1 Cognitive Impairment and Rehabilitation in Alzheimer's Disease

Theodoros Angelopoulos, Dorothy Martha Scordilis, and Christos Tsagkaris

Abstract

A wealth of evidence emphasizes on the link between Alzheimer's disease (AD) and cognitive impairment (CI). CI is generally accepted as a decline in memory, learning capacity, concentration, or decision-making, leading to functional impairment. The role of mild cognitive impairment (MCI) as a predictive factor of AD and the CI linked to the establishment and progression of AD have been discussed in the context of epidemiology, genetics, pathophysiology, pathology, and clinical practice. AD-associated CI has been also addressed as a source of socioeconomic burden urging for the development of therapeutic interventions. Cognitive rehabilitation (CR) is a complementary non-pharmaceutical treatment for AD consisting of cognitive stimulation and training methods. Based on the neuronal plasticity concept, CR aims at increasing AD patients' functional status and retarding their mental decline. Although the method has encouraging results in several studies, there is still controversy as far as its efficacy is concerned and further research ought to be conducted before incorporating CR in AD's treatment plan globally. CR drawbacks should be addressed and counteracted in this context, while the current CR approach may be ameliorated through errorless learning techniques.

T. Angelopoulos · C. Tsagkaris (✉)
Faculty of Medicine, University of Crete, Heraklion, Greece
e-mail: med3618@edu.med.uoc.gr

D. M. Scordilis
Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria

G. M. Ashraf, A. Alexiou (eds.), *Biological, Diagnostic and Therapeutic Advances in Alzheimer's Disease*, https://doi.org/10.1007/978-981-13-9636-6_1

1.1 Introduction

Someone in the world develops dementia every 3 s. There were an estimated 46.8 million people globally suffering from dementia in 2015, and this number is believed to double every 20 years. Much of the growth is due to developing countries. At present, 58% of people with dementia live in low- and middle-income countries, but by 2050, this will increase to 68% (Baumgart et al. 2015). Alzheimer's disease (AD) is nowadays the leading cause of dementia, and it consists of progressive cognitive decline. Although researchers and health professionals focus on AD-associated memory deficits, in the recent years, it has become clear that AD is strongly linked to an overall cognitive decline and may also be predicted by mild cognitive impairment. A new therapeutic attitude known as cognitive treatment has been developing over the past three decades. With these facts, cognitive rehabilitation (CR) appears promising and is further investigated.

The purpose of this chapter is to discuss aspects of CI and CR in AD context. We first provide definitions of the important terms of this chapter, then we proceed with an overview of CI from a preclinical and clinical point of view, and finally we move to CR elaborating on its background, its efficacy, and practical aspects of its implementation.

1.2 Cognitive Impairment in AD

Alzheimer's disease (AD) is an irreversible, progressive brain disorder. It is the most common cause of dementia, a general term for memory loss. It is a type of dementia that causes problems with memory, thinking, and behavior. Dementia, a syndrome with many causes and types, is defined as an acquired deterioration in cognitive abilities that are serious enough to impair the successful performance of activities of daily life. While many people have trouble with memory, this does not mean they have Alzheimer's, taking into consideration the many different causes of memory loss (Larson et al. 1992; Mufson et al. 2012).

1.3 Cognition

Cognition refers to a brain activity such as awareness, perception, reasoning, and thinking. Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life. Experts divide the types of cognitive impairment into four categories: mild intellectual disability, moderate intellectual disability, severe intellectual disability, and profound intellectual disability, the most debilitating of the categories. Amnesia may coexist with CI or not (amnestic and non-amnestic type) (Takao 2012).

Although in the past years there was significant controversy concerning the characterization and the detection of CI's stages, nowadays it is widely known that mild cognitive impairment has been usually observed as a "prodromal" stage of AD

development, whereas it is also deteriorated along with the progression of the disease. CI may alter the treatment options for AD.

1.4 Clinical Significance

Physicians must take a multidisciplinary approach when working with patients, family members, or caregivers of cognitive impairment (CI). Alzheimer's disease has shown to follow a characteristic pattern of events; however, in the early stages of AD, it may be difficult to diagnose. Physicians must not only be aware of the important risk factors and family history associated with the disease but must also have knowledge of the various initial signs and symptoms which may offer suspicion of AD. Early recognition of signs and symptoms offers substantial benefits to diagnosis, which can therefore lead to early-stage therapy and prevention, giving value to prognostic information and rehabilitation.

Another key consideration in the diagnosis of AD is patient education. AD is a disorder that is renowned worldwide, and the average population knows the common pathological features of it. The importance of patient education is another key factor in distinguishing early diagnosis. The more family members and spouses understand and accept the initial symptoms, the earlier a diagnostic intervention can ensue.

1.5 Cognitive Impairment (CI) and Alzheimer's Disease (AD)

AD is the most common cause of dementia, which is defined as a syndrome of global CI (https://www.ncbi.nlm.nih.gov/pubmed/1599598). The link between AD and CI is supported by (1) *epidemiology, genetics*, (2) *pathophysiology*, (3) *neuropathology*, and (4) *clinical evidence*. Some investigators claim that essentially all patients with MCI have AD neuropathologically, while others believe that many of these patients develop AD but that is not mandatory. At the same time, the amnestic subtype of mild cognitive impairment has a high risk of progression to Alzheimer's disease, and it could constitute a prodromal stage of this disorder, while the clinical presentation of AD is highly compatible with CI.

1.5.1 Epidemiology

The majority (>95%) of patients who develop AD disease are over 65 years of age (also known as late-onset AD), and up to 5% of all people with Alzheimer's have early-onset AD, normally appearing in the late four or early five decades of life. The two forms of AD cannot be easily clinically distinguished but they comply with different patterns of genetic epidemiology (de Souza-Talarico et al. 2016). The early-onset form displays more severe symptoms and shows higher progression rates than the late-onset form. The most important risk factor for Alzheimer's disease is

advanced age. Every 5 years after the age of 65, the risk of suffering from the disease nearly doubles. Prevalence rates in less developed countries are reduced. In the USA, where the Hispanic population has a 30% decreased risk than the non-Hispanic white people, the chance of dying from Alzheimer's disease is 26% higher among the non-Hispanic white population than among the non-Hispanic black population (Jicha and Carr 2010; Takizawa et al. 2014).

1.5.2 Genetics and Pathophysiology of CI and AD

Cognitive impairment is often correlated with autosomal dominant inheritance. Several genes identified in AD pathogenesis are also supposed to play a role in MCI or CI. APOE genotype, as well as rare mutations in PS1, PS2, and APP, can cause familial forms of AD.

1.5.2.1 Early-Onset Alzheimer's Disease: Familial Alzheimer's Disease (FAD)

Three causative genes have been linked to autosomal dominant familial AD which include the APP itself and PSEN1 and PSEN2 which encode proteins required for APP breakdown and Aβ formation. Mutations in these three genes on chromosomes 21(APP), 14(PSEN1), and 1(PSEN2) are responsible for Aβ aggregation formation and early-onset disease. As a result, the dominant component of amyloid plaques in the brains of AD patients is amyloid-β (Aβ) (De Strooper et al. 1998). The mutations on APP spread Aβ levels (Aβ40, Aβ42, or both) increasing APP expression or activity of β-secretase and α-secretase inhibition.

Somatic variants in autosomal dominant genes like APP are a rare cause of AD. Mutations affect particularly the aβ production process, since they are most commonly located in or near the proteins coding exons (APP exons 16 and 17). Lastly, all three causal AD genes cause a common pathogenic AD pathway, directly affecting Aβ (Scheuner et al. 1996).

