REVIEW ARTICLE

# Perspectives for future research on cognitive rehabilitation

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**Abstract**

Rehabilitation techniques are developed in line with the progress of medical science. The usefulness of rehabilitation for patients undergoing treatment in intensive care units (ICUs), where strict physical management is required, has been widely recognized, and rehabilitation services are now provided by professionals from the very early stage even in ICU. Rehabilitation in the past was mainly positioned as the tertiary prevention, and activities in the recovery process from diseases and disabilities were the main focus of rehabilitation service. Recentry, the importance of rehabilitation in the community as well as in hospitals and facilities has been pointed out. With the aging of society, the proportion of elderly people in the world is rising, and the number of dementia patients is increasing accordingly. In Japan, too, the National Dementia Policy has been formulated, focusing on "prevention and coexistence" of dementia, and the establishment of a comprehensive community care system is urgently needed. Originally, rehabilitation is a process of working with the subject to restore the subject's dysfunctions, and the subject's proactive effort is the key of the success or failure of the rehabilitation. In order for rehabilitation services to be effective, it is necessary for the subject to understand the significance of rehabilitation, to recognize its necessity, and to take the initiative. In the development of rehabilitation for hyperacute patients and rehabilitation for prevention, techniques to understand the cognitive function and to promote the subject's independent efforts will be required. Although cognitive rehabilitation is a relatively new term, the number of articles on cognitive rehabilitation retrieved from PubMed has increased rapidly since 2005, and an interest in cognitive rehabilitation has been growing. This paper summarizes the concept of cognitive rehabilitation and suggests what goals should be pursued in research. In addition, after introducing the authors' previous research works, an overview of cognitive rehabilitation research in the world will be reviewed. Finally, the authors propose a research agenda that we consider to be important.

***Key words:*** *Cognitive rehabilitation, cognitive function, dementia, cognitive reserve, cognitive behavioral therapy*

## IMPORTANCE AND USEFULNESS OF EARLY REHABILITATION

Recent advances in medical technology have made it possible to save critically ill patients, and the survival rate and long-term prognosis from serious illnesses have improved. However, an increase in the number of saved patients means that more will be left with long-term complications and functional disability. It is well known that poor general health is a factor that leads to significant disability and the need for long-term rehabilitation (De Jonghe, 2007; Herridge, 2003; Schweickert, 2007). In critically ill patients, neuropsychiatric disorders as well as physical disabilities are often observed. Intensive care unit (ICU) delirium has been reported in many patients treated in the ICU, and delirium has also been reported to be associated with increased severity of the primary illness (Ely, 2004) and prolonged hospital stay (Ely, 2008).

It is known that restoration of the awakening rhythm by systematic interruption of sedative administration (Schweickert, 2008) and maintenance of physical exercise by physiotherapy (Bailey, 2007; Thomsen, 2008) are helpful in improving the prognosis of patients admitted to the ICU. In fact, it is possible to start physiotherapy services after the fourth day of ventilator introduction, and several reports have shown that this intervension improves prognosis of the ICU patients (Angus, 2001; Bailey, 2007).

In 2009, the results of a randomized controlled study of the effects of early intervention with physical

and occupational therapy were reported (Schweickert, 2009) comparing a group of 104 patients admitted to the ICU within 3 days of induction of a ventilator at two university hospitals in the United States who received exercise and physical activity interventions by physical and occupational therapists with a control group reported a clear effect of early rehabilitation. Of the 104 patients in the study, 29 (59%) in the intervention group and 19 (35%) in the control group were discharged from the hospital with the ability to live independently, but the number of days spent in hospital before discharge was significantly shorter in the intervention group (Figure 1). It was also reported that significantly more patients in the intervention group returned to independent living, and that the degree of improvement was higher in many ADL items (Figure 2).

The report that the onset of delirium was suppressed in the intervention group and that the number of days on the ventilator was reduced further indicates that early introduction of rehabilitation is safe, suppresses the onset of delirium, and reduces the number of days in the hospital, even for patients who are on ventilators in the ICU. Based on this report, the importance and necessity of early rehabilitation for hospitalized patients has been shared by medical professionals, and innovations in early rehabilitation have been made.

However, it is not clear whether all the current rehabilitation professionals are capable of such early intervention. It goes without saying that rehabilitation for hyperacute patients requires ingenuity because it is difficult to obtain voluntary cooperation from patients.

## COMPREHENSIVE COMMUNITY CARE AND REHABILITATION FOR PEOPLE WITH DEMENTIA

The number of dementia patients in Japan is rapidly increasing due to the elongation in life expectancy and the growing elderly population. The prevalence of dementia among the elderly aged 65 years and over in 2020 is estimated to be 16.7%, which means that one in six elderly people, or 6.02 million people, have dementia. The increase in the number of dementia patients is a major social issue, and in developed countries, society as a whole is taking action, such as the National Dementia Strategy in the United Kingdom and the National Alzheimer's Plan in the United States. In Japan as well, the "National Dementia Strategy" has been formulated with the aim of realizing a society in which people with dementia can continue to live in their own way in a good local environment as long as possible. In addition, a comprehensive community care system is being developed to support elderly people to live in their own com-

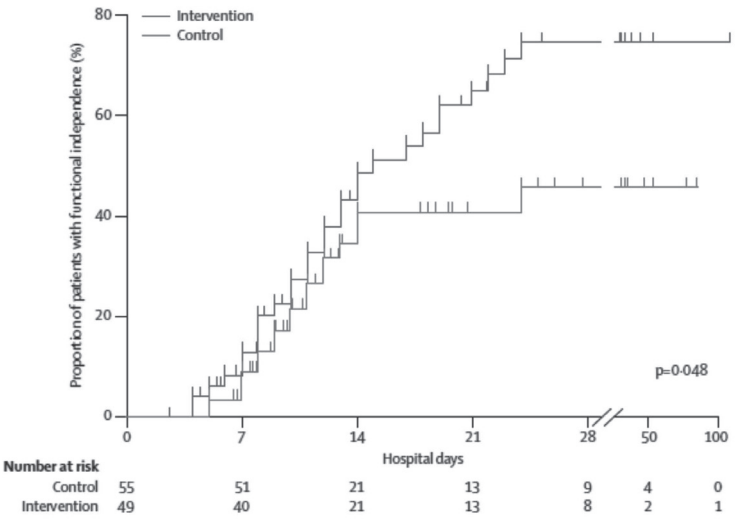


**Figure 1.** Probability of return to independent functional status in intervention and control group.
From Schweickert WD, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet, 373,1874–1882, 2009

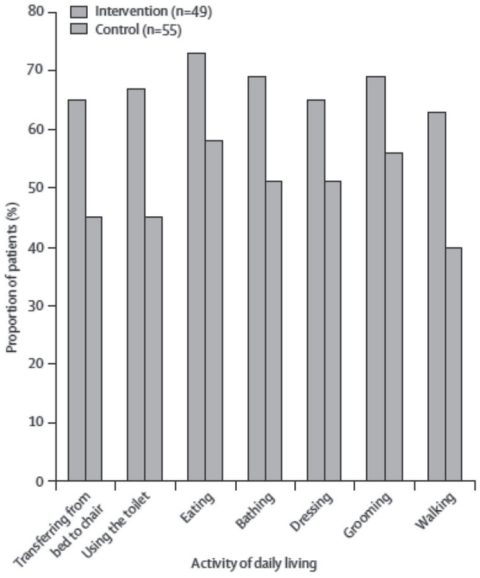


**Figure 2.** Proportion of patients able to perform activities of daily living and to walk independently at hospital discharge.
From Schweickert WD, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet, 373,1874–1882, 2009

munities even if they have dementia. Rehabilitation specialists are now required to provide rehabilitation services to people with dementia and their families who live in the community.

Rehabilitation professionals working in the community are strongly required to enhance rehabilitation services for people with dementia and their families. It goes without saying that the willingness of the rehabilitation subject to proactively participate in the therapeutic intervention is important in rehabilitation to begin with, and rehabilitation professionals are required to have a "heart that accompanies the subject" and to increase the subject's willingness to participate in rehabilitation therapy. Considering that rehabilitation is an intervention technique that aims to change behavior in an effective direction, rehabilitation services for dementia patients require more advanced techniques than those for those without cognitive dysfunction.

