REVIEW ARTICLE

Cognitive reserve and sex difference in vulnerability to Alzheimer disease

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Abstract
Cognitive reserve is a concept proposed to explain the gap between neuropathological findings and clinical phenotypes of cognitive impairment. Education, occupation and leisure activity can be proxy-based factors affecting cognitive reserve, which are difficult to quantify objectively. Recent development of *in vitro* study of structural and functional evaluation has led to more precise quantification of cognitive reserve by residual-based measures. Cognitive reserve might be useful in understanding the pathogenesis of age-related cognitive decline, including neurodegenerative dementia. This paper examines the meaning of cognitive reserve and brain reserve with the aim of resolving the question of the sex difference in the incidence of Alzheimer disease.

Key words: *Alzheimer disease, cognitive aging, cognitive reserve, gender difference, sex difference*

Introduction

Cognitive ageing is observed as a physiological change in elderly people. This physiological cognitive decline varies greatly among individuals owing to different life-long lifestyle factors including home-rearing, education, occupation, and social interaction. Differences in these life-long experiences may result in various levels of cognitive decline in the later life. Some older people may show significant cognitive decline in old age, which is considered pathological, and are diagnosed with dementia. Alzheimer disease (AD) accounts for 60%-70% of dementia in later life.

Dementia increases rapidly after the age of 65 years, and the prevalence of dementia almost doubles with each 6-year age increment thereafter. The reported prevalence rate is 7% at 75–59 years, 12% at 80–84 years, 20% at 85–89 years, and 40% at 90–94 years (Alzheimer's Disease International, 2015). Considering the more than 50% prevalence rate of dementia in people over the age of 100 years, any human being may develop dementia if he/she lives long enough.

Sex differences exist in relation to the onset of dementia; two-thirds of patients with AD in clinical settings are women. Even after adjustment for the longevity of women, the incidence of AD in women is still 1.4 times higher than that in men. Being a woman is the second largest risk factor for developing AD after age, but the reason for this sex difference is unclear.

One possible reason why women are more susceptible to AD may be the effects of female hormones. In fact, women with long secretion periods of female hormones (those with late menopause) are less likely to develop AD. Though estrogen replacement therapy has been tried as a treatment for AD, it is still unclear whether estrogen suppresses the development of AD because clinical trials of estrogen replacement therapy were stopped prematurely owing to the increased risk of developing cancer (Zec, 2002). Additionally, apolipoprotein E4 (ApoE4) is a well-known risk factor for AD (Roses, 1996), and its effect is thought larger in women, but this requires confirmation. With this background, we discuss the underlying mechanism of the higher risk of AD in women from the perspective of cognitive reserve (CR).

1. Age-related changes in the brain

Cognitive decline due to age-related changes in the brain is the first factor to play an important role in the onset of dementia. Generally, human cognitive function begins to decline after the age of 40, but some brain areas are more easily affected by ageing than others, showing differing vulnerability to ageing process. In psychology, intelligence is divided into two types: fluid intelligence, which has a large decline due to ageing, and crystalized intelligence, which has almost no decline due to ageing. Considering cognitive functions by functional region, there is signifi-

cant decline in attention, working memory, language reproduction, reasoning, ability to perform complex tasks, task switching, and reaction suppression with age, because they each depend on processing speed, processing amount, and synergistic cognitive processing (Harada, 2013; Park, 2002). However, cognitive functions, such as dictionary knowledge, so-called common sense, and vocabulary are more easily maintained (Baltes, 1993).

Looking at the changes in brain morphology due to ageing, the volume of the brain decreases after the age of 40. As for gray matter, the volume decrease with ageing is large in the hippocampus, the caudate nucleus, the globus pallidus, the prefrontal cortex and in other sites involved in cognitive function (Raz, 2005; Tamnes, 2013). Additionally, prefrontal white matter also decreases with age (Gunning-Dixon, 2009; Raz, 2005). These changes may cause decline in cognitive function due to the loss of functional connectivity of each part of the brain.