1.5.2.2 Secretases and Amyloid-Beta (Aβ) Plaques

Brain amyloid-beta (Aβ) plaques are a hallmark damage of patients with a clinical diagnosis of aMCI or AD. The distribution of Ab deposits changes in accordance with the evolution of the disease and reflects the spread of extracellular amyloid aggregates in the diseased brain. The distribution of amyloid deposits in MCI appears to be intermediate between the changes seen in the people with cognitive function (or NCI) and AD brain (Bagyinszky et al. 2016; Gouras et al. 2015).

Normally, in people not suffering from the AD disease, the dominant form of αβ is 40-amino-acid long and is called Aβ40. Aβ42 has two additional amino acid residues at the C-terminus and is lower than Aβ40. Increased proportion of Aβ42 appears to be responsible for EOAD. Aβ 42 is more easily oligomerized and forms fibrils than the Aβ40 peptide that is found in higher levels. The APP protein can be cleaved by three different secretases: α, β, or γ. Amyloid beta (Aβ or Abeta) denotes peptides of 36–43 amino acids that are derived from the amyloid precursor protein

(APP) after cleavage by beta secretase (first) and gamma secretase (second cleavage of the β-secretase product) to produce Aβ. The point of cleavage by γ-secretase determines the kind of aβ produced (Aβ40 or Aβ42). Both b- and γ-secretases are proteolytic proteins that increase in response to cellular stress such as oxidative stress, ischemia, and energy loss. β-Secretase1 requires the presence of glycosaminoglycans for effective cleavage. It is important to note that the function and the normal biological activity of αβ are not yet fully understood. Both the amyloidogenic and non-amyloidogenic pathways exist in healthy people, with AD presumably being caused through increased amyloidogenic cleavage or decreased Aβ turnover. Clots created in the presence of Aβ have an abnormal structure and are resistant to clearance (Bagyinszky et al. 2016). The amyloid plaques are extracellular deposits found in the brains of AD patients. The plaques are made of a hodgepodge of normally fibrillar aggregates known as amyloid fibers, a protein fold shared by other peptides, for example, the prions linked to protein misfolding diseases (Nicolas et al. 2018; Wu et al. 2012).

1.5.2.3 Late-Onset Alzheimer's Disease

Late-onset AD has been linked to genes that are not inherited in a Mendelian pattern. First-degree relatives of patients with late-onset AD are two times more likely to have the expected lifetime risk of this disease of individuals without an AD-affected first-degree relative. The fact that AD is more common in monozygotic than in dizygotic co-twins gives good reason to assume an important genetic contribution to this disorder (Jicha and Carr 2010; Reitz et al. 2011; Pierce et al. 2017).

1.5.2.4 ApoE

ApoE, one of the principal apolipoproteins in the brain that is expressed in humans as one of three common isoforms, transports both lipids and Aβ. The three ApoE variants, ApoE-ε2, ApoE-ε3, and ApoE-ε4, are encoded by three different alleles. The ApoE-ε2 allele is protective against AD, while ApoE-ε4 allele is the greatest risk factor. The *APOE* gene has been associated with late-onset AD and is located in chromosome 19, belonging in a cluster together with the genes encoding translocase of outer mitochondrial membrane 40 (TOMM40), apolipoprotein C1, and apolipoprotein C2. *APOE ε4* is responsible for as much as 20–30% of AD risk. The presence or absence of an *APOE ε4* allele determines the risk of AD and the age of AD onset by approximately 6 years for each allele (Myers et al. 1996; Kurz et al. 1996). The appearance of a single *APOE ε4* allele triples the risk of the disease, while the two copies are associated with a fivefold increase of it. In addition, the presence of this allele links up with memory impairment, MCI, and progression to dementia.

ApoE plays a significant role in many potential causes of AD, including Aβ plaque formation, τ-tangle formation, oxidative stress, lipid homeostasis deregulation, inflammation, synaptic plasticity loss, and cholinergic dysfunction. ApoE-ε4 allele has a low ability to remove Aβ plaques in contrast with ApoE-ε3 and ApoE-ε2 alleles. In patients with AD, ApoE is present in senile plaques (polymorphous

beta-amyloid protein deposits), vascular amyloid, and neurofibrillary tangles and binds to APP (Liu et al. 2013; Corder et al. 1993; Bekris et al. 2010).

1.5.2.5 Further Risk Variants: SORL1

As it is already mentioned, the recycling of the amyloid precursor protein (APP) from the cell membrane (plasma membrane) through the endocytic pathways is crucial for the formation of amyloid β-peptide (Aβ) in Alzheimer's disease. SorL1 is one of the five type I transmembrane receptors often found in the CNS and contains a luminal, extracellular vacuolar protein sorting ten domains and is a specific receptor for APP holoprotein. SORL1 results in APP recycling preventing cleavage by beta-secretase. Dysfunction or absence of sortilin-related receptor SORL1 caused by inherited variants increases αβ production as the APP holoprotein can no longer be recycled. Aβ plaques accumulating on cortical and subcortical brain structures linked to cognitive functions lead to a dysfunction interpreted as CI (Nicolas et al. 2018; Rogaeva et al. 2007; Behrman et al. 2017).

1.5.3 Neuropathology

1.5.3.1 Mild Cognitive Impairment (MCI)

The pathologic and molecular features of patients with MCI are not entirely understandable. The neuropathological changes don't seem to follow a direct linear path. MCI is characterized by a complex background that includes plaque and tangle pathology and also significant morphological alterations of cells and molecules (Stephan et al. 2012). These changes are highly associated with cognitive deficit together with the compensatory responses to the development of the disease. The neuronal disconnection syndrome that is associated with MCI is variable indicating that there is no one and only unique event which precipitates this early stage of AD. It is possible that neuronal damage observed in MCI is deteriorated in AD enhancing a pattern of decline (Takao 2012; Petersen et al. 2014).

1.5.3.2 Characteristics of Brains in MCI

The cortical gyral and sulcal patterns have not shown any discernible difference between amnestic MCI (aMCI) and non-amnestic MCI brains. In aMCI and mild AD, the cerebrum is characterized by a widening of sulci, such as the ventral ramus of the lateral fissure along with a blunting of the anterior tip of the temporal pole in comparison with specimens from patients without MCI. As the disease evolves into AD, the morphological changes noted in aMCI are enlarged and extended to other cortical zones (Mufson et al. 2016; Larson et al. 1992).

1.5.3.3 Neuropathological Evidence of CI in AD Patients

Positive and negative neuropathological features occur on the brains of people with CI. Positive characteristics of the disease include neutrophil threads, plentiful amyloid plaques, and neurofibrillary tangles and dystrophic neurites involving hyperphosphorylated tau (p-tau) combined with additional astrogliosis and massive

microglial irritation. Congophilic amyloid angiopathy is frequently an additional feature. Positive characteristics also include brain damage present in MCI and AD that mainly affects hippocampal formation. In the hippocampus, we can generally observe the major presence of Hirano bodies and granulovacuolar degeneration. As for the negative neuropathological lesions of MCI, these are characterized by significant losses of neurons, neutrophil, and synapses. All these damages have a unique distribution, for example, the plaques dominate the cortical mantle, and the tangles are mainly found in limbic and associated cortices. The early damages in the cortex and in particular in the entorhinal and the perirhinal area, then in the hippocampus proper, later in the association cortex, and finally in the primary neocortex represent a highly specific model of the neurofibrillary degeneration that occurs among brain regions (Jeong 2017).

All the above neuropathological characteristics are major diagnostic markers for AD. It needs to be added that the advancing degeneration of the basal forebrain, the limbic system, and the neocortical areas of the brain cannot be separated from the CI in Alzheimer's patients. More precisely, neuronal degeneration seems to be proportionate to CI. The pathological evolution of AD initiates with alterations to the synapses, proceeds with retrograde degeneration of the axons, and eventual results in atrophy of the dendritic tree and perikaryon. CI in patients with AD appears linked to neocortex and limbic system lesions. These brain areas are crucial components of the Papez circuit taking part in the genesis and consolidation of short-term memory processes, and hence their damage results in deficits identified in CI. The lesion's evolution inferiorly and posteriorly in the temporal lobes affects brain structures decisive for semantic memory. Anterior spread has the effect of involvement of subcortical areas including the cholinergic projections. Neuropsychiatric and behavioral characteristics of AD have resulted from the engagement of the anterior cingulate, amygdala, and other limbic structures in the basal forebrain. Eventually, AD as well as other neurodegenerative diseases starts focally and evolves outward, affecting gradually the entire brain in the end stage of disease and causing the typical phenotype in AD from normal cognition to end-stage disease (Stephan et al. 2012).

