



**Mental Capital and Wellbeing:
Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-EI I
Early Detection of Mild Cognitive Impairment and Alzheimer's Disease:
An example using the CANTAB PAL**

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Summary

Among age-related cognitive disorders, dementia is at the forefront in terms of personal, social and economic costs. For example, the Alzheimer's Society (2007) estimated that dementia currently affects more than 700,000 people in the United Kingdom. Age is a key risk factor and so, as populations age worldwide, these prevalence rates can be expected to increase. Alzheimer's disease (AD) is the most common of the dementias. From a clinical perspective, mild AD patients usually present with a difficulty in new learning and memory. Unfortunately, substantial neuropathological change may have occurred before a diagnosis is made, particularly as DSM IV diagnostic criteria require that the clinical symptoms are sufficiently severe to cause impairment in occupational or social functioning.

Individuals in the earlier stages are generally considered to suffer from amnesic mild cognitive impairment (MCI). Cognitive abilities are mildly impaired, and neuropathological damage is still limited to hippocampal regions in MCI. There is increasing interest in diagnosing MCI early and implementing interventions which may slow the progression to full dementia. Early detection of dementia and the diagnosis of MCI currently require a full balanced clinical assessment of the case using history, psychological tests, investigations and clinical judgment, which is not routinely performed. Therefore, finding a relatively discriminatory psychological test would be advantageous to assist this process and to enable routine performance of a balanced clinical assessment. This review therefore discusses one such example. The Paired Associates Learning test from the Cambridge Neuropsychological Test Automated Battery (CANTAB PAL) is a visuospatial associative learning test that acts as a functional probe of the early hippocampal formation neuropathology in MCI and early AD. Accumulating evidence demonstrates the sensitivity and specificity of the CANTAB PAL for early and differential diagnosis of Alzheimer's disease. Therefore, the CANTAB PAL may be a very useful biomarker to detect dementia early, before the neuropathological damage is done and an individual's functioning in daily activities as well as quality of life have become significantly impaired.

Early detection provides many treatment options as, for instance, mental activation and/or pharmacological therapy. There are currently drugs (e.g. cholinesterase inhibitors) to treat cognitive symptoms of Alzheimer's disease, and further pharmacological treatments are in development by industry. Some of these newer treatments currently in development are neuroprotective agents that will modify the underlying disease process. Therefore, it is essential to have good means of early detection of MCI and AD so that treatment interventions are given early for the greatest benefit for mental health and wellbeing.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia over age 65 (Yaari and Corey-Bloom, 2007). The underlying cause is a progressive neurological disease, leading to irreversible loss of neurons, which in turn causes dementia (Braak et al., 1999). Currently, the diagnosis of probable AD relies on the criteria as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (1994) and includes memory impairment as well as aphasia and/or apraxia, agnosia or impairment in executive function. These deficits must also be accompanied by a significant impairment in social or occupational functioning and must constitute a change from a previous level of performance. Since the underlying disease is a progressive neurological disorder, the occurrence of these deficits is not an all-or-nothing process. Several stages in the disease process can be discriminated, in which global cognitive function declines more rapidly compared to healthy ageing (Petersen, 2004).

Probable AD according to the DSM IV criteria, as outlined above, is usually diagnosed at the start of the final, or advanced, stage. The neurological disease is already present in earlier stages, but the symptoms are not sufficiently pronounced to meet DSM IV criteria for probable AD (McKhann et al., 1984). Individuals in the earlier stages are generally considered to suffer from amnesic mild cognitive impairment (MCI) (McKhann et al., 1984). Previously, MCI has been given several labels, including 'Questionable Dementia' (e.g. Blackwell et al., 2004; Swainson et al., 2001) but is currently commonly known as MCI (Petersen et al., 1999; Petersen, 2004). MCI is defined as a brain disorder in which cognitive abilities are mildly impaired. Individuals with the disorder are able to function in everyday activities, but have memory difficulties (Sahakian et al., 1988). Since these individuals are in the early stages of the dementia glidepath and the underlying neurological disease is progressive, cognitive abilities of people with MCI will continue to decline, and they will eventually be diagnosed with AD. Around 7-15% per annum of a sample meeting criteria for MCI will 'convert' to meet criteria for probable Alzheimer's disease; several-fold the conversion rate expected in a general population (Bennett et al., 2002; Celsis, 2000; Petersen, 2004).

