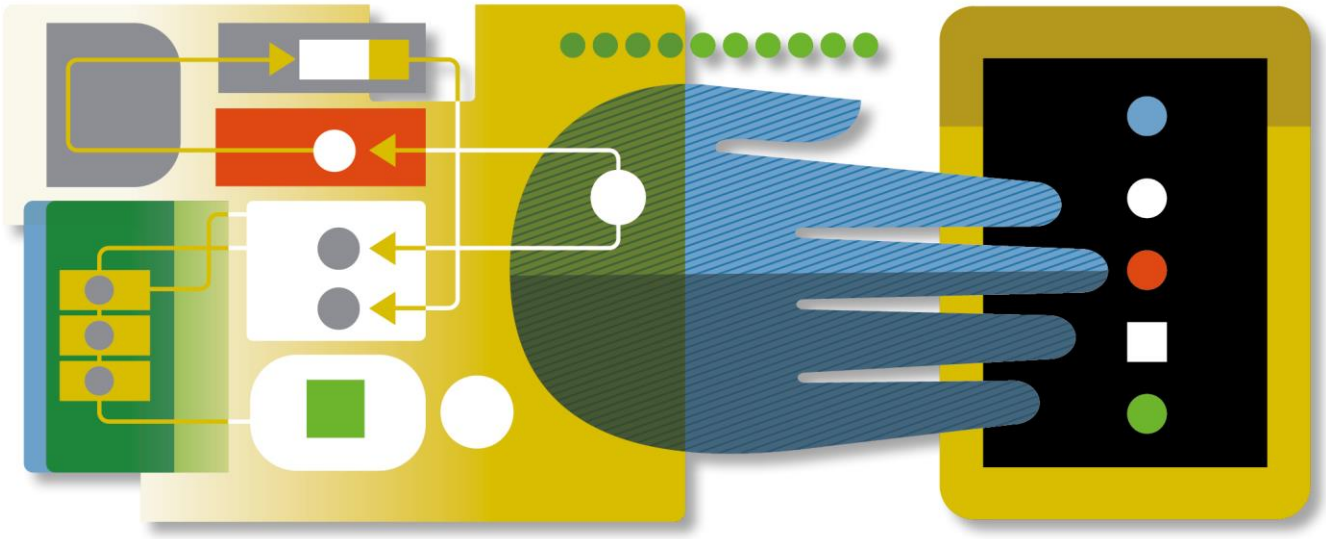
CAMBRIDGE COGNITION

CANTAB Insight

A Scientific and Clinical Review

24th February 2016 v1.0



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Contents

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Introduction

CANTAB Insight is a CE approved Class II Medical Device from Cambridge Cognition. Approved for use from age 18, it measures an individual's cognitive health across five key domains:

- Executive function - central control, planning, strategy, and flexible thinking;
- Processing speed - the ability to perform mental tasks quickly and efficiently;
- Attention - the ability to concentrate and actively process information;
- Working memory - how we hold information while processing or acting on it, which is key for reasoning, comprehension and learning;
- Episodic memory – memory of events and experiences (what happened, where and when). This function is most likely to be affected by a neurological disorder.

These domains are assessed using three cognitive tests:

- Match to Sample Visual Search (MTS) or 'Matching Patterns Test';
- Spatial Working Memory (SWM) or 'Working Memory Test';
- Paired Associates Learning (PAL) or 'PAL Memory Test'.

An in-built depression scale (GDS) also assesses the current mood of the person taking the test.

Assessments are simple to set up and use, typically taking around 20 minutes to complete. An audio soundtrack guides individuals taking the test through each step and the results, which are adjusted for age, gender and education, are automatically scored and recorded in a report.