It is essential to highlight that the complete definition of anatomic disease progression is clearly in evolution. Clinicopathological correlation studies played a decisive role to develop a hypothetical model about the pathophysiology of the disease. The models are based on the existence of a continuum between normal aging and AD dementia and on the observation that the amyloid plaque formation is taking place principally before the onset of cognitive deficits, while neurofibrillary tangles, neuron loss, and particularly synaptic loss equally extend the progression of cognitive decline (Mufson et al. 2012).

1.5.3.4 Macroscopic Features

The visual examination of the AD brain has no diagnostic value. Nevertheless, most patients display certain clinical features as the considerable expansion of the lateral ventricles and specifically of their temporal horns. The excessive *accumulation* of CSF is a result of cortical atrophy affecting medial temporal lobes and primary

sensory, motor, and visual cortices that characterize dementia. Additionally, the presence of several lacunar infarcts in the basal ganglia, cortical microinfarcts, and demyelination of the periventricular white matter is frequent due to the cerebrovascular disease that is more prevalent in older people and hence is correlated with cognitive impairment. It is also noteworthy that possible existence of a concurrent severe cerebral amyloid angiopathy would have a profound effect on brain morphology affecting especially the posterior parietal and occipital lobes and causing from cortical microbleeds to even substantial lobar hemorrhages. AD, dementia, and cognitive impairment are characterized by the death of dopaminergic neurons in substantia nigra. Only when Lewy bodies are present in the above cases, the substantia nigra has an abnormal coloration. Finally, the locus coeruleus is noticeably affected in the early stages of AD (Behrman et al. 2017).

1.6 Microscopic Features

1.6.1 Neurofibrillary Tangles: Tαu Protein

The neurofibrillary tangles (NFTs) are formed in the perikaryal region of pyramidal neurons. The NFTs are principally produced by paired helical filaments (PHFs) that are fibrils of $\approx$ 10 nm in diameter that outline pairs with a helical tridimensional conformation according to a standard repetitive pattern. A small number of fibrils in the NFTs remain unpaired and form straight filaments, a different kind of abnormal filament (Dos Santos Picanço et al. 2016). There are cases where filaments in NFTs include transition between a paired helical and a straight segment. Leaving structural units aside, the main component of NFTs is tau protein that has become defective. This protein normally stabilizes microtubules and is plentiful in neurons and less common in astrocytes and oligodendrocytes of CNS. Cognitive impairment, dementia, and AD are often characterized by microtubule instability secondary to tau protein deficiency. The abnormal tau protein originates from the pathological phosphorylation of tau and has the effect of the transformation of normal adult tau into PHF (paired helical filament)-tau and NFTs. Generally, the stabilization of the microtubules requires the effective interaction of tau protein isoforms with tubulin via phosphorylation (Jeong 2017). Lastly, the primarily responsible hyperphosphorylated tau isoforms are often caused by mutations affecting tau function and expression or even perhaps by increased protease action or interplay between polyanions and tau protein (Takahashi et al. 2017; Bagyinszky et al. 2016; Bloom 2014; Goedert 2015; Reitz et al. 2011).

Recent studies show that NFT formation is directly proportional to molecular and conformational changes in the tau protein before and during NFT development and maturation. The pathologic expansion of the NFTs from the MTL to the neocortex is defined by the Braaks. The topographic spread involves six stages according to the current location and the severity of the damaged neurons (transentorhinal stages I–II, clinically silent cases; limbic stages III–IV, incipient AD; neocortical stages V–VI, fully developed AD). Patients with CI as well as individuals without

CI demonstrate many potential Braak staging scores from stage 0 that shows total nonexistence of NFTs to stages V–VI indicating AD. The use of the Braak staging criteria seems not to clearly differentiate the normal and the CI brains. Nevertheless, a study suggests that Braak scores are very effective in categorizing amnestic MCI from non-amnestic MCI (ref) (Takahashi et al. 2017; Mufson et al. 2016; Behrman et al. 2017).

1.7 Protective Factors

1.7.1 Diet

Although diets higher in antioxidants and polyunsaturated fatty acids (PUFAs) have been shown in several studies to lead to decreases in the risks of dementia and AD, age-related cognitive decline, and MCI (more PUFA, less disease) (Yehuda et al. n.d.), other studies discovered no clear relationship between dietary PUFAs and cognitive impairment (Chiu et al. 2008). PUFAs are mostly found in vegetables, fish, and fruit. In some other studies, individuals with high levels of vitamins E and C were less susceptible to develop dementia than those with low levels of these vitamins. Antioxidants like vitamin C can prevent cell damage by oxidation, and vitamin C may help to revive other antioxidants, such as vitamin E (Engelhart et al. 2002; Morris et al. 2002). However, larger studies have not been able to determine such associations (Laurin et al. 2004).

Currently, clinical trials concerning dietary supplementation with omega-3 PUFAs have found no complete consequence on cognition in patients with MCI or AD. On the other hand, docosahexaenoic acid supplementation has a benign effect on cognitive function in patients harboring the *APOE ε4* allele and in the beginning of the AD.

A Mediterranean-type diet (MeDi) reduced the incidence of AD with the aim of reducing the risk of MCI and progressing from MCI to AD (Singh et al. 2014). A 2013 systematic review reached similar conclusions, and also found a negative association with the risk of progressing from mild cognitive impairment to Alzheimer's, but acknowledged that only a limited number of studies had been done on the topic. The principal aspects of this diet include proportionally high consumption of legumes; olive oil as the primary source of monounsaturated fat, unrefined cereals, fruits, and vegetables; moderate to high intake of fish; moderate consumption of dairy products (mostly as cheese and yogurt); moderate amount of wine consumption (mostly red); and conservative poor consumption of red non-fish meat goods. A following cohort study in France showed that Mediterranean-type diet doesn't affect the performance on the Isaacs Set Test, the Benton Visual Retention Test, or the Free and Cued Selective Reminding Test in contrast with high MMSE scores mentioned (Féart et al. 2009).

Several prospective studies exploring the effect of alcohol on dementia risk concluded that light to moderate alcohol consumption was associated with a reduction in the risk of AD and dementia (Xu et al. 2017).

1.8 Physical Activity

Researchers examining the link between objective measures of complete periodic physical activity and incidence of Alzheimer's disease are lacking. Recent experimental reports show that physical exercise possibly promotes brain health (Abbott et al. 2004).

Physical activity could affect cognition in many ways. Aerobic exercise (cardio) – a physical exercise of low to high intensity which – raises cerebral blood flow, oxygen extraction, and glucose utilization and activates growth factors that cause structural brain changes, such as an increase in capillary density. Furthermore, studies show that physical activity reduces the amyloid plaque formation (Fratiglioni et al. 2004; Féart et al. 2009).

1.8.1 Daily Intellectual Activity

Taking part in intellectual activities, such as reading, learning a new hobby, and playing board games and card games or even using the opposite hand when brushing your teeth, may delay or prevent dementia in older adults, even if these habits and practices take place in late life, according to the latest research. New researches suggest, for example, elderly people with greater levels of education had a lower incidence of dementia than those with no education. Cognitive activity was suggested to decrease the risk of cognitive decline by increasing cognitive reserve. However, it is important to point out that the exact effect of cognitive exercise on the risk of dementia remains unclear (Ball et al. 2002; Bidzan et al. 2016; Takizawa et al. 2014; Acevedo and Loewenstein 2007).

