Validation of the Cantab Paired Associates Learning (PAL) test in measuring Alzheimer’s Disease (AD) and Mild Cognitive Impairment (MCI)
Contents

Scientific rationale 2
Paired Associates Learning: an overview 3
Cognitive decline over the lifespan 4
Cognitive decline in Mild Cognitive Impairment 6
Cognitive decline in Alzheimer’s Disease 8
PAL and Biomarkers/Neuroimaging in MCI and AD 10
Ecological and concurrent validity 12
Psychometric considerations 13
References 14
Contact us 15
Scientific Rationale

Alzheimer’s disease (AD) is characterised by an insidious onset with progressive cognitive decline. Mild Cognitive Impairment (MCI) is a state of cognitive functioning below what is expected for normal aging, associated with increased risk of progression to dementia.

Early cognitive difficulties patients with AD commonly experience include deterioration in visuospatial/episodic memory. This is also the most common cognitive impairment seen in patients with MCI who progress to a diagnosis of AD dementia (Albert et al., 2011). Tests of episodic memory are especially sensitive to AD pathology because they rely heavily on the brain regions first affected in the progression of Alzheimer’s pathology (Braak & Braak, 1991).

The Cantab Paired Associates Learning (PAL) test assesses visual associative learning and memory, both of which are dependent on the functional integrity of the temporal lobe, particularly the entorhinal cortex (Owen et al., 1995).

PAL has sound preclinical validation and task performance is sensitive to pharmacological manipulation. For example, scopolamine impairs PAL performance in rhesus monkeys (Taffe et al., 2002). In addition, PAL task performance can differentiate subjects with AD and MCI from subjects with depression, and healthy volunteers (Swainson et al., 2001).
Paired Associates Learning (PAL): An Overview

- PAL assesses visual associative learning and memory

- Boxes are displayed on the screen and are automatically opened in a randomised order to show a number of patterns. Participants must learn to associate the patterns with locations on the screen. After all the boxes have been opened each pattern is then shown in the centre of the screen and the participant must touch the box where that pattern was located.

- If the participant makes an error, the patterns are re-presented to remind the participant of their locations. The difficulty level increases with the number of patterns to be remembered, thereby making the test suitable for use in both high-functioning individuals and patient populations.

- For participants who fail to complete all levels, an adjusted total is calculated that allows for errors predicted in the stages that were not attempted.

- PAL is a non-verbal test that utilizes abstract stimuli. This allows research to be comparable across a diverse range of cross-cultural populations to support multi-centre, global studies.
Cognitive Decline over the Lifespan

Different cognitive domains show characteristic lifecourse functions. Figure 1 contrasts the age-related performance on the Cantab Paired Associates Learning (PAL) test, a task depending upon medial temporal lobe function. Cognitive performance on this test declines with age, and the rate of decline increases significantly from age 50.

![Graph showing PAL performance across the lifespan.](Image)

Figure 1. Cantab normative data indicating change in PAL performance across the lifespan.

Focusing specifically on older adults, Figure 1 maps this significant decline in PAL performance across later life, based on cross-sectional performance of healthy volunteers aged 48 to 89 years. This normative sample excludes individuals showing signs of dementia (as screened by an extended Mini Mental State Examination (MMSE)).

Regression analysis demonstrates a mean increase in PAL total error (adjusted) score of 1.6 errors per year. More rapid deterioration was seen between the ages of 60 and 80, where performance declined by 2.3 errors per year. This decline would be exacerbated in patients with increased likelihood of developing dementia, for example in MCI, or in patients with risk factors such as poor cardiovascular health, low education or vitamin deficiency.
The effects of education on PAL decline can be seen in Figure 3. Individuals who left school prior to age 16 show greater error scores at all ages, and their decline with age is somewhat greater than those who remained in education after age 18.

Figure 3. Normative data: PAL total errors (adjusted) for healthy older adults stratified by level of education (age of leaving education)
Cognitive Decline in Mild Cognitive Impairment

Cognitive deterioration has been recorded in patients with MCI in a number of Cantab studies. For example, Figure 4 shows the performance of 62 undifferentiated MCI patients on the Cantab PAL task, over the course of 80 weeks. In this study, a subgroup of 'deteriorating' patients with questionable dementia showed significant worsening of memory performance assessed using the PAL test within 6 months of screening, and cognitive decline continued over a period of 2 years (Fowler et al., 2002) (see decliners in Figure 4).

![Figure 4. Performance on PAL (total errors adjusted) for stable and deteriorating patients with MCI (Fowler et al., 2002).](image)

These findings are replicated in a more recent one and a half year follow up of prodromal AD (Visser et al., 2012), where PAL shows sensitivity to the deterioration in these patients (see Figure 5).
Figure 5. The number of errors made on the PAL memory task over 1.5 years, for a group of subjects fulfilling the criteria of prodromal AD (Visser et al., 2012), compared to healthy older adults.

A separate longitudinal study by Chamberlain et al. (2011) replicated these findings but with a lesser degree of deterioration in patients with subjective memory impairment (SMI). The SMI group (N=43; aged 64.9 ± 9.1 years) is characterised by subjective report of memory complaint without the requirement for a 1.5 standard deviation deficit on formal neuropsychological testing. These patients showed decline in PAL performance (total errors adjusted) at a rate of 3.7 errors over 8 months (see Table 1). Furthermore, a sub-sample of patients with SMI who followed a converting versus stable trajectory showed elevated rates of decline in PAL performance (see Table 1).