For more information visit www.CANTAB.com/insight

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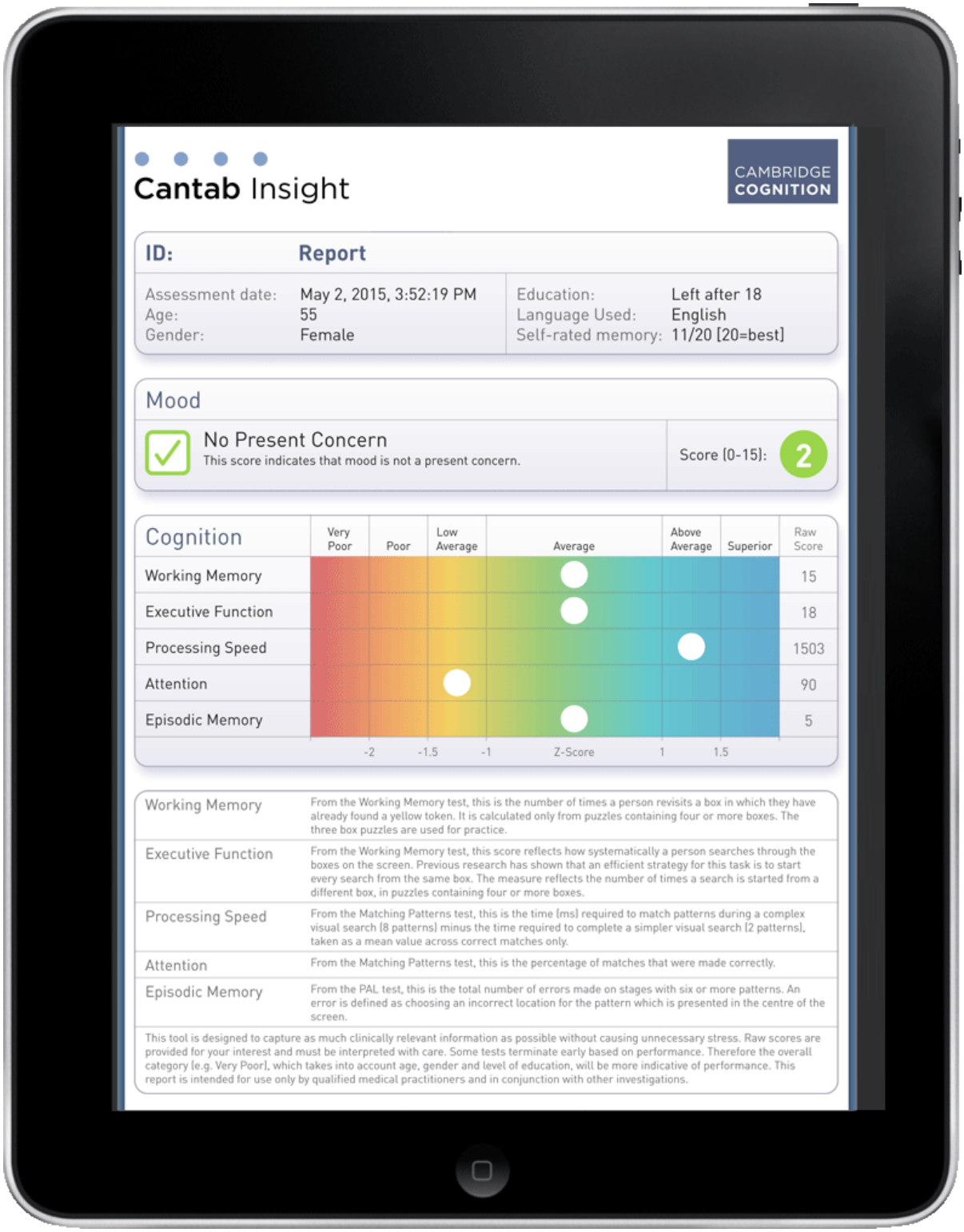
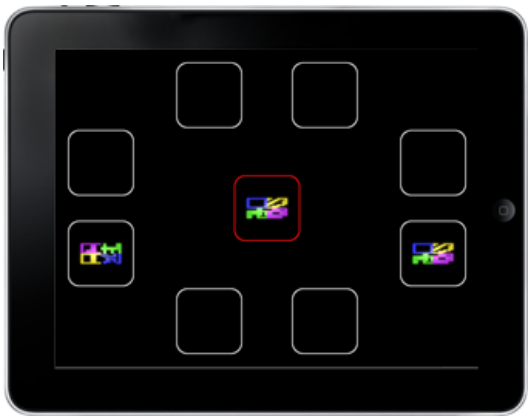
Example CANTAB Insight report



Match to Sample Visual Search (MTS)

In CANTAB Insight, the Match to Sample Visual Search test is referred to as the 'Matching Patterns Test'. The outcomes of this test are Processing Speed and Attention in the CANTAB Insight report.

This is a matching test, with a speed/accuracy trade-off. It is a simultaneous visual search task with response latency dissociated from movement time.



Description of the test

The sample stimulus is an abstract pattern, composed of four coloured elements. This is displayed within a red square, in the middle of the screen. After a brief delay, a varying number of similar patterns are shown in a circle of white boxes around the edge of the screen. Only one of these patterns matches the sample pattern in the centre of the screen. The subject must indicate which it is by touching it.

In some trials only two patterns are shown in the white boxes around the edge of the screen (see image above), and in other trials all eight boxes have a pattern inside. There is always only one pattern in the white boxes that matches the sample pattern in the red box. When a subject responds by touching a pattern the task immediately moves on to the next trial – no feedback is given.

Key outcome measures

Measures	Definition
Percent correct ('attention')	The number of correct responses expressed as a percentage (higher is better).
Relative slowing ('processing speed')	The difference between the time taken to respond to a two pattern problem, compared to an eight pattern problem

Ageing

Ageing has little effect on the accuracy measure of MTS until old age (80+ years; see Figure 1). In contrast, both absolute response speed and processing speed ('relative slowing') are domains which are heavily affected by age.