1.9 Economic and Social Burden

Dementia is one of the major causes of disability and dependency among the elderly. It is overwhelming not only for the people who have the syndrome but also for their caregivers and families. There is often a lack of awareness and understanding of dementia, which results in stigmatization and barriers to diagnosis and care. The impact of dementia on caregivers, family, and societies can be physical, psychological, social, and economic (Dementia 2017).

Before evaluating the cost of AD, cost terminology should be defined. The costs of dementia to society come from all goods and services that are given up to anticipate, diagnose, heal, or in other respects cope with dementia. Individuals, families, and carers are affected both economically and in terms of quality of life. Alzheimer's disease (AD) – the most common cause of dementia – is associated with a valuated health-care cost of US$172 billion annually (Alzheimer's Association 2010). The basic Alzheimer's disease (AD) symptoms including progressive cognitive, behavioral, and functional impairment have a direct influence on the patients, families, and the public health system. AD affects both indirect and direct costs. During the

early stages of AD and for the community-dwelling patients, indirect costs (such as the serious adverse impact on patients and family members' financial situation) are the highest costs. The evolution of the disease leads to an increase of the direct costs (equally medical treatment and social services) when the patient is hospitalized or services of a caregiver are required. Although the drug therapies increase the direct costs they can reduce, other expenses are also involved. A number of studies have shown that there are total economic benefits to society while using drug therapies, and all related cost are considered, where results rely on specific patient and care setting characteristics. Indicatively, direct medical costs per year for mild AD ranged from €5476 in France to €27,380 in Spain. A good health system should take greater account of dementia, and governments must prepare a plan to tackle AD based on treatment options that are proportionate to the burden of the disease (Marešová and Zahálková 2016; Takizawa et al. 2014).

1.10 Diagnosis of Cognitive Impairment in AD

To standardize the diagnostic process, several major medical organizations have created diagnostic criteria for AD. In clinical practice, diagnosis of dementia (or neurocognitive disorder) is required prior to diagnosis of probable AD. The first one is the International Statistical Classification of Diseases and Related Health Problems (ICD), listed by the World Health Organization (WHO). The second one is the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association (APA) (Sachdev et al. 2014). Both are used interchangeably worldwide, and preference of usage depends on the country, member states, and the physician's organization. The latter, for example, serves as the principal authority for psychiatric diagnoses in the USA. Another organization that has diagnostic criteria is the National Institute on Aging-Alzheimer's Association (NIA-AA) (Albert et al. 2011).

The range of disorders associated with CI is evident, highlighting that modern diagnostic procedures pay attention to cognitive deficits. For instance, DSM-5 diagnostic criteria for dementia have been renamed and split into "major neurocognitive disorder" (previously dementia) and "mild neurocognitive disorder," which is equivalent to mild cognitive impairment (MCI) (Wetterling et al. 1996). A short comparison between normal aging, MCI, and major neurocognitive disorder can be found in Table 1.1.

1.10.1 Diagnostics

1.10.1.1 Intro

When an individual has symptoms of dementia, a physician must conduct tests to identify the underlying brain disease or other condition that is causing these symptoms. Different types of dementia are associated with distinct symptom patterns and brain abnormalities (Langa and Levine 2014).

Table 1.1 Normal aging vs. mild and major neurocognitive disorder

Normal aging	Mild neurocognitive disorder	Major neurocognitive disorder
Primarily intact cognition	Inefficiency in daily activities	Needs help with daily activities
Subtle processing speed is decreased	Decline from lifelong abilities in one or more areas of thinking	Substantial decline in one or more cognitive abilities
Less efficient attention and executive reasoning	[a]ADLs progressively decreased and [b]IADLs decreased	ADLs severely decreased and IADLs not feasible

[a]Basic activities of daily living (ADLs): bathing, dressing, eating, transferring from bed to chair, continence, toileting

[b]Instrumental activities of daily living (IADLs): transportation, shopping, cooking, using the telephone, managing money, taking medications, housecleaning, laundry

CI changes of AD follow a characteristic pattern, beginning with memory impairment and progressing to language and visuospatial deficits. However, approximately 20% of patients with AD present with non-memory complaints such as word finding, organizational, or navigational difficulties. In other AD patients, upstream visual processing dysfunction (referred to as posterior cortical atrophy syndrome) and a progressive "logopenic" aphasia are the primary manifestations of AD for years before progressing to involve memory and other cognitive domains. Furthermore, other patients may present with an asymmetric akinetic–rigid–dystonic ("corticobasal") syndrome or a dysexecutive "frontal variant" of AD. Loscalzo MD, Phd, 2015 (Casper et al. 2015; Fratiglioni et al. 2004).

1.10.2 Approach to Diagnosis: Evaluation of the Patient

Physicians may have multiple objectives with alternating degrees of importance during their consultations with patients. These goals include, but are not limited to, the interpretation of signs and symptoms into diagnoses, assessing the stability or change in known conditions, providing information and counseling for future prevention, and the continuation or adjustment of therapeutic interventions. A general health check will increase the number of diagnoses for a patient, but it may not affect overall morbidity and mortality (Krogsboll et al. 2012).

The interaction between the patient and the physician represents not only a scientific encounter but also a social practice centered on the point of control and meeting each other's expectations. Patients expect that their health-care needs and concerns will be addressed efficiently. Physicians also have expectations: a need to feel that they have not missed something important in addressing diagnostic challenges, a need to put limits on the time available for each interaction, and a need to maintain open-mindedness so that their evaluations and recommendations are not clouded by any emotional feelings about the patient. The expertly performed rational clinical examination enhances the expected social practice and the likelihood of acquiring relevant data. It also optimizes the physician's ability to understand the patient's symptoms and concerns, as well as to facilitate the healing process (Verghese et al. 2011).

Table 1.2 Overview- approach to evaluating a patient with dementia: routine evaluation and optional diagnostic tests

Routine evaluation	Optional focus tests	Occasionally helpful tests
History	Psychometric testing	EEG
Physical examination	Chest X-ray	Parathyroid function
CT/MRI	Lumbar puncture	Adrenal function
Laboratory tests: thyroid function (TSH), vitamin B12, complete blood count, electrolytes	Other tests: liver function, renal function, urine toxin screen, HIV, apolipoprotein E, RPR or VRDL	Other tests: urine heavy metals, lab screen for autoantibodies, RBC sedimentation rate, angiogram, brain biopsy, SPECT, PET

Abbreviations: *CT* computed tomography, *EEG* electroencephalogram, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *RBC* red blood cell, *RPR* rapid plasma reagin (test), *SPECT* single-photon emission computed tomography, *TSH* thyroid-stimulating hormone, *VDRL* Venereal Disease Research Laboratory (test for syphilis)
Source: Casper et al. (2015)

Table 1.3 Overview- approach to evaluating a patient with dementia: diagnostic categories

Reversible causes	Irreversible/degenerative dementias	Psychiatric disorders
Examples: Hypothyroidism Thiamine deficiency Vitamin B12 deficiency Normal pressure hydrocephalus Subdural hematoma Chronic infection Brain tumor Drug intoxication Autoimmune encephalopathy	Examples: Alzheimer's disease Frontotemporal dementia Huntington's Dementia with Lewy bodies Vascular dementia Leukoencephalopathies Parkinson's disease	Examples: Depression Schizophrenia Conversion reaction

Table 1.4 Overview- approach to evaluating a patient with dementia: associated treatable conditions

Depression	Agitation
Seizures	Caregiver "burnout"
Insomnia	Drug side effects

When it comes to patients with dementia, including patients suffering from CI in AD context, three major points should be kept in focus: (1) What is the best fit for a clinical diagnosis? (2) What component of the dementia syndrome is treatable or reversible? (3) Can the physician help alleviate the burden on caregivers? A broad overview of the approach to evaluating a patient with dementia including optional diagnostic tests (Table 1.2), diagnostic categories (Table 1.3), and associated treatable conditions (Table 1.4) can be found under Tables 1.2, 1.3, and 1.4.