2. Pathological changes in the brain

The accumulation of pathological changes is a second factor causing rapid decline in cognitive function. For example, amyloid plaques, neurofibrillary tangles, and neuronal loss are regarded as hallmarks of AD, which accounts for 60%-70% of dementia in elderly people. Amyloid plaque is composed of a deposit of β-amyloid in the center and degenerative neurites around it. Neurofibrillary tangle is a polymerized form of excessively phosphorylated tau protein. Recent developments in biomarker technology have made it possible to search for accumulated amyloid and tau in the brain with positron emission tomography (PET) long before the clinical onset of AD reflecting AD pathology (Jack, 2013). Quantification of β-amyloid and (phosphorylated) tau in cerebrospinal fluid also show changes in biomarkers of preclinical AD individuals without any cognitive decline. Whether an individual with positive biomarkers should be considered to have a disease or not, with due consideration of the ethical implications, is a subject of wide debate (Dubois, 2016).

3. Continuity between physiological ageing and pathological changes in the brain

Physiological changes also increase with age, including spongiosis, deposition of lipofuscin, Hirano body, amyloid body, pseudo-calcification, and fibrosis. Although these changes increase with age, they do not directly lead to cognitive impairment. Changes with more pathological significance include neurofibrillary tangles, amyloid plaques, and Lewy bodies, but it should be noted that these characteristic pathological protein deposits affect elderly people in general, even those with normal cognitive function. Normal ageing to pathological ageing of the brain is a continuous change. A characteristic pathological change below a certain amount of threshold value does not therefore immediately indicate cognitive impairment, i.e., dementia. Even in healthy elderly people after sixty years of age, neurofibrillary tangles in the hippocampal CA1 region and amyloid plaques in the cerebral cortex are observed, and increase with age (Guillozet, 2003). This may explain the decline in cognitive function with ageing, but it should not be directly linked to diagnosis of dementia. Figure 1 shows the staging of neurofibrillary tangles in the brain reported by Braak & Braak (Braak, 1993). Stage 0 is the young brain, Stages I and II are normal elderly people in which neurofibrillary tangles are confined to the hippocampus and parahippocampal gyrus. The presence of those localized neurofibrillary tangles does not warrant diagnosis of dementia. When the distribution of neurofibrillary tangles extends beyond the parahippocampal gyrus to the medial temporal lobe and cerebral cortex, mild cognitive impairment and dementia are diagnosed (Figure 1).

4. Proposal of cognitive reserve (CR)

As described above, normal aging changes in the brain and AD pathological changes are continuous. Meanwhile, there is a period during which a subject positive for AD biomarkers shows normal cognitive function. The CR hypothesis has been proposed as a concept to explain the situation where the pathological findings do not match an individual's cognitive state (Stern, 2012). The underlying hypothesis is that some individuals with AD pathology may maintain cognitive function by driving a neural circuit against dysfunction caused by pathological findings. CR is the ability of individuals to antagonize the effects of pathological processes or those of the ageing process in order to maintain normal cognitive function.

CR is expected to antagonize the age-related or pathological changes in the brain, which may delay the onset of dementia. People with high CR are more resistant to the age-related changes and AD pathology than those with low CRs at the onset of symptoms of dementia. The rate of cognitive decline, however, of the people with high CR is faster than that of those with the low CR (Figure 2). How CR affects the entire course of dementia, i.e., mortality, is not

