REVIEW ARTICLE

Cognitive aging and cognitive reserve

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Abstract
A patient's behavior and cognition are important considerations in psychiatric practice. Elderly people show wide range of differences in cognition and behavior. Along with other physical effects of aging, there are morphological and biochemical changes in the brain that affect age-related cognitive decline. Elderly people have accumulated a variety of differing psychological and social experiences throughout their lifetime, including childhood and educational experiences, experiences in their working lives, and other psychological and social experiences. Individual differences among elderly people can therefore be so great that it is inappropriate to group them together into a dichotomy of normal or abnormal aging, and it is perhaps better to view aging as a spectrum with a series of continuities from health to disease. 'Successful and unsuccessful aging' is a concept which considers a wide spectrum of cognitive decline, in which dementia may be placed at the extreme end of the spectrum of 'unsuccessful aging'. The importance of cognitive reserve has been pointed out as the ability to maintain cognitive function against aging and pathological changes in the brain. Although the concept of cognitive reserve is not yet fully formed, clinicians should always give it broad consideration in the psychiatric treatment of elderly people.

1. Behavior and cognition

Behavior might be considered the currency of an individual's social life. People perceive stimuli from the outside world and make comparison with internal information stored in the brain, such as memories and emotions, to determine their own behavior. Even if the external stimuli are the same, both the cognitive process and the internal information differ from person to person, resulting in a variety of behaviors. People living within a society are expected to appropriately recognize and act upon the behaviors expressed by others and thus behavior is considered as a social currency which psychiatrists can make use of to understand the human behavior.

"*Omote*" is a Japanese term that means 'surface'- we may not understand the activities in the brain and mind (the inner world), but we can objectively observe human behavior. For psychiatry to be a science, objective facts are important, and the evidence should be sought in observable behavior. Psychiatrists must therefore devote themselves to behavioral observation in order to gain some understanding of their patients' minds. Behavioral abnormalities exhibited by patients with psychiatric disorders could be said to reflect the pathophysiology of the disease, and that objective science be constructed only by careful observation of patients' behavior (Figure 1).

1-1. Diagnostic and Statistical Manual of Mental Disorders introduction and behavior

These ideas had a major impact on psychiatric practice in Japan with the introduction of the *Diagnostic and Statistical Manual of Mental Disorders, third revision* (DSM-III) in 1980 because it recommended seeking diagnostic clues and evidence in the patient's expressive behavior rather than making an inference on the patient's inner world.

Before DSM-III, psychiatry was basically concerned with mental illness. The criterion for inclusion in psychiatry was whether or not the patient could be understood to have a disease, and there was a reluctance to include abnormal behavior that was not caused by a disease within the framework of psychiatry. Psychiatric research was built around psychopathology based on diagnostic systems, and the emphasis was on qualitative and quantitative evaluation of mental abnormalities and interpretation of their pathological structures within the framework of

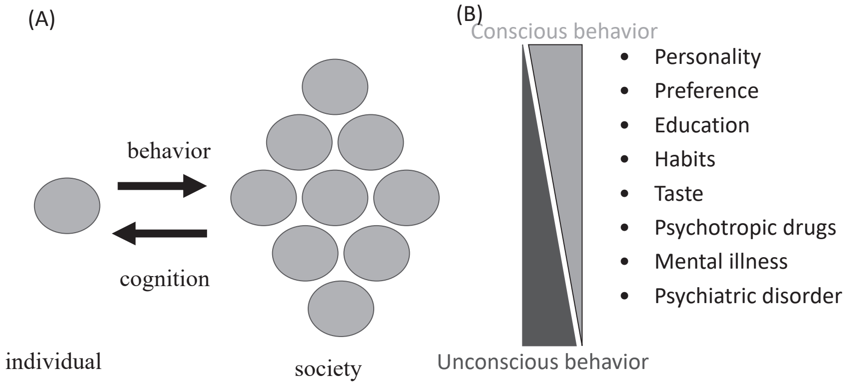


Figure 1. Human Behavior and Cognition
(A)The humans live their lives by using behavior as the currency does in the society. An individual expresses 'behavior' to affect the society, and the individual perceives the societal response by 'cognition'.
(B)The behavior is composed of conscious behavior and unconscious behavior.

empirically accumulated diagnostic systems. Psychiatry was thus the study of mental disorders, and the behavior of so-called 'normal people' was considered to be outside the scope of psychiatry.