## INCREASING INTEREST IN COGNITIVE REHABILITATION

Recently, the possibility of rehabilitation techniques for brain functions, in other words, rehabilitation techniques for cognitive functions, has been studied. A search for the term "cognitive rehabilitation" in the PubMed database shows that the number of articles on cognitive rehabilitation has increased rapidly since 2005, and the number of papers will exceed 5,000 per year by 2020 (Figure 3).

## CONCEPT OF COGNITIVE REHABILITATION

The term "cognitive rehabilitation" has been not yet fully recognized by society, but here we explain our thoughts on the term "cognitive rehabilitation research," We believe that cognitive rehabilitation research is effective for devising and improving new rehabilitation techniques, and that it is the most necessary research topic in the rehabilitation field in near future. The authors propose that cognitive rehabilitation research has the following three implications.

(1) Rehabilitation of brain functions

Firstly, it has the meaning of rehabilitation to improve the cognitive function. In the field of physical therapy, rehabilitation has been divided into motor disorders, internal disorders, and others according to the target organ of rehabilitation. In addition, rehabilitation of brain functions has come to be considered necessary, and the mental and psychological division of the Japan Physical Therapists Association has been active in this field. In this area, an academic society named "Cognitive Rehabilitation Study Group" is already active. However, the cognitive rehabilitation research that the authors are considering encompasses rehabilitation of cognitive functions but has even greater implications, including the following meanings as described below.

(2) Rehabilitation for people with dementia

The term "cognitive rehabilitation" is often associated with dementia and rehabilitation. We would like to consider how rehabilitation services should be provided to people with cognitive impairment throughout the life cycle, and it is true that the most common target of rehabilitation services is dementia in the elderly. As a direct goal of rehabilitation services, it is a major objective to develop knowledge and skills for effective rehabilitation of people with dementia. Rehabilitation professionals (physical, occupational, and

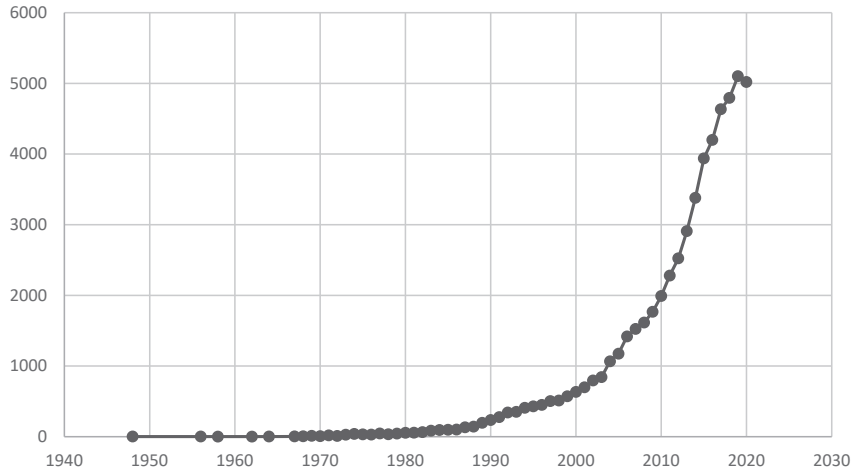


**Figure 3.** Number of articles found in PubMed database for cognitive rehabilitation.

speech therapists) are expected to provide services to people with dementia as shown in the diagram (Figure 4).

In the course of the research involved with pathogenesis of dementia, the authors have pointed out the importance of the concept of cognitive reserve.

Amyloid deposition, neurofibrillary changes, and neuronal loss are thought to be the basic pathology of Alzheimer's disease, but they are also expressions of brain aging observed in the brains of healthy elderly people, although not in as large a quantity as in Alzheimer's disease. In fact, it is known that some individuals with Alzheimer's disease pathology detected by postmortem brain examination did not show cognitive decline before death, and that amyloid deposition and neurofibrillary changes do not correlate completely with cognitive decline. Thus, the "cognitive reserve" hypothesis has been proposed, which acts to maintain cognitive function by antagonizing the pathological process of Alzheimer's disease and the aging process of the brain. In this sense, intervention to maintain and increase cognitive reserve is highly relevant to cognitive rehabilitation for people with dementia.

(3) Cognitive-behavioral therapy (behavior change through improvement of cognitive function)

As a goal of rehabilitation, it is required to devise theories and techniques to foster the subject's awareness and motivation toward rehabilitation and to maximize the effectiveness of rehabilitation. For this purpose, it is thought to be effective to work on the cognitive functions of the subject and to promote behavioral change in the subject. Cognitive therapy or cognitive-behavioral therapy has been established in the clinical practice of psychiatry and psychosomatic medicine to correct cognitive distortions and lead to behavioral change. However, little attempt has been made to utilize cognitive-mediated behavioral change in rehabilitation. The aim of the "Cognitive Rehabilitation Research" is to improve the effectiveness of rehabilitation by examining the cognitive function of the subject, and to develop effective rehabilitation techniques through behavioral change via improvement of cognitive function.

As shown in Figure 5, "cognitive rehabilitation research" is a term with triple meanings. It is not yet widely recognized, but we hope to make it widely known to society in the future.

The practical aims of cognitive rehabilitation research can be summarized as follows.

(1) To understand the mechanism and pathophysiology of cognitive function

Cognitive function is an important brain function that defines human behavior, and is often divided into the following categories: attention, executive function, memory and learning, language function, perceptual-motor function, and social cognition. Cognitive dysfunction can be caused by a variety of disorders and diseases throughout infancy, childhood, adolescence, young adulthood, adulthood, early old age, and old age. It is hoped that by deepening our understanding of the pathophysiology of cognitive dysfunction caused by various causes and its impact on social functioning throughout the life cycle, we can develop rehabilitation techniques that can provide effective rehabilitation services for people with a variety of cognitive dysfunction. It is expected to develop rehabilitation techniques that can consider how to provide effective rehabilitation services for subjects with various cognitive impairments.

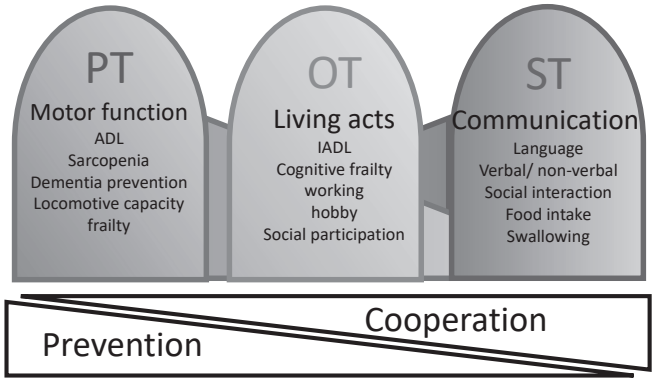


**Figure 4.** Rehabilitation Service to people and family with dementia by physical therapis t(PT), occupational therapist (OT), and speech therapist (ST).

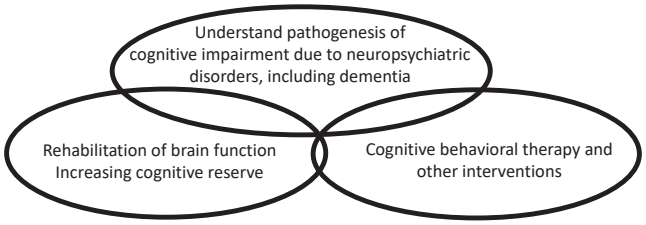


**Figure 5.** Conceptual diagram of "Cognitive Rehabilitation Research."

(2) To acquire the latest scientific knowledge on dementia patients

The rate of brain weight loss increases after the age of 60 years, and by the age of 100 years, brain weight is reduced by about 20% compared to the younger age even in healthy individuals. Among the cerebral cortex, the frontal and temporal lobes show the greatest atrophy, and the age-related brain atrophy is different by brain area. The cortical density decreases early in the regions where myelinization ends early, while the gray matter density decreases slowly in the regions where myelinization continues late, such as the frontal and parietal lobes. These age-related changes in brain morphology result in changes in brain function. Information processing speed, declarative memory, short-term memory, and working memory decline with age, whereas semantic memory continues to increase without declining with age. The episodic memory among the declarative memory declines with age, while the semantic memory and the nondeclarative memories such as priming and procedural memory do not decline significantly with age.

Dementia is a disease in which a specific part of the cerebrum is damaged, not the whole brain. Considering these points, dementia is a disease in which memory impairment and cognitive dysfunction result in impaired judgment and impairment of social life functions. In other words, dementia is an extremely social disease, and psychological and sociological perspectives are important in addition to biological perspectives in dealing with it. In addition to the biological perspective, the psychological and sociological perspectives are also important in dealing with dementia. The latest knowledge of functional brain imaging, cellular biochemistry, and molecular genetics regarding cognitive decline in dementia will enable us to tackle cognitive rehabilitation.

