Edinburgh Research Explorer

From Cognitive Science to Dementia Assessment

From Cognitive Science to Dementia Assessment

Robert H. Logie[1], Mario A. Parra[1,2], & Sergio Della Sala[1]

[1] Human Cognitive Neuroscience and Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology Department, University of Edinburgh, United Kingdom

[2] Scottish Dementia Clinical Research Network, NHS Scotland, Psychology Department, University of Edinburgh, United Kingdom.

Abstract

Alzheimer's disease is a degenerative disease of the brain that impairs mental skills and abilities and undermines independent living. It is estimated to affect over 44 million people worldwide, and 5.3 million in the US at an estimated cost of $226 billion. The numbers of people affected are expected to increase dramatically over the next few decades along with increased life expectancy, and costs are expected to be over $1 trillion by 2050. There is currently no cure, and accurate diagnosis in primary care is hampered by a lack of widely available, reliable, and specific forms of assessment. Accurate diagnosis is essential to avoid inappropriate and expensive clinical follow-up, to evaluate new treatments when these become available, to avoid underestimating or overestimating prevalence of the disease, and to inform policy priorities on resource allocation for health care and for research. We argue that the cognitive and behavioral sciences offer an important route to developing widely available, inexpensive, reliable and specific assessment tools for the disease.

What is Alzheimer's Disease and why is it a policy issue?

Alzheimer's Disease (AD) is the most frequent form of dementia that occurs mainly, but not exclusively, in older adults. It is a degenerative disease of the brain that affects mental skills and abilities, in particular memory function, as well as behavior, emotion and personality. As the disease progresses, it presents significant challenges for independent living, placing a major burden on families and the healthcare system. With increased life expectancy across the population comes an increased number of people suffering from the disease. In 2013, an estimated 44.35 million people were living with dementia worldwide, predicted to be 75.62 million by 2030, and 135.46 million by 2050 (Alzheimer's Disease International, Policy Brief for Heads of Government: The Global Impact of Dementia 2013-2050. http://www.alz.co.uk). Currently, in the US, an estimated 5.3 million people have AD, most of whom are over 65. In 2015, AD costs to US society are estimated to total $226 billion. These costs are shared almost equally between Medicare and individual families, and are expected to soar to over $1.1 trillion by 2050 (US Alzheimer's Association, http://www.alz.org/).

Addressing the current and future massive personal, societal and financial burdens of AD raises a wide range of major policy issues. These include how to set priorities within political agendas, how to support families and individuals affected at home and in the workplace, and how projected costs may be met. Equally important are questions about how to facilitate the development of treatments, and how to develop accurate and reliable assessments for diagnosis and for evaluations of the effectiveness of proposed treatments. This last issue might sometimes be seen as less salient when setting policy priorities. However, accurate and reliable assessment of AD is crucial to avoid (a) under-estimating or over-estimating its prevalence in society, (b) the serious consequences of misdiagnosis and inappropriate treatment, and (c) the adoption and costs of proposed treatments that in reality fail to offer the claims for prevention or slowing of disease progression. In this article we discuss examples of how the behavioral and cognitive sciences can inform policy by generating evidence-based assessments that are inexpensive as well as accurate and reliable as aids to AD diagnosis.

The Challenges for Clinical Practice and Policy

The challenges presented by AD are exacerbated by the lack of a cure and by the fact that there is no widely available gold standard for diagnosis. Considerable resources are being directed towards developing possible treatments. However, assessing the effectiveness of such treatments requires accurate diagnosis when selecting participants for clinical trials, and reliable measures of changes in the severity of the disease. These requirements help ensure that any observed slowing of the progression of AD, or an improvement in the condition can be detected and confidently attributed to the treatment, rather than resulting from mistaken inclusion of participants who do not have the disease, or a problem with the reliability or accuracy of the measures. Should such a treatment generate strong evidence of effectiveness, then it is likely to be more successful if started at an early stage of the disease. This would require early diagnosis and a means for assessment of the progression of the disease over time. Moreover, the diagnostic criteria have to be specific for AD, the symptoms of which are similar to those of other forms of dementia, similar to chronic depression, and similar to some features of normal aging. Early diagnosis also helps to inform families while the individual with AD still has the mental capacity to be involved in the planning and organization of their care. Misdiagnosis can lead to unnecessary concern or misleading reassurance, incorrect treatments, and possibly unnecessary referral for expensive analysis of spinal fluid samples or brain scans.

A note of caution is that diagnosing the disease many years in advance of its development may not be welcomed given implications for health insurance. Moreover, the wide availability of such advance knowledge across the population might lead to unnecessary high levels of personal or public expenditure on new products that are marketed as helping to prevent the onset or progression of the disease, but with little or no supportive evidence as to the claimed benefits. While medical science and healthcare policy would be helped by identification of factors that could predict development of AD several decades in the future, many individuals and families might simply prefer not to know until the early symptoms of the disease begin to emerge (e.g., Mattsson, Brax & Zetterberg, 2010). However, when symptoms such as worrying memory failures begin to appear, then linking the onset of those symptoms unambiguously with a specific disease would most likely be welcomed by individuals, families and health professionals alike.

Individuals who go on to develop AD typically seek initial help in primary care when they or a close friend or family member notice unusual errors in their behavior, thinking, language or

memory (e.g., Smith, Della Sala, Logie & Maylor, 2000). Currently, diagnosis of AD is based on a clinician taking a medical history, carrying out a physical examination, and taking blood samples or referring the patient for a brain scan (if facilities are available) in order to rule out other possible causes of the symptoms such as a vitamin deficiency, infection, or brain tumour. In the absence of an alternative diagnosis, the patient might be referred to a memory or geriatric clinic for further assessment. Therefore, initial assessment is based on excluding other possible causes. The diagnosis of possible AD is then based on assessment of mental status using cognitive markers, together with biological markers from body fluid analysis or brain scans if these are available or affordable.