The major degenerative dementias can usually be distinguished by the initial symptoms; neuropsychological, neuropsychiatric, and neurological findings; and neuroimaging features.

Table 1.5 Patient's medical history

Description of the patient: Age, gender, ethnic background, occupation, chief reason for seeking medical care, state the purpose of the evaluation (usually in the patient's words)
Other physicians involved in the patient's care: Include the clinician that the patient identifies as his/her primary provider or the physician who referred the patient. Record contact information for all physicians who should receive information about the visit
History of the reason for seeking medical care: In chronologic fashion, determine the evolution of the indication for the visit and then each major symptom. It is best to address the patient's reason for seeking care first rather than what the physician ultimately believes is most important
Be careful to avoid "premature closure," in which a diagnosis is assumed before all the information is collected
Past medical and surgical history: List other illnesses and previous surgeries not related to the current problem. List all prescribed and OTC medications with dosages. Remember to ask about vitamin and herbal supplements
Allergies and adverse reactions: List allergic reactions to medications and food. Record the specific reaction (e.g., hives). Distinguish allergies from adverse reactions or intolerance to medication (e.g., dyspepsia from NSAIDs)
Social, occupational, and military history: Describe patient's current family and a typical day for the patient. The occupational history should focus on current and past employment as it might relate to the current problem
Risk factors: Include history of tobacco use, alcoholism, illegal drug use, and risk factors for sexually transmitted diseases (e.g., HIV and hepatitis)
Family history: History of any diseases in first-degree relatives and a list of family members with any conditions that could be risk factors for the patient (e.g., CVD, known genetic disorders, malignancy)
Review of systems (see Table 1.6)

Abbreviations: *CVD* cardiovascular disease, *HIV* human immunodeficiency virus, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OTC* over-the-counter

1.10.3 History

The history begins by asking the patients to describe, in their own words, the reason for seeking medical care (Table 1.5). Although patients may have many reasons for initiating a visit to the physician, they should be encouraged to select the most important or top two most important concerns they have and state them. The physician should reassure the patient that other concerns will not be ignored but that it's important to understand what is the most concerning to the patient at that moment.

The history should concentrate on the onset, duration, and tempo of progression when it comes to dementia and AD. For example, an acute or subacute onset of confusion may be due to a different cause like delirium and should trigger the search for intoxication, infection, or metabolic derangement. An elderly person with slowly progressive memory loss over several years is likely to suffer from AD. Nearly 75% of patients with AD begin with memory symptoms, but other early symptoms include difficulty with managing money, shopping, driving, following instructions, navigating, or finding words. The latter symptoms are really important in the frame of CI.

The history should be taken in a stepwise manner, and the spoken approach should also be taken into consideration. We should begin with acquiring the history of the present illness or concern at large. Open-ended questions produce a description of the patient's concerns in the patient's own words, whereas specific questions fill in gaps and help clarify significant points. These questions should be asked in an order lead by the story the patient tells and targeted to fit the individual problem. Important questions to consider include description of onset and chronology, location of symptoms, quality (character) of symptoms, intensity, and precipitating, aggravating, and relieving factors. Ask if this problem or similar problems occurred before and, if so, whether a diagnosis was established at the time.

After taking the history of the present illness, we should ask about past medical and surgical history, a list of current medications including prescriptions, herbal drugs, over-the-counter medications, and vitamins. Next, we may attempt to assess social and occupational history, along with risk factors. Social history can help us understand the patient's values and support systems. Information that can influence risk factors for disease should be gathered including occupational history, substance abuse, and sexual history. Marital status and the living situation of the patient are as important as risk factors for disease and help determine how to provide the best care for the patient.

An intelligent physician is aware that patients may not report all their problems because they may have forgotten or simply may not want to discuss them.

The family history is never diagnostic, but it allows risk stratification and it may indicate signs of CI which will not be mentioned by the patient (Goldman and Schafer 2012). Studies of family history say that if you have a close relative who has been diagnosed with AD, your risk increases by 30%. This is a relative risk increase, meaning a 30% rise in your existing risk. This means your risk may be higher, but not that much higher, if you consider the absolute numbers. The risk of being diagnosed with AD is 2% per year if you are over the age of 65. Family history then raises this 2% by 30%, to about 2.6% per year. Age raises the chances of AD more than family history considering that people above the age of 70 have a 5% chance of being diagnosed. Family history would again raise this by 30%, making 5% go to 6.5%. Nevertheless, a positive family history of AD should always be taken into consideration. The review of systems is the structural assessment of each of the major organ systems and can help elicit symptoms or signs that are not covered or may be overlooked in the history of the present illness (Table 1.6).

1.10.4 Screening

1.10.4.1 Cognitive and Neuropsychiatric Examination

Cognitive and neuropsychiatric examinations, or mental status testing, evaluate memory, ability to solve simple problems, and other thinking skills. Such tests give an overall sense of whether a person is aware of symptoms; knows the date, time, and where he or she is; or can remember a short list of words, follow instructions, and do simple calculations.

Table 1.6 Review of systems[a]

Focus all questions on a specific time frame (e.g., within the past "month" or "now") and on items not already addressed during the clinical examination
Change in weight or appetite, change in vision, change in hearing, new or changing skin lesions
Chest discomfort or sensation of skipped beats, shortness of breath, dyspnea on exertion
Abdominal discomfort, constipation, melena, hematochezia, diarrhea, difficulty with urination
Depression; joint or muscle discomfort; sensation of unsteadiness when walking, standing, or getting up from a chair; problems with sleep; difficulty with sexual function

[a]Clinicians may start with this basic list and adapt the items to their specific patient population by considering factors such as age, gender, medications, and the problems identified during the examination. The process is facilitated by developing a routine personal approach to these questions, typically going through the systems from "head to toe"

Brief screening tools such as the Mini-Mental State Examination (MMSE), Mini-Cog test, Montreal Cognitive Assessment (MOCA), and Cognistat can be used to capture dementia and follow progression. None of these tests is highly sensitive to early-stage dementia or discriminates between the different dementia syndromes. In most patients with MCI and some with clinically apparent AD, bedside screening tests may be normal and therefore may require a more comprehensive set of neuropsychological tests to be conducted.

The MMSE is a questionnaire designed to test a range of everyday mental skills. It is a 30-point test of cognitive function, with each correct answer being scored as 1 point, making a maximum MMSE score of 30 points. It includes tests in the areas of orientation (e.g., identify season/date/month/year/floor/hospital/city/state or region/country); registration (e.g., name and restate three objects); recall (e.g., remember the same above mentioned three objects 5 min later); and language (e.g., name pencil and watch; repeat "no if's, and's, or but's"; follow a three-step command; and write a sentence and copy a design). A score of 20–24 suggests mild dementia, 13–20 suggests moderate dementia, and less that 12 indicates severe dementia. On average, the MMSE score of a person with Alzheimer's declines about 2–4 points per year.

The Mini-Cog test is a 3-min instrument to screen for cognitive impairment in older adults. The Mini-Cog is scored in two parts: the first part uses a three-item recall test for memory and the second part is a simply scored clock-drawing test (CDT) (Fig. 1.1). These are then added together for a total score. The maximum score for the item recall test is 3, and the maximum score for the clock-drawing test is 2, with the complete total score being a maximum of 5. A total score of 3, 4, or 5 indicates lower likelihood of dementia but does not rule out some degree of cognitive impairment.

