesis further using more difficult reversal tasks where the shift may occur over several trials, which might bring a small orbitofrontal activation suprathreshold; alternatively, the present paradigm may be more successful with imaging modalities with finer temporal resolution, such as fMRI. This experiment, however, does exemplify the importance of cross-validation between different types of neuroimaging modality, as well as with neuropsychologic studies in humans and nonhuman primates, to identify critical neural circuitry.

Visual recognition memory: delayed-matching-to-sample

In the CANTAB, short-term visual recognition memory is assessed using the DMTS task. Performance on this task is particularly affected by temporal lobe excisions (Owen et al., 1995b) and by Alzheimer's disease (Sahakian et al., 1988), which affects posterior cortical regions. Unlike the tests described above, there is relatively little evidence that performance on this test requires the integrity of frontal cortical function, although there is evidence that

DNMTS task performance in monkeys depends on intact ventromedial prefrontal function (see Murray, 1992).

A variation of this task has been used in a PET study by Elliott and Dolan (1998) in an effort to investigate the neural network underlying short-term visual memory. The underlying experimental paradigm was that subjects were presented with a test stimulus composed of four subelements and then, after a short delay of a few seconds, four choice stimuli made of similar subelements. Depending on the condition, the subelements of the choice stimulus were either the same shape as those of the test stimulus but of a different color (*color-only* condition), the same color as those of the test stimulus but of a different shape (*shape-only* condition) or, a mixture of these two (*conjunction* condition). The subjects had to remember and recall the test stimulus on the basis of either the colors of the subelements, the shape, or both the color and the shape of the subelements. The control task was designed to match the perceptual and motor demands of the experimental tasks but lacked a visual memory component. Subjects were presented with four choice stimuli, which were also made up of four subelements but did not bear any resemblance to the preceding test stimuli. The subjects were explicitly instructed not to remember the test stimuli and to respond to the four choice stimuli by simply pressing a prespecified response button.

By subtracting the perceptuomotor control from all of the memory conditions combined, Elliott and Dolan (1998) were able to isolate regions specific to short-term visual memory. These regions included the extrastriate cortex, medial and lateral parietal cortex, anterior cingulate cortex, inferior frontal cortex, and the thalamus. In contrast to many of the tests reviewed above, the DMTS paradigm did not produce a widespread pattern of activation in the prefrontal cortex, congruent with the relative lack of effects of frontal lobe excisions on this task (Owen et al., 1995a). Subtracting the color-only and shape-only conditions from each other showed that these conditions were associated with subtly different activation patterns. However, the conjunction condition was found not to activate any regions that were not already active in the color-only or shape-only condition. This finding suggests that, at least in short-term visual memory, there are no specific cortical regions that are responsible for remembering perceptual conjunctions between features. Rather, there may be specific posterior areas that are responsible for remembering specific types of feature. From their observations, Elliott and Dolan (1998) suggest that the left lingual gyrus may be involved in the memory of color whereas the medial occipital gyrus, right inferior parietal cortex and precuneus may be specifically associated with memory for shape.

Summary and future directions

The use of functional neuroimaging has greatly increased the power of the CANTAB by enabling the definition of specific neural networks that are necessary for the adequate performance of the different tasks (Fig. 21.2). These data help to validate the neural assumptions of the battery, which are based on studies of humans or monkeys with brain lesions, and also help to isolate discrete cognitive components of the tests, with consequent implications for theories of their underlying cognitive processes. We have also illustrated the use of the tests for analyzing further the nature of the cognitive deficits exhibited in disorders such as depression or Parkinson's disease, a list we can expect to grow longer and to include neurodevelopmental disorders. The particular attractions of CANTAB for this purpose includes (i) its relationship to the existing animal neuropsychologic literature; (ii) its lack of dependence on language functions; and (iii) its componential nature, which is just as well suited to the gradual development of cognitive function as its gradual decline (as occurs in the dementias, which provided the initial impetus for the construction of the battery).