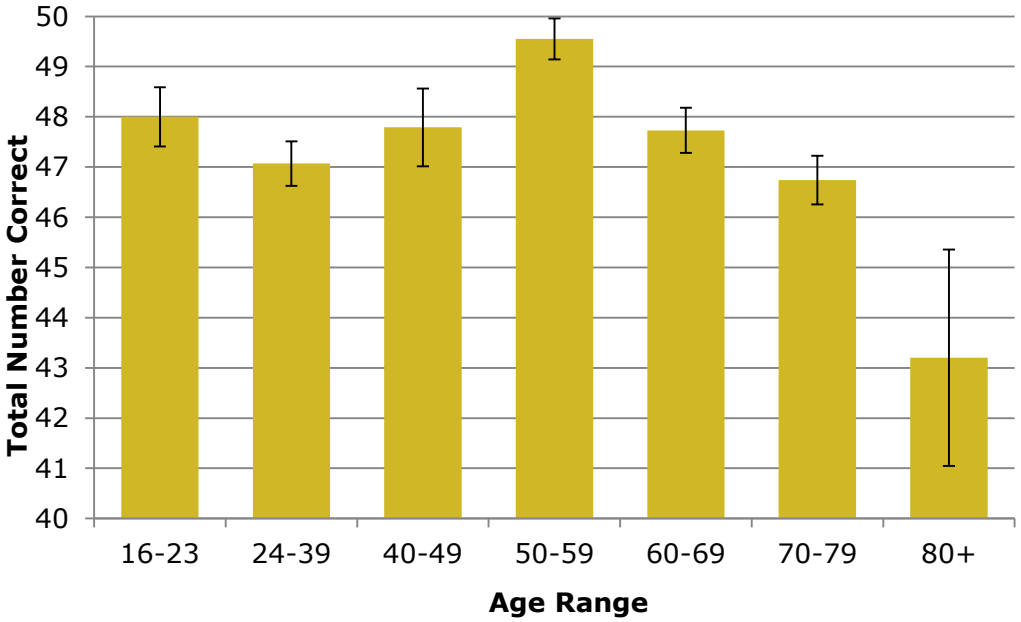


Figure 1. Scores on CANTAB MTS total number correct across the adult lifespan (mean +/- SE).

Sensitivity to impairment in clinical populations

Dementia and MCI

People with subjective memory complaints, with amnestic MCI, and with Alzheimer's disease all show significant slowing on MTS compared with controls (Saunders 2010). Among patients with MCI, those who progressed to a dementia over 20 months, or continued to show MCI, were significantly slower on MTS than those who showed a cognitive recovery and healthy controls (Summers 2012).

Psychiatric and mood disorders

Patients with major depressive disorder show impairments in MTS compared with matched controls (Herrera-Guzmán 2010). A mean z-score of -1.4 when symptomatic and -1.3 when in remission was reported by (Egerhazi 2013). Depressed individuals who performed better on the MTS were more likely to respond to the antidepressant buproprion (Herrera-Guzmán 2008).

Among patients with schizophrenia and schizoaffective disorder, 30mg of the neurosteroid pregnenolone taken for 8 weeks improved performance on MTS percent correct (Ritsner 2010). A similar trial with L-theanine produced no change over 8 weeks (Ritsner 2011).

Neurological and movement disorders

As would be expected, patients with prominent motor dysfunction such as those with motor neurone disease (Chari 1996) or Huntington's disease (Lawrence 2000) show slower absolute response speeds on the MTS task. This is one of the reasons why proportional slowing (i.e. slowing related only to the processing of a larger number of visual stimuli) is the measure used in CANTAB Insight. Accuracy is nonetheless often spared, for example in Huntington's disease (Lawrence 2000).

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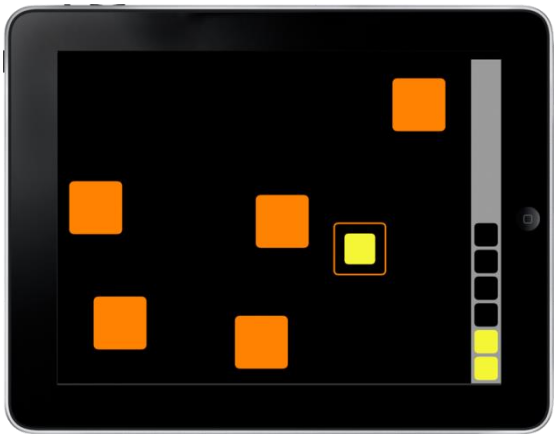
Spatial Working Memory (SWM)

In CANTAB Insight, the Spatial Working Memory test is referred to as the 'Working Memory Test'. The outcomes of this test are Working Memory and Executive Function in the CANTAB Insight report.

The Spatial Working Memory test (SWM) taxes the key aspects of working memory: storage of information over short periods of time and the updating and manipulation of that information to guide action. It also provides an index of strategy use, thereby indexing executive function in addition to working memory capacity.



Description of the test

SWM measures the ability to retain spatial information and manipulate it in working memory. It is a self-ordered task that also assesses the use of strategy. Subjects must search for blue tokens by touching the coloured boxes to open them. The task becomes more difficult as the number of boxes increases. The critical instruction is that the subject must not return to a box where a token has previously been found.