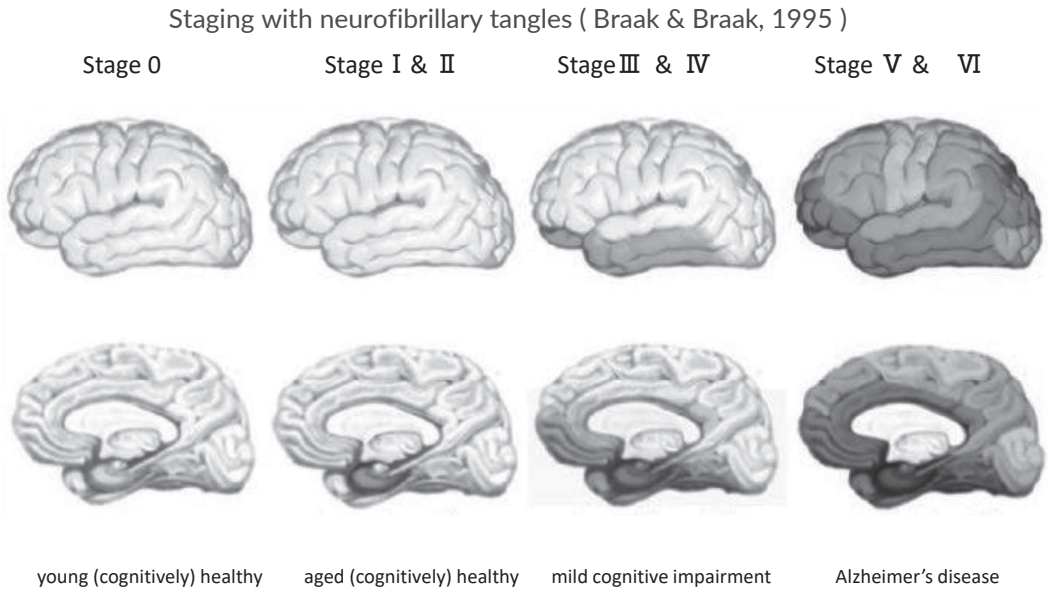


Figure 1. Braak & Braak stages of AD neuropathology based on the pattern of neurofibrillary change
Although clinic-pathological correlations were not made, Braak and Braak speculated that the entorhinal stage (I-II) represents clinically silent periods of the disease with neurofibrillary tangles involvement confined to trans-entorhinal layer pre-alpha. Limbic stages (III/IV) correspond with clinically incipient Alzheimer disease, and neurofibrillary tangles involvement of CA1, and neocortical stages (V/VI) represent fully developed Alzheimer disease, with neurofibrillary tangle involvement of all areas of association cortex.

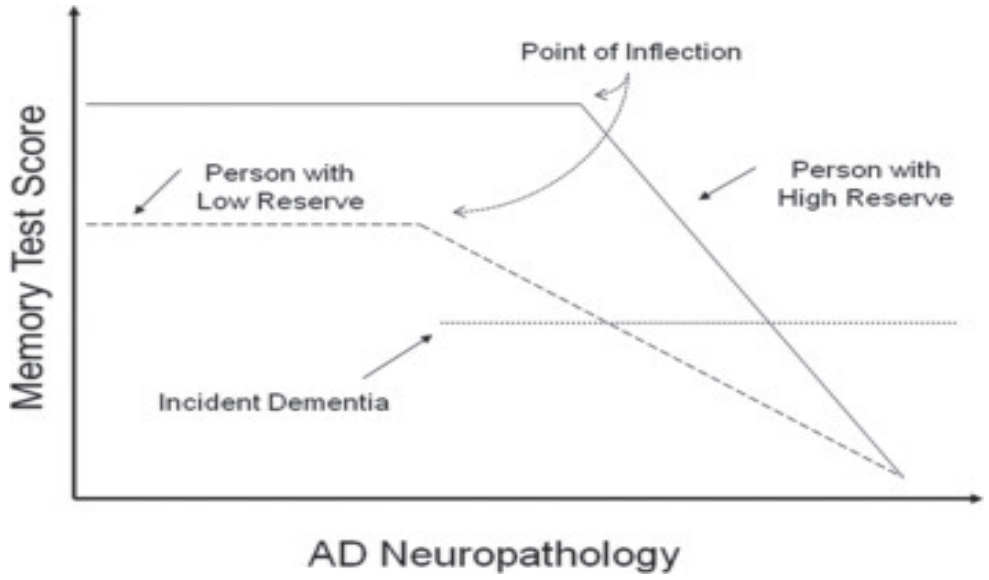


Figure 2. Cognitive reserve (CR) and cognitive decline

well understood (Bruandet, 2008; Qiu, 2001), but the entire course after the onset of dementia should be compressed. Considering the faster rate of cognitive decline, it is speculated that people with high CR may die earlier (Cheng, 2014). The extent to which high CR delays the onset of dementia is unclear. Delay of the onset for a year or two of the public prevalence of dementia is hypothesized to have significant effect in reducing the number of patients, which is just one of the reasons why research on CR is required.