(3) To elucidate the biological basis of cognitive reserve

Amyloid deposition, neurofibrillary changes, and neuronal loss are considered to be the basic pathology of Alzheimer's disease, but they are also expressions of brain aging that are observed in the brains of healthy elderly people, although not in as large a quantity as in Alzheimer's disease. In fact, it is known that some individuals with Alzheimer's disease pathology detected by postmortem brain imaging did not show cognitive decline before death. It is also known that amyloid deposition and neurofibrillary changes may not correlate with cognitive decline, and the "cognitive reserve (CR)" hypothesis has been proposed as an explanation for the discrepancy between pathological findings and cognitive function (Scarmeas, 2003; Stern, 2003).

The concept of brain reserve (BR) has long been used to understand the level of cognitive and life functions in children with intellectual disabilities. It was thought that a certain level of development in cognitive and life functions could be expected with appropriate training and nurturing, but that the degree of development was determined by brain reserve, which depended on brain size, number of neurons, and number of synapses. By developing this passive concept of brain reserve, "cognitive reserve" in the elderly has been proposed, and active effects defined by neural networks, types of neural circuits involved, and neural circuits to be newly mobilized have been considered (Stern, 2020).

Cognitive reserve is the ability to maintain cognitive functions by antagonizing the aging and pathological processes of the brain and is considered to be an action that intervenes between pathology and clinical symptoms in the brain to maintain cognitive functions. Cognitive reserve is thought to be influenced by psychosocial factors such as intelligence (IQ), educational background, work, hobbies, and social participation (Nucci, 2012), but the biological basis of cognitive reserve has not been fully elucidated.

Cognitive decline of the elderly usually progresses slowly with age. People with high cognitive reserve can resist the pathological process to some extent and protect their functional decline, but once functional decline begins, it progresses rapidly. People with high cognitive reserve have a longer time to develop dementia than those with low reserve, but the rate of cognitive decline after the onset of dementia is faster. In other words, cognitive reserve can delay the onset of cognitive decline.

Older people are highly individualistic. Although we are all born as similar babies, we experience different families, education, and work throughout our lives, and individual differences increase as a result of various biological, psychological, and social factors in old age. Given this diversity of the elderly, it is not sufficient to simply categorize the elderly into two groups: normal or ill. Dementia is a representative of unsuccessful aging, and the actual elderly are positioned somewhere on the spectrum from "unsuccessful aging" to "successful aging." Successful aging has been proposed as a term to describe desirable older adults in such a spectrum (Butler, 1974). A hierarchical model has been proposed to

describe the requirements for successful aging, which include (a) physical health, (b) normal cognitive function, (c) life satisfaction (well-being), and (d) social activities. (a) Physical health is the absence of physical diseases and is considered to be the most basic requirement. In addition, (b) cognitive function is an important requirement for people to lead a social life, and it is necessary to have a healthy mind and body and to maintain cognitive function in order to achieve (c) life satisfaction and wellbeing, and (d) social activities and social productivity (Figure 6).

However, recent studies have shown that there is an interrelationship between (b) normal cognitive function, (c) life satisfaction (wellbeing), and (d) social activity and social productivity. (c) Life satisfaction (wellbeing), and (d) social activity and social productivity are interrelated, and the hierarchical structure is not necessarily simple. It has been shown that experiencing life satisfaction helps to maintain cognitive function, and furthermore, that participating in society and continuing social activities are important for maintaining cognitive function. Taking these points into account, the left side of Figure 6 shows the old model.

As shown on the right of Figure 6, it is better to consider that cognitive function, life satisfaction, and social activities influence each other (Takeda, 2020). From this perspective, life satisfaction and participation in social activities, which enable successful aging, can be considered as one of the factors that enhance cognitive reserve. The concept of cognitive reserve is proposed from the viewpoint that maintaining sufficient cognitive reserve may help maintain cognitive function even in the presence of Alzheimer's pathology, and the idea is to foster sufficient reserve and use it to prevent dementia by improving lifestyles.

(4) Preventive Rehabilitation Practice and Research Initiatives

To extend healthy life expectancy, physical therapists play a major role in disease prevention, recurrence prevention, and care prevention in cooperation with related professions. Physical therapists are expected to develop preventive physical therapy in clinical and community rehabilitation. The practice of such preventive rehabilitation requires the technique of behavioral change through intervention on cognitive functions.

Occupational therapists are expected to focus on assisted-living activities that help primary prevention of dementia by preventing social isolation of the elderly by improving life functions and promoting human interaction and social participation in the community.

Speech-language pathologists are expected to contribute to the prevention of dementia by preventing social isolation through the use of rehabilitation to improve and maintain the communication function of the elderly, and to contribute to the prevention of aspiration pneumonia through the use of rehabilitation techniques that help maintain and improve the swallowing and chewing function of the elderly.

(5) Community rehabilitation for primary and secondary prevention

In the future, rehabilitation professionals are required to promote rehabilitation activities for local residents in collaboration with local governments, while responding to new medical, nursing, and welfare systems. Rehabilitation professionals who can provide community rehabilitation services with a broad perspective are needed, so that they can always be aware of the broad perspective of community rehabilitation and the structures of community physical therapy, community occupational therapy, and commu-

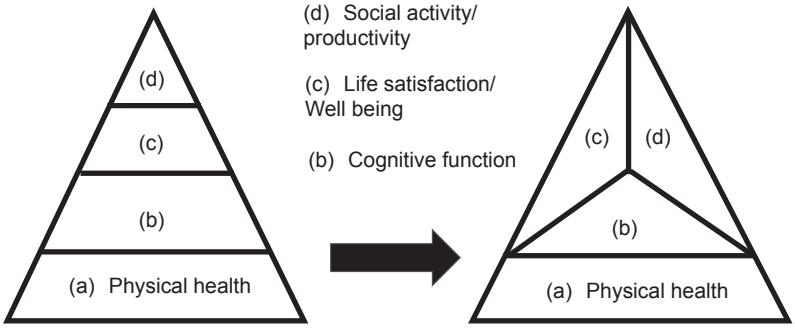


**Figure 6.** Interrelationship among cognitive function, well-being, and social activity
Above (a) physical health, which is a *sine qua non* for (b), (c), and (d).

nity speech and hearing therapy within that context. In addition, through these studies, research activities are needed to lay the foundation for thinking and acting on what kind of system will benefit the public and what kind of effective services will be provided in the new medical and nursing care system.

## RESEARCH EXPERIENCE

### Pain and Movement Disorders

Imai has been engaged in the study of postoperative pain since he was a graduate student. Recently, he has devised a new evaluation method because of the problems of evaluation in the acute postoperative period. The tools that clinicians commonly use to predict the risk for chronic pain include the numeric rating scale (NRS) and the Visual Analogue Scale (VAS). One risk factor for chronic post-surgical pain (CPSP) is pain that persists for longer than 1 month (Lovich-Sapola, 2015), and, pain intensity after surgery in acute phase are determined as a red flags for CPSP (Althaus, 2012). However, Chapman et al. revealed that VAS and NRS scores show a high degree of variability among patients, making it extremely difficult to predict the prognosis of a case with only a single point of pain intensity. (Chapman, 2011). Moreover, the NRS and VAS are too imprecise to characterize an individual patient's postoperative pain meaningfully at a specific date (e.g., 1, 3, or 5 days post-surgery). In fact, looking at the changes in pain at rest and pain during exercise over time in 57 postoperative patients with distal radius fractures that we evaluated, it is clear that there is a large degree of variability (Imai, 2020a). As a solution to these problems, Chapman (2011) fit the values of pain intensity during the first 6 days after surgery to a linear function (X-axis: days, Y-axis: pain NRS) and calculated the slope (= degree of pain improvement) and intercept (= initial postoperative pain intensity) obtained from the function. Using this method, we measured the pain intensity of patients after total knee arthroplasty (TKA) and calculated the slope and intercept. As a result, it was clarified that this pain trajectory predicted the pain intensity one year after surgery (Imai, 2021). Furthermore, a decision tree analysis was performed, and the probability of developing CPSP at 1 year after surgery was 33.3% when the slope was 2.8 or higher. When age, slope and intercept were combined, the probability of developing CPSP at 1 year postoperatively was 36% if the slope was between -9.5 and 2.8 and the age was 77 years or older. The results of this study indicate that the combination of VAS and age at 1 week after surgery can predict CPSP at 1 year after surgery, which may be a clinically useful method.