Biological and cognitive markers of AD

Biological markers or 'biomarkers' for AD include analysis of a sample of fluid taken from the spine and analysis of brain scans. These biomarker tests have been shown to be sensitive and specific for Alzheimer's disease, although they are not fully reliable and have not been wholly satisfactory in differentiating AD from other forms of dementia (e.g., Blennow, Dubois, Fagan, Lewczuk, de Leon & Hampel, 2015; Frisoni et al., 2010; Johnson, Fox, Sperling & Klunk, 2012; Swan, Waddell, Holloway, Bak, Colville, Khan & Pal, 2015). There is a substantial research effort directed towards refining the use of such biomarkers, which are viewed as the best forms of assessment available. As such, clinical policy views biomarkers as a form of 'gold standard' for assessment of AD. However, these techniques can be invasive, painful (e.g. a needle in the spine) and/or expensive (brain imaging). Moreover, they are only available in specialist centers and hospitals with highly trained staff. This means that they are not widely available, and the cost of setting up and running the necessary facilities, coupled with the very large volume of older people who seek medical help for their memory problems make current biomarkers an impractical solution for routine assessment. Hence, clinical policy and practice cannot rely on current biomarkers. Moreover, due to their still limited specificity, biomarkers are currently recommended as research tools only rather than for routine clinical use (Sperling & Johnson, 2013).

Assessments of Mental or Cognitive Functions

Typically, diagnosis and monitoring of progression of AD is assisted by the use of generic assessments of 'cognitive' functions, namely memory, learning, attention, perception, thinking and language. These assessments are non-invasive, inexpensive, portable and, unlike assessment of spinal fluid samples and brain scans, they are widely available in clinical

settings and can be used in primary care with minimal waiting time for the testing or for receiving the results. The outcome of this clinical assessment is often used to refer the patient to a specialist or for further assessment, such as a brain scan when the facilities are available and affordable. Or they may assist in the diagnosis of conditions such as depression that can be treated, at least initially, in primary care. However, cognitive assessments in current clinical use can only detect that there is a general impairment in mental ability. They cannot identify the underlying cause of that impairment. Therefore, these assessments may lead to uncertain diagnosis, or inappropriate clinical follow-up.

Tests of cognitive function also have a range of other limitations. The most frequently used forms of assessment are dementia severity scales, notably the Mini-Mental State Examination (MMSE - Folstein, Folstein & McHugh, 1975). This can be a useful tool to categorise patients according to how severe is their general cognitive impairment, but it has been known for some time that it is not reliable (e.g., Cossa, Della Sala, Musicco, Spinnler & Ubezio, 1997), nor is it specific for AD (e.g., Boustani, Peterson, Hanson, Harris & Lohr, 2003; Tariq, Tumosa, Chibnall, Perry, & Morley, 2006) and has poor sensitivity for detecting impairments in individuals with high levels of education (Vertesi, Lever, Molloy, Sanderson, Tuttle et al., 2001). Other dementia severity scales such as the Milan Overall Dementia Assessment (Brazzelli, Capitani, Della Sala, Spinnler, & Zuffi, 1994), and the Addenbrooke's Cognitive Examination (e.g., Hsieh, Schubert, Hoon, Mioshi & Hodges, 2013), have been shown to be more reliable and sensitive. However, poor performance on these collections of short tests is not an indicator of any particular disease.

More extensive batteries of tests assessing cognitive functions are also available, notably ADAS-Cog or CANTAB. These are commonly used in aiding diagnosis as well as in clinical trials of pharmaceutical treatments for AD. ADAS-Cog (Rosen, Mohs, & Davis, 1984) is widely used in the US and consists of 11 tests covering a range of cognitive functions, not just those affected specifically by AD. However, it has been shown to suffer from unreliability and a lack of sensitivity (e.g., Connor & Sabbagh, 2008; Karin, Hannesdottir, Jaeger, Annas, Segerdahl, Karlsson, Sjörgen, Rosen & Miller, 2014). CANTAB (e.g., Sahakian & Owen, 1992) is one of the best-known test batteries for cognitive impairment in the UK. This also is a suite of tests to measure a wide range of cognitive functions that offers a profile of which cognitive abilities are impaired and which are relatively spared in individuals. It is continually under development with an ongoing research program, but its

strength lies in detecting that impairments are present, not what is causing those impairments, and so it is not specific for AD. It involves extended time for testing each patient, and performance on the tests is affected by healthy aging. It is also expensive relative to other forms of cognitive testing.

These test batteries were developed in the 1980s and 1990s, when theories of human mental abilities were much more preliminary than they are now, and the batteries involve multiple different tests that require extensive training to administer and score. The test batteries were also developed when there was limited understanding of the link between specific cognitive abilities and specific structures and networks in the brain that become less efficient with healthy aging, or fail to function as a result of specific brain diseases or brain injury. These widely used test batteries may be useful in measuring the severity of the cognitive impairment and in identifying the kinds of abilities that are impaired or are spared in a given individual. This information could be extremely helpful when advising individuals and their carers about the possible effect of cognitive impairments on everyday life. However, they are limited as aids to diagnosing the underlying cause of those impairments, and as such they are not effective aids to identifying that the individual is suffering from AD rather than showing the signs of healthy aging, or other disorders such as chronic depression or other forms of dementia.

There is widespread consensus that the main clinical criterion for referring a patient for further diagnostic tests is the presence of memory problems. Indeed, the hallmark of AD is widely considered to be a deficit in memory (Dubois, Feldman, Jacova, DeKosky, Barberger-Gateau et al., 2007; Perry, Watson & Hodges, 2000), and memory problems are well established as being associated with, and being very sensitive to the early stages of the disease. Unfortunately memory problems also occur in many other disorders, including depression, and even in healthy normal aging, leading to diagnostic uncertainty (e.g., Pfennig, Littmann & Bauer, 2007; Wright and Persaud, 2007). Moreover, the early sensitivity to AD of memory tests is coupled with performance that becomes too poor after the disease has progressed to allow for reliable or repeated measurement (e.g., Frisoni, Ghiretti, Catricala, Pomati, Marcone et al., 2010) to track the progression of the disease or evaluate efficacy of treatment. On the other hand, in less severe patients and in healthy volunteers, many memory tests tend to show effects of improvement simply due to practice across repeated test sessions (e.g., Rabbitt, Diggle, Holland & McKinnes, 2004). This practice effect could mistakenly be

interpreted as a benefit from a treatment (see discussion in Foley, Cocchini, Logie, & Della Sala, 2015). People who show early signs of memory deterioration do not necessarily go on to develop AD, and AD is not an inevitable consequence of aging: more than 50% of people who live into their 80s and 90s do not develop the disease, even if they show a decline in memory ability for other reasons. So, memory tests are sensitive but they are not specific to the disease. Indeed, there may be a danger of over-diagnosing dementia in patients who suffer from other disorders, including chronic depression, that have similar symptoms such as memory loss. Such over-diagnosis has implications for healthcare costs of inappropriate assessments and inappropriate treatments, and implications for the everyday lives and concerns of individuals and their families (Le Couteur, Doust, Creasey & Brayne, 2013). We would argue then that one reason that cognitive assessments are seen by clinical policy makers as less promising than biomarkers as a means to help diagnose the disease is because biomarkers are typically designed to be specific to particular disorders and in many cases have been demonstrated to be so. Cognitive assessments typically are designed to be sensitive to the presence of a disorder, not to identify what that disorder might be. Therefore, even if they are much less expensive and more practical for large numbers of people, traditional tests of memory are not ideal for developing AD-specific assessments. More recent evidence from the cognitive and behavioral sciences has pointed towards approaches that might combine the convenience, sensitivity, and low cost of cognitive assessments with much greater specificity for the disease.