Psychiatry now focuses its studies on human behavior as a whole, beyond the framework of disease, and it has come to include all human behavioral abnormalities. This trend was further accelerated by the introduction of DSM-III and subsequent editions as the diagnostic system for psychiatry, which became widely accepted in clinical psychiatry and expanded the scope of psychiatry from disease to behavior. Modern psychiatry is now based in the integration of objective findings of brain events and behavioral manifestations. In a sense, psychiatry has become less dependent on speculation and inference about brain events, and instead uses human behavioral manifestations as direct clues.

1-2. Conscious and unconscious behavior

Human behavior includes both conscious and unconscious actions. Many people believe they are acting upon their own initiative to make decisions and they are unaware of their unconsciously determined actions. Unconscious behavior nonetheless accounts for a significant portion of a person's behavior (Figure 1). Personality, preferences, education, and other factors influence a person's behavior and manifest themselves as a person's unique behavior without the individual being aware of it. Meanwhile, mental illness and psychotropic drugs can also influence behavior and manifest as person-unique behavior.

Mental illnesses can even cause individuals to behave against their own will. Each psychiatric disorder forms a specific behavioral pattern that is a characteristic manifestation of the disorder and a clue to the diagnosis. The observer attempts to arrive at a diagnosis of a mental disorder by observing the characteristic behavior of the patient and by detecting cues common to the disorder.

1-3. Behavior and cognition

Humans are social animals and always determine their own behavior in the context of social life with others. They recognize the actions of others, can often understand the meaning and nuances of those actions, and determine their own appropriate behavior in response. In this sense, action and cognition are a set, and naturally we are to some extent aware of how our actions are perceived by others. Our own behavior is then determined by inferring the content of others' perceptions (of our own behavior). It is through this feedback between action and cognition that people lead their social lives. Cognitive functions are then perhaps more fundamental and behavior is merely an expression of them.

2. Biopsychosocial diversity of elderly people

People are born as almost identical organisms. Even if there are some individual differences in physical characteristics, most physiological functions are similarly immature and there are few individual differences. After birth, people live through various stages of life and accumulate a wide variety of experiences. Elderly people have accumulated various psychological and social experiences throughout their lives, including their childhood experiences, their education, their working life and interactions with others, and a variety of psychological and social experiences. Individual differences among elderly people are therefore great, and it is inappropriate to broadly group them into a dichotomy of 'normal' or 'abnormal'. Aging is perhaps better viewed as a spectrum with a series of continuities from health to disease.

People tend to show age-related cognitive decline after their 40s as their brains age. The concept of 'successful' and 'unsuccessful' aging has been proposed to envision a spectrum of cognitive decline. Whether dementia is normal aging or pathological aging was once debated, but more recently it has come to be considered that brain aging can be expressed as a position on a spectrum of brain aging from 'successful' to 'unsuccessful' aging, with dementia positioned at the pole of unsuccessful aging on the spectrum.

2-1. Age-related changes in cognitive function

Cognitive function is the process by which humans take in information from the outside world and integrate it with internally-stored memory information to proactively determine the best course of action for the time, place and situation. In a broad sense, this function can be considered to be carried out by the entire cerebrum, but in a narrower sense, it is carried out by the sensory association cortex, the motor association cortex, and the limbic system. Cognitive function is a complex assemblage that broadly includes social cognition, theory of mind, etc. However, in a relatively narrow sense, it is examined in terms of the prefrontal cortex-striatal circuit and the medial temporal-hippocampal circuit, which are thought to be important neural circuits involved in cognitive function (Figure 2).