Key outcome measures

Measures	**Definition**
Between errors ('working memory')	The total number of times the subject revisits a box in which a token has previously been found in the same problem (calculated for assessed problems only).
Strategy ('executive function')	For assessed problems with six boxes or more, the number of distinct boxes used by the subject to begin a new search for a token, within the same problem.

Brain systems

Data from patients with brain lesions demonstrate that SWM performance is impaired by damage to the prefrontal cortex, especially the dorsolateral prefrontal cortex (Manes et al. 2002; Owen et al. 1990).

Versions of the test adapted for use in brain scanning have been used to shed further light on the neural substrates mediating SWM performance. Positron emission topography indicated that the dorsolateral and mid-ventrolateral prefrontal cortices are particularly recruited (Figure 2: Mehta et al. 2000).

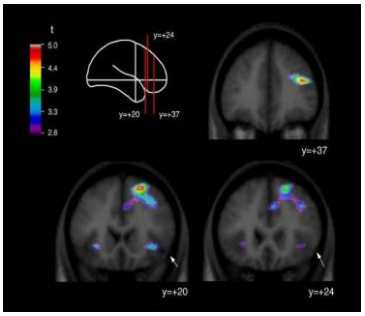


Figure 2. Control participants performing this task show activation in the VLPFC and DLPFC

Ageing

Consistent with the protracted development of the prefrontal cortex through childhood and adolescence, and its sensitivity to normal ageing, performance on the SWM test shows both clear developmental and ageing effects, particularly in the between-search errors index (Figure 3).

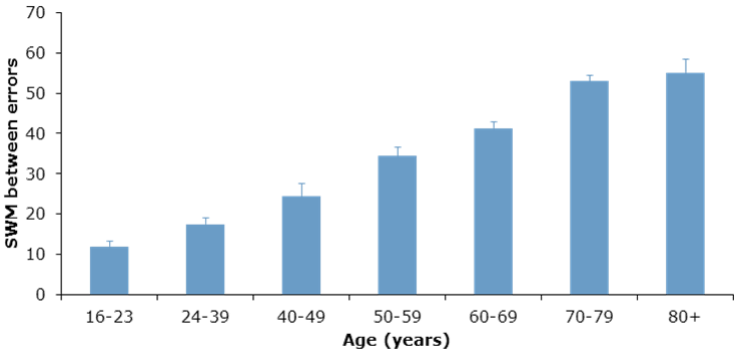


Figure 3: Normative trajectory of performance in the SWM test. Higher scores indicate worse performance

Sensitivity to impairment in clinical populations

Dementia and MCI

In addition to affecting episodic memory, Alzheimer's disease (AD) affects working memory, which is dependent on frontal and temporal lobe structures. Patients have been found to perform worse than healthy controls on SWM (Sahgal et al. 1992). The pattern of performance is such that there is a steep decrease in performance as task difficulty increases in both AD patients and controls, although AD performance is worse than that of controls at all stages of the task (Figure 4). This highlights the suitability of this test even in cases with mild dementia, as performance does not reach floor levels early on in the test.

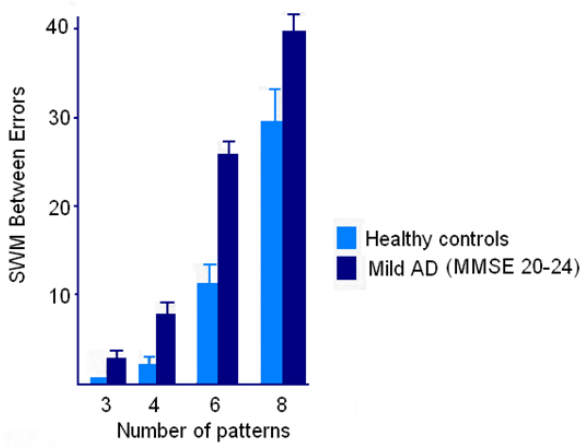


Figure 4: Sahgal et al., 1992

SWM contributes to discrimination of MCI from normal ageing in combination with other measures of memory, attention and executive function (Klekociuk & Summers 2014c). Significant differences in working memory capacity have been found between subgroups of MCI, with those with a-MCI+ (amnestic MCI with additional deficits in other domains) making more errors than those with purely amnestic MCI (Klekociuk & Summers 2014b; Saunders & Summers 2011). The strategy score also showed significant differences between MCI sub-groups, again with the a-MCI+ performing worse than the a-MCI group. (Klekociuk & Summers 2014a). SWM strategy scores were significantly higher at baseline compared to 10-month and 20-month follow-up periods (Saunders & Summers 2011).

There is less data regarding the profile of cognitive performance in other forms of dementia. Nevertheless, there is some evidence to suggest that working memory is impaired. Rahman et al. (1999) used CANTAB to profile the cognitive dysfunction of patients with frontal variant fronto-temporal dementia (fvFTD). Small groups of fvFTD and age-matched controls (n=8 in each group) were compared on a number of CANTAB tests: pattern and spatial recognition, spatial span, spatial working memory and set-shifting. In this study, fvFTD subjects were relatively unimpaired on the spatial working memory task, although differences were found in more complex CANTAB measures of executive function.