AD-Specific Cognitive Markers

In summary, the ideal cognitive test for aiding the diagnosis of AD should:

- Not show effects of healthy ageing
- Be sensitive and specific to the very early stages of AD
- Not show improvement solely as a result of repeated testing
- Be useable in Primary Care and in intervention trials with minimal training for administration and scoring
- Avoid very low performance levels when the symptoms become severe
- Be targeted at cognitive impairments shown in AD but not in other disorders
- Be non-invasive with minimal discomfort to the patient
- Be quick to administer and inexpensive
- Be insensitive to the cultural background and literacy levels of those assessed

- Be able to identify impairments in daily living

Finally, tests of impairments in mental abilities are likely to be more specific to particular disorders if they arise from scientific theories validated from empirical evidence of human mental ability and the links between different mental abilities and structures and networks in the brain that are damaged by those disorders. Over the last two decades, there has been a substantial accumulation of scientific evidence that has allowed the development of such validated theories. These advances have led to the design of cognitive tests that go a long way to meeting the above criteria for AD-specific cognitive markers.

Free and Cued Selective Reminding test

One cognitive test that has been proposed as a candidate for a specific cognitive marker for AD, is the Free and Cued Selective Reminding test (FCSRT) (Grober, Buschke, Crystal, Bang, & Dresner, 1988; Dubois, Feldman, Jacova, Cummings, DeKosky et al., 2010). This is a memory test that typically involves first presenting a set of items that participants are then required to recall, first with no cues given, and then in response to specific cues for each item that they had previously failed to recall. The use of the cue procedure is a key characteristic that is not present in traditional memory tests. A consensus conference (Dubois et al., 2007) argued that a version of this task involving memory for arrays of presented pictures of objects, has high predictive value for the progression towards AD. For example, in a study by Sarazin, Chauvire, Gerardin, Colliot, Kinkingnehun et al. (2007), 251 participants considered at risk of developing dementia were tested initially and followed at six-month intervals for up to three years. A total of 59 of them developed AD. Out of the tests that were included in that study, the most sensitive and specific for diagnosis of early AD was the FCSRT. However, it remains unclear if the test would meet all of the criteria mentioned above. In particular, a well-established literature has shown that the FCSRT is affected by healthy ageing (e.g. Grober, Hall, Lipton, Zonderman, Resnick et al., 2008; Grober, Lipton, Katz, & Sliwinski, 1998), and it is unknown as to whether or not performance is affected by repeated testing. Thus, poor performance in FCSRT may not offer the best indicator of AD (Carlesimo, Perri, & Caltagirone, 2011; Gainotti, Quaranta, Vita, & Marra, 2014).

Temporary Memory Binding

An alternative approach to the development of cognitive markers has come from clinical and experimental evidence showing that patients in the early stages of AD have problems dealing

with multiple sources of information (e.g., Della Sala, Foley, Parra & Logie, 2011; Foley et al., 2015; Logie, Cocchini, Della Sala, & Baddeley, 2004). A specific form of this on-line cognitive processing is known as temporary binding. This refers to the processes by which different aspects of stimuli such as colors and shapes are bound together on a temporary basis as an integrated object (i.e., a colored shape) (Allen, Baddeley & Hitch, 2006; Logie, Brockmole & Vandenbroucke, 2009; Luck & Vogel, 1997, Treisman 2006). To perform this kind of task, it is essential to keep track of the rapid changes in the environment such as the colors and types of cars about to overtake us on the freeway, or whether we have just taken the yellow oval pill or the white oval pill, or who said what during a conversation. People have to keep track of continually changing temporary bindings in their daily lives, so a breakdown in the ability to do so can undermine independent living. Holding and updating these rapid changes around us is thought to be a function of a system in the brain known as working memory (Baddeley, 2007; Baddeley & Logie, 1999; Logie, 2011) that can hold information for a few seconds and continually update its contents to help us reason, think, solve problems, navigate, hold conversations and generally interact with the world moment to moment.

Holding color-shape combinations for just a few seconds is very different from learning stable associations that are a function of long term memory, such as an object and its location, a face with a name, or that the typical receptacle for mail in the UK is red and cylindrical, but in the US is blue and rectangular with a rounded top. Evidence suggests that temporary binding and the learning of associations are each supported by a different memory process (Colzato, Raffone & Hommel, 2006; Logie et al. 2009; Parra, Della Sala, Logie & Morcom, 2014; Parra, Fabi, Luzzi, Cubelli, Hernandez et al., 2013; Treisman 2006) and are differentially affected by brain damage and aging (Parra, Abrahams, Fabi, Logie, Luzzi et al., 2009a; Parra, Della Sala, Logie, & Abrahams, 2009b).

It has been demonstrated repeatedly that the learning of associations between stimuli (including objects and colors, word pairs, or patterns and spatial location) is affected in AD (e.g., Buschke et al., 1999; Fowler, Saling, Conway, Semple & Louis, 2002; Gallo, Sullivan, Daffner, Schacter & Budson, 2004). This associative learning has been shown to be dependent on a specific area of the brain known as the hippocampus in the temporal lobe (see Figure 1) and damage to this region is thought to be the hallmark of AD (e.g., Lowndes & Savage, 2007). However, associative learning (and hippocampal function) also declines as

part of the normal aging process (de Jager, Blackwell, Budge & Sahakian, 2005; De Jager, Milwain & Budge, 2002; Old & Naveh-Benjamin, 2008) and in other disorders common in older adults namely chronic depression (Gainotti, Marra, Villa, Parlato & Charotti, 1998; Fossati et al., 2004; Kaschel, Logie, Kazén, & Della Sala, 2009). The lack of specificity of this deficit limits the use of associative learning tasks in the assessment and diagnosis of AD.
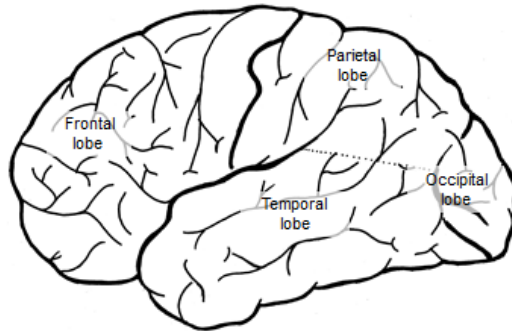