5. Concept of cognitive reserve

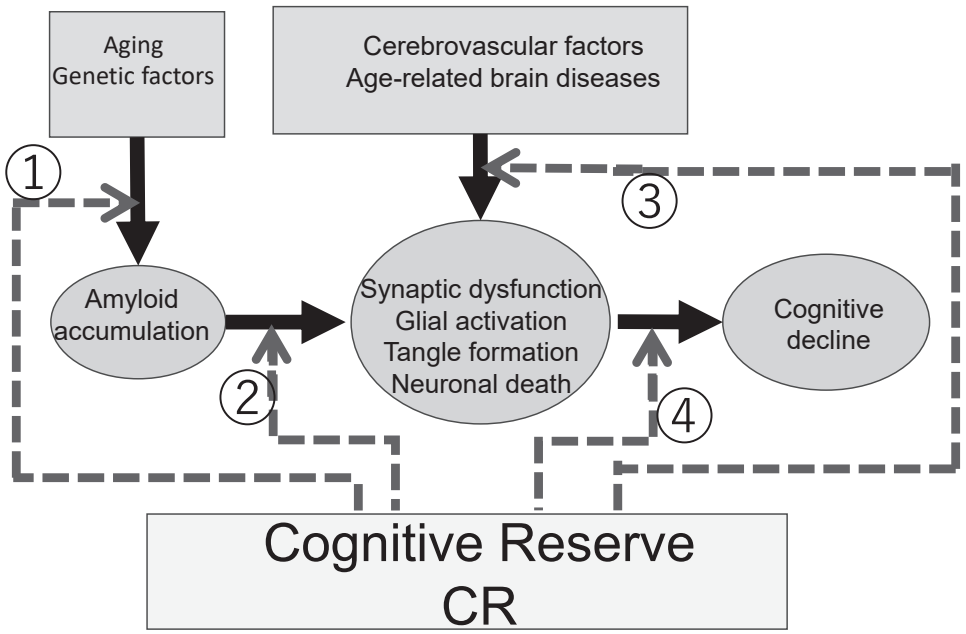
As discussed above, the greatest characteristic of elderly people is heterogeneity. People are in the relatively similar state when they are born as babies, but as they age, they live their lives experiencing a wide variety of different family, education, and work environments, and can have widely different biological and/or psychological influences throughout their lives. Individual differences in old age increase because of these different psychological and social fac-

tors. There are greater individual differences in mental and cognitive functions that are more susceptible to psychosocial factors than physical functions.

CR refers to the ability to maintain cognitive function by counteracting functional decline caused by brain ageing and AD pathology. The human brain can develop sufficient reserves through lifestyle. Cognitive decline in elderly people tends to begin when they are in their 40s and progresses slowly with age, but there are individual differences in the rate of decline. People with high CRs can to some extent resist pathological processes in the brain and prevent their functional decline. However, even a person with a high CR will rapidly decline in cognitive function once the decline begins. It is necessary to investigate which point(s) of the pathological process of AD are modified by CR (Figure 3).