Table 1. Absolute change from baseline PAL performance (total errors adjusted) for patients with subjective memory impairment (Chamberlain et al., 2011)

<table>
<thead>
<tr>
<th></th>
<th>Subjective memory impairment</th>
<th>Subjective memory impairment - converters</th>
<th>Subjective memory impairment – stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 months</td>
<td>+3.7 ± 22.0</td>
<td>+13.4 ± 28.4</td>
<td>+0.5 ± 19.0</td>
</tr>
</tbody>
</table>
Cognitive Decline in Alzheimer’s Disease

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 (see Figure 6). For example, PAL total error score (adjusted) declined by an average of 24 errors over one year in patients with dementia of the Alzheimer’s type (Fowler et al., 2002) (see Figure 6).

Research conducted by Swainson et al. (2001) also demonstrated that individuals with questionable dementia committing more than 20 errors at the 6-pattern stage were likely to go on to develop AD over the next 32 months while none of those committing fewer than 20 errors went on to develop AD (Figure 7). Therefore, poor PAL performance is a good indicator of those likely to progress to an AD diagnosis.
Figure 7. Paired associates learning test identifies individuals who are likely to develop AD (Swainson et al., 2001).

The OPTIMA study revealed that paired associates learning error scores have a sensitivity of 0.83 and a specificity of 0.82 when differentiating individuals with mild cognitive impairment from healthy older adults (Chandler et al., 2008).

In clinical trials, PAL’s sensitivity to pharmacological manipulation in AD allows for shorter and smaller clinical trials than those required for less sensitive cognitive tests. Figure 8 shows data from a relatively small (N=72) study in patients with mild to moderate AD. In this 12-week study, PAL performance deteriorated by an average of 7 points in the placebo-treated group, while no significant change was detected on the ADAS-cog (Greig et al., 2005).

Figure 8. Performance on PAL and ADAS-cog for patients with mild to moderate AD following 12-week treatment with the cholinesterase inhibitor phenserine or placebo.
PAL and Biomarkers/Neuroimaging in MCI and AD

A recent review by Jack et al. (2010) proposed a model of the different temporal profiles of a number of AD biomarkers (see Figure 9). Deposition of Aβ was posited to occur very early in the disease process, with a lag phase of as yet unknown duration before the onset of cognitive symptoms. Meanwhile, biomarkers of neurodegeneration, such as tau, are thought to occur later in the disease and correlate with clinical symptom severity.

Figure 9. Dynamic biomarkers of the Alzheimer’s pathological cascade (Jack et al. 2010).

Figure 10 shows that an increase of Aβ in CSF has a detrimental effect on patients’ ability to perform PAL, and therefore we can infer deterioration of their visuospatial/episodic memory.
Finally, brain atrophy assessed using magnetic resonance imaging (MRI) is seen later still in the disease process. Therefore, CSF Aβ$_{1-42}$ represents a biomarker for AD potentially present in patients with preclinical dementia and MCI. In patients with MCI, the combination of reduced CSF Aβ$_{1-42}$ and increased CSF total tau (T-tau) was found to predict conversion to AD with a sensitivity of 95% and a specificity of 83% over three years (Hansson et al. 2006).

Figure 11 shows bilateral hippocampal activation during PAL encoding for MCI patients and healthy controls (de Rover et al., 2011). The hippocampus, located in the medial frontal lobe, is one of the first brain regions affected in the onset of AD (Braak & Braak, 1991). This fMRI study therefore clearly demonstrates that PAL ‘taps in to’ cognitive domains (visual associative learning and memory) which are dependent on the functional integrity of this brain region, particularly the entorhinal cortex (Owen et al., 1995).

Figure 10. Paired associates learning performance is associated with CSF beta amyloid and total tau levels (unpublished data) (error bars indicate standard errors of the mean).
Ecological and Concurrent Validity

Performance on PAL is highly correlated with other measures of cognition in patients with AD, including all sub-scales of the Cambridge Behavioural Inventory (CBI) and the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) (see Figure 12; unpublished data).

Figure 11. Bilateral hippocampal activation during PAL encoding for MCI patients and healthy controls (de Rover et al., 2011).

Figure 12: Significant correlation between PAL (total trials adjusted) and CBI memory score (left) and ADAS-cog score (right).
Psychometric Considerations

Test-retest reliability

Findings from a healthy volunteer study carried out by Harrison and colleagues (N=100; 43.6 ± 16.4 years; unpublished) attest to the moderate-to-high test-retest reliability of the cognitive tasks included in this document. Test-retest reliability would be expected to be greater in patients with MCI and AD than in healthy controls. For example, Fowler et al. (1995) recorded one-month test-retest reliabilities of 0.64 (healthy controls), 0.71 (MCI) and 0.88 (AD) for PAL (total errors).

Dynamic Range

PAL increases in difficulty across the task and is therefore suitable for use in highly impaired and high-functioning individuals. This test has a large dynamic range and so we expect there to be minimal floor or ceiling effects. Furthermore, the PAL test is non-verbal and utilizes abstract stimuli to allow research to be comparable across a diverse range of cross-cultural populations to support multi-centre, global studies.
References


Detecting dementia before the damage is done. Makes sense.