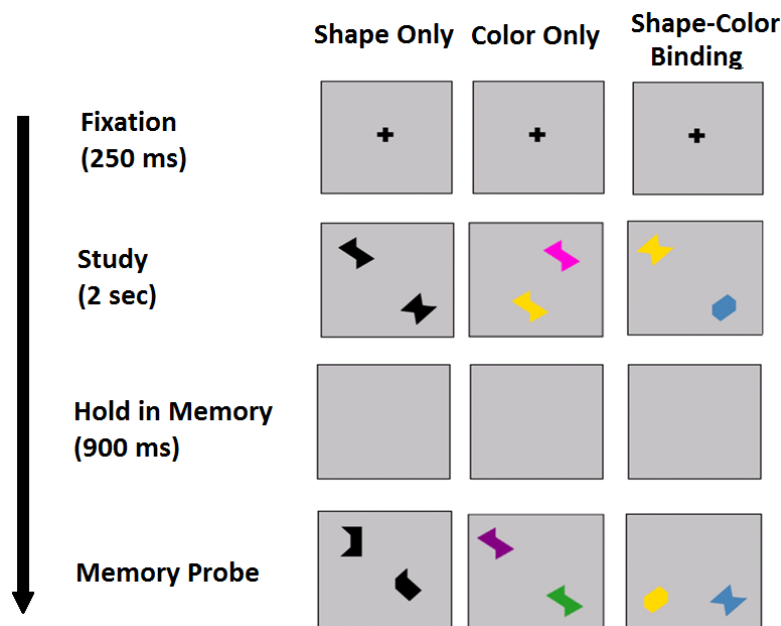Figure 1. The major lobes of the cerebral cortex of the human brain.

Figure 2. Test for temporary memory of two shapes, of two colors, or of two colored shapes. Participants decide if the memory probe matches their memory for the display that they saw 900 milliseconds previously. They would be given multiple trials with different shapes, colors, or colored shapes on each trial. On half of the occasions there is a match, and on the other half of the occasions they do not match, as shown here.

In a series of studies we have demonstrated that poor performance on tests of *temporary* binding is indicative of the very early stages of AD. Crucially, unlike other tests, impairments in temporary binding appear to be specific to the disease. We have developed a range of tasks

to measure this function through the temporary retention of shapes and colors. The tasks enable the comparison of memory for single features (shapes or objects) and combinations of bound features (colored objects). A typical task is illustrated in Figure 2.

We demonstrated a selective temporary binding deficit in a group of individuals with AD in comparison to healthy age-matched older adults (Parra et al. 2009a). The AD group showed a disproportionate deficit in the temporary retention of colored shapes in comparison to memory for a color alone or a shape alone. Remarkably, this selective temporary binding deficit was also present in people with a genetic mutation that invariably leads to early-onset AD (age around 45-50 years), but who were tested at age 30-35 years, that is ten years or more before they were showing symptoms of the disease (Parra et al. 2010. The task combined more sensitivity and specificity for AD than either associative learning tasks or other standard memory tasks. The task has the added advantage that, because of its reliance on simple shapes and colors, it can be used with people who have impaired language. Moreover, it is not affected by repeated testing (Logie et al, 2009), or by the level of education (Parra et al., 2010), so it can be used to test people with low levels of literacy as well as to test people who are highly educated.

Temporary binding impairments have also been shown to be specific to AD. This binding ability is preserved in healthy older adults who show no difference in memory ability for bindings between colors and shapes compared with memory for colors alone or shapes alone. (Parra et al. 2009a, b). This contrasts with associative learning that is vulnerable to the effects of age (e.g., Old and Naveh-Benjamin, 2008). Moreover, we have shown that the task also differentiates between AD and chronic depression as well as between AD and healthy aging (Parra et al. 2010). Depression is common in older adults, and poor performance on standard memory tests is characteristic of both AD and depression. We demonstrated that only the AD patients performed poorly on the shape-colour binding condition, whereas people with depression and healthy older people showed no difference between remembering single features (colors or shapes) and temporary bindings of features (colored shapes). Moreover our most recent work has demonstrated that this temporary binding deficit was not present in other forms of dementia, highlighting that it is specific to AD. Individuals with Vascular Dementia, Lewy Body Dementia, Frontal Lobe Dementia, and Dementia associated with Parkinson's Disease showed a profile of impairment in memory, attention, executive dysfunction and visuospatial dysfunction on standard neuropsychological testing (Della Sala,

Parra, Fabi, Luzzi, & Abrahams, 2011). However, as shown in Figure 3, only those with AD showed a specific temporary memory binding deficit compared with memory for single features.
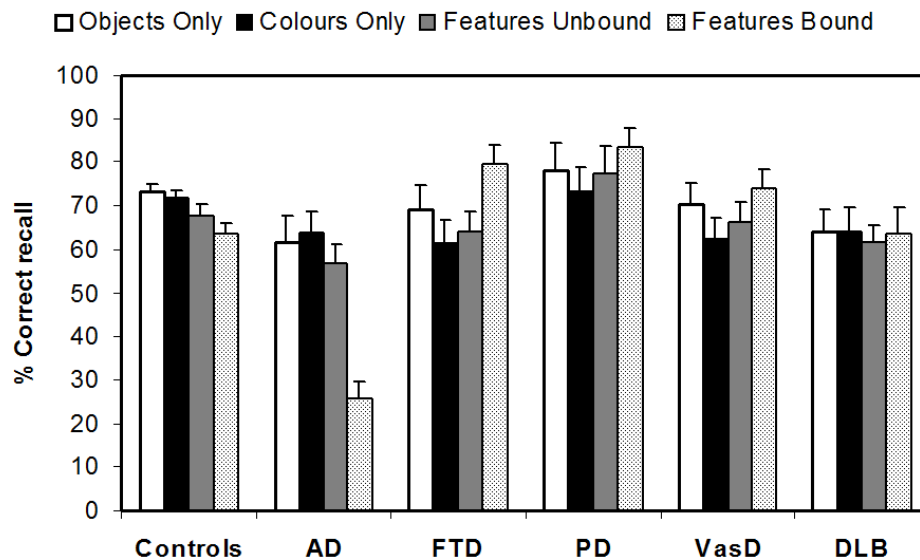