6. The Nun Study: an example of CR

The Nun Study, a well-known cohort study, showed that written ability at a young age affects cognitive function after 60 years. The study partially answers the question of why some nuns did not develop dementia despite living in a similar environment as those that did, which explains an implication of the CR hypothesis. The results of the first Nun Study were reported in 1996. Cognitive function (ages 75–95) and autopsy brains (ages 75–95 at death) of 93 nuns were compared with their written ability at age 22, approximately 58 years before (Snowdon, 1996). Written ability was evaluated for idea density and grammatical complexity using the last ten sentences of an autobiographical statement of about 300 words per page written at the time of their admission to the monastery. The nuns who had low written ability when they were young were clearly shown to have had low cognitive function when they became elderly. The ideal density number had a higher effect than the grammar ability. Autopsy findings revealed 14 subjects with low conceptual density showed AD pathology, but no AD pathology in nuns with high conceptual density. Written ability early in life was thus found to be a predictor of cognitive impairment (onset of AD) in later life. The Nun Study has continued since the first report above, collecting data for 678 people as of 2003, and many results have been reported using this cohort. Among the participants of this cohort study, the neuropathological assessment showed that 33.9% had mixed dementia, 43.2% had AD, 2.5% had vascular dementia, and 20.4% had other causes of dementia (including diffuse Levy body disease, meningioma, primary hydrocephalus, and trauma) (Snowdon, 2003). The Nun Study demonstrated correspondence between the nun's cognitive function and pathological brain processes in autopsy. In many cases, the severity of dementia can be explained by the neuropathological findings of the autopsied brain. Nevertheless, there was a small number of cases in which cognitive decline was hardly observed before death, but the autopsied brains had some degree of



(adopted from Sperling R et al. Alzheimers Dement 7(3), 280–292, 2011, modified by Takeda)

Figure 3. Cognitive reserve and amyloid cascade hypothesis

neuropathological findings of AD or vascular dementia. Primarily, dementia can be defined by the degree of pathology, but secondly, it was shown that there are certain factors determining the extent to which the neuropathological findings show clinical symptoms (Snowdon, 2003).

7. The conceptualization of CR

Correlation between intracerebral pathology and cognitive function is low and there is a divergence between the two (Chui, 2006; Mungas, 2002). For example, AD pathology is observed in autopsy in up to 20% of elderly people without cognitive decline before death (Bennett 2006; Discoll, 2006; Schimitt, 2000). Similarly, magnetic resonance imaging (MRI) shows cerebral infarction in approximately 20% of elderly people without cognitive decline (DeCarli, 2005; Longstreth, 1998). CR was hypothesized to be the ability to antagonize ageing and brain pathology and to maintain cognitive function (Satz, 1993; Stern, 2019). Although the biological nature has not been elucidated, additional neurons and synapses in structure, and there is assumed to be extra plasticity and compensatory ability in function (Stern, 2015). CR varies from individual to individual, and experience that requires cognitive function is considered to be important for CR formation.

Prior to CR, there was the concept of brain reserve (BR) (Katzman, 1993). BR is a rather passive reserve defined by the morphological parameters of the brain, such as brain volume, and number of nerve cells among others. It is a threshold model, intended to explain individual differences in whether the symptoms may or may not occur due to differences in brain reserve, considering the notion that dysfunction appears when brain disorders exceed the threshold. CR is an active concept, however, implying coping activity with a disorder by utilizing the remaining neural circuit and surrounding neural circuits. In this sense, there is no idea that CR has any threshold, more specifically CR tends to have more interested to the kind of response the subject is trying to adopt. The characteristics of BR and CR are shown in Table 1. Furthermore, CR has been further divided into two components, neural reserve and compensation (Stern, 2019). Neural reserve is an individual difference in the cognitive processing process in healthy subjects, while neural compensation is usually mobilized to cope with disability, referring to the mobilization of unused circuits.

8. Quantification of CR

The fundamental issue of CR is the question of how to quantify this theoretical concept. Initially, it was evaluated by proxy-based measures such as years of education, complexity of occupation and other social factors. Years of education were reported to be inversely correlated with prevalence (Canadian Study of Health and Aging Working Group, 1994; Zhang 1990) and incidence (Cobb, 1995; Karp, 2004) of dementia. However, an individual's experience of education is complex in its own right, and has been demonstrated to reduce the risk of many illnesses (Grossman, 1997) and affects health-affecting income and access to health care (Deaton, 1999; Grossman, 1997; Kaplan, 1987). Low level of education is actually a risk factor of heart disease, diabetes, strokes (Borrell, 2006; Liu, 1982; Wong, 2002), hypertension, smoking and obesity (Kaplan, 1993), all of which are in turn risk factors for development of dementia. Occupational complexity (Andel, 2006; Potter, 2008) and leisure intellectual activity (Wilson, 2002; Verghese, 2003) have also been used as alternatives, but have similar problems to evaluation by level of education.