However, Sahgal et al (1995) assessed differences in cognitive profiles between subjects with AD and those with dementia of the Lewy Body type (DLB). They examined spatial working memory in a small subset of their sample (AD, n=8; DLB, n=8), and found a differential pattern of errors.

Control subjects made the fewest between-search errors, followed by AD patients, and DLB patients made the greatest. For within-search errors, DLB patients were significantly impaired in comparison with AD and controls (these two groups did not differ). This differential pattern of impairment on SWM is thought to reflect dysfunctions in non-mnemonic processes mediated by fronto-striatal circuits, which are more severely damaged in DLB.

Psychiatric and mood disorders

A recent meta-analysis of studies of depressed participants using CANTAB showed that there was a significant deficit in spatial working memory, relative to controls. This impairment was present even in unmedicated and remitted participants (Rock et al. 2013), suggesting that this is potentially an important cognitive variable in depression.

Cognitive Impairment Associated with Schizophrenia (CIAS) is an important determinant of functional outcome, and working memory impairment is a core component of this. Impairments have been seen across the range of chronicity and severity of schizophrenia. In hospitalised patients with chronic schizophrenia, Pantelis et al. (1997) found deficits in SWM relative to healthy controls. In addition, comparison between patients with schizophrenia and those with frontal lobe lesions showed equivalent impairments on SWM, with increased between-search errors. Patients with schizophrenia were unable to develop a systematic strategy to complete this task, relying instead on a limited visuospatial memory span.

Elliot et al. (1998) considered neuropsychological deficits in schizophrenic patients with preserved intellectual function (IQ >90) in order to examine the specificity of their cognitive impairment independent of global decline. On SWM, the patients showed impairment on both mnemonic and strategic components of the task, in contrast to temporal lobe patients (mnemonic impairment only) and frontal lobe patients (strategic impairment only) (Owen et al, 1995). Thus the data presented in this study confirm the many previous findings of mnemonic and executive dysfunction in schizophrenia, but do not suggest primacy of one over the other.

Deficits are present even earlier in the course of the disease, before the cumulative effects of medication have had an impact. Hutton et al. (1998) researched executive function in first-episode schizophrenia, in 30 patients and 30 healthy volunteers matched for age and National Adult Reading Test (NART) IQ. Patients with schizophrenia showed the greatest impairments on tests of executive functioning, including SWM.

The potential importance of SWM in the cognitive phenotype of schizophrenia is highlighted in a study of patients before the onset of diagnosed schizophrenia. Wood et al. (2003) explored the relationship between working memory and negative symptoms in patients who had been referred to the Personal Assessment and Crisis Evaluation Clinic, Melbourne, Australia, as being at high risk of developing psychosis. There were 38 high-risk patients (9 of which later become psychotic at least 12 months from baseline assessment) and 49 healthy controls. The high-risk group performed significantly more poorly than the healthy controls, and those who went on to develop psychosis performed more poorly than those who did not, but this did not reach significance. However, for the group that went on to develop psychosis, there was a significant association between their SWM errors score and their total score on the Scale for Assessment of Negative Symptoms.

Neurological and movement disorders

SWM performance is impaired in Parkinson's disease (PD) (Owen et al. 1997; Owen et al. 1992). This impairment is thought to be driven by dopaminergic dysfunction in PD. L-dopa withdrawal impairs SWM task performance in patients with PD (Lange et al. 1992). Neuroimaging evidence suggests that the beneficial effect of L-dopa is mediated by improved efficiency in the dorsolateral prefrontal cortex (Cools et al. 2002).

SWM performance has been found to be impaired in patients with multiple sclerosis relative to controls (Figure 5: Foong et al. 2000; Foong et al. 1997). Furthermore, performance at the more difficult 6-box and 8-box stages of this test correlated significantly with frontal lobe lesion load determined using MRI in patients with multiple sclerosis (Foong et al., 1997), again indicating the sensitivity of this measure to frontal lobe impairments.

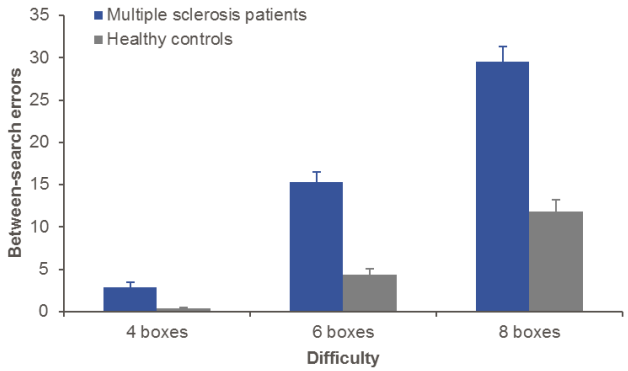


Figure 5: Patients with multiple sclerosis show impaired spatial working memory relative to controls at all levels of difficulty (Foong et al., 1997).