Figure 3. A deficit in temporary binding is shown for AD but not in healthy older people (Controls) or in other forms of dementia. FTD-Frontotemporal dementia. PD-Parkinson's Disease. VasD-Vascular Dementia. DLB-Lewy Body Dementia

Neuroanatomy of Temporary Binding

Cerebral changes very early in the course of AD are selective. Analyses of structural brain scans using Magnetic Resonance Imaging (e.g., Busatto et al., 2003) have shown shrinking of the brain in specific areas (known as focal brain atrophy), mainly in the medial and lateral temporal lobe regions. Figure 4 shows a scan of a healthy brain on the left, and of a brain with temporal lobe atrophy, including the hippocampus, on the right. The brain atrophy then spreads to other areas of the brain. However, it is not the only brain damage characteristic of AD.
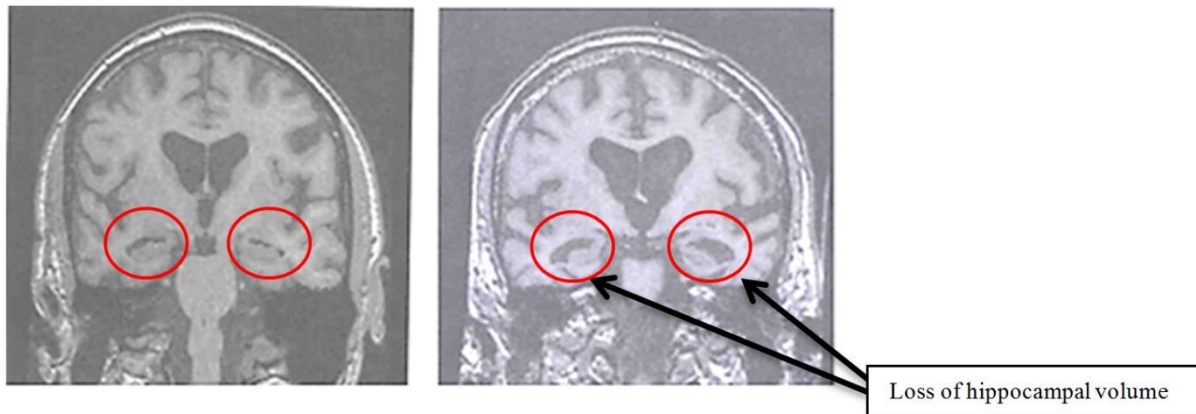
Figure 4. A scan of a healthy brain (left) and of a brain with focal atrophy (darker areas). particularly the medial temporal lobe, including the hippocampus.

The different areas of the brain normally communicate with one another via a network of connections known as white matter tracts; in the course of AD such connections become progressively thinner and more inefficient particularly between the front (or anterior) and the back (posterior) areas of the brain (e.g., Bokde, Ewers & Hampel, 2009). Colors and shapes are known to be processed by different areas of the brain (Van Essen & Drury, 1997), and binding colors and shapes together requires communication and integration between those areas (O'Reilly, Busby, & Soto, 2003). Therefore one plausible hypothesis as to why temporary binding shows a specific deficit in AD is because it is dependent on the integrity of communication along these white matter tracts (Parra et al., 2015).

As mentioned above, the hippocampus is well known to be crucial for memory and learning, and to be one of the structures affected first by the brain atrophy that accompanies AD (Braak & Braak, 1991). Due to its prominent role in learning and memory, and to the observation that the earliest symptoms referred to by patients with AD appear to reflect memory impairment, most memory tests developed to date have aimed at tests of the efficiency of the hippocampus (Schobel, Buxton, Witter, & Barnes, 2011). However, focusing too much on the assessment of hippocampal-related memory may delay the diagnosis of AD (see Sperling et al., 2001). In particular, the hippocampus undergoes significant structural and functional changes as people grow older whether or not they will develop AD (Yang, Goh, Chen, & Qiu, 2013). This overlap with changes in healthy aging prevents the early identification of deficits specific to AD, even with highly validated tests. Nevertheless, recent guidelines continue to emphasize tests of associative learning and memory functions as promising

markers for the early detection of AD (Auriacombe et al., 2010; Dubois et al., 2010; Dubois et al., 2007).

More recently, it has been suggested that memory tasks that target the stages of AD that occur prior to major changes in the hippocampus may be more promising in supporting early detection of the disease, than those that target the hippocampal stages (Didic et al., 2011; Das et al., 2015; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013; Stark, Yassa, Lacy, & Stark, 2013). Before affecting the hippocampus, AD brain pathology seems to impact on other regions that are close to the hippocampus (extra-hippocampal regions), known as the entorhinal and perirhinal cortex (Braak, Braak, & Bohl, 1993; Juottonen et al., 1998). Although this evidence is not entirely new, the role of these regions in supporting memory and development of cognitive tasks that are suitable to assess their function have become clear only over the last decade (Mayes, Montaldi, & Migo, 2007; Montaldi, Spencer, Roberts, & Mayes, 2006). The hippocampus supports learning for associative memory such as remembering details about an object or person encountered before. In contrast, the extra-hippocampal regions appear to support memory for more arbitrary memories for information not explicitly associated with particular details, such as recognizing something as familiar but not remembering where or when it has been encountered. The arbitrary combination of color and shape in temporary binding, shown to be sensitive and specific to AD, would also be an example of this latter form of memory. There is now evidence supporting the notion that associations in memory are different from more arbitrary memory for something being familiar. We will consider three lines of evidence for this difference.

First, studies using functional magnetic resonance imaging (fMRI) scans of the brains of healthy young volunteers have revealed that a temporary memory binding task does not rely on the function of the hippocampus. This task activates a network involving specific regions of the brain but not including the hippocampus (Parra, Della Sala, Logie, & Morcom, 2014). This evidence converges with previous fMRI studies which also assessed similar forms of temporary binding (Xu, 2007; Song & Jiang, 2006; Shafritz, Gore, & Marois, 2002). When more associative information becomes relevant (e.g. the location of an object), the involvement of the hippocampus becomes apparent (Piekema, Rijpkema, Fernandez, & Kessels, 2010).

A second source of evidence for the difference in memory types comes from studies of individual cases of people with specific and focused brain lesions. One individual known by the initials AE (Parra et al., 2013), suffered from a stroke resulting in damage to the right hippocampus. The person had a striking deficit in associative binding, but had completely preserved temporary binding. Preserved temporary binding ability but impaired associative binding in the presence of damage to the hippocampus has also been observed in an individual known as Jon (Baddeley, Allen, & Vargha-Khadem, 2010).