9. Quantification of CR by residual-based measure

The concept of CR has recently been pushed forward to evaluate the quantitative aspect of CR. Not

Table 1. Characteristics and differences between cognitive reserve (CR) and brain reserve (BR)

	Brain Reserve; BR	Cognitive Reserve; CR
characteristics	Physical, mechanistic	Functional
factors	Brain size, neuron number, synapse number	Plasticity, adaptability and compensation of neural circuits
mode	Passive	Active
threshold	yes	no
limitation	Loss of reserve when stress overloaded	Maintained reserve without limitation
nature	Basically quantitative	Qualitative plasticity and compensation
PC analogy	hardware	software

(adopted from Stern Y Neuropsychologia 47(10), 2015–2028, 2009)

relying on a proxy-based measure, CR is quantified (as a residual-based measure) based on the difference between the cognitive function expected from each individual's brain pathology and their actual cognitive function.

Cognitive function can be defined by several factors. Owing to the recent development of brain imaging techniques, the most reliable information on brain structure is from MRI imaging. For example, cerebral volume, white matter intensity, and gray matter thickness have all been demonstrated to co-relate with cognitive function. The parameters of cerebral volume and others can therefore be used to estimate the subjects" cognitive function.

Variation in cognitive function (for example, episodic memory performance) can be separated into three factors: brain imaging data, personal background, and others. The third factor, which represents residual components of cognitive function, can be used as the CR index (Reed, 2010). By this means of definition, those who show good cognitive function expected from the brain pathological images have high CR, while those who have lower cognitive function than expected from the brain pathological image have CR. In other words, CR can be interpreted as a difference from cognitive function expected from brain pathology, and is thought to reflect cognitive function undefined by known factors.

10. Sex differences in AD onset from the viewpoint of CR

Women are at higher risk of developing AD than men. Here, we examine whether there is a difference in CR between men and women, and whether any difference in CR can explain the higher risk of developing AD in women, with reference to a recent paper (Subramaniapillai, 2021).

10-1. Sex differences in education

Educational history is a predominant factor in determination of CR. Many studies have reported that people with a long history of formal education are comparatively less likely to develop AD than those with shorter length of formal education. Four longitudinal studies and three AD cross-sectional studies have reported sex differences. A longitudinal study studied the prevalence of AD, while (Fratiglioni, 1991), and another (Letenneur, 1999) studied the incidence of AD. Neither study reported sex difference in incidence of AD as an effect of educational history. In contrast, recent reports have shown that a long education history reduces the risk in women but not in men (Launer, 1999; Letenneur, 2000). From these reports, it can be concluded that the effect of education can be more easily observed in women than in men. Three cross-sectional studies comparing patients with AD with healthy individuals show the effect of sex on educational history. According to a report on the effect of sex and ApoE4, in which outpatients with AD (146 women and 68 men) were observed for 4 years, the educational history of women was slowed down and ApoE4 was accelerated (Oliveira, 2016).

Another study investigated 39,451 patients with AD (25,643 women and 13,808 men) and stated that the educational history was a more significant factor in suppression of onset of AD in men than in women. No pathological data were investigated, so pathology was potentially greater in the women, and if so, the pathology may have progressed to the extent that the effect of the educational history was negated in the women (Pradier, 2014). Elsewhere 1,098 healthy individuals with mild cognitive impairment and AD were observed for 2.5 years. High tau levels were associated with left hippocampal atrophy and impaired performance in women but not in men. This correlation was not affected by educational history. Decreased cerebrospinal fluid Aβ also correlated with left hippocampal atrophy, episodic memory, and decreased performance in women. Education was also involved to some extent, suggesting that Aβ has a greater effect in less educated women (Koran, 2017).