Prefrontal-striatal circuit

The characteristics of cognitive function in elderly people are known to include a decline in working memory, a tendency toward retention, and increased susceptibility to interfering stimuli. These characteristics of cognitive decline in elderly people may suggest similarities with patients with frontal lobe disorders. The prefrontal cortex is assumed to be involved in age-related changes such as working memory decline, retention sequencing, and non-inhibition of interfering stimuli. The prefrontal cortex is the area that shows the greatest age-related changes in brain morphology, and in particular, the volume of the lateral prefrontal cortex is the area that shows the greatest decline with age. This is very different from the areas of brain atrophy caused by Alzheimer's disease. In Alzheimer's disease, medial prefrontal atrophy is also observed in the later stages of the disease, but the age-related decrease in prefrontal volume is thought to be mainly due to a decrease in the number of prefrontal synapses, not due to neuronal loss.

Striatal volume also declines with age, and magnetic resonance imaging (MRI) comparisons of the striatal cross-sectional area show that striatal volume declines by 3% per decade with age. Dopamine levels, dopamine transporters, and dopamine receptor density have also been shown to decrease with age. After the age of 40, the density of dopamine D2 receptors declines by 8% per decade. Regarding age-related cognitive changes and changes in the

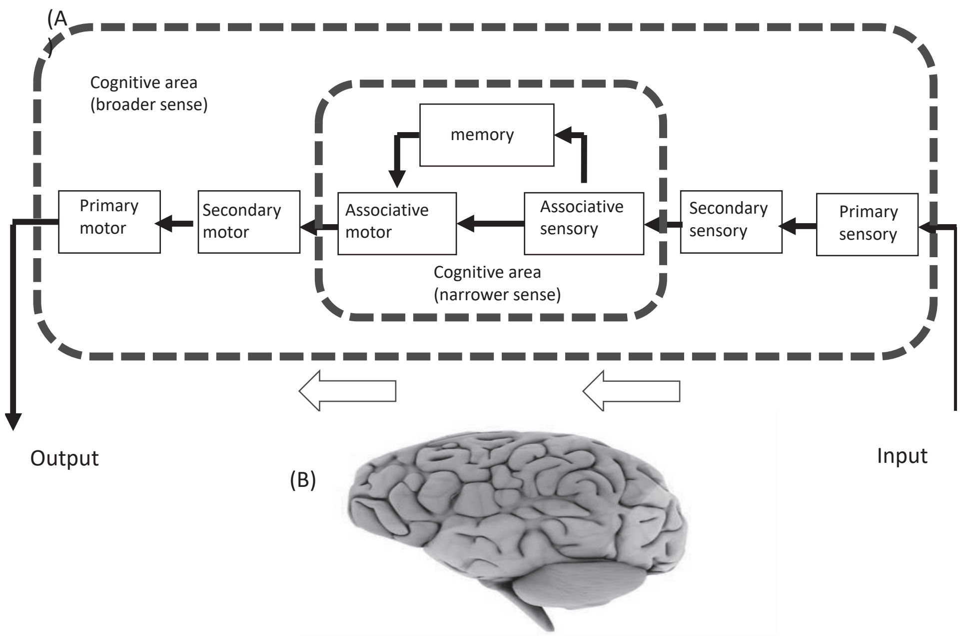


Figure 2. Definition of Cognitive Function
Cognitive function can be defined as that of the whole cerebrum in broader sense, or as the function of associated motor, associated sensory, and memory areas in narrower sense.

biological parameters of the prefrontal-striatal circuit, prefrontal volume in elderly people was reported to be inversely proportional to the Wisconsin card sorting test retention error and that age-related prefrontal atrophy defines the decline in fluid intelligence seen in positron emission tomography (PET) studies in elderly people (Schretlen, 2000). Elsewhere, the number of dopamine D2 receptors was reported to correlate well with attentional function, response inhibition, and Wisconsin card sorting test performance in PET studies of elderly people, and such functional decline in elderly people is reportedly due to a decrease in dopamine neuron function (Volkow, 1998). There has also been a report that the number of D2 receptors in the striatum correlates more with information processing speed in elderly people than with actual age (Baeckman, 2000).