A third source of evidence comes from studies, mentioned earlier, of groups of individuals who have a genetic mutation that is known to result in the development of AD when they are in their late 40s. Genetic testing can identify these individuals many years before they show any cognitive or other impairments associated with the disease, for example when they are between 30 and 40 years of age. Despite showing no evidence of impairments on standard memory and other cognitive tests, these individuals perform poorly on temporary binding tests, specifically temporary binding of color and shape. However, they show normal levels of performance on associative binding tests, such as learning pairs of words (Parra et al., 2011; Parra et al., 2010).

In sum, this neuroanatomical evidence supports the recent proposal that temporary binding tasks that appear to require the use of extra-hippocampal regions in the brain may be more promising for the early detection of AD than traditional memory tasks that rely heavily on intact functioning of the hippocampus. This novel evidence may help explain why the temporary memory binding task has proved insensitive to healthy ageing. In contrast to the hippocampus that shrinks as we grow older, brain regions along the lower areas of the brain, known as the ventral stream, such as the fusiform gyrus, enthorinal cortex and ventral prefrontal cortex seem to undergo functional reorganization with age and allow the maintenance of performance on temporary binding tasks (Grady & Craik, 2000). Moreover, because temporary binding of color and shape does not rely on former associations, nor does it lead to learning or require support from previous knowledge, it is not influenced by repeated exposures (Logie et al., 2009; Colzato et al., 2006) or the cultural background or educational level of the assessed individual (Parra et al., 2011).

Conclusions for research, clinical practice and policy

Neuropsychological assessment plays a vital role in the diagnosis of dementia. Although it is recognized that memory changes are a primary feature of AD, diagnosis is often difficult because several disorders that are common in older adults (including cerebrovascular disease, depression, other types of dementia) and even healthy aging, also manifest with memory dysfunction. The identification of a sensitive and specific cognitive marker of AD will ultimately aid in differential diagnosis and early detection of the disease. Accurate and early diagnosis will ensure that appropriate drug interventions are administered, will aid in tailored care plans being implemented at a timely stage, and will ensure correct classification of patients for appropriate placement within clinical trials. Improving early diagnosis and care of patients with dementia is a current primary target for the National Institutes of Health in the US and for the National Health Service within the UK, and will no doubt continue to be a national and international priority.

To date the findings suggest that temporary binding may be a promising tool to help differentiate AD from other dementias and from disorders common in older adults including chronic depression. It has the advantage of being based on solid behavioral, cognitive, and neuroanatomical evidence, and offers an example of how such evidence might help drive future policy and clinical practice in combining the advantage of both cognitive and biomarkers in the diagnosis of AD. More broadly, it serves as an example of how scientific developments in the behavioral and cognitive neuroscience can inform clinical approaches and evidence-based policies to address major health challenges.

Author Notes

Robert H. Logie, Mario A. Parra, and Sergio Della Sala, Human Cognitive Neuroscience, and Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK. Mario A. Parra is also associated with the Scottish Dementia Clinical Research Network, NHS Scotland, Psychology Department, University of Edinburgh, United Kingdom.

Correspondence concerning this article should be addressed to Robert H. Logie, Human Cognitive Neuroscience, Department of Psychology, University of Edinburgh, UK, e-mail rlogie@staffmail.ed.ac.uk or Sergio Della Sala, Human Cognitive Neuroscience, Department of Psychology, University of Edinburgh, UK, e-mail sergio@ed.ac.uk.

Reference List

Allen, R. J., Baddeley, A. D., & Hitch, G. J. (2006). Is the binding of visual features in working memory resource-demanding? *Journal of Experimental Psychology: General*, *135*, 298-313.

Auriacombe, S., Helmer, C., Amieva, H., Berr, C., Dubois, B., & Dartigues, J. F. (2010). Validity of the free and cued selective reminding test in predicting dementia: the 3C study. *Neurology, 74*(22), 1760-1767.

Baddeley, A. D. (2007). *Working memory, thought and action*. Oxford: Oxford University Press.

Baddeley, A., Allen, R., & Vargha-Khadem, F. (2010). Is the hippocampus necessary for visual and verbal binding in working memory? *Neuropsychologia, 48*(4), 1089-1095.

Baddeley, A. D., & Logie, R. H. (1999). Working memory: The multiple component model. In A. Miyake & P. Shah (Eds.), *Models of working memory* (pp. 28-61). New York: Cambridge University Press.

Blennow, K., Dubois, B., Fagan, A. M., Lewczuk, P., de Leon, M. J., & Hampei, H. (2015). Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. *Alzheimer's and Dementia*, *11*, 58-69.

Bokde, A. L., Ewers, M., & Hampel, H. (2009). Assessing neuronal networks: understanding Alzheimer's disease. *Progress in Neurobiology, 89*(2), 125-133.

Boustani, M., Peterson, B., Hanson, L., Harris, R., & Lohr, K. N. (2003). Screening for dementia in primary care: A summary of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*, *138*, 927-937.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathology, 82*(4), 239-259.

Braak, H., Braak, E., & Bohl, J. (1993). Staging of Alzheimer-related cortical destruction. *European Neurology, 33*(6), 403-408.

Brazzelli, M., Capitani, E., Della Sala, S., Spinnler, H., & Zuffi, M. (1994). A neuropsychological instrument adding to the description of patients with suspected cortical dementia: The Milan overall dementia assessment. *Journal of Neurology,Neurosurgery, and Psychiatry*, *57*, 1510-1517.

Busatto, G. F., Garrido, G. E., Almeida, O. P., Castro, C. C., Camargo, C. H., Cid, C. G. et al. (2003). A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiology of Aging, 24*(2), 221-231.

Buschke, H., Kuslansky, G., Katz, M., Stewart, W. F., Sliwinski, M. J., Eckholdt, H. M. et al. (1999). Screening for dementia with the memory impairment screen. *Neurology, 52*(2), 231-238.

Carlesimo, G. A., Perri, R., & Caltagirone, C. (2011). Category cued recall following controlled encoding as a neuropsychological tool in the diagnosis of Alzheimer's disease: A review of the evidence. *Neuropsychology Review*, *21*(1), 54-65.

Colzato, L. S., Raffone, A., & Hommel, B. (2006). What do we learn from binding features? Evidence for multilevel feature integration. *Journal of Experimental Psychology: Human Perception and Performance, 32*(3), 705-716.