The three-item recall score is simply 1 point for each word recalled without cues, scoring 1, 2, or 3. The clock-drawing is scored as 2 points for a normal clock or 0 (zero) points for an abnormal clock-drawing. A normal clock must include all numbers (1–12), each only once, in the correct order and direction (clockwise). There

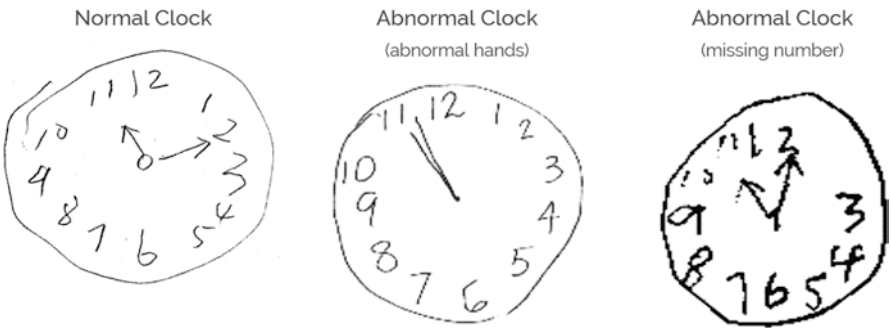

Fig. 1.1 Example of normal and abnormal clock-drawing test (CDT)

must also be two hands present, one pointing to eleven (11) and one pointing to two (2). Hand length is not scored in the Mini-Cog algorithm.

1.10.5 Physical Examination

1.10.5.1 Physical and Neurologic Examination

A comprehensive general and neurological examination is fundamental in diagnosing dementia, AD, and any signs of cognitive impairment. The physical and neurological examination is essential evidence when it comes to documenting the progression of cognitive decline. It is also useful for the discovery of other signs of nervous system involvement and to search for clues that may suggest an underlying cause that may be responsible for the cognitive disorder.

A classic medical workup consists of medical history, diet, nutrition, use of alcohol, review of medications, blood pressure check, temperature, pulse, auscultation of heart and lungs, and collection of blood or urine samples for laboratory testing. Information obtained from the physical examination and laboratory tests can help identify health issues that can cause symptoms of dementia, like conditions other than Alzheimer's that could cause confusion, trouble focusing, memory problems, and thinking problems which include anemia, infection, diabetes, hepato-renal disease, cardiovascular disease, lung disease, or vitamin and hormonal abnormalities.

A classic neurological examination consists of testing reflexes, coordination, muscle tone and strength, eye movement, speech, and sensation. The neurological examination may also include a brain imaging study depending on the outcome of the physical examination, symptoms, and patient concerns. The typical neurological examination is done in order to closely evaluate the patient for problems that may signal brain disorders other than Alzheimer's. It is important to look for signs of small or large strokes, Parkinson's disease, brain tumors, fluid accumulation in the brain, and other illnesses that may impair memory or thinking.

Typical AD spares the motor systems until later on in the course, whereas frontotemporal dementia (FTD) patients usually develop axial rigidity, supranuclear gaze palsy, or a motor neuron disease reminiscent of amyotrophic lateral sclerosis (ALS). In dementia with Lewy bodies (DLB), the initial symptoms may include the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, festinating gait), but DLB most often starts with visual hallucinations or dementia. Creutzfeldt–Jakob disease (CJD) is advocated by the presence of an akinetic-mute state, diffuse rigidity, and prominent, startle-sensitive myoclonus.

1.10.6 Laboratory, Microscopic, and Imaging Findings

There are no definitive laboratory tests available that will positively diagnose AD during life. Currently, the only definite diagnosis of AD is to microscopically examine a section of the person's brain tissue after death. Histopathologists will look for senile plaques and neurofibrillary tangles which are characteristic of AD. Since plaque and tangle formation are also seen in the normal aging process, the sample must be compared to a control sample of normal, non-AD brain tissue from a person of the same age.

A physician may use a range of traditional laboratory tests to rule out other conditions and deficiencies that could be affecting the patient's memory. They may also look for overmedication and may use imaging tools such as computed tomography (CT) and magnetic resonance imaging (MRI) scans in order to look for evidence of tumors, trauma, or stroke that could cause dementia symptoms. Imaging can also help look for brain atrophy or shrinkage that may be seen later in the AD progression. The American Academy of Neurology recommends the routine measurement of a complete blood count, electrolytes, renal and thyroid function, a vitamin B12 level, and neuroimaging studies (CT or MRI).

1.11 Differential Diagnosis

Common causes of dementia include Alzheimer's disease, which is the number one cause. Vascular dementia, alcoholism, and drug/medication intoxication are other common causes. Less common causes of dementia include vitamin deficiencies, endocrine and other organ failure, other psychiatric disorders, degenerative disorders, chronic infections, head trauma and diffuse brain damage, intracranial hypotension, neoplasm, toxic disorders, and others.

Differential diagnosis should always be in mind when the physician is taking a history. Personality change, disinhibition, and weight gain or compulsive eating suggest frontotemporal dementia (FTD), for example, and not AD. Early visual hallucinations, parkinsonism, and rapid eye movement (REM) behavior disorder (RBD; the loss of skeletal muscle paralysis while dreaming) may suggest diagnosis of dementia with Lewy bodies (DLB). Rapid progression with motor rigidity and myoclonus suggests Creutzfeldt–Jakob disease (CJD). Seizures may indicate

strokes or neoplasm but also occur in AD, particularly early-age-of-onset AD (Casper et al. 2015). Furthermore, a history of stroke with irregular progression suggests vascular dementia. Vascular dementia is also commonly seen in the setting of hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. Therefore, in patients with cerebrovascular disease, it can be difficult to determine whether the dementia is due to AD, vascular disease, or a mixture of the two because many of the risk factors for vascular dementia, including diabetes, high cholesterol, and lack of exercise which are also presumptive risk factors for AD.

1.12 Treatment Options for AD Patients with CI

The treatment options for MCI and CI are either pharmacological or psychological. Currently, the FDA has not approved any medication for MCI treatment since AD medication has not been proved effective as far as preventing or delaying the deterioration of MCI is concerned. Several psychological or occupational interventions have shown encouraging results; however, most of them should be personalized, while their efficacy depends on the experience of the therapist, the compliance of the patient, and the support of the carers.

CI in AD patients is treated with pharmacological agents on the grounds of CI's pathophysiology knowledge. More specifically cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) antagonists are considered as the first-line therapy for global cognitive impairment. Several studies indicate the benefits of psychological approaches in combination with pharmaceutical treatment. In this frame several approaches have been developed. To name just a few, we may shortlist cognitive behavioral therapy, stimulation training, cognitive training, cognitive stimulation, and cognitive rehabilitation. The latter consists of both stimulation and training techniques and focuses on cognitive aspects of the patient's disorder.

1.13 Cognitive Rehabilitation in AD

1.13.1 Introduction

Cognitive rehabilitation (CR) has been defined as a comprehensive program aiming to cognitive enhancement. It includes several training approaches, and it has been developed as a method of rehabilitation for people with cognitive impairment of various etiologies. CR is an individualized treatment in accordance with the principles of biopsychosocial approach. CR has been studied as a part of the treatment of several conditions including traumatic brain injury (TBI), cerebral vascular accident, cerebral palsy, Down syndrome, Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), and developmental disorders such as autism, schizophrenia, and Parkinson's disease (Choi and Twamley 2013).

Due to the low efficacy of pharmacological approaches up to this day, CR is expected to play an important role in AD's treatment. In CR, all facets of

neuropsychological deficits are approached in the context of behavior and social functioning. Practitioners pay special attention to cognitive stimulation and training. Clare and Woods published their work on cognitive enhancement in AD back in 2004 and grouped the various treatments into three broad categories: cognitive stimulation, cognitive training, and cognitive rehabilitation (Clare and Woods 2004).