However, since, in the earlier stage of the dementia glidepath, the cognitive decline is not easily discriminated from healthy cognitive ageing and other neuropsychological disorders, MCI is very difficult to diagnose (Petersen, 2004). These difficulties have led to a debate about the validity of MCI as a diagnosis for a 'pre-AD' stage (e.g. Chong and Sahadevan, 2005; Dierckx et al., 2007; Panza et al., 2005) which in turn hampers treatment options. Importantly, significant irreversible neuropathology may already be present in MCI patients (Karas et al., 2004; Visser et al., 1999). As outlined in more detail below, accurate diagnosis of the earlier stages or, in other words, identifying those MCI patients who have incipient AD, would enable preventive treatment to avoid any further neuropathology and ensuing cognitive decline. Thus, the progressive and devastating nature of the underlying disease has created an urgent need for diagnosis of the earlier stages of the dementia glidepath. Recent research has made important progress in discriminating between those MCI patients who will go on to develop AD and those who will not (Blackwell et al., 2004; Swainson et al., 2001).

2. Dementia and the brain

Amyloid-rich senile plaques and neurofibrillary tangles in the brain characterise progressive dementia (Braak and Braak, 1991). The causes of these plaques and tangles are thought to be both environmental and genetic (Anderton, 2002; Yaari and Corey-Bloom, 2007). However, whether it is the plaques or the tangles, or both, that cause neuronal death leading to AD, is currently still unresolved (e.g. Anderton, 2002; St George-Hyslop and Rossor, 2001).

Neuronal loss, plaques and tangles occur initially in selective regions, first in the transentorhinal cortex, later spreading to the entorhinal cortex and hippocampus proper (Braak and Braak, 1991). Ultimately the effects of AD impact the entire brain, with regional emphasis (Fox et al., 1999). Neuronal loss leads to disruption of multiple major neurotransmitter systems, which also characterises AD. Cholinergic innervation of the brain originates almost exclusively from the nucleus basalis and innervates almost the whole brain via long projections (Selden et al., 1998). Since these projections run largely through those brain areas among the first affected by plaques and tangles, the cholinergic system is the first and most prominent neurotransmitter system showing disruptions in MCI and AD (Bartus, 2000; Mesulam, 2004).

3. Risk factors and occurrence

AD is mainly a late-onset disorder so ageing is the main risk factor for the disease (Yaari and Corey-Bloom, 2007). It is already a major health problem in developed countries, and prevalence rates can only be expected to increase since populations are ageing worldwide. The number of people with Alzheimer's

dementia currently exceeds 700,000 in the UK, which is generally considered to be an underestimation due to under-reporting (Alzheimer's Society, 2007). The amyloid-rich senile plaques and neurofibrillary tangles in the brain that characterise AD are also present in the brain of the healthy ageing elderly, but in much smaller numbers than are found in AD (Anderton, 1997). This observation triggered the debate on the possibility that AD is the relatively early, but inevitable consequence of ageing (Anderton, 2002).

The alternative view in this debate is that a combination of genetic and environmental factors will determine whether or not an individual will develop AD, regardless of the age to which they live (e.g. Yaari and Corey-Bloom, 2007). The latter view is mainly based on the discovery of the genes described below, that contribute to the risk for developing AD (Myers et al., 2000). Considering environmental factors that play a role in the development of AD, there is some evidence that brain injury might increase the risk (Mehta et al., 1999; Plassman et al., 2000; Salmond et al., 2005), whereas education, vascular health and psycho-social activity might reduce the risk (Barnett et al., 2006; Schmand et al., 1997; Stern et al., 1994; Wolozin and Bednar, 2006). Further, brain exercise products, like 'Brain Age' by Nintendo, may prove useful (Nature Neuroscience editorial, 2007), in line with the idea that, when it comes to mental capital, one must 'use it or lose it' (Orrell and Sahakian, 1995). However, whilst these products provide mental activity, research is needed in order to first validate them as a means of cognitive enhancement and then to determine their neural mechanism of action (see also Barnett and Sahakian, 2008 in this Foresight project). Possibly, vascular health and psycho-social activity may increase cognitive reserve, thus compensating for the consequences of AD (Barnett and Sahakian, 2008 in this Foresight project; Barnett et al., 2006; Stern et al., 1994).