Whereas the $H_2{}^{15}O$ PET method is powerful, it is likely that it will be supplanted, or at any rate augmented, by alternative neuroimaging methods with greater temporal or chemical specificity. Reference was made to the possibility of using fMRI to resolve some interesting issues for the attentional set-shifting task. So far, this method with its improved temporal resolution has not often been used with the CANTAB; however we expect this to change in the near future in cognitive activation studies, especially with the better prospects offered for imaging children using fMRI than PET (because of the ethical constraints imposed by the latter, see Chapter 2). It is useful to note that there has been a recent study of the "one touch" Tower of London task using fMRI that largely confirmed the results obtained using PET reviewed above (Baker et al., 1996). The "easy" and "difficult" conditions both produced a significant activation of the dorsolateral prefrontal cortex. Dorso–ventral and anterior–posterior extensions of these activations were associated with the increased working memory load involved in planning more difficult solutions (Granon et al., 1998).

It has also proved possible recently to correlate the performance of several of the CANTAB tests, including the Tower of London and spatial span, with levels of dopamine

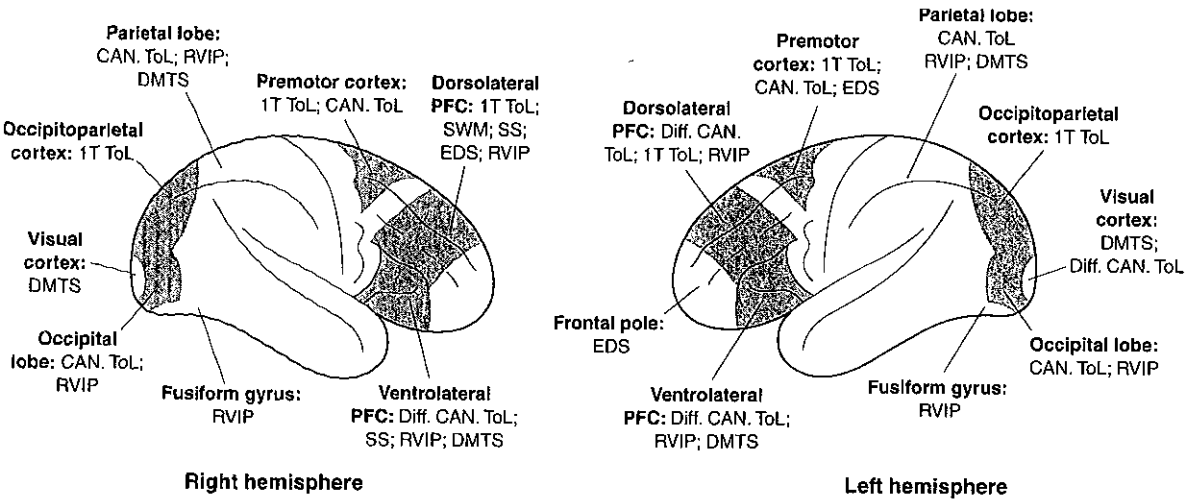

Fig. 21.2. Summary of the cerebral cortical locations of the main activations described for the CANTAB tests described in this chapter. RVIP, rapid visual information processing; SWM, spatial working memory; SS, spatial span; DMTS, delayed-matching-to-sample; CAN. ToL, CANTAB version of the Tower of London; Diff. CAN. ToL, difficult problems (four or more moves) of CAN. ToL; IT ToL, one-touch Tower of London; EDS, extradimensional shift on the attentional set-shifting paradigm; PFC, prefrontal cortex (see text for further details).

D_1 and D_2 receptor ligands in the caudate and putamen of patients with Huntington's disease (Lawrence et al., 1998b), suggesting an approach to understanding the neurochemical basis of performance on some of the tasks. The approach here was one of straightforward correlation of performances on several neuropsychologic tests, including those from CANTAB, measured outside the scanner with indices of ligand binding obtained via PET. This might be expanded still further in light of the exciting recent demonstration of displacement of a dopamine D_2 receptor ligand from binding sites in the ventral striatum by performance of a video game by healthy men (Koepp et al., 1998). A complementary approach is suggested by the results of several recent psychopharmacologic investigations of tests from CANTAB, including effects of adrenergic (clonidine; Coull et al., 1995), cholinergic (scopolamine (hyoscine); Robbins et al., 1997), and dopaminergic agents (methylphenidate, Elliott et al., 1997c). It would obviously be of interest to locate the specific sites at which these drugs are exerting their effects by observing changes in rCBF that correlate with the drug effect. With the availability of specific ligands, including for these drugs themselves, the question of neuroanatomic localization of drug effects can be addressed more directly than has previously been feasible. This will obviously be of considerable significance for our attempts to localize the neural sites of action of compounds, such as methylphenidate, that have special significance for developmental cognitive and behavioral disorders.

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