10-2. IQ and sex difference

Cognitive function is generally evaluated by intelligent quotient (IQ), which is the relative value of an individual's function to resolve problems. IQ is composed of crystallized intelligence and fluid intelligence which can constitute a reserve force. In an investigation into the relationship between IQ and the onset of AD and related dementia, (ADRD) of 43,014 men and 42,479 women, 50 years after measurement of their IQ, high IQ during puberty reduced the incidence of ADRD in both men and women. The effect of IQ was the same for both men and women (Huang, 2018). Another study investigated pre-symptomatic IQ in relation to memory function; when examined by dividing into four groups according to sex and IQ, there was no difference in verbal episodic memory between the four groups. Men with both high- and low IQ had delayed development of language memory impairment, while women were shown to have superior spatial memory (Beinhoff, 2009).

10-3. Occupation and sex difference

The level of complexity of an individual's occupation may affect their reserve capacity. There are three studies on occupation and sex differences in relation to the onset of AD. Some types of work were shown to be more related to the prevention of onset of AD than the complexity of the actual occupation, especially in women. In a study of 919 healthy subjects (695 women and 218 men) divided by age and educational history of eight years or more, engaging in manual work of lighter mental complexity increased the onset of AD, and this was observed in women more than in men (Qiu, 2003). Classifying occupations into seven types (homemaker, farmer, domestic work, blue-collar worker, white-collar worker, craftsperson, and professional occupation), another paper studied the effects of each type of work by sex. Women tended to have a lower risk of developing AD if working as a craftsperson, while men had an increased risk (Helmer, 2001). The effect of different occupations has also been studied, classifying them into four types (white-collar, blue-collar, domestic work, and farmer). Farmers had the highest AD prevention effect, and this effect was higher in women (Santabarbara, 2019).

10-4. Bilingual and sex difference

Bilingual people have been shown to have high levels of intelligence and social communication ability. The onset of AD was reported to be delayed by 5 years in both men and women with the ability to speak more than one language (Craik, 2010).

10-5. Brain Reserve (BR) and sex difference

Brain reserve (BR) can be measured by structural and functional parameters of MRI, such as cerebral volume, white matter intensity, cerebral blood flow and cerebral metabolism. AD pathology progresses accordingly, with decrease in cerebral blood flow or cerebral metabolism. If cerebral blood flow or cerebral metabolism is larger in either men or women, it could be assumed that the sex with a larger decrease has a larger reserve capacity. Three studies have compared sex difference in patients with equivalent cognitive function, using cerebral blood flow and cerebral glucose metabolism as indicators reflecting AD pathology. Significantly reduced glucose metabolism in the right hemisphere (inferior frontal gyrus, superior temporal gyrus, hippocampus, island) in 43 men and 50 women by FDG-PET in patients with similar AD; men had a higher reserves than women (Perneczky, 2007). Using data from the ADNI study, another study investigated the relationship between temporal lobe glucose metabolism and verbal memory (recent, delayed) by FDG-PET. The subjects were 390 healthy subjects (196 women, 194 men), 672 with amnesic mild cognitive impairment (aMCI; 276 women, 396 men), and 254 with AD (101 women, 153 men). Among the patients with aMCI, women had higher language memory ability, suggesting that women with aMCI have higher reserves than men, but no sex difference was observed in the stage of AD (Sundermann, 2016). Glucose metabolism in 225 healthy subjects and 282 patients with AD (123 men, 159 women) was studied, with sex, education level, and occupation as independent variables. In healthy subjects, educational history and occupation were correlated with glucose metabolism in various parts of the brain (the anterior limbic system and the performance circuit in women, the posterior associative field in men). Among patients with AD, education and occupation were inversely correlated with glucose metabolism in both men and women (the frontal lobe and the limbic system in women, the parietal temporal region in men). From these results, the parts corresponding to the reserve capacity were considered to be different between men and women (Malpetti, 2017).

11. Conclusion

Human cognitive function is influenced by the experience throughout of life. Human cognitive function is influenced by biological and psychosocial factors, such as genes, personality traits, educational history, occupation, physical activity, and social activities, and others. The concept of CR is proposed to explain the gap between brain pathology and actual cognitive function. Regarding gender, in addition to biological sex, gender involvement from a psychosocial perspective is also conceivable. Psychosocial factors may also be involved in the fact that women are at an increased risk of developing AD.

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