

## Cognitive Changes in cognition

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### Abstract

The clinical hallmark of Alzheimer's disease (AD) is a gradual decline in cognitive function. For the majority of patients the initial symptom is an impairment in episodic memory, i.e., the ability to learn and retain new information. This is followed by impairments in other cognitive domains (e.g., executive function, language, spatial ability). This impairment in episodic memory is evident among individuals with mild cognitive impairment (MCI) and can be used to predict likelihood of progression to dementia, particularly in association with AD biomarkers. Additionally, cognitively normal individuals who are likely to progress to mild impairment tend to perform more poorly on tests of episodic memory than do those who remain stable. This cognitive presentation is consistent with the pathology of AD, showing neuronal loss in medial temporal lobe structures essential for normal memory. Similarly, there are correlations between magnetic resonance imaging (MRI) measures of medial temporal lobe structures and memory performance among individuals with mild cognitive impairment. There are recent reports that amyloid accumulation may also be associated with memory performance in cognitively normal individuals.

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**Keywords:** Alzheimer's disease; Dementia; Cognition; Cognitive testing; Cognitive function; Memory; Biomarkers

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### 1. Introduction

The clinical hallmark of Alzheimer's disease (AD) is a gradual decline in cognitive function. This decline occurs over years and ultimately leads to overt dementia, in which multiple cognitive domains are sufficiently impaired such that the individual is no longer capable of functioning independently. The pattern of decline in cognition is relatively consistent in the majority of patients. This reflects the fact that AD is a neurodegenerative process that follows a relatively predictable pattern, with specific brain regions affected early (e.g., the medial temporal lobe), while others are spared until late in the course of disease (e.g., sensorimotor areas). The role of biomarkers for AD ultimately will be to measure the neurobiological changes associated with this process in a sufficiently reliable manner that they can be

used to detect, track, and predict the disease course over time.

### 2. Patients with AD dementia

The initial neuropsychological studies pertaining to patients with Alzheimer dementia focused on identifying the cognitive domains that are impaired among mildly demented patients, based on the assumption that this would provide information about the cognitive phenotype of AD. These studies led to a general consensus that the majority of patients have a deficit in the learning and retention of new information. This difficulty, known as an episodic memory impairment, is evident in day-to-day activities where retention over a delay is needed (such as remembering conversations and appointments) and on tasks that require an individual to learn something new (e.g., a shopping list or a news event) and then retain it over a delay. In the laboratory, episodic memory is assessed by a range of tasks including the learning and retention of stories, word lists, and paired-associates. Most of the initial studies compared Alzheimer dementia patients with healthy older controls,

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and demonstrated a striking episodic memory impairment in the patients (Butters et al., 1988; Flicker et al., 1984; Hart et al., 1988; Moss et al., 1986; Petersen et al., 1994; Sahakian et al., 1990; Storandt and Hill, 1989; Welsh et al., 1991, 1992; Wilson et al., 1983).

Comparisons between Alzheimer dementia patients and patients with other causes of dementia (e.g., frontotemporal dementia, Huntington's disease, Lewy body dementia), subsequently showed that the ability to retain information over a delay is more impaired in patients with AD than in other dementing disorders (Connor et al., 1998; Hamilton et al., 2004; Hodges et al., 1990; Lange et al., 1995; Milberg and Albert, 1989; Moss and Albert, 1988; Raskovsky et al., 2002; Tröster et al., 1993).

In addition to memory problems, mildly demented patients with Alzheimer dementia were shown to be substantially impaired with regard to a set of abilities collectively known as "executive functions." This includes impairments on tasks that involve coordinating 2 concurrent tasks (Baddeley et al., 1986), as well as tasks requiring shifting between stimulus dimensions (Baudic et al., 2006; Filoteo et al., 1992; Parasuraman et al., 1992; Sahakian et al., 1990; Sebastian et al., 2008). Mild-to-moderately demented Alzheimer patients also demonstrate executive function deficits (Becker, 1988; Bondi et al., 2002; Lafleche and Albert, 1995; Morris and Baddeley, 1988; Nestor et al., 1991; Stokholm et al., 2008). The evidence suggests, based on studies that compared very mildly demented Alzheimer patients with controls on tasks assessing a range of cognitive domains, that executive function deficits precede deficits in language and spatial function in the majority of individuals (e.g., Amieva et al., 2004; Grady et al., 1988; Lafleche and Albert, 1995).