Connor, D. J., & Sabbagh, M. N. (2008). Administration and scoring variance on the ADAS-Cog. *Journal of Alzheimer's Disease*, *15*, 461-464.

Cossa, F. M., Della Sala, S., Musicco, M., Spinnler, H., & Ubezio, M. C. (1997). Comparison of two scoring systems of the minimental state examination as a screening test for dementia. *Journal of Clinical Epidemiology*, *50*, 961-965.

Das, S. R., Pluta, J., Mancuso, L., Kliot, D., Yushkevich, P. A., & Wolk, D. A. (2015).
Anterior and posterior MTL networks in aging and MCI. *Neurobiology of Aging, 36,
Supplement 1*(0), S141-S150.

de Jager, C. A., Blackwell, A. D., Budge, M. M., & Sahakian, B. J. (2005). Predicting
cognitive decline in healthy older adults. *American Journal of Geriatric
Psychiatry.13(8):735-40.*

de Jager, C. A., Milwain, E., & Budge, M. (2002). Early detection of isolated memory
deficits in the elderly: the need for more sensitive neuropsychological tests.
Psychological Medicine, 32(3), 483-491.

Della Sala, S., Foley, J. A., Parra, M. A., & Logie, R. H. (2011). Dual tasking and memory
binding in Alzheimer's. *Journal of Alzheimer Disease, S23*, 22-24.

Della Sala S., Parra M. A., Fabi K., Luzzi S., & Abrahams S. (2012). Short-term memory
binding is impaired in AD but not in non-AD dementias. *Neuropsychologia* 50, 833–
840

Didic, M., Barbeau, E. J., Felician, O., Tramoni, E., Guedj, E., Poncet, M. et al. (2011).
Which memory system is impaired first in Alzheimer's disease? *Journal of
Alzheimer's Disease., 27*(1), 11-22.

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau,
P. et al. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet
Neurology, 9*(11), 1118-1127.

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J.
et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the
NINCDS-ADRDA criteria. *Lancet Neurology, 6*(8), 734-746.

Foley, J., Cocchini, G., Logie, R., & Della Sala, S. (2015). No dualtask practice effect in
Alzheimer's disease. *Memory*, *23*, 518-528.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975) "Minimental state". A practical
method for grading the cognitive state of patients for the clinician. *Journal of
Psychiatric Research*, *12*, 189-198.

Fossati, P., Harvey, P. O., Le, B. G., Ergis, A. M., Jouvent, R., & Allilaire, J. F. (2004).
Verbal memory performance of patients with a first depressive episode and patients
with unipolar and bipolar recurrent depression. *Journal of Psychiatric Research,
38*(2), 137-144.

Fowler, K. S., Saling, M. M., Conway, E. L., Semple, J. M., & Louis, W. J. (2002). Paired
associate performance in the early detection of DAT. *Journal of the International
Neuropsychological Society, 8*(1), 58-71.

Frisoni, G. B., Galluzzi, S., Signorini, M., Garibotto, V., Paghera, B., Binetti, G., ... Perani,
D. (2010). Preliminary evidence of validity of the revised criteria for Alzheimer
disease diagnosis: Report of 2 cases. *Alzheimer Disease and Associated Disorders*,
24, 108-114.

Gainotti, G., Marra, C., Villa, G., Parlato, V., & Chiarotti, F. (1998). Sensitivity and
specificity of some neuropsychological markers of Alzheimer dementia. *Alzheimer
Disease and Associated Disorders, 12*(3), 152-162.

Gallo, D. A., Sullivan, A. L., Daffner, K. R., Schacter, D. L., & Budson, A. E. (2004).
Associative recognition in Alzheimer's disease: evidence for impaired recall-to-reject.
Neuropsychology, 18(3), 556-563.

Grady, C. L., & Craik, F. I. (2000). Changes in memory processing with age. *Current
Opinion in Neurobiology, 10*(2), 224-231.

Grober, E., Buschke, H., Crystal, H., Bang, S., & Dresner, R. (1988). Screening for dementia
by memory testing. *Neurology, 38*(6), 900-903.

Grober, E., Hall, C. B., Lipton, R. B., Zonderman, A. B., Resnick,

S. M., & Kawas, C. (2008). Memory impairment, executive dysfunction, and intellectual

    decline in preclinical Alzheimer's disease. *Journal of the International*

    Neuropsychological Society, *14*(2), 266-278.

Grober, E., Lipton, R. B., Katz, M., & Sliwinski, M. (1998). Demographic influences on free

    and cued selective reminding performance in older persons. *Journal of Clinical and*

    Experimental Neuropsychology, *20*(2), 221-226.

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the

    Addenbrooke's Cognitive Examination III in frontotemporal dementia and

    Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *36*, 242-250.

Johnson, K. A., Fox, N. C., Sperling, R. A., & Klunk, W. E. (2012). Brain imaging in

    Alzheimer Disease. Cold Spring *Harbour Perspectives in Medicine, 2*.

    doi:10.1101/cshperspect.a006213.

Juottonen, K., Laakso, M. P., Insausti, R., Lehtovirta, M., Pitkanen, A., Partanen, K. et al.

    (1998). Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease.

    Neurobiology of Aging, 19(1), 15-22.

Karin, A., Hannesdottir, K., Jaeger, J., Annas, P., Segerdahl, M., Karlsson, P., . . . Miller, F.

    (2014). Psychometric evaluation of ADAS-Cog andNTB for measuring drug

    response. *Acta Neurologica Scandinavica*, *129*, 114-122.

Kaschel, R., Logie, R. H., Kazén, M., & Della Sala, S. (2009). Alzheimer's disease, but not

    ageing or depression, affects dual-tasking. *Journal of Neurology,* 256(11), 1860-1868.

Le Couteur DG, Doust J, Creasey H, & Brayne C. (2013). Political drive to screen for pre-

    dementia: not evidence based and ignores the harms of diagnosis. *British Medical*

    Journal, 347:1–6.

Logie, R. H. (2011). The functional organisation and the capacity limits of working memory. *Current Directions in Psychological Science*, *20*(4), 240-245.

Logie, R., Brockmole, J. R., & Vandenbroucke, A. R. E. (2009). Bound Feature Combinations in Visual Short Term Memory are Fragile but Influence Long-Term Learning. *Visual Cognition, 17*(1/2), 160-179.

Logie, R. H., Cocchini, G., Della Sala, S., & Baddeley, A. D. (2004). Is there a specific executive capacity for dual task co-ordination? Evidence from Alzheimer's disease. *Neuropsychology*, *18*, 504-513.

