Chapter 1

Overview

Old age cognitive impairment is a set of syndromes that affect memory, thinking ability, language skills, and daily functioning. With increasing age, the incidence of cognitive impairment gradually rises. According to the Chinese Expert Consensus on Cognitive Impairment in the Elderly (2022), cognitive impairment refers to varying degrees of impairment in one or more cognitive areas due to various reasons, such as orientation, memory, calculation, attention, language, executive function, reasoning, and visuospatial function. These impairments can affect the social function and quality of life of patients to varying degrees, and can even lead to death in severe cases. The severity of cognitive impairment is usually classified based on its impact on an individual's daily functioning. According to the Chinese Expert Consensus on Cognitive Impairment in the Elderly (2022), cognitive impairment can be divided into Mild Cognitive Impairment (MCI) and Dementia. MCI refers to progressive decline in memory or other cognitive functions, but does not affect daily living abilities, and does not meet the diagnostic criteria for dementia. MCI can be further subdivided into single-domain amnestic MCI, multi-domain amnestic MCI, single-domain non-amnestic MCI, and multi-domain non-amnestic MCI. These classifications are based on the affected cognitive domains and whether memory functions are impaired. Amnestic MCI is

primarily characterized by memory loss, while non-amnestic MCI is characterized by impairment in cognitive functions other than memory. Dementia, on the other hand, is a more severe form of cognitive impairment that significantly affects an individual's daily functioning. The severity of dementia is typically categorized into three stages: mild, moderate, and severe. In the mild stage, individuals may experience memory loss, difficulty completing familiar tasks, language problems, and decreased judgment. In the moderate stage of dementia, symptoms worsen and individuals may require assistance from others for daily activities such as dressing and eating. In the severe stage of dementia, individuals may be completely dependent on others for care, lose their ability to speak, and be unable to control bodily functions like walking and swallowing.

The etiology of dementia is diverse and complex, with Alzheimer's disease (AD) being the most common type, accounting for 50% to 70% of all dementia cases. Other types include vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), Parkinson's disease dementia (PDD), etc. Risk factors include age, low education level, smoking, alcohol abuse, decreased cognitive activity, lack of physical activity, reduced social interaction, stroke, depression, traumatic brain injury, hearing loss, air pollution, cardiovascular metabolic risk factors, and a family history of dementia. Dementia is a complex clinical syndrome involving multiple mechanisms, including genetic, environmental, lifestyle, and pathophysiological factors. The key mechanisms include: 1. β-amyloid cascade

hypothesis, 2. tau protein pathology, 3. inflammation and immune mechanisms, 4. neurotransmitter imbalance, 5. vascular dementia (VaD), 6. genetic factors, and 7. environmental and lifestyle factors. Additionally, residing in a noisy environment for a long time may increase the risk of dementia. Furthermore, cardiovascular diseases and unhealthy lifestyles may also be associated with the onset of dementia.

Currently, our methods for evaluating cognitive impairment in the elderly include rapid screening scales and comprehensive assessment scales. Commonly used rapid screening scales include the Clock Drawing Test (CDT), the Mini-Cog, and the 8-Item Interview to Differentiate Aging and Dementia (AD8). Comprehensive assessment scales include the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog), the Clinical Dementia Rating (CDR), and the Activities of Daily Living (ADL) scale. The evaluation process includes general information collection, medical history collection, physical examination, rapid screening for cognitive impairment, comprehensive assessment for cognitive impairment, specific cognitive domain function assessment (optional), Activities of Daily Living (ADL) assessment, and evaluation of Behavioral and Psychological Symptoms of Dementia (BPSD). This process helps to consider the individual's medical history, physical examination, and auxiliary examination results comprehensively in order to make a clinical diagnosis and develop subsequent intervention and follow-up plans.

The diagnosis of dementia involves the assessment of clinical symptoms, including blood tests, cerebrospinal fluid analysis, neuroimaging (such as MRI or CT scans), and other necessary laboratory tests to exclude other conditions that may cause cognitive impairment. With the increasing elderly population in our country, the diagnosis and treatment of cognitive impairment in the elderly are particularly important.

The treatment of dementia is a comprehensive management process that includes drug therapy, non-drug therapy, and psychosocial support. Currently, there are four FDA-approved drugs for improving clinical symptoms of Alzheimer's disease (AD), including cholinesterase inhibitors (such as donepezil, rivastigmine, galantamine) and N-methyl-D-aspartate receptor antagonists (such as memantine). These drugs can improve cognitive function, enhance daily living abilities, and overall clinical changes, but memantine may be a more suitable choice for moderate to severe AD patients. In addition, the new drug Lecanemab, as an anti-amyloid beta protein drug, has been launched in China, providing a new treatment option for early-stage AD patients by clearing toxic Aβ proteins in the brain to reverse the pathological progression of AD. Non-pharmacological interventions (NPIs) play an important role in dementia treatment, including cognitive training, exercise, sensory stimulation therapy, non-invasive brain stimulation, multi-component therapy, etc. Cognitive training can be done with paper and pen or computer assistance, aiming to improve performance in specific cognitive domains. Exercise such as Tai Chi, yoga, qigong, traditional

Chinese exercises, has been shown to improve cognitive function in MCI patients. Additionally, mindfulness meditation therapy, cognitive training, and physical exercise are also considered beneficial for preclinical AD patients. Psychological support and counseling for dementia patients are very important. Cognitive behavioral therapy (CBT) and other psychological therapy methods may have a small positive impact on depression, quality of life, and daily living activities in dementia or mild cognitive impairment (MCI) patients.