The Tampa Scale for Kinesiophobia (TSK) and the Fear-Avoidance Beliefs Questionnaire (FABQ) have traditionally been used to assess fear of movement (Knapik, 2011; Waddell, 1993). Fear of exercise is more frequently used as a clinical assessment than pain intensity, because fear of movement leads to poor motor performance. However, in the acute phase, fear of movement has not been assessed objectively and quantitatively. Therefore, we investigated the possibility of objectively quantifying fear of movement by capturing the movements for patients in the acute phase after surgery (Imai, 2018). A video camera was used to record the flexion and extension movements of the fingers of postoperative patients with distal radius fractures. The recorded images were divided into frames, and the number of frames at the time when the speed reached zero (maximum extension and maximum flexion) was measured. The evaluation was conducted on 1, 3, 5, 7, 14, 21, and 30 days after surgery. As a result, we observed that the point at which the speed became zero, i.e., the time to switch movements, improved (shortened) over time. We defined this phenomenon as "movement hesitation." We found a significant difference in exercise hesitation time on the day after surgery and a significant difference in exercise speed one week after surgery between patients with poor and good improvement after distal radius fracture surgery (Imai, 2020b).

### Cognitive dysfunction in mental disorders

Inoue has been studying cognitive dysfunction in patients with schizophrenia. Cognitive dysfunction (attention, memory, processing speed, etc.) is a core symptom of schizophrenia along with positive symptoms and negative symptoms. The severity of cognitive dysfunction in patients with schizophrenia ranges from -1.0 to -1.5 standard deviations compared to healthy controls, which is less than moderate severity (Reichenberg ,2007, 2010). In addition, cognitive impairment is most closely related to the ability to work and social functioning of patients with schizophrenia (Green, 2004), and it has been reported that cognitive impairment at baseline explains 50% of social functioning as a factor affecting the ability to live in society at 9 months in patients with first-episode schizophrenia (Nuechterlein, 2011). With regard to the incidence of cognitive impairment in schizophrenia, a comparison of pre-onset IQ by JART25 and post-onset full IQ by WAIS-III in 456 patients revealed a mean difference of 16.3, with 69.3% of patients decreasing

10 points or more (Fujino, 2016).

Cognitive remediation therapy (CRT) is expected to be a treatment for such cognitive dysfunction in schizophrenia. The effect size of CRT for schizophrenia on cognitive dysfunction was about 0.45 in meta-analysis of 39 studies in a randomized design (Wykes ,2011). As described above, the effect size of CRT on the severity of cognitive dysfunction in schizophrenia is still insufficient, and improvements are still needed in the therapy.

Electrophysiological indices are useful as indicators to judge the effects of cognitive rehabilitation. Electroencephalography (EEG) and magnetoencephalography (MEG) have higher temporal resolution than fMRI and SPECT and can evaluate minute changes in neural activity. The P300 component elicited by the auditory oddball task, which is one of the event-related potentials (EEG), reflects selective attention and has been found to be weaker in schizophrenic patients than in normal subjects (Doege, 2009). In addition, neural synchrony, which contributes to memorization and recollection in working memory tasks, is reduced in schizophrenia (Zhao, 2011).

CRT using PC-based cognitive tasks for schizophrenia improves performance on neuropsychological tests, which are desk-based behavioral tests, but little improvement has been observed in electrophysiological indices such as those described above. We are currently testing the effect of CRT using the event-related potentials.

There is growing interest in CRT that address cognitive dysfunction at lower levels of perception. In particular, the amount of improvement in cognitive function by auditory-perceptual training was very large (+0.86), and that such auditory-perceptual training caused changes in the EEG and magnetoencephalogram of patients with schizophrenia (Fisher, 2009; Kariofills, 2014). In addition, covariance structure analysis suggests that auditory perceptual processing ability is associated with event-related potentials and explains neurocognitive functioning, negative symptoms, and social life functioning (Thomas, 2016). Therefore, it may be necessary to combine interventions at lower levels, such as auditory-perceptual training, with other intervention techniques, such as PC tasks, in order to increase the effectiveness of cognitive rehabilitation.

**Changes in EEG and autonomic nervous system function by occupational therapy**

Shiraiwa is conducting a study on “Changes in electroencephalography and cardiac autonomic function during craft activities: experimental evidence for the effectiveness of occupational therapy”. Occupational therapy often uses craft activities as therapeutic tools, but their therapeutic effectiveness has not yet been adequately demonstrated. The aim of his study was to examine changes in frontal-midline theta (Fmθ) rhythms and autonomic nervous responses during craft activities and to explore the physiological mechanisms underlying the therapeutic effect of occupational therapy. To achieve this, he employed a simple craft activity as a task to induce Fmθ and performed simultaneous EEG and ECG recordings. Twenty-eight healthy volunteers participated in this study. Of these, nine participants (three males and six females; age range = 20–25 years, $M$ = 22.4, $SD$ = 1.6) who clearly showed Fmθ during the task were included in the analysis. Nine participants exhibited Fmθ while performing the task. Fmθ was defined as a rhythmic waveform measured at a frequency of 5-7 Hz that lasted more than 1 s and had a maximum focal distribution near the frontal midline of the EEG (Ishihara,1972). In this study, theta waves lasting more than 1 second were also selected. For cardiac autonomic function, the R-R interval (RRI) was recorded and the Cardiac Vagal Index (CVI), an index of the parasympathetic nervous system, and the Cardiac Sympathetic Index (CSI), an index of the sympathetic nervous system, were calculated using the Lorenz plot method (Toichi, 1997). The mean RRI values were also calculated. The experiment consisted of a 3-minute resting condition followed by a 7-minute manual handling condition. Corresponding t-tests were performed on the CSI, CVI, and RRI mean values in the resting and Fmθ conditions. Correlation analysis was also performed for the number of occurrences of Fmθ and power values with CSI, CVI, and their respective changes in each period. Both parasympathetic and sympathetic indices increased with the appearance of Fmθ compared to during resting conditions, and RRI mean values were not significantly different compared to the resting condition. Correlation analysis showed that the power value of Fmθ was positively correlated ($r$ = 0.78) with the amount of change in CSI, and the number of Fmθ appearances was positively correlated with CVI in the resting condition ($r$ = 0.76) and CVI in the manual handicraft condition ($r$ = 0.82).

Although an increase in CSI is usually associated with a decrease in the mean RRI value, the mean RRI value did not change in this study. These results indicate that a state of relaxation equivalent to that at rest is achieved during craft activities. In addition, the increase in CVI buffered the effect on CSI, resulting

in no change in the mean RRI value. This suggests that an appropriate level of concentration to perform manual activities can result in a state of physical relaxation comparable to that at rest. Furthermore, the appearance of Fmθ was positively correlated with parasympathetic activity, and theta-band activity in the frontal region was associated with sympathetic activity; the current source of Fmθ is the anterior cingulate gyrus cortex (Ishii, 1999), and regulation of autonomic function is also believed to use this network via the anterior cingulate cortex (Critchley, 2004). This suggests that there is a close relationship between cardiac autonomic function and Fmθ activity. The results of the present study confirm that concentrating on craft activities produces a relaxed state, and provide one of the evidences for the effectiveness of occupational therapy using handicrafts.

**Incompleteness and reliability of eyewitness memory**

Matsuo conducts research in an area of eyewitness memory. Eyewitness memory plays an important role in the police investigations, and it is critical to obtain as many accurate memories as possible. However, memory is so fragile that can be contaminated by various factors such as repetition of memory recollection and information received after witnessing an event (post-event information). One of the techniques to obtain many accurate memories is Cognitive Interview (CI) (Geiselman, 1984). There are four techniques in the CI: mental reconstruction of context, report everything, recollection in a different order, and recollection from another person's point of view. A number of studies has shown that the effectiveness of the CI that eyewitnesses can recall more memory when they receive the CI compared to an ordinary interview (e.g., Geiselman, 1986). A meta-analysis of 55 studies showed that accurate memory increased 40% and inaccurate memory also increased 61% (e.g., Köhnken, 1999).

Although the CI is an effective method and it has been introduced in the police around the world, there are concerns about the time and human costs. For example, the police usually interview eyewitnesses some time after witnessing an incidence; therefore, they may forget and receive some post-event information, which may result in fewer and contaminated memories being recalled. Human costs include the investigators to find the good eyewitnesses and the training of conducting the CI. In particular, when a major incident or accident occurs, those costs would be significant due to the large number of eyewitnesses.