Sterr et al. (2006) showed a trend for poorer SWM performance in patients with symptomatic traumatic brain injury (TBI) relative to non-symptomatic TBI patients and healthy controls. Performance on SWM was significantly associated with symptom severity. A study by McAllister et al. (2001) showed that TBI patients demonstrate different activation patterns of working memory circuitry on fMRI relative to healthy controls. A further review by McAllister (2006) suggests that patients with TBI have problems in the activation and allocation of working memory, and that these may be secondary to reduced catecholaminergic function.

Both individual studies (e.g. Kempton et al. 1999; McLean et al. 2004), and meta-analysis (Chamberlain et al. 2011), have shown extensive impairments in SWM in Attention Deficit Hyperactivity Disorder (ADHD). These are evident both in terms of between-search errors and strategy scores. Methylphenidate significantly improves performance on SWM in children and adults with ADHD as well as in healthy volunteers (Kempton et al. 1999; Mehta et al. 2001; Mehta et al. 2000; Turner et al. 2005).

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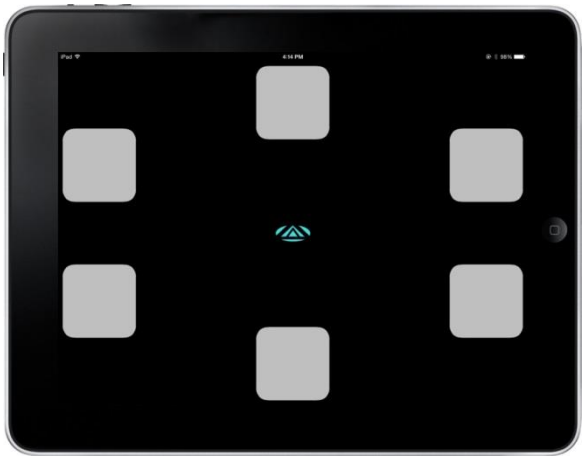
Paired Associates Learning (PAL)

In CANTAB Insight, the Paired Associates Learning (PAL) test is referred to as the 'PAL Memory Test'

PAL assesses visual memory and new learning, and is a sensitive tool for accurate assessment of episodic memory.



Description of the test

The PAL test consists of a number of stages. For each stage, boxes are displayed on the screen, which open one at a time in a randomised order. One or more of them will contain a pattern. After all the boxes have opened, the patterns shown in the boxes are then one at a time displayed in the middle of the screen, and the subject must touch the box where the pattern was originally located.

If the subject makes an error on a stage, all the patterns are re-presented as a reminder of their locations. For each stage, the same patterns may be re-presented up to a set number of times. When the subject gets all the locations correct, they proceed to the next stage. The test is adaptive so that if a stage is not completed despite multiple attempts, the test automatically terminates and the error score calculated includes an adjustment for errors at those stages that were not attempted.

The patterns are designed to be difficult to verbalise so that verbal rehearsal cannot be used as a strategy. Their nonverbal nature also allows the test to be used in international studies without the need for stimuli translation.

Key outcome measure

Measure	Definition
Total errors adjusted	The number of times the subject chose the incorrect box for a stimulus on assessment problems but with an adjustment for the estimated number of errors they would have made on any problems, attempts & recalls they did not reach due to failing or aborting the test.

Cognitive domains assessed

PAL is designed to assess visual episodic memory and learning. Tests of convergent validity have shown that there is a modest correlation between the PAL and story recall (-.19 immediate; -.21 delayed recall. Smith et al., 2013). However, the verbal component to story recall does limit the comparability of these tasks. In terms of the ecological validity of the measures, there is strong correspondence between PAL and self-reported memory problems (Swainson et al., 2001), as well as other measures of memory.

Brain systems

Successful performance on the PAL test is dependent on functional integrity of the temporal lobe, particularly the entorhinal cortex, but is also affected by resections of the frontal lobe (Owen et al., 1995). Impairment on the PAL test correlates with hippocampal volume loss in schizophrenia (Kéri et al., 2012).

The PAL paradigm has been modified for use in the MRI scanner, allowing direct assessment of the brain areas involved in performance (Figure 6). This has consistently shown involvement of the medial temporal lobe, particularly the hippocampus and parahippocamal regions (de Rover et al., 2011; Owen et al., 1995). de Rover et al. (2011) further showed that there were differences in the pattern of hippocampal activation during PAL in MCI patients compared to normal controls. These data support the use of this measure as a sensitive marker of hippocampal function.

Ageing

Consistent with the early development of the medial temporal lobes, episodic memory improves rapidly in early childhood and remains relatively stable through mid-life, before worsening in later life (Figure 7). Gender and education have also been found to impact on error scores, such that women and those with higher educational attainment perform better on the task. However, there are no significant interactions between age, education and gender.