1.13.2 Neuropsychological Background

The idea of cognitive treatments for AD is based on the concept of neuronal plasticity. A continuous loss of cerebral capacity including neuromodulation has been related to aging. Accumulating evidence recommends that the sensory system is capable of altering its structural and hence its functional pattern in accordance with various stimuli. To put it in plain words, this means that the mind has the capacity for rebuilding itself so as to adjust to changing conditions or novel stressors. This feature has been established through plasticity promoting studies in ordinary old individuals (Choi and Twamley 2013).

Training appears as a promising method of inducing brain plasticity since it involves individuals in stimulating cognitive, sensory, and psychomotor tasks. The rationale behind this statement has been established from the level of neurons to the level of cortical representations. Training represents a repeated stimulus which enhances signaling pathways and eventually gene expression in molecular and cellular levels (Limond and Leeke 2005).

On these grounds, we assume that neurons which undergo these procedures can act as an assembly enhancing memory patterns and networks. This applies to existing memory patterns, which are enhanced and may also be able to form new patterns. A very important aspect of this concept is that minority neuron circuits may be enhanced, and in functional level, this signifies that an individual who faces a working memory impairment could witness an improvement of his daily life through cognitive training (Winocur et al. 2000; Choi and Twamley 2013).

Several neuropsychological experiments or clinical studies support the efficacy of training. Most of these studies focus on visual stimuli and suggest that the main cerebral areas affected by training experiments are the right fusiform face area, right parahippocampal cortex, right temporal parietal junction, and right medial prefrontal cortex. The efficacy of training could be assessed through either higher or lower activation of neural circuits. Higher activation has been correlated with higher functionality, whereas in different studies, lower activation is considered an encouraging finding suggesting that a task can be accomplished easier (Ginarte-Arias n.d.).

More specifically, Heiss et al. conducted a PET study of 70 patients with mild AD comparing social support and pharmacological and/or cognitive treatment. Their results suggest that a combination of cognitive training and pharmacological treatment (phosphatidylserine or pyritinol) was associated with increased brain glucose metabolism in temporal–parietal brain areas during a task based on recognition of visual stimuli (Heiss et al. n.d).

Moreover, a single-blind randomized controlled trial consisting of CR and relaxation therapy versus no treatment in mild AD conducted by Clare et al. in 2010 found an increase in blood oxygen level-dependent signals in the CR group in areas forming part of the network for visual associative encoding and learning, whereas individuals in the no-treatment control group showed reduced BOLD activity over time (Clare et al. 2010).

Other studies showed a progressive decrease in the neuronal activity associated with the accomplishment of a task upon training. Haier et al.'s study included young individuals performing repeatedly a complex visuospatial/motor task. The individuals underwent brain PET scans before and after practice which revealed a decrease in regional subcortical glucose metabolic rate with practice may reflect changes in cognitive strategy that are a part of the learning process (Haier et al. 1992).

Such findings formulate the neuropsychological background of CR allowing respective studies to be conducted. They support CR's scientific rather than empirical character, they provide practitioners with constant updates to improve their practice, and they also establish a feedback network between practitioners and researchers. All in all, this accumulating evidence is an added value to cognitive rehabilitation and its role in AD treatment (Limond and Leeke 2005; Petersen et al. 2014).

1.13.3 Cognitive Rehabilitation in AD Methods

Cognitive rehabilitation (CR) is defined as a comprehensive cognitive enhancement program, which puts under the same roof cognitive stimulation (CS), cognitive training (CT), and other approaches. In this point, it would be useful to provide a short definition of cognitive stimulation and cognitive training given that these methods have been developed for patients suffering from AD of different stages. CS focuses on the engagement of the patient in discussions about familiar to him everyday affairs in order to stimulate mental activity. More impaired AD patients and mainly inpatients in proper facilities are usually treated with CS. On the other hand, CT consists of various tasks designed to exercise specific cognitive functions or to work on patients with a relatively fair cognitive status so as to support its impaired aspects. Consequently, patients who have enough cognitive resources for a therapist or a computer program to guide them are usually treated with CT (Kelly and Maria 2015).

As a combination of the aforementioned methods, CR functions as a model of treating the cognitive decline depending on the assessed behavioral and social disability rather than focusing on specific cognitive deficits. In this frame CR not only alleviates cognitive deficits working closely on them, but it also creates compensatory mnemonic pathways so as to restore the functionality of the patient to the greatest extent. This compensation ranges from training the patients to dealing with finances in such a way that the monthly utility bills are easier to remember to learning how to use virtual or paper aids to organize and recall important information (medication, appointments, etc.). Verbal instructions along with physical

Table 1.7 An overview of CR patterns

Guiding principles	Recall strategies	Specific interventions
Effortful processing dual	Mnemonics	Face-name recall
Cognitive support	Cueing	Number recall
Errorless learning	Chunking	Story recall
	Method of loci	List/object recall
	Spaced retrieval	Procedural memory
		Fluency training
		Semantic impairments

An overview of principles, strategies, and intervention in the frame of CR (Kelly and Maria 2015)

demonstration and support items are used to teach the patient how to develop methods applicable to its own cognitive deficits. The outcomes of CR can be observed and assessed during the interaction between the patient and his/her environment (Clare et al. 2010).

To this point, the exact methods of CR seem to be opaque. Some clarifying examples can be found in clinical studies on CR and in health associations' guidelines papers. Hence, we should briefly review the guidelines of the Alzheimer's Society of Ireland and a CR therapy study conducted by Loewenstein et al. back in 2004.

According to the guidelines, CR is a tripartite pattern consisting of guiding principles, recall strategies, and specific interventions (Table 1.7).

To our knowledge, CR is performed on an individual basis although many studies group AD patients with a similar impairment score. The majority of the CR approaches belong to three different categories: (a) techniques without external memory aids, (b) techniques with nonelectronic external memory aids, and (c) techniques using electronic technologies. Studies have recorded everyday items and electronic applications, notepads, alarm clocks, traditional computer games such as Tetris, or more sophisticated electronic applications used in cognitive rehabilitation settings. The selection of these supportive items varies depending on availability, personal experience of the health professionals practicing CR, and familiarity of the patient with any given item. Familiarity is also linked to the optimal treatment setting given that space is another important feature of CR interventions (Ginarte-Arias n.d; (Choi and Twamley 2013).

A comfortable setting such as the patient's home plays an important role concerning the efficacy of the intervention. Moreover, CR ought to be perceived as a dynamic procedure in which the patient and his family/carers are actively involved, assisted, and coordinated by the health professional who acts as therapist. The patient should be encouraged to practice the strategies he/she elaborated on during the session on his own and apply them to as many of his daily activities as possible. At the same time, the family/carers should be debriefed after each session and also be instructed with strategies for practice outside the CR sessions (Kelly and Maria 2015).

Evidence suggests that the outcomes of CR should be assessed in the beginning and in the end of each CR session, in the short and in the long term. Moreover, it is considered useful for the health professional and for the family/carers of the patient to take notes so as to observe better the capacity of the patient to deal with everyday tasks. Although scientific studies observe and evaluate systematically the efficacy of any tested approach, such an individual monitoring appears as an essential part of each treatment plan, and it seems to be helpful as far as the personalization of CR, the commitment of the patient, and the therapist–patient communication are concerned (Kelly and Maria 2015; Ginarte-Arias n.d)

1.14 Efficacy of CR in AD patients

The efficacy of CR in AD has been debated for a long time. Back in 1999, an NIH resolution pointed out that few studies are available, and even these studies are greatly diverse as far as their methods are concerned or present data from a small number of patients. Even though evidence has grown since then, the approaches remain diverse, and it was difficult to group all studies. We provide the main categorization system of these studies and present the results of three representative ones:

1. Studies targeting techniques without external memory aids
2. Studies targeting techniques with nonelectronic external memory aids
3. Studies focusing on the use of assistive electronic technologies

Germain et al. conducted an observational, prospective study in a sample of 52 patients. CR sessions were facilitated by experienced therapists once weekly during 3 months at home and once monthly contact for 9 months. Patients with mild AD dependence and caregiver's burden were evaluated immediately after the intervention and had follow-ups at 6 months and 1 year. The dependence of the patients with regard to adapted activity as well as the caregiver's burden was decreased at 3 months, 6 months, and 1 year. Moreover, global cognition slightly decreased in a 1-year interval. The results of this observational study are encouraging for patients with mild AD and their caregivers, given the fact that patients' dependence decreased and the global cognitive decline is limited (Germain et al. 2018).