In order to solve such problems, a new method has been developed based on the technique of the CI. Self-Administered Interview© (SAI©) is a paper-and-pencil questionnaire that eyewitnesses are able to report by themselves in writing according to the instructions written in the questionnaire (Gabbert, 2009). By distributing the SAI to eyewitnesses at the scene of an incident or accident, investigators can save a great deal of time and manpower by allowing witnesses to report what they have seen at their own pace. The SAI begins with a mental reconstruction of the context followed by seven sections: recollection about (A) the entire event, (B) the person, (C) the scene, (D) other witnesses, (E) the car or vehicle, (F) the degree of witnessing, and (G) other information. In the section C, eyewitnesses are asked to draw pictures of the scene, which is one of the features of the SAI. The SAI is effective for recollection of more memory (Gabbert, 2009), memory retention (Hope, 2014) compared to free-recall. The SAI is also effective to prevent the memory contamination by post-event information (Paterson, 2015).

Matsuo (2017) developed the Japanese version of the SAI and investigated the effects of the Japanese SAI as well as reporting method of sketching. Participants watched a video and recalled their memory through the SAI, the CI, or free recall (writing) immediately or one week after watching the video. The results revealed the main effect of time that the correct memories were significantly more recalled in the immediately condition than one week condition. There was also a main effect of the recall method that the SAI obtained more accurate memories than the CI and free recall. However, when the memories reported in the sketch section was excluded, there was no significant difference in the recall methods. In addition, the SAI was significantly more likely than the other two groups to obtain inaccurate memories, and these results were similar with those conducted in the original English version. The results suggested that the Japanese version of the SAI is as effective as the original version on memory recollection and that sketching is an effective method to recall eyewitness memories.

Although several studies demonstrated that the SAI promoted memory recollection and retention, it is unknown the mechanism of such effects in the SAI. Another study examined whether the effects of the SAI was due to the instruction in the SAI or the reporting method (handwriting). After watching the video, participants recalled their memory through the

SAI-writing, SAI-speaking, or free recall (speaking) (Time 1). In the SAI-speaking condition, participants were given the instruction printed in the SAI verbally and reported their memory verbally. All participants returned to the experiment about one week later and reported the content of the video verbally again (Time 2). The result showed that the SAI-writing condition recalled significantly more correct memories than the other two conditions, and the SAI-speaking condition recalled significantly more correct memories than the free recall condition in Time 1. In Time 2, the SAI-writing condition recalled significantly more correct memories than the other two conditions, and there was no significant difference between the SAI-speaking and free recall conditions. Moreover, there were no differences among the three conditions on the accuracy rate. The results suggested that both the method of handwriting and instructions in the SAI were effective on the recollection of eyewitness memories, and the method of handwriting contributed to the retention of eyewitness memories. The results on the accuracy rate suggested the possibility that increment of memory recollection does not necessarily deteriorate the quality of memory.

## SOME CURRENT RESEARCH TOPICS ON COGNITIVE REHABILITATION

Cognitive rehabilitation is defined as “a systematic series of treatment techniques aimed at improving cognitive function” by the American Congress of Rehabilitation Medicine, and its treatment measures are categorized as: (1) reconstruction of behaviors patterns learned in the past. (2) construction of new cognitive patterns to supplement the damaged nervous system, (3) construction of new neural activity patterns that can use external aids and environmental support, and (4) adaptation to self-cognitive impairment to improve various aspects of life and improve quality of life (Cicerone, 2005).

### Stroke and traumatic brain injury

Looking back at the history of cognitive rehabilitation, the first targeted subjects were stroke or traumatic brain injury patients. The cognitive areas selected for cognitive rehabilitation were mostly attention, executive function, memory, and social function. The Ministry of Health, Labor and Welfare of Japan, depicted four domains of cognition (attention disorders, executive dysfunctions, memory disorders, and social behavior disorders) as the major domains for higher brain dysfunction, often observed with stroke or cerebral trauma patients.

In stroke or traumatic brain injury, the area of injury or damaged brain area by disorder is limited, and damage to specific neural circuits can be assumed. In addition, the damaged site can be identified by a brain imaging such as MRI or CT, and the damaged neural circuit can be identified by a brain functional imaging such as fMRI or NIRS. In stroke or traumatic brain injury patients, brain function other than the injured area is regarded to be normally maintained, and neurorehabilitation to the injured area has been applied to restore motor and cognitive function.

Neurorehabilitation based on findings from neuroscience is actively applied as an attempt to improve motor and cognitive functions. Synaptic transmission efficiency is not fixed but dynamic. Synaptic activity repels and interacts with other synaptic inputs resulting in dynamic changes. In other words, synaptic connections change in an activity-dependent manner, which is the physiological basis of motor or cognitive learning. Transcranial electrical stimulation (tES) including transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) are introduced as non-invasive brain stimulation methods, combined with rehabilitation to increase synergistic synaptic plasticity. The effect of rTMS on nerve activity differs depending on the stimulation frequency. The frequency 5 Hz or higher increases synaptic activity, whereas low frequency below l Hz suppresses it. For patients with synaptic disorders, it is necessary to increase the neural activity of the site that compensates for the disorder function. An approach of applying high-frequency rTMS to the cerebral hemisphere containing the functional compensation site is often combined with application of inhibitory low-frequency rTMS to the contralateral cerebral hemisphere. The latter attenuates the interhemispheric inhibition from the stimulated cerebral hemisphere to the function-compensating site and indirectly activates the function-compensating site by releasing it from the interhemispheric inhibition. The non-invasive brain stimulation is often used in the field of cognitive rehabilitation.

In addition, many types of computer-based cognitive rehabilitation programs have come to be used. Virtual reality has been shown an effective rehabilitation tool for stroke patients. The Elements system with customized surface computing and tangible interfaces is shown to have therapeutic effects on upper limb and cognitive function after brain trauma. Stroke patients (21 adults; 42-94 years old) in the subacute phase were randomized to receive 4 weeks

of virtual rehabilitation with Elements system (three 30-40 minutes sessions per week) plus usual care (conventional occupational and physical therapy) or usual care alone. Upper extremity skills, cognitive function, and participation in daily life were assessed before and one month after the training. Rates of recovery were two- to three-fold higher than in the control group, and there was a better transition to daily motor, cognitive, and communicative behaviors. (Rogers, 2019).

On the other hand, neurofeedback therapy (NFT) using physiological parameters of brain activity such as EEG has also been incorporated into cognitive rehabilitation. NFT is widely applied as a measure of cognitive rehabilitation for stroke patients. A number of studies found improvements in participants' cognitive impairments after the treatment. but due to the limited quality of the studies and strength of the evidence, the conclusions regarding the effectiveness of NFT cannot be generalized to a larger number of stroke patients. Further research to strengthen methodological quality and study design is needed aiming for the standardized NFT protocols to understand the dose-response relationship between NFT and improved functional outcomes (Renton, 2017).

Effectiveness of various intervention measures aiming for cognitive rehabilitation of stroke or traumatic brain injury patients can be summarized as below.

Direct training that stimulates attention function is effective for attention disorders themselves. In addition, time pressure management for attention disorders is useful. (When the information processing speed is slow, a device to secure sufficient time) is also effective.

Goal management training is effective in training with guidance that enables "planning and structuring" in order to realize the intended behavior for executive dysfunction.

Utilization of compensatory means for memory impairment has high evidence for the effectiveness of training and errorless learning.

Cognitive behavioral therapy and social skill training are effective for social behavioral disorders. In recent years, the effect of Positive Behavior Supports, which induces positive behavior in response to events and environments that precede problem behaviors, is reported.

Comprehensive / Milieu-oriented / Multi-professional / Holistic approach is regarded effective in improving physical disability, cognitive disability, social behavioral disability, financial problems, schooling/ working problems, etc. while the social environment is important in which the patient is placed. On the other hand, the effect has been established in a rehabilitation system in which multiple occupations provide holistic and comprehensive support.

**Parkinson's disease and neurodegenerative disorders**

Cognitive rehabilitation techniques have come to be applied to neurodegenerative diseases including Parkinson's disease and Alzheimer's disease. Parkinson's disease, in particular, was initially thought to be a movement disorder mainly consisting of extrapyramidal symptoms, such as muscle rigidity, tremor, and rigidity. In recent years, various non-motor symptoms such as cognitive, emotional, and autonomic symptoms have attracted attention. Many Parkinson's disease patients exhibit cognitive dysfunction at the same time or even before the onset of motor dysfunction. Parkinson's disease is caused by neurodegeneration of dopaminergic neurons in the basal ganglia, localized to the substantia nigra striatum.