Mild-to-moderately impaired Alzheimer dementia patients also have impairments in language function. Some investigators have argued that these deficits are the result of a broader impairment in semantic memory, defined as "that system which processes, stores and retrieves information about the meaning of words, concepts and facts" (Warrington, 1975). Semantic memory abnormalities in patients with Alzheimer dementia have been documented using a range of tasks that include category fluency (Chan et al., 1993; Hodges et al., 1992; Martin and Fedio, 1983; Tröster et al., 1989), category membership (Grossman et al., 1998), confrontation naming (Grossman et al., 1998; Hodges et al., 1992; Martin and Fedio, 1983), and similarity judgments (Chan et al., 1993, 1995, 1997). In addition, several studies of word priming (Glosser et al., 1998; Milberg et al., 1999; Salmon et al., 1988) have reported significant deficits in Alzheimer dementia patients, although other studies have failed to find this effect (Nebes and Brady, 1988). For a recent review of this area, see Altmann and McClung (2008).

Visuospatial function is impaired in the course of Alzheimer dementia. On simple copying tasks, such as drawing

a clock or a triangle, mildly demented Alzheimer patients do not differ from controls (Karrasch et al., 2005; Rouleau et al., 1992). However, visuospatial impairments are common among mild-to-moderately impaired patients (Kurylo et al., 1994; Rouleau et al., 1996).

It should be noted that, although the findings above are characteristic of the majority of patients, at least 2 other clinical presentations have been described among patients with Alzheimer dementia: (1) individuals with gradually progressive impairments in spatial ability (sometimes referred to as having posterior cortical syndrome); and (2) individuals with gradually progressive language deficits. The former set of patients typically has AD pathology on autopsy, which is particularly striking in visual association pathways (e.g., Hof et al., 1997; Renner et al., 2004). The latter group of patients is more challenging to diagnose correctly, because their pattern of deficits overlaps that seen in a form of frontotemporal lobar degeneration (FTLD) known as primary progressive aphasia (PPA) (Mesulam et al., 2008).

### 3. Individuals with prodromal Alzheimer's disease dementia

It is now widely accepted that there is a transitional phase between normal function and Alzheimer dementia, during which cognitive impairment is progressing. The term most commonly used to characterize individuals in this prodromal phase of disease is mild cognitive impairment (MCI) (Petersen, 2004; Petersen et al., 1999).

The feasibility of studying this transitional phase is based on the fact that the hallmark of AD is a progressive decline in cognition. To study this phenomenon, many research groups recruited nondemented individuals with mild cognitive impairments and followed them over time. The general design of the studies was to evaluate a range of cognitive functions in the participants when they were first evaluated, and then to follow them over time to determine which cognitive changes were the best predictors of progressing from mild impairment to frank dementia.

Among these studies there is considerable consensus that tests of episodic memory are significantly different among nondemented individuals with mild memory deficits who subsequently receive a diagnosis of Alzheimer dementia on follow-up, as compared with those who also have memory problems but do not progress to dementia within a few years (Albert et al., 2001; Blackwell et al., 2004; Bondi et al., 1994; Chen et al., 2000; Dierckx et al., 2009; Howieson et al., 2003; Jacobs et al., 1995; Kluger et al., 1999; Newmann et al., 1994; Petersen et al., 1994; Rabin et al., 2009; Rubin et al., 1998; Sarazin et al., 2007; Small et al., 1995; Tabert et al., 2006; Tierney et al., 1996; Tuokko et al., 1991).

A number of studies have reported that executive function abnormalities are also evident in the prodromal stage of Alzheimer dementia (Albert et al., 2001, 2007; Chen et al.,

2000, 2001; Grady et al., 1988; Grober et al., 2008; Sahakian et al., 1990; Tierney et al., 1996). Others have reported declines in naming are more likely to be impaired among those destined to develop Alzheimer dementia (e.g., Saxton et al., 2004), though these findings are less consistent.