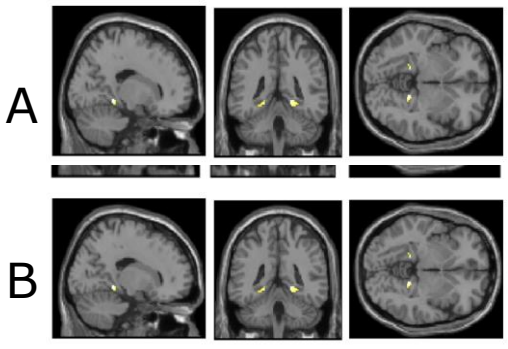


Figure 6: Significant bilateral hippocampal and parahippocamal activation during the encoding (A) and retrieval (B) of PAL in elderly subjects (de Rover et al. 2011)

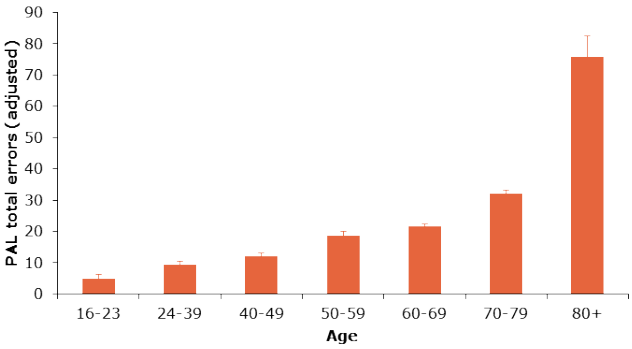


Figure 7: Age profile of PAL errors showing an increase in errors with age in healthy participants

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Sensitivity to impairment in clinical populations

Dementia and Mild Cognitive Impairment

The medial temporal lobes are susceptible to Alzheimer's pathology, particularly early in the course of the disease (Smith et al., 2002) and problems with episodic memory can be the first warning signs of AD. The sensitivity of PAL to hippocampal function has led to the suggestion that it may be used for the early and differential diagnosis of AD (Blackwell et al., 2004; de Jager et al., 2008). Across studies, the sensitivity and specificity indices were 0.94 and 0.91 respectively for detecting AD compared to elderly non-demented controls. The predictive ability for detecting incipient AD in populations with mild cognitive impairment (MCI) is discussed below.

As would be expected, the rate of decline in PAL performance in AD is greater than that seen on average in MCI or healthy elderly populations. For example, PAL total error score (adjusted) increased by an average of 24 errors over one year in patients with dementia of the Alzheimer's type (Fowler et al., 2002).

Differentiating MCI from normal ageing is challenging, since MCI represents a heterogeneous group, with only certain individuals progressing to Alzheimer's or another underlying cognitive disease. Nonetheless, PAL scores have a sensitivity of 0.83 and a specificity of 0.82 in differentiating adults with MCI from healthy older adults (Chandler et al., 2008). In a study at the University of Tasmania, patients with amnestic MCI showed poorer performance on PAL than either controls or non-amnestic MCI patients at baseline. When reassessed 10 months later, patients with amnestic MCI had worsened by an average of four errors at the six-pattern stage. In contrast, the PAL scores of patients with non-amnestic MCI, who are at lower risk for Alzheimer's disease, changed by less than one error (Saunders & Summers, 2011).

An important issue in the study of MCI is predicting which participants will go on to develop AD and which will not. A meta-analysis of 19 longitudinal studies has reported that approximately 10% of MCI cases per year progress to develop dementia (Bruscoli & Lovestone, 2004). PAL has shown considerable promise in this regard. Swainson et al. (2001) examined the ability of PAL to distinguish AD from controls and those with "questionable dementia" (QD) over 24 months. At baseline, both AD and QD participants were impaired on PAL, and there was a significant correlation between MMSE and PAL. The PAL 6-pattern error score was able to classify group membership with 98% accuracy. At baseline, those with QD appeared to be split into two distinct groups: one whose PAL scores resembled those with AD and one that resembled control subjects. These patients were followed up 6-12 months later, by which time the QD subjects had split into 2 groups: those whose performance had declined similarly to AD, and those whose performance had remained stable. By 24 months, all patients with poor and deteriorating performance had received a diagnosis of AD.

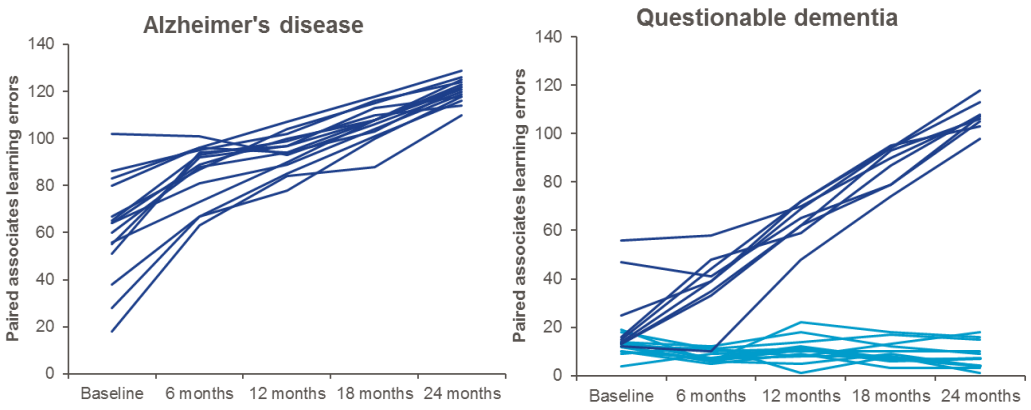

Figure 8: Paired Associates Learning decline over 24 months in individuals with questionable dementia (Fowler et al., 2002).