Clare et al. conducted a single-blind *randomized controlled trial* (RCT) comparing CR supported by practical components with relaxation therapy and no treatment. Sixty-nine individuals from a community – outpatient setting (41 women and 28 men), mean age 77.78 years (standard deviation 6.32, range = 56–89), and who have been diagnosed with AD or mixed AD and *vascular dementia* and have a *Mini-Mental State Examination score* of 18 or above – were also included. All patients were treated pharmacologically (stable dose of acetylcholinesterase-inhibiting medication). Eight weekly individual sessions of CR were held, and goal performance and satisfaction were assessed. The assessment was based on the Canadian Occupational Performance Measure; questionnaires assessing mood, quality of life, and carer strain; and a brief neuropsychological test battery. CR was associated with

significant improvement in ratings of goal performance and satisfaction. An imaging study (fMRI) supported the behavioral changes in a subset of the CR group. Hence, these findings suggest that the item which assisted CR may be effective against early-stage AD (Clare et al. 2010).

Loewenstein et al. conducted an RCT of CR against mental stimulation facilitated by computer puzzle games. According to their findings, CR ameliorated orientation, learning and recalling faces and names for at least 3 months. The CR group also made noticeable improvements on an untrained functional task at a level of statistical significance. However, only informant patients in the CR condition noted a significant improvement in memory function on the Informant Questionnaire of the Cognitive Decline in the Elderly scale. These results suggest that long-term outcomes may be achieved provided that CR intervention focuses on everyday life – real-world affairs – and the patient is aware of his condition and motivated to ameliorate it (Loewenstein et al. 2004).

All in all, although CR interventions have encouraging results, they are still considered somewhat controversial. Many researchers claim that CR is beneficial only for a short time and that the results are mainly reported in patients with mild- or early-stage AD. Moreover, a Cochrane review focusing on individuals with early-stage AD or vascular dementia assumes that the available evidence is not strong enough for the application of such interventions because limited randomized controlled trials (RCTs) are available and considerable methodological limitations have been identified. The efficacy of individual CR approach appears even more opaque because of a complete absence of relevant RCTs. Further and more comprehensive research ought to be conducted in order to properly assess the efficacy of CR. This fact has a negative impact on the future incorporation of CR in clinical practice for the forthcoming patients with AD (Winocur et al. 2000; Jacquemin 2009; Bahar-Fuchs et al. 2013a).

1.15 Benefits and Drawbacks of CR on Patients with AD

CR is considered beneficial for various reasons. First of all, it is a non-interventional, non-pharmaceutical treatment, and thus it does not share the side effects of these treatments. Moreover, CR is a personalized treatment adjusted to the mental status and the specific needs of the patients. In this concept it engages both the patient and the carers in the therapeutic procedure, and thus it enhances doctor's and patient's communication according to the principles of biopsychosocial healthcare. What is more a wide spectrum of health professionals can be trained and qualified to perform CR, and thus many patients in different settings will have access to CR. More specifically, CR may be performed by an occupational therapist, a physical therapist, a speech/language pathologist, a neuropsychologist or other psychologist, or a neuropsychiatrist, psychiatrist, or other physician (Bottino et al. 2005; Viola et al. 2011; Bahar-Fuchs et al. 2013a).

On the other hand, CR is due to several drawbacks with regard to the method in general and the application of the method to patients with AD in particular. In the

first category, we may list the variable efficacy of the method depending on the experience of the therapist, the ambivalent efficacy – which discourages health professionals from considering it as a treatment for their patients – and the fact that carers should be engaged to achieve optimal compliance and efficacy (Kelly and Maria 2015).

In the second category, we may refer to indigenous factors of the disease. Factors such as the progressive mental status decline, the patient's low understanding, or even awareness of the illness and the highly prevalent depression among geriatric patients have been shown to alter the potential outcomes of CR. As a result of this, the purpose of CR in AD is to slow down this cognitive decline offering to the patient some months of independent or less dependent function (Hwang et al. 2015). Even though this is considered as a huge benefit in terms of quality of life and care-associated direct and indirect costs, it does not meet the expectations of the patients' carers, and this results in a lower level of carers' engagement, weakening the overall efficacy of the treatment. A more detailed overview of obstacles has been presented by Choi et al. (Choi and Twamley 2013).

1.16 Cost and Overall Implementation Overview

Not all the patients with AD are guaranteed access to CR. Reviewing many US-based insurance brands, it is evident that there is a consensus not to cover CR expenses in patients suffering from different conditions than traumatic brain injury (TBI) and cerebral vascular accident. Medicare documents also reveal a similar attitude of the US public sector toward CR in AD. The background of this attitude is an NIH resolution in 1999 which concluded that CR has not been proved effective in conditions such as cerebral palsy, Down syndrome, Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), and developmental disorders such as autism, schizophrenia and Parkinson's disease. Hence, it appears that influential health-care systems are not willing to fund CR interventions as a counteract to AD's cognitive impairment (Winocur et al. 2000; Limond and Leeke 2005; Bahar-Fuchs et al. 2013b).

The cost of CR interventions varies accordingly to the methods applied. Interventions based on computer programs cost more than interventions based on simple notepads. Nowadays studies investigate cost–benefit aspects of the low-cost CR. Their findings are encouraging; nevertheless, more evidence concerning AD in particular and the impact on CR on direct and indirect treatment cost will be published in due time.

In the future, in case CR is approved for insurance coverage, it seems that the criteria will be strict. Taking into account the procedure for patients with TBI and HIV-associated encephalitis, patients with AD should prove their impaired cognitive status on the grounds of:

1. Neuropsychological testing leading to neuropsychological results which will be used in treatment planning and directing rehabilitation strategies.

2. Neuropsychiatric and neuropsychological evaluation.
3. Ability of the patient to actively participate in a cognitive rehabilitation program (e.g., is not comatose or in a vegetative state).
4. An expected significant amelioration of the patient's cognitive status (*Cognitive Rehabilitation Therapy* | TRICARE n.d).

1.17 Toward an Optimal CR

Errorless learning approach has been suggested as a promising CR intervention by several researchers. Errorless training prioritizes avoidance of errors during sessions and consequently targets the participants it is supposed to study and immediately reproduces any piece of given information. It appears that this feature prevents participants from attempting to retrieve target information from long-term memory. In this frame, both everyday materials and sophisticated computer software may be effective. However, error elimination could be a significant pitfall leading to a gradual impairment of retrieval practice ability and thus confusing the patients further, discouraging them and their carers, and eventually weakening CR treatment plan. (Petersen et al. 2014; Germain et al. 2018). Errorless learning has been designed to make sure that the patient memorizes accurately and correctly in order to achieve an appropriate level of functionality as long as possible. This approach appears as the most promising one and is expected to reform all existing kinds of CR (Middleton and Schwartz 2012).

1.18 Conclusion

All in all, the significance of CI in AD has been more and more acknowledged during the past years. This knowledge has been incorporated in contemporary research and diagnostics, while the CR treatment model has been developed to counteract AD's cognitive features (Hwang et al. 2015). Several factors from the current understanding of pathophysiology to the patients' compliance interfere with the investigative, diagnostic, and therapeutic procedures (Choi and Twamley 2013). In the future, further and more comprehensive research ought to be conducted in order to enhance the understanding of CI in AD context and to establish the most efficient treatment models.

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