#### 4. Relevance to pathology and biomarkers

Taken together, these studies of cognition are consistent with the neuropathological findings in patients with Alzheimer dementia and in MCI. The striking impairment in episodic memory now considered to be the cognitive hallmark of AD is thought to result from the pathological alterations (including synaptic dysfunction, neuronal loss, and presence of neurofibrillary tangles and neuritic plaques) that are seen in medial temporal lobe regions early in the course of disease (Hyman et al., 1984; Selkoe, 2005). These alterations are particularly evident in the entorhinal cortex and CA1 region of the hippocampus (Gómez-Isla et al., 1996), brain regions critical for normal memory (Squire and Zola, 1996).

Findings from biomarkers that assess brain structure and function are also consistent with this hypothesis. As discussed in detail below, structural studies using magnetic resonance imaging (MRI), as well as functional studies using positron emission tomography (PET) show both cross-sectional and longitudinal alterations that appear to reflect the accumulation of AD pathology in medial temporal and temporoparietal regions. Likewise, the functional MRI (fMRI) studies described below that have shown consistent differences between controls and patients with AD dementia or individuals with MCI have used functional MRI activation tasks involving learning and retention of new information, thus capitalizing on the episodic memory deficit that is the hallmark feature of Alzheimer dementia.

PET studies using radiotracers that measure beta-amyloid (A $\beta$ ) accumulation have also reported relationships between episodic memory performance and degree of A $\beta$  accumulation. For example, it has been reported that, using  $^{11}\text{C}$ -PET-Pittsburgh Compound B (PiB/PET), neocortical A $\beta$  burden is correlated with episodic memory performance in subjects with MCI (Morimino et al., 2009; Pike et al., 2007), as well as with decline in episodic memory performance over the preceding 6–10 years (Villemagne et al., 2008). Correlations between PiB uptake and memory performance are reported to be less strong among patients with Alzheimer dementia (Pike et al., 2007).

#### 5. Cognitively normal individuals at risk for developing mild impairment

Accumulating evidence indicates that some individuals who are cognitively normal show the hallmark pathological features of AD in their brain (i.e., neuritic plaques and neurofibrillary tangles). The percentage of individuals with evidence of substantial AD pathology appears to vary with

age (Bennett et al., 2006; Hulette et al., 1998; Knopman et al., 2003; Price and Morris, 1999; Schmitt et al., 2000;). Approximately 1-third of the oldest individuals have these pathological changes. Despite abundant pathology, most investigators have, however, not reported that these individuals have significant neuronal loss. These findings suggest that there may be a “window of opportunity” to prevent Alzheimer dementia, if treatments can be initiated when individuals are cognitively normal despite evidence of some AD pathology in their brain.

Recent studies have therefore sought to determine if cognitive testing can be used to predict which cognitively normal individuals will subsequently develop cognitive decline and dementia. Though the number of studies is small, the majority have found that measures of episodic memory are significant predictors of future cognitive decline (Blacker et al., 2007; De Jager et al., 2005; Johnson et al., 2009; Kawas et al., 2003) or that tests of episodic memory are correlated with degree of pathology in normal individuals (Bennett et al., 2006; Schmitt et al., 2000). One study has reported that a composite measure of visuospatial ability, most of which were assessed by speed of performance, are significant predictors of which normal individuals will subsequently develop cognitive decline (Johnson et al., 2009). These findings suggest that the presence of AD pathology may be having a subtle influence on cognition, even though it is in the normal range.

#### 6. Relevance to biomarkers

Studies using amyloid imaging have reported findings consistent with this hypothesis. For example, it has been reported that episodic memory performance is correlated with neocortical A $\beta$  accumulation, as measured by PiB, in normal controls (Pike et al., 2007) and with decline in episodic memory performance (as well as working memory and visuospatial ability) (Storandt et al., 2009). Reports concerning the correlations between MRI measures of brain volume and cognitive performance in normal individuals suggest that the relationship may be complex. One study reported that episodic memory performance among controls with elevated PiB binding is associated with smaller hippocampal volume (Storandt et al., 2009), while another did not (Morimino et al., 2009). Subsequent analyses suggested that the sequential pattern of these changes may alter the associations that are seen at any 1 point in time (Morimino et al., 2009). Additional studies in this area should clarify these issues.

#### Conflict of interest statement

The author discloses no conflicts of interest.

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