Similar findings have been reported in a series of studies by Fowler et al. (1995, 1997, 2002). They demonstrate that PAL is able to predict which participants with memory problems will go on to have AD two years later. The authors found that while participants with poor performance and declining trajectories went on to have a diagnosis of probable AD, those with higher baseline scores and stable performance did not (Fowler et al., 2002. See Figure 8). Using PAL alongside a test of naming, patients with relatively high baseline scores remained dementia-free at 32 months; while all of those impaired on both tests at baseline went on to receive a diagnosis of probable AD (Blackwell et al., 2004). Using PAL alongside the Addenbrooke's Cognitive Evaluation (ACE), Mitchell et al. (2009) obtained a sensitivity to conversion to AD of 94%. This compared to other cognitive tests, such as measures of semantic memory and executive function, which showed very low sensitivity to conversion, ranging from 0-25%. These and similar findings have led to the suggestion that PAL may be a useful marker for the subsequent conversion of MCI to AD (Blackwell et al., 2004; Sahakian et al., 1988).

Recent studies examining the profile of impairment in different subtypes of MCI have found that participants with amnestic MCI (a-MCI) show poorer performance than those with non-amnestic MCI on PAL (Klekociuk & Summers 2014a; Saunders & Summers 2011). Together with other measures (including indices from the Rapid Visual Information Processing (RVP) task, SWM and MTS), PAL scores contributed significantly to the discrimination of MCI cases from controls (Klekociuk & Summers, 2014c).

Less common subtypes of dementia (and other rarer neurodegenerative conditions) are associated with a range of cognitive, behavioural and functional deficits, and there are a number of different clinical diagnostic criteria, of which memory is a part. While memory assessment can be helpful in earlier stages of assessment in these diagnoses, it may not be a presenting symptom until later stages of other disease progression.

For Lewy Body Dementia (LBD), there is one study showing that patients performed poorly on the PAL task. Interestingly, in this study their performance was more severely impaired than patients with AD, which suggests that PAL may have sensitivity to memory symptoms associated with LBD (Galloway et al., 1992). Fronto-temporal dementia (FTD) is often a complex presentation and memory loss is not typically a key feature in the early stages. Nevertheless, from the few studies conducted, there is some evidence that PAL performance is impaired in the early stages of FTD presentation (e.g. Deakin et al., 2003; Lee et al., 2003).

Psychiatric and mood disorders

There is some debate regarding the sensitivity of PAL to depression. Swainson et al. (2001) showed that older adults with major unipolar depression had PAL scores similar to age-matched healthy controls, with little overlap between these groups and patients with mild AD. Similarly, Sweeney et al. (2000) did not find a significant difference in PAL performance between their young unipolar depressed patients and healthy controls, but did find that mixed/manic patients made more errors than healthy subjects. O'Brien et al. (1993) found that patients with seasonal affective disorder were significantly impaired in terms of number of trials to reach criterion on PAL, compared both to healthy controls and to their own performance once recovered.

A recent meta-analysis of studies using CANTAB tests in depressed patients (Rock et al., 2013) brought together these and similar studies and revealed that, while PAL performance was reduced in medicated currently depressed patients, no significant change was seen in a smaller number of studies of those not currently medicated.

Patients with schizophrenia show a level of impairment similar to that seen in AD (Gabrovska-Johnson et al., 2003). In addition, there was a significant correlation between right hemisphere ventricle size and performance on the PAL in patients with schizophrenia. Bartók et al. (2005) compared the performance of the patients to that of the CANTAB standardization database. The performance of the prepsychotic patients was significantly lower compared to the healthy individuals on the PAL test ($p<0.001$), as well as in tests of frontal lobe function.

Neurological and movement disorders

Patients with multiple sclerosis (MS) performed significantly worse than controls on PAL. In addition, in MS patients, performance was associated with levels of disease-specific markers (glutamate) in the hippocampus, thalamus and cingulate (Muhlert et al., 2014). This again demonstrates the sensitivity of the test to pathology of the hippocampus.

TBI patients make more errors than controls on the PAL test (Salmond et al. 2005), and the degree of impairment is associated with increased atrophy in the hippocampal formation, as measured by white matter density (Salmond et al., 2006), again implicating this structure as a key area mediating successful performance. A later study examining changes in brain structure outside the hippocampus found a statistically significant negative correlation between measures of white matter integrity in the corpus callosum on diffusion weighted imaging and memory performance ($r = -0.588$, $P = .005$) (Holli et al., 2010).

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