

## From Normal to Pathological Ageing – The Spectrum of Mild Cognitive Impairment and Alzheimer's Disease

a report by

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### Introduction

Human ageing is joined by various physical, social and cognitive-mnemonic changes, which can differ considerably both inter- and intra-individually. Cognitive-mnemonic changes are caused by processes in the central nervous system, but they are also determined by genetic factors, education, profession, lifestyle, intellectual and physical activity and, especially, general physical condition.

Reliable norms about cognitive and mnemonic functions in older people are usually lacking. Many tests just indicate norms for a group older than 60 years. In geronto-psychological literature, a differentiation is sometimes made between 'young olds' (65–75 years), 'old olds' (75–85 years) and 'eldest olds' (greater than 85 years) in order to define the clinical heterogeneity of ageing in the elderly.

### Study Design

There are also problems in study design. In cross-sectional studies, age-dependent impairments are often overestimated, while in longitudinal studies they are underestimated. Since the neurons of the central nervous system lose their ability to replicate, irreversible destructive processes cumulate over the course of the years.<sup>1</sup>

After the age of 30, the human brain begins to lose weight; this can be demonstrated in computed tomography (CT) and magnetic resonance imaging (MRI). The enlargement of cortical sulci and ventricles increases 20% per decade after the age of 50 in men and after the age of 60 in women.

Not only shrinkage and loss of neurons, but also changes in the energy metabolism of the neurons can restrict cell function.

A reduction of density of the synapses and the 'dying back' of axonal branching, increases of plaques and tangles and changes in the cholinergic and dopaminergic transmitter systems have all been

described. There is little experience in the age-sensitivity of the approximately 50 different transmitter systems.

Cognitive-mnemonic changes are described in the elderly.<sup>2</sup> Intelligence deficits can be ascertained in distinguishing between crystalline and fluid intelligence.<sup>3</sup> Components of the crystalline intelligence can remain preserved or even increase until late age, while fluid intelligence decreases.<sup>4</sup> This means that older people act successfully in routine situations and that their knowledge and vocabulary remains stable. In contrast, there is a successive loss in the processing speed of new information.

The flexible adaptation to new situations and problem-solving can become difficult. Older people frequently complain about memory deficits. The extent of mnemonic problems largely depends on age, the material to learn and the task to solve.

Memory performances are hampered more strongly in abstract material than in everyday familiar material. There are also problems in free recall. Memory performance in recognition tasks worsens later, but to a small extent only.

Attention task performance, especially processes in selective and divided attention, is impaired. Verbal and communicative abilities may pass as being relatively stable in age, but communication can be disturbed by sensory deficiencies like hearing deficits.

A decline in abstraction ability and cognitive flexibility, as well as an increased susceptibility to interference can be found in older people.

Deceleration of reaction time in cognitive information processing is a universal phenomenon in older people and is one of the main causes of cognitive dysfunction. Reaction time in 60-year-olds compared to 30-year-olds is thought to be reduced by 20%.

Except for some subtypes of vascular dementia, cognitive decline in dementia starts slowly and sneakily, and the leap from normal cognitive decline in age and the beginning of dementia is often very difficult to define. In different classification schemes, the diagnostic uncertainty is described in terms of 'age-related cognitive decline', 'mild neuro-cognitive disorder', 'age-associated memory impairment' and 'mild cognitive impairment' (MCI).

### Mild Cognitive Impairment

MCI is a heterogeneous phenomenon characterised by a loss of cognitive abilities beyond normal aging.<sup>5</sup> According to Petersen et al., patients with MCI can be classified into those with amnesic MCI or non-amnesic MCI on the basis of their leading symptoms.<sup>6</sup> The criteria for amnesic MCI are specified by Petersen et al. as:

- memory complaints (preferably corroborated by an informant);
- objective memory impairment on a delayed recall test;
- relatively normal general cognitive function, except for memory (other cognitive domains may be impaired but only to a minimal degree);
- normal or only minimally impaired activities of daily living (ADLs) (below the threshold required for a diagnosis of dementia); and