In a meta-analysis of articles reporting the results of RCTs on the efficacy of cognitive rehabilitation for Perkinson's disease, cognitive impairment was the most common symptom targeted in patients with Parkinson's disease. Thirteen articles reported the results of RCTs on cognitive rehabilitation for Parkinson's disease, 6 articles on cognitive function by cognitive rehabilitation, 2 articles on brain morphology by MRI, and 5 articles on long-term effects on cognitive function over 6-12 months were reviewed, which all demonstrated the positive results (Díez-Cirarda, 2018).

In 2021, a study was reported on the long-term effects of cognitive training in patients with Parkinson's disease. Sixty-four Parkinson's disease-MCI patients were assigned to a cognitive training group (*n*=33) or a regular exercise therapy group (n=31) for a 6-week, twice-weekly, 90-minute intervention, and cognitive function was assessed 1 year later. Verbal and nonverbal memory improved after 6 months, but the significant difference disappeared after 12 months, indicating that there was a certain improvement in memory function but no effect on executive function (Schmidt, 2021).

One of the locomotor symptoms in Parkinson's disease patients is the tendency to fall. A report examined whether the effects of trunk balance training on 53 patients with Parkinson's disease in stages 2-3 of the Hoehen-Yahr classification were affected by cognitive reserve as examined by CRIq. It was reported that the improvement in balance ability was greater in

the elderly, and that the improvement in balance ability was greater in those with lower cognitive reserve (Piccinini, 2018).

The meta-analysis on effectiveness of music-based interventions is reported with stroke and Parkinson's disease patients. Music-based intervention was categorized into 1) instrumental-based intervention studies (*n*=10), 2) listening-based intervention study (*n*=1), 3) rhythm-based intervention study (*n*=3), walking and arm exercises were performed to music, and 4) multi-factor-based intervention study (*n*=5), listening, singing, playing, and moving were combined. This review concludes that there are certain effects of music-based interventions, although no effect size calculations or meta-analyses have been conducted due to the wide range of differences between studies (Mounmdjian, 2017).

Impairments in motor-cognitive dual-tasking (e.g., walking while talking) are common in people with neurological disorders, and the effects of motor-cognitive dual-task training (DTT) on mobility and cognition in people with neurological disorders compared with usual care have been reviewed. There were 14 studies reporting the effect of DTT including gait or balance outcomes. The subjects were brain injury, Parkinson's disease, and Alzheimer's disease patients. Intervention protocols included cued walking, cognitive tasks combined with gait, balance, and strength training, and virtual reality and games. DTT improved single-task walking speed and stride length in Parkinson's disease, and Alzheimer's disease, and dual-task walking in Parkinson's disease, Alzheimer's disease, and brain injury. Speed and stride length improved in Parkinson's disease and Alzheimer's disease. This review states that improvements in dual-task ability in neurologically impaired individuals may lead to improvements in gait, balance, and cognition, and that motor-cognitive dual-task deficits in neurologically impaired individuals may be amenable to training (Fritz, 2015).

**Alzheimer's disease and dementia**

We are practicing various rehabilitation techniques to dementia patients in clinical and caring settings. In many cases, the goals of rehabilitation to dementia people are to delay the progression of dementia and to suppress the newly onset of symptoms rather than the cure itself.

(a) Music therapy with relaxing effect

Music is an effective memory of information. A mood or nostalgic music recalls past memories with relaxation effect. In addition to melody, music requires understanding of singing voice and lyrics. Effective rehabilitation for dementia requires physical function and thinking ability, and a state in which one can confidently perform them. In that sense, music therapy is also very effective in regaining the memory and cognition of the brain and the resulting calmness of the mind.

(b) Animal therapy, opening heart with contact

Animal therapy (animal-assisted therapy) is often used for dementia care settings which may stimulate self-confidence, family trust, or reducing anxiety by contacting with animals.

Pet animals are fundamentally open to humans and have an unconditional attachment. This peculiar property of pet animals allows patients to remember their desire to take care of others and the self-confidence they need.

(c) Horticultural therapy

Horticultural therapy developed as a means of rehabilitation and introduced in Japan in the early 1980s, mainly for the purpose of functional recovery training in elderly care facilities. Horticultural therapy is suitable for elderly dementia people with some effect in six areas: acquisition of association, maintenance of sociality, maintenance of living ability, calmness and improvement of motivation, however with little scientific evidence.

Although the usefulness of horticultural therapy for cognitive function has not been confirmed, it is highly expected to be effective to strengthen well-being in community-dwelling elderly people.

(d) Reminiscence therapy, slowing down the progression of memory loss

Reminiscence therapy is a part of reality orientation, based on the principle "memories of the distant past are hard to lose." The subjects are asked to talk personal stories, from childhood to school, stories of hardships, friends, and fun. The idea is to present the patient with a hint of memory, such as an album, a movie poster, a picture, or a photo, and talk with them.

(e) Occupational therapy, rehabilitating comfortably in your daily life

For brain dysfunction, behavior therapy is often implemented, which is effective for "conversing normally with people" and "getting motivated and peaceful spirit and vitality on a daily basis." Light tasks such as handicrafts, calligraphy, or solving puzzles with fingertips that require light cognitive function can be chosen. For adults, cooking, washing, and cleaning are more routine. It will be a training to reconstruct the order of such basic work in the brain again.

**Elderly people in community**

Based on these experiences, the effectiveness of cognitive rehabilitation for patients with Alzheimer's disease and dementia people in community was investigated. The following findings are available regarding the usefulness of exercise and music therapy.

Exercise that targets modifiable risk factors and neuroprotective mechanisms can slow normal age-related cognitive decline and protect against changes associated with neurodegenerative diseases such as Alzheimer's disease and other dementias. Based on the role of exercise in neuroprotection and cognitive function, implementing exercise programs is beneficial for older adults. Evidence from both animal and human studies indicates that exercise improves brain metabolism, structure, and function and plays a role in maintaining cognitive function in older adults. Results from observational studies support a neuroprotective relationship between physical exercise and cognitive function in older adults. Some clinical trials of exercise interventions have shown a positive effect of exercise on cognitive performance, while other trials have shown little or no effect. Although further research is needed, physical exercise interventions aimed at improving brain health through neuroprotective mechanisms hold promise for maintaining cognitive function (Kirk-Sanchez, 2013).

A review study of the cognitive, emotional, and neurological effects of free musical activities in the daily lives of patients and their caregivers, including healthy older adults, found that active musical activities, such as playing a musical instrument or singing in a chorus, were more effective than passive musical activities, such as listening to music In a study of healthy older adults. Studies in healthy elderly people have shown that choral singing and playing musical instruments can improve short-term QOL and reduce anxiety and depression. In stroke patients, singing has been shown to facilitate verbal expression in patients with aphasia and to increase intelligibility in patients with dysarthria. In Parkinson's disease patients, it has been reported that choral singing reduced their sense of social isolation. Furthermore, in patients with dementia, singing rather than listening to music has been shown to enhance working memory and reduce stress in both patients and caregivers (Särkämö, 2018).

## PROPOSAL OF RESEARCH PROTOCOL

**Purpose**

Dementia is considered to be the most malignant disease of the 21st century due to the number of patients, duration of the disease, and severity of the disability. The Japanese Government has announced the National Dementia Strategy with the aim of realizing a society in which people with dementia can continue to live their own lives in their local environment as long as possible. The basic concepts of the policy are "prevention" and "coexistence", and the aim is to delay the onset of dementia and to create a society in which people with dementia can live their daily lives with hope.