Medial temporal lobe and hippocampus

Although the medial temporal lobe and hippocampus are involved in declarative memory, the volume changes in the medial temporal lobe and hippocampus are less pronounced with age than in the prefrontal cortex and white matter. The hippocampus and parahippocampal gyrus actually show no volume change and almost no neuronal loss with age, and the volume loss of the hippocampus and parahippocampal gyrus by MRI is about 2-3% per decade. The rate of atrophy is slower than that of the prefrontal cortex and striatum. However, the rate of atrophy speeds up in old age (over 70 years of age), reaching about 1% per year. In terms of hippocampal regions, the volume of the entorhinal cortex and hippocampal CA1 region shows almost no age-related volume loss, while the subiculum and dentate show a certain amount of age-related volume loss and atrophy. In response to such atrophy, fMRI studies have also reported lower activation of the left hippocampus in response to tasks in elderly people, which may correspond to atrophy of the subiculum and dentate. The amygdala, which forms part of the limbic system, does not show much volume loss with age, but fMRI studies have reported reduced responses to negative emotions in elderly people.

Taken together, these findings suggest that normal aging-related changes in the hippocampus and medial temporal lobe are less morphological, and aging changes in the medial temporal lobe-hippocampal circuit are not uniquely important. Rather, it is better to assume that age-related changes also appear in the functions involving this region in conjunction with the prefrontal cortex. Cognitive functions involving the medial temporal lobe-hippocampus vary widely, especially in elderly people. In addition to biological aging changes, differences in life experiences, genetic predisposition, and vulnerability to neuropathological processes affect the cognitive function of elderly people. In extreme cases, it is possible that there may be two major groups: high cognitive function group and another in which it is easy to slip into decline in cognitive function (Rapp, 1992).

White matter

Diffusion tensor imaging (DTI) is considered to be a parameter that reflects white matter function, and DTI studies of elderly people have shown a decrease in white matter density in the prefrontal cortex and anterior corpus callosum. Such reductions in white matter function have been shown to affect processing speed, executive function, reasoning, and immediate and delayed playback, but are not related to overall IQ. The changes in white matter function observed in elderly people can nonetheless affect the connections between the prefrontal cortex and the hippocampus or striatum, and these white matter changes affect their cognitive function.

3. Aging changes in cognitive processes

3-1. Fluid and crystalline intelligence

Psychology divides human intelligence into fluid and crystalline intelligence, and states that fluid intelligence declines with age, while crystalline intelligence does not decline with age, but rather increases, albeit slowly, even in old age. Fluid intelligence is the ability to quickly and flexibly process the resources necessary for cognition using working memory and processing speed, and this type of fluid function declines with age. Conversely, information stored in the human body, such as personal experience and general knowledge, accumulates with age, while crystalline function does not decline.

Elderly people with high cognitive reserve may have higher fluidity of function. Although there is no significant difference in the amount of information stored in the brain between individuals with high and low cognitive reserve, significant differences are observed in the ability to appropriately utilize this district-theorized information (Figure 3).

3-2. Changes in memory representations with aging

Although cognitive functions that utilize knowledge, common sense, and stored memories improve with age, episodic memory declines with age. As mentioned above, there is a significant difference between semantic memory and episodic memory with age, but the mechanism behind this difference in aging has not been clarified. The memory process has three components: inscription, memory representation, and retrieval. The changes in inscription and retrieval with age have been widely reported, and the age-related changes in memory representation are also being investigated.

At present, the prevailing hypothesis is that elderly people form memory representations with too much information compared with younger people due to cognitive decline and inhibition (Armer, 2021). When cognitive and inhibitory mechanisms are working effectively, memory representations are formed by selecting only targeted information from irrelevant information, but in elderly people, these mechanisms are weakened and irrelevant information that has been recently used, past knowledge induced by tar-