Lowndes, G., & Savage, G. (2007). Early detection of memory impairment in Alzheimer's disease: a neurocognitive perspective on assessment. *Neuropsychology Review, 17*(3), 193-202.

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, *390*, 279-281.

Mattsson, N., Brax, D., & Zetterberg. (2010). To know or not to know: Ethical issues related to early diagnosis of Alzheimer's disease. *International Journal of Alzheimer's Disease*, Article ID 841941, 4 pages, http://dx.doi.org/10.4061/2010/841941

Mayes, A., Montaldi, D., & Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Science, 11*(3), 126-135.

Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus, 16*(5), 504-520.

Old, S. R., & Naveh-Benjamin, M. (2008). Differential effects of age on item and associative measures of memory: a meta-analysis. *Psychology and Aging, 23*(1), 104-118.

O'Reilly, R. C., Busby, R. S., & Soto, R. (2003). Three Forms of Binding and their Neural Substrates: Alternatives to Temporal Synchrony. In A.Cleeremans (Ed.), *The Unity of*

Consciousness: Binding, Integration, and Dissociation (pp. 168-192). Oxford: Oxford University Press.

Parra, M. A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S., & Della Sala, S. (2009). Short term memory binding deficits in Alzheimer's disease. *Brain*, *132*, 1057-1066.

Parra, M. A., Abrahams, S., Logie, R. H., Mendez, L. G., Lopera, F., & Della Sala, S. (2010). Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain, 133*(9), 2702-2713.

Parra, M. A., Della Sala, S., Abrahams, S., Logie, R. H., Mendez, L. G., & Lopera, F. (2011). Specific deficit of colour-colour shortterm memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia*, *49*, 1943-1952.

Parra, M. A., Della Sala, S., Logie, R. H., & Abrahams, S. (2009). Selective impairment in visual short-term memory binding. *Cognitive Neuropsychology*, *26*, 583-605.

Parra, M. A., Della Sala, S., Logie, R. H., & Morcom, A. M. (2014). Neural correlates of shape-color binding in visual working memory. *Neuropsychologia, 52*(0), 27-36.

Parra, M. A., Fabi, K., Luzzi, S., Cubelli, R., Hernandez-Valdez, M., & Della Sala, S. (2013). Relational and conjunctive binding functions dissociate in short-term memory. *Neurocase,* 21(1):56-66.

Parra, M. A., Saarimäki, H., Bastin, M. E., Londoño, A. C., Pettit, L., Lopera, F. et al. (2015). Memory binding and white matter integrity in familial Alzheimer's disease. *Brain, 138, 1355-1369.*

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: Relationship to episodic and semantic memory impairment. *Neuropsychologia*, 38, 252-271.

Pfennig, A., Littmann, E., & Bauer, M. (2007). Neurocognitive impairment and dementia in
mood disorders. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*,
373-382.

Piekema, C., Rijpkema, M., Fernandez, G., & Kessels, R. P. (2010). Dissociating the neural
correlates of intra-item and inter-item working-memory binding. *PLoS.ONE., 5*(4),
e10214.

Rabbitt, P., Diggle, P., Holland, F., & McInnes, L. (2004). Practice and drop-out effects
during a 17-year longitudinal study of cognitive aging. *The Journals of Gerontology
Series B: Psychological Sciences and Social Sciences*, *59*, P84-P97.

Rentz, D., Parra, M. A., Amariglio, R., Stern, Y., Sperling, R., & Ferris, S. (2013). Promising
developments in neuropsychological approaches for the detection of preclinical
Alzheimer's disease: a selective review. *Alzheimer's Research & Therapy, 5*(6), 58.

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's
disease. *American Journal of Psychiatry*, *141*, 1356-1364.

Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using
CANTAB. *Journal of the Royal Society of Medicine*, *85*, 399-402.

Sarazin, M., Chauvire, V., Gerardin, E., Colliot, O., Kinkingnehun, S., de Souza, L. C. et al.
(2010). The amnestic syndrome of hippocampal type in Alzheimer's disease: an MRI
study. *Journal of Alzheimer's Disease, 22*(1), 285-294.

Shafritz, K. M., Gore, J. C., & Marois, R. (2002). The role of the parietal cortex in visual
feature binding. *Proceedings of the National Academy of Sciences, 99*(16), 10917-
10922.

Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011, print). A
pathophysiological framework of hippocampal dysfunction in ageing and disease.
Nature Reviews Neuroscience, 12(10), 585-601.

Smith, G., Della Sala, S., Logie, R.H. & Maylor, E.A. (2000). Prospective and Retrospective Memory in Normal Aging and Dementia: A Questionnaire Study. *Memory*, 8, 311-321.

Song, J. H., & Jiang, Y. (2006). Visual working memory for simple and complex features: An fMRI study. *Neuroimage, 30*(3), 963-972.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M. et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280-292.

Sperling, R., & Johnson, K. (2013). Biomarkers of Alzheimer disease: current and future applications to diagnostic criteria. *Continuum (Minneapolis Minnesota), 19-2* Dementia, 325-338.

Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. L. (2013). A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia, 51*(12), 2442-2449.

Swan, A., Waddell, B., Holloway, G., Bak, T., Colville, S., Khan, Z., & Pal, S. (2015). The diagnostic utility of 99m Tc-HMPAO SPECT Imaging: A retrospective case series from a tertiary referral early-onset cognitive disorders clinic. *Dementia and Geriatric Cognitive Disorders*, *39*, 186-193.

Treisman, A. (2006). Object tokens, binding, and visual memory. In H. D. Zimmer, A. Mecklinger, & U. Lindenberger (Eds.), *Handbook of binding and memory* (pp. 315-338). Oxford: Oxford University Press.

Van Essen, D. C., & Drury, H. A. (1997). Structural and Functional Analyses of Human

    Cerebral Cortex Using a Surface-Based Atlas. *The Journal of Neuroscience, 17*(18),

    7079-7102.

Wolk, D. A., Mancuso, L., Kliot, D., Arnold, S. E., & Dickerson, B. C. (2013). Familiarity-

    based memory as an early cognitive marker of preclinical and prodromal AD.

    Neuropsychologia, 51(6), 1094-1102.

Xu, Y. (2007). The Role of the Superior Intraparietal Sulcus in Supporting Visual Short-Term

    Memory for Multifeature Objects. *The Journal of Neuroscience, 27*(43), 11676-

    11686.

Yang, X., Goh, A., Chen, S. H. A., & Qiu, A. (2013). Evolution of hippocampal shapes

    across the human lifespan. *Human Brain Mapping, 34*(11), 3075-3085.