The "prevention" does not mean preventing the onset of dementia, but delaying the onset of dementia. Strategies are required to select individuals at high risk of developing dementia and to delay the onset

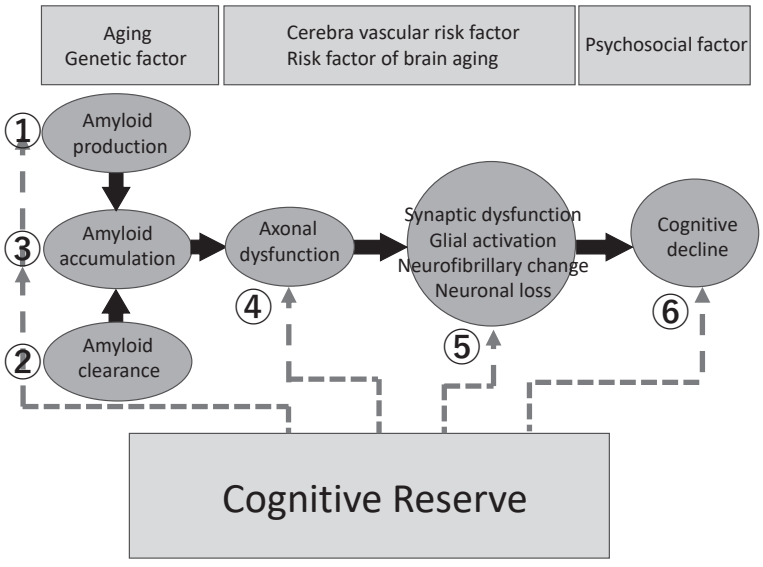


**Figure 7.** Alzheimer pathological process and cognitive reserve.

of dementia as long as possible. We have been involved with research to delay the onset of dementia and have pointed out the importance of enhancing cognitive reserve. Cognitive reserve is the ability to maintain cognitive function against aging and pathological processes in the brain, which can be identified between brain pathology and clinical symptoms to maintain cognitive function. However, the biological basis of cognitive reserve has not been elucidated. We speculate the biological processes (4), (5), and/or (6) in Figure 7 are the most closely related to cognitive reserve, and the core questions of this study are to clarify which of (4), (5), and/ or (6) defines cognitive reserve and to develop a program to prevent cognitive decline by increasing the cognitive reserve.

**Characteristics of cognitive reserve and implementation of new technology**

Cognitive decline in the elderly progresses slowly with age. People with high cognitive reserve are able to resist pathological processes and protect themselves from functional decline to some extent, but once functional decline begins, cognitive function declines more rapidly than those with lower cognitive reserve. As shown in Figure 8, people with high cognitive reserve are able to maintain cognitive function even after pathology accumulates to some extent, and the period until the onset of dementia is longer. However, it is also known that once dementia develops, it progresses more rapidly in people with higher cognitive reserve than those with lower cognitive reserve.

We have shown that enhancing cognitive reserve may reduce the decline in brain function, but we have not yet proposed a program to improve cognitive function. In this study, we assess the cognitive reserve of community-dwelling elderly people and conduct an intervention program for the groups with high and low cognitive reserve.

The cognitive decline in each group will be assessed using biomarkers corresponding to each process of (4), (5), and (6) in Figure 7; neurofilament L (nf-L) by Simoa for (4), peripheral blood apolipoprotein E (ApoE), apolipoproteinA1 (ApoA1), complement C3, and transthyretin (TTY) for (5), and analysis of verbal response digital information by dialogue with AI Avatar (Figure 9) for (6).

First, the cognitive reserve of elderly people living in the community is assessed using the cognitive reserve assessment table Ver3.2, and a six-month intervention program is provided according to the cognitive reserve of the subject. Along with the evaluation of cognitive functions, the point of transition from stage (1)-(2) to stage (2)-(3) in Figure 10 can be accurately identified by analyzing data on voice, language, and facial expressions through dialogue with avatars on a PC using AI.

The main feature of this study is that the group with high cognitive reserve antagonizes cognitive decline until a certain period of time, but when the threshold is exceeded, the rate of cognitive decline is greater in the group with high cognitive reserve than in the group with low cognitive reserve. For this purpose, we measure neurofilament L (nf-L), which is discharged when a neural axon fiber collapses, to accurately determine the point (2) in each group. For this purpose, we will measure neurofilament L (nf-L), which is discharged when nerve axon fibers disintegrate. We will use a new technique to quantify nf-L levels in peripheral blood using Single Molecule Assay (Simoa) technology (Quantex), which has recently become available.

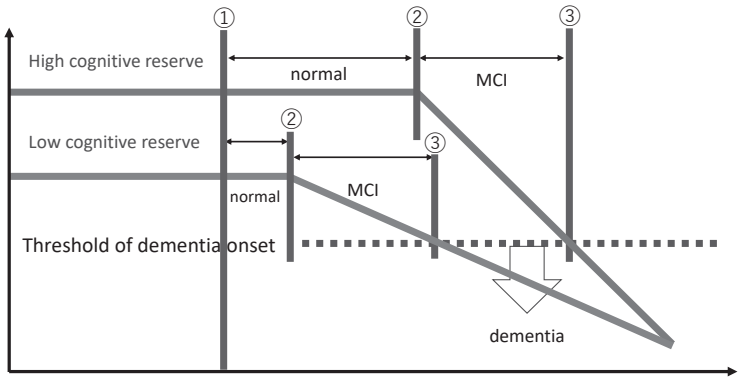


**Figure 8.** Course of Cognitive decline with subjects of high and low cognitive reserve.
① the time of entry to the project
② the time of mild cognitive impairment (MCI) onset
③ the time of dementia onset

**Figure 9.** A subject is talking to Avatar on PC.

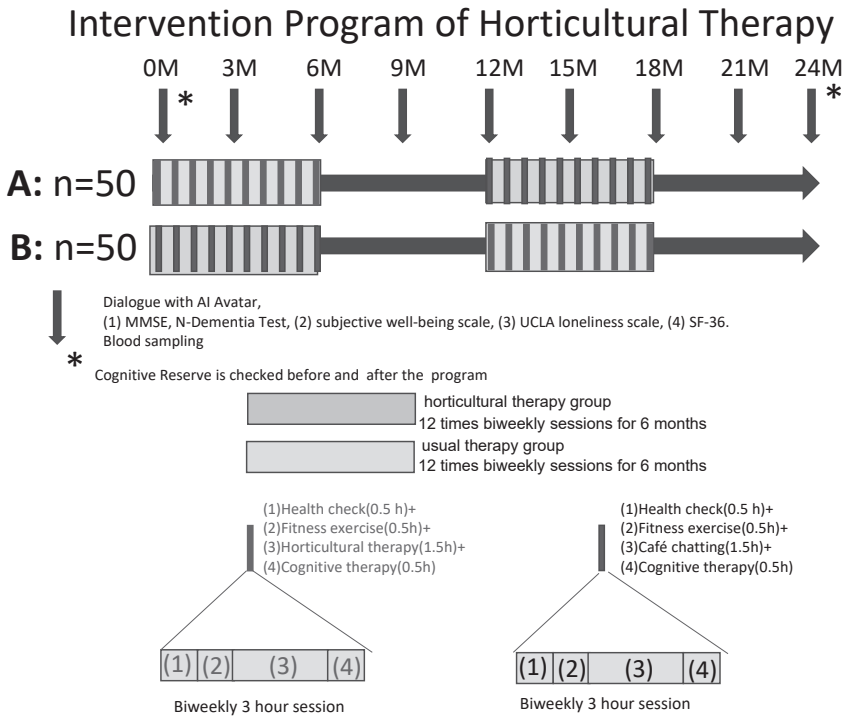


**Figure 10.** Protocol of horticultural therapy intervention.

**Intervention program**

This study is a two-year longitudinal intervention study in which about 120 participants are recruited once a year. At the time of participation and after the completion of the study, the cognitive reserve of the participants will be assessed by the cognitive reserve assessment scale Ver. 3.2 developed by our university. Participants will be assessed at 3-month intervals by interacting with AI Avatar, as well as by blood sampling and various scales. As shown in Figure 10 participants are evaluated by providing digital information of voice, language, and facial expression through the dialogue with avatars on the PC.

Participants chose either horticultural therapy or café talk and participated in a total of 12 biweekly programs over a 6-month period. Each program is divided into two groups: Group A: health check (30 minutes) - fitness exercise (30 minutes) - horticultural therapy (1 hour) - cognitive behavioral therapy (45 minutes), and Group B: health check (30 minutes) - fitness exercise (30 minutes) - café talk (1 hour) - cognitive behavioral therapy (45 minutes). Those who participate in the second year will be assigned to a group other than the one they chose in the first year. Since horticultural therapy can be divided into a six-step process of goal setting, planning, work, harvesting, evaluation, and planning for the next time, and the complexity of each process can be adjusted, in this study, the participants were divided into 20 participants in the high group, 20 participants in the medium group, and 20 participants in the low group according to their cognitive reserve. The main feature of this study is to adjust the complexity of the horticultural therapy. In addition, the cognitive-behavioral therapy conducted at the end of each session is conducted for each 20 participants classified according to the height of their cognitive reserve regarding the problems, issues, and improvements in the implementation of horticultural therapy each time.