In terms of genetic make-up, four genes have been shown to be associated with increased risk for AD: amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2) and apolipoprotein E (APOE) (St George-Hyslop, 2000a, 2000b). These four genes together account for approximately 50% of the genetic risk for AD, and have already helped in the unravelling of the disease process (St George-Hyslop and Rossor, 2001). The genes contributing to the risk of developing AD have been found by studying several families with high occurrence of the condition (Cruts and Van Broeckhoven, 1998). These studies had a major impact on the still ongoing unravelling of the disease process, providing new targets for drug development (see also Morein-Zamir et al., 2008 in this Foresight project).

4. Mental capital and wellbeing

The impact of AD on the mental capital and wellbeing of its many sufferers is enormous. As the disease progressively causes memory to fail and memories to fade, with eventual complete loss of identity, AD literally degrades mental capital in its patients. The course of the disease is unpredictable: periods of rapid decline followed by periods of relative stability of cognitive function (Rabheru, 2007). During the stable periods, patients often realise their inevitable decline, which hugely impacts on their wellbeing. Not only the mental capital and wellbeing of AD patients themselves is affected, but the toll on the wellbeing of their families is enormous. Role reversal, in which adult children must care for their dependent parents, is common – drawing heavily on both patients' as well as their children's wellbeing. Moreover, the majority of patients in the UK live at home, constantly requiring intensive care from their spouses and children. Such circumstances have been shown to cause sadness, grief, guilt and anger and to increase the risk for depression and related disorders in family members and caregivers, thus impacting on their mental capital and wellbeing (Mittelman et al., 2006).

Further, AD is associated with substantial financial costs. Institutionalisation of patients is currently the main financial burden recognised by governments. However, there are huge hidden costs associated with the care required by dementia patients when living at home. In order to provide appropriate care, functioning family members often have to give up their jobs and sacrifice many of their social activities. Lost government revenues in the form of taxable income and healthcare costs for the caregivers, such as counselling and

treatment for depression, are not routinely included in estimates for dementia costs. Obviously, the toll on family members who suddenly find themselves playing a parental role is both financially daunting as well as emotionally incalculable.

5. Early detection

In contrast to symptom treatment, prevention can only be accomplished in the early stages of dementia. Once the relevant neurons have died, they cannot be recovered, and thus it would be advisable to prevent cell death at early stages of dementia before the symptoms occur. There is therefore increasing interest in diagnosing MCI early and implementing interventions which may slow and ultimately prevent the progression to full dementia. The early detection of dementia and diagnosis of MCI currently requires a full balanced clinical assessment using case history, psychological tests, investigations and clinical judgment. Using a psychological test that would be sensitive to the functioning of precisely those regions affected first would assist in diagnosis, treatment and future research. This review therefore discusses one such example.

For research purposes, early detection would be useful because it would provide enriched samples for investigating possible neuroprotective agents and novel treatments. This research is currently mainly carried out in the general elderly population and, since only a small percentage of the general population convert to AD over time, these studies are usually not cost-effective. Studies would generally be much more viable with good quality early detection such that research can be directed to the people who need it: relatively healthy elderly who will convert to AD over a relatively short period of time without preventive treatment.

Several longitudinal studies have shown some promising results regarding the relative sensitivity of various neuropsychological tests for AD in its prodromal phase. A group of 63 asymptomatic individuals at risk of autosomal dominant Alzheimer's disease were followed over a six-year period (Fox et al., 1998). Ten subjects in this group developed dementia during this time, and *post hoc* analysis showed that these individuals had already demonstrated cognitive impairments at first assessment, when they were ostensibly unaffected. As a group, the patients who went on to receive a probable AD diagnosis had significantly reduced verbal memory scores and, to a lesser degree, reduced IQ performance. However, in terms of age, family history and initial Mini-Mental State Examination scores, these subjects did not differ from the individuals who remained unaffected over the six-year period. First assessment was typically two to three years before symptoms were manifest and four to five years before a diagnosis of probable AD was made. This result clearly illustrates the potential sensitivity of cognitive testing. Thus, the earliest cognitive deficits seen in AD may include objective episodic memory impairments that may even precede the onset of subjective memory complaints.

Other longitudinal studies in elderly subjects generally dovetail into these results. 'Preclinical' deficits in verbal recall preceded clinical diagnosis of AD in some cases by more than six years (Elias et al., 2000; Linn et al., 1995). Similarly, in the Bronx ageing study, two tests of verbal memory (delayed recall from the Buschke Selective Reminding Test and recall from the Fuld Object Memory Evaluation) were found to predict a subgroup of people who would go on to develop AD (Masur et al., 1994; see also Albert et al., 2001; Artero et al., 2003).