**Table 1: Tests and Scales Useful in Diagnosing MCI and Dementia**

<b>Scales</b>	
Global deterioration scale (GDS)	(23)
Clinical dementia rating scale (CDR)	(24)
<b>Screening</b>	
Mini-mental-status-test	(25)
DemTect®	(26)
Clock drawing	(27)
7 minute screening test	(28)
<b>Memory tests</b>	
California verbal learning test (CVLT)	(29)
Auditory verbal learning test (AVLT)	(30)
Complex figure test (CFT)	(31)
<b>Memory test batteries</b>	
Wechsler memory scale (WMS-R)	(32)
Rivermead behavioral memory test (RBMT)	(33)
Inventar zur Gedächtnisdiagnostik (IGD)	(34)
<b>Dementia test batteries</b>	
Consortium to establish a registry for Alzheimer's disease (CERAD)	(35)
ADAS-cog	(36)
Dementia rating scale (DRS)	(37)
Dementia test	(38)

The conversion rate is approximately of 15% per year.<sup>7</sup> AD pathology has already been demonstrated in these patients.<sup>8</sup> Currently discussed predictors of

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- not demented (that is, in the opinion of the investigator, the patient does not meet criteria for dementia).

Non-amnesic MCI can be further classified by the impairment of a single domain (language, executive function, visuo-spatial relations) or in multiple domains (combination of cognitive dysfunctions).

Patients with amnesic MCI are more likely to develop Alzheimer's disease (AD) than non-amnesic MCI patients.

dementia development are typical signs of AD, including the type and extension of memory of executive dysfunction,<sup>9</sup> cerebrospinal biomarkers such as beta-amyloid or tau,<sup>10-11</sup> genetic analysis, especially the apolipoprotein E (APOE) allele,<sup>4-12</sup> reduced volume of the hippocampus,<sup>13-14</sup> hypo-metabolism in AD relevant (especially entorhinal and tempoparietal) cortical areas and reduced cortical cholinergic activity.<sup>15-17</sup>

Episodic memory impairment in MCI has primarily been attributed to hippocampal atrophy

and to cholinergic dysfunction.<sup>18-19</sup> In contrast, executive impairment in MCI may rely more on the impairment of prefrontal functions, which are suspected to be predominantly dependent on dopaminergic neurotransmission.<sup>5,20</sup>

One major 'Petersen criteria' is that MCI-patients have normal or minimal impairment in ADLs. This separates MCI from dementia. Recent studies have shown that impairment of ADLs may already be present in MCI. Intact ADLs cannot be used as a criterion to define the syndrome of MCI.<sup>21</sup> MCI is also associated with characteristic neuropsychiatric symptoms, such as dysphoria (39%), apathy (39%), irritability (29%) and anxiety (25%). The definition of MCI varies considerably, depending upon the test used for case definition.<sup>22</sup>

an overview of common tests and scales used for the early diagnosis of memory impairment and the stages of dementia.

AD is the most common cause of dementia and is characterised by an insidious onset and a slow deterioration in cognition, functional ability (e.g. ADLs), behaviour and mood.

While in the early stage of AD, assistance may be necessary with complex tasks, such as managing financial problems and calculations, behavioural disturbances are not evident until the middle stages of AD.

Behavioural disturbances can be characterised by a mini-mental-state examination (MMSE) score of

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### Alzheimer's Disease

'Dementia syndrome' is a generic term describing symptoms of chronic or progressive impairment of cortical and sub-cortical function that results in complex cognitive decline. These cognitive changes are commonly accompanied by disturbances of mood, behaviour and personality.

At the beginning of the disease, a correct differential diagnosis is necessary to separate age-associated cognitive changes, mild cognitive impairment and dementia syndrome. Clinical estimation must be focused on neuropsychological assessment of disturbed function. *Table 1* provides

between 20 and 10 points. The need for help by relatives and professionals often increases and makes independent living impossible. It poses a considerable burden on carers, which often results in secondary morbidity.

Valuable therapeutic options are provided by the three approved cholinesterase inhibitors donepezil, rivastigmine and galantamine, as well as the partial glutamate antagonist memantine.

In randomised clinical trials, these drugs have shown considerable results in reducing cognitive decline and behavioural disturbances and improving ADLs. ■

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