Participants in either group will be asked to interact with AI Avatar and have blood drawn every 3 months, and will be assessed before, 3, and 6 months after the intervention on (1) cognitive function tests (MMSE and N-Dementia Test), (2) subjective well-being scale, (3) UCLA loneliness scale, and (4) QOL scale using the Japanese version of SF-36.

**Why the research protocol should be implemented now**

For the past six years, we have collaborated with the city of Kaizuka, where the university is located, to hold the "Tsugesan Health Check for Mind and Body" at three community halls in the city, and have conducted health promotion activities for about 100 elderly people living in the community every year. We are building a new research building with the Frontier

Rehabilitation Center on the first floor currently under construction. This will allow us to conduct more research than we have done in the past and to conduct intervention studies for the prevention of dementia.

The Finger study, a representative longitudinal intervention study, has shown that health checks, exercise, and cognitive training as a whole can help prevent dementia (Kivipelto, 2018), but unfortunately, the Finger study did not identify which specific interventions are the most effective.

On the other hand, horticultural therapy has been widely implemented in Japan and abroad for various diseases and disorders including dementia and psychiatric disorders. Although the empirical benefits of horticultural therapy have been recognized, there is no scientific evidence on its mechanism. Relaxation, a sense of accomplishment, and collaborative work have been pointed out as suggesting the usefulness of horticultural therapy, but few studies have presented evidence based on the findings of brain science.

This study aims to clarify the usefulness of horticultural therapy by assessing the degree of cognitive reserve and changes in biomarkers (nf-L in plasma) using digitally phenotyped data of "voice, words, and facial expressions" of question and answer in dialogue with AI-based avatars. It is highly original and may provide scientific evidence for horticultural therapy interventions.

Assuming the participation of approximately 120 community-dwelling elderly people per year (240 people in total over 2 years), and after assessing their cognitive reserve, we will conduct an intervention study twice a month for 6 months to determine the usefulness of horticultural therapy with different levels of complexity for high, medium, and low cognitive reserve groups. The purpose of this study is to identify which older adults with which cognitive reserve are most likely to benefit from the intervention and at what time of the year.

The specific objectives of this study are (1) to assess cognitive function in the elderly and identify the beginning point of mild cognitive impairment (MCI) through machine learning of digital information of voice, language, and facial expression by interacting with AI avatars, (2) to determine biological factors that define cognitive reserve by identifying trends in cognitive function and biomarkers, (3) to test whether intervention effects of horticultural therapy differ according to differences in cognitive reserve, and (4) to evaluate the effects of AI technology as new end-of-life interventions.

**Preparatory works for the research implementation**

In 2018, we have established the Research Center for Cognitive Reserve (Director: Masatoshi Takeda) and started research on cognitive reserve, and we launched an English- journal "Cognition & Rehabilitation" to present the results of our research in 2020. In April 2022, we will open the Frontier Rehabilitation Center (FRC) on the first floor of the new Graduate School building. Health-checking and rehabilitation equipment will be installed in there, and local residents will be able to visit the center on a regular basis for health promotion activities.

The university is located along the mountains in Kaizuka City and has been teaching horticultural therapy to students who will become rehabilitation professionals for the past 15 years in the "First Enable Garden" on the university grounds and the vast "Second Enable Garden" 10 minutes' walk from the university campus. Therefore, we chose horticultural therapy as the main intervention method.

We have been working at the Cognitive Reserve Research Center to develop a cognitive reserve assessment scale and to identify biological basis that determine cognitive reserve. In addition, our team has been in charge of a health checkup project for elderly people living in the community for six years. We are ready to tackle this project by utilizing their experience and data.

A characteristic of horticultural therapy is that the degree of difficulty and complexity can be adjusted according to the subject's ability, sense of accomplishment, and initiative, from appreciating seasonal flowers and plants to growing crops for maximum harvest. Since a cognitive-behavioral therapy approach is assumed to be useful for modifying and improving behaviors that utilize such complex cognitive functions, research collaborator Professor Nobuo Oshima of Tokyo Metropolitan University is preparing to apply cognitive-behavioral therapy, which has been used in the rehabilitation field, to the elderly.

Professor Nakamura and Dr. Tanaka of Nara Institute of Technology have proposed a technology for early detection of dementia using a dialogue system in which the voice, words, and facial expressions of an elderly person's question and answer are input as digital phenotyping data, and a machine learning model is constructed by inputting images and neuropsychological test data at the same time. They propose a technology for early detection of dementia using a dialogue system. Kitamura (2015) have attempted to detect dementia through interactive ques-

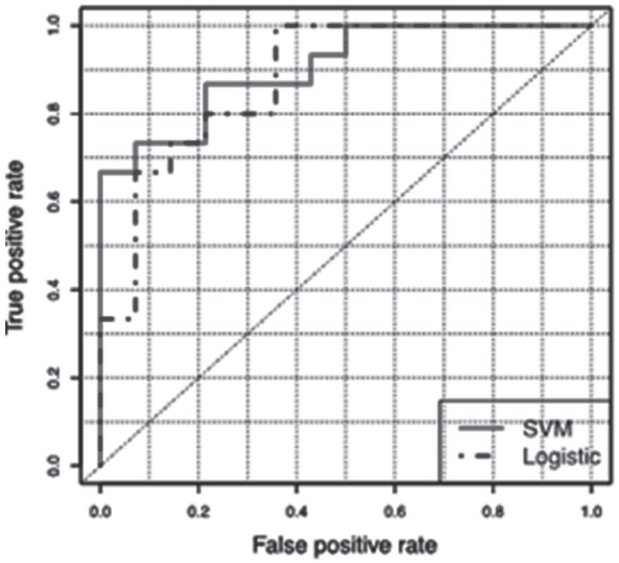


**Figure 11.** ROC curve of dementia discrimination (AUC: 0.9).

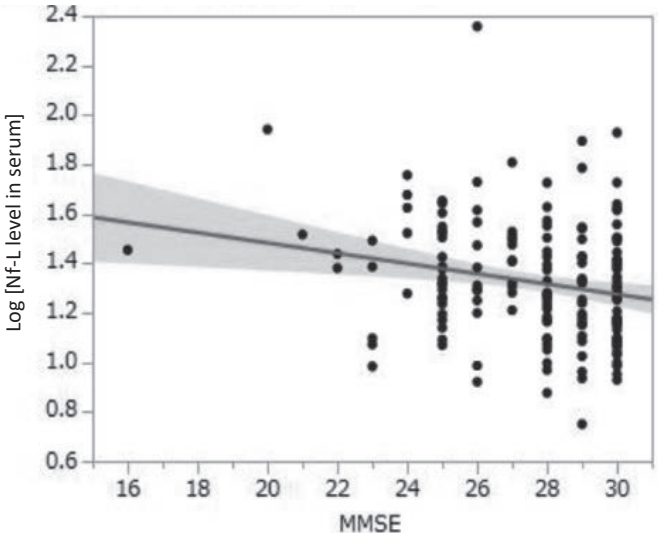


**Figure 12.** Serum level of Nf-L measured by Simoa and MMSE score.

tion and answer sessions between Avatar and elderly people, and reported that they could distinguish dementia from non-dementia with a probability of more than 90% by building a machine learning model from the recorded question and answer sessions of elderly people (Figure 11). They have developed a system that makes it possible to identify signs of cognitive decline by continuing conversations with avatars on a daily basis (Tanaka2017), and empirical results are expected in elderly people living in the community.

To investigate the biological basis determining cognitive reserve, we have typed and quantified apolipoprotein E4, a polymorphism in kinesin light chain 1 (KLC1vE), apolipoprotein A1, complement C3, and transthyretin. Nf-L is a small amount of cytoskeletal protein that is shed when nerve axon fibers disintegrate by neurodegeneration. The amount of Nf-L is so little and it was difficult to quantify in peripheral blood. However, the introduction of the Single Molecule Assay (Simoa) technology has made it possible to quantify Nf-L in peripheral blood. Professor Takashi Kudo and his colleagues at Osaka University conducted a pilot study and reported that the amount of Nf-L in plasma by Simoa technology showed a certain correlation with cognitive function, as shown in Figure 12

(This paper is the product of five times meetings among MT, KS, RI, TI, and KM once a month from May to September 2021)

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