One example of progress in early detection is the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB paired associates learning (PAL) test was developed for the early detection of AD and assessing the functional integrity of the hippocampal formation (Sahakian et al., 1988). A longitudinal study showed that individuals with a declining CANTAB PAL performance had a poor prognosis and an increased likelihood of a diagnosis of AD. On the other hand, individuals with stable PAL performance had a good prognosis and remained unimpaired (Fowler et al., 1997; 2002). A later longitudinal study found that assessing stability of PAL performance was not even necessary. PAL performance as

assessed at one time point alone, when used in conjunction with the graded naming test together with age, could be used to accurately predict which individuals from a questionable dementia group would go on to develop AD (Blackwell et al., 2004; Swainson et al., 2001). More research is needed to verify the link between changes in brain function related to these tests of learning and memory, and the prognosis.

Recently, brain imaging methods have been used to directly identify the pathological processes in the brain, independent of symptoms. Structural Magnetic Resonance Imaging (MRI) shows right medial temporal lobe atrophy in MCI patients (Pennanen et al., 2005) and volume reductions in the entorhinal cortex and hippocampus in MCI and AD patients (Du et al., 2001). Entorhinal cortex atrophy was suggested to precede hippocampal atrophy in early AD (Pennanen et al., 2004). This is in line with earlier findings – that neurofibrillary tangles and neuropil threads are found in the entorhinal cortex earlier in the pathological process and spread to the hippocampus in a later stage (Braak and Braak, 1991). However, medial temporal atrophy is not an AD-specific feature, thus hampering its use as a diagnostic tool (Laakso, 2002). While neuropsychological assessment seems to be more reliable in predicting subsequent progression of patients to AD, the use of structural MRI as a diagnostic tool remains a controversial issue (Laakso, 2002). Mapping a number of regions and defining a pattern of atrophy in order to increase the specificity of the method have been advanced as a potential approach to circumvent this problem (Laakso, 2002).

Another approach to increase the specificity of brain imaging techniques as a diagnostic tool is to involve *functional* measurements. Not surprisingly, learning and memory have been the functional measurements of choice, because a main symptom in AD is difficulty in new learning and memory (Sahakian et al., 1988). Notably, brain activity during episodic memory has been studied, because this is most affected in AD (Welsh et al., 1992).

Functional brain imaging techniques are especially useful for showing the plasticity-related mechanisms compensating for pathology-induced brain damage during new learning and episodic memory. MCI patients show increased functional MRI (fMRI) responses in the posterior hippocampal, parahippocampal and fusiform regions in an associative encoding task of novel picture-word pairs (Hamalainen et al., 2007). Hippocampal volume is decreased in MCI compared to controls, and hippocampal volume is negatively correlated with parahippocampal activation in MCI patients only (Hamalainen et al., 2007). Thus, the hippocampal atrophy in MCI patients seems to be compensated for by increased fMRI responses (Hamalainen et al., 2007).

Further, fMRI has been used to show changes in brain function as the pathological process progresses. During encoding of novel face/name pairs, mildly impaired MCI subjects show hyperactivation of the hippocampus compared with controls, whereas more severely impaired MCI subjects demonstrate significant hypoactivation, similar to the levels observed in mild AD subjects (Celone et al., 2006). These data indicate that, in less impaired MCI patients, hyperactivation of the hippocampus during new learning and memory compensates for pathological damage, while in more impaired MCI patients, compensatory mechanisms break down, possibly because the damage has become too extensive, leading to the first AD-related symptoms.

As described above, the CANTAB PAL task has been shown to be a very useful research tool in the early detection and the differential diagnosis of prodromal AD. In order to directly link these neuropsychological results to functional brain deficits, the PAL task was also used in fMRI experiments. Gould and colleagues (2003) used a variant of the task and found that increasing cognitive demands or task difficulty involves the same, rather than an additional, network of brain regions being relatively more active. Use of the same paradigm, whilst controlling for confounds of varying task difficulty and subsequent performance, yielded remarkably similar brain activations during successful paired associate learning in AD patients and healthy controls (Gould et al., 2005). The pattern of brain activity in patients with AD performing an easy version of the task was indistinguishable from that of controls performing a harder version of the task when task

difficulty was not matched (Gould et al., 2006). These data support greater recruitment of the same brain regions in the patients as in age-matched controls, as a means of compensating for neuropathology and associated cognitive impairment in AD (Gould et al., 2006). It remains to be investigated whether this is also the case in MCI patients, and whether this may prove to be a useful additional diagnostic tool in clinical settings, as part of a comprehensive approach to assessment.