The field of neural modulation technology is developing rapidly in the medical field. It regulates the nervous system through physical or chemical means to improve patients' neural function and quality of life. As research on elderly cognitive disorders progresses, neural modulation technology has shown potential in improving cognitive function in the elderly. Currently, the treatment options for Alzheimer's disease (AD) are limited, with limited effectiveness and often accompanied by side effects. Therefore, neural modulation technology, as an emerging treatment method, is highly anticipated. Neural modulation technology includes non-invasive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), as well as invasive deep brain stimulation (DBS), optogenetic stimulation, and others.

Transcranial magnetic stimulation (TMS), transcranial direct current stimulation(tDCS) and transcranial alternating current stimulation(tACS) regulate the activity and excitability of cortical neurons by changing the membrane potential of nerve

cells. Clinical studies have shown that these three non-invasive methods can to some extent improve cognitive impairments in AD patients. However, due to low spatial precision and varying effect sizes, the optimal stimulation target areas, parameters, and patterns of these two methods have not been unified. Transcranial magnetic stimulation (TMS) is a non-invasive neuroregulation technique that modulates neuronal excitability by applying rapidly changing magnetic fields to the brain cortex through the scalp. TMS has shown potential effects in the treatment of age-related cognitive impairments, especially in Alzheimer's disease (AD) and other related disorders. TMS can also modulate brain networks associated with cognitive functions, such as the default mode network (DMN) and the executive control network (ECN). By improving the functional connections of these networks, TMS helps enhance cognitive functions. Additionally, TMS therapy can increase the levels of brain-derived neurotrophic factor (BDNF), which plays a crucial role in neuroplasticity and memory formation. By elevating BDNF levels, TMS may help protect neurons from damage and promote their repair.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that modulates cortical excitability by applying weak direct current through electrodes on the scalp, thereby influencing cognitive functions. Studies have shown that tDCS can improve cognitive functions in AD patients, including memory, attention, and executive functions. Anodal tDCS is typically used to increase cortical excitability, while cathodal tDCS is used to decrease cortical excitability. In

this way, tDCS can enhance neuroplasticity in the brain, promote the formation of new neural networks, and improve cognitive functions. tDCS is considered a safe treatment with minimal side effects. Any discomfort during treatment, such as mild headaches or scalp sensations, is usually temporary. Besides its potential in improving cognitive functions, tDCS has been found to effectively reduce the incidence of postoperative delirium in elderly patients, suggesting an important role for tDCS in perioperative management of elderly patients.

Transcranial alternating current stimulation (tACS) is a non-invasive neurostimulation technique that involves applying alternating current to target brain areas through electrodes placed on the scalp, modulating endogenous brain oscillations to influence cognitive functions. tACS can impact neural oscillations in the brain by specific frequencies of electrical current, thereby improving cognitive functions, especially in the gamma frequency range (30-80 Hz), with particularly significant effects observed at 40 Hz. In the treatment of age-related cognitive dysfunction, tACS has shown promising potential. Studies have indicated that tACS can enhance cognitive functions by modulating oscillatory activities in the brain cortex, promoting local or long-range synchronization within cortical networks. For instance, 40 Hz tACS can enhance visual and auditory perception, memory, as well as fluid intelligence in healthy individuals, and in populations with cognitive impairments such as mild cognitive impairment (MCI) and Alzheimer's disease (AD), tACS can improve memory and cognitive functions of patients.

Deep brain stimulation improves cognitive function in AD

patients by modulating neural circuits associated with cognition. Optogenetic stimulation, on the other hand, precisely regulates the activity of specific neurons and neural circuits through genetic and optical means. These two innovative approaches provide a theoretical basis for identifying the pathogenic mechanisms of cognitive impairments in AD and therapeutic targets.

The future development of neural modulation technology will be more personalized, precise, and intelligent. With the advancement of medical technology and the elucidation of neural network mechanisms in brain functional disorders, neural modulation technology will continue to develop, providing new ideas and methods for the treatment of elderly cognitive impairment. Furthermore, neural modulation technology is not only a therapeutic approach, but also an important tool for researching disease mechanisms, helping to deepen our understanding of the regulatory physiology and pathology of the brain. Neural modulation technology has shown great potential and application prospects in the treatment and research of elderly cognitive impairment. With the continuous advancement of technology and a deeper understanding of the cognitive control mechanisms of the brain, there may be more neural modulation methods developed in the future to help elderly individuals improve cognitive function and enhance their quality of life.