6. Pharmacological treatment: current situation, future options and cost-effectiveness

Current available treatment options mainly constitute cholinesterase inhibitors (Birks, 2006). Because of the damage to the cholinergic pathways in the brain, the amount of released acetylcholine in target areas is decreased in AD (Bartus, 2000; Mesulam, 2004). Treatment with cholinesterase inhibitors reduces the breakdown of the released acetylcholine, thereby normalising the cholinergic tone in the target brain areas (Lanctot et al., 2003; Trinh et al., 2003) and possibly functioning as a neuroprotective agent as well (Ballard et al., 2007). Obviously, this treatment method requires that the cholinergic pathways, at least in part, still be intact. Treatment with cholinesterase inhibitors of patients in a relatively early stage of the disease can increase mental capital and wellbeing of both patients and their close relatives, and delay cognitive impairment of patients for at least six months (Takeda et al., 2006).

Medications currently under development include neurotrophic agents, ampakines and other cognitive enhancers (Herrmann, 2007; Kuipers and Bramham, 2006; Morein-Zamir et al., 2007; Robbins et al., 1997). Further new opportunities for future therapies are vaccines and stem cell therapy (see Barker, 2008 in this Foresight project; Melnikova, 2007). Vaccines may trigger a process in the immune system to remove amyloid-rich senile plaques from the brain (Maier et al., 2006). This new approach appears promising, but it is anticipated that it will be at least six years before the vaccine becomes available (Nikolic et al., 2007). In contrast to symptom treatment, the new developments focus on preventing neuronal death and, thus, not only halting the disease process but even possibly preventing or reversing it.

Medication is currently considered by the National Institute for Health and Clinical Excellence (NICE) to be cost-effective only in moderate stages of AD – not in advanced, nor early stages of the disease. Therefore, NICE has restricted the use of cholinesterase inhibitors by the NHS to moderate stages of AD and currently faces legal challenges over this decision. It is argued that the present use of MMSE scores as a rigid diagnostic tool discriminates against certain groups of patients, and that the role of cholinesterase inhibitors requires reconsideration (Liffe, 2007). Specifically, it has been shown in a post-mortem study that amyloid-rich senile plaques are up to 70% lower in dementia patients treated with cholinesterase inhibitors, compared to untreated patients (Ballard et al., 2007). These results suggest that cholinesterase inhibitors modify the disease and so, in order to slow down its progression, it is advised to prescribe such treatment in early stages (Ballard et al., 2007). Further, as outlined above, cholinesterase inhibitors depend on at least part of the cholinergic system being intact, which is likely to be the case in the early stages of the disease.

Cost-benefit analyses could usefully be refined with the use of better tools than quality-adjusted life-years, and the policy implications of restricting treatments in a progressive neurodegenerative disorder would benefit from careful reconsideration (Liffe, 2007). Preserving mental capital and wellbeing, that is halting the disease process before widespread neuronal death, which will also delay institutionalisation, should be weighed more heavily in such calculations, as this can only be done by treatment in an earlier phase (Liffe, 2007).

7. Conclusions

AD is a neurological disorder inextricably tied to the proportional increase of the ageing population. It has a major and increasing impact on health and wealth in the UK, since the number of AD patients is growing rapidly. Not only are the mental capital and wellbeing of the AD patients themselves affected, but the toll on the wellbeing of their families is enormous.

Thus, increased resources are needed to meet these escalating needs. This is not only a social problem, but also a problem at the individual level, for AD patients and also for the people providing support for them. Sooner or later, almost everybody will have to deal with AD, directly or indirectly. Although much has been accomplished, additional effort and resources are necessary to address this disease at both the individual and society level.

Great progress has been made in early detection, and implementing these results would offer a platform for developing more effective therapies. Increased emphasis on treatment in the early stages is required, when the disease process may still be halted without significant loss of mental capital and wellbeing. Additional research would play an important role in linking the results of early diagnosis to the development of more effective therapies.

Cost-benefit analyses of such therapies could usefully be improved, taking a wider societal approach which takes into account the preservation of mental capital and wellbeing of both patients and caregivers.

Declaration of interest

Professor Barbara Sahakian consults for several pharmaceutical companies and for Cambridge Cognition. She also has shares in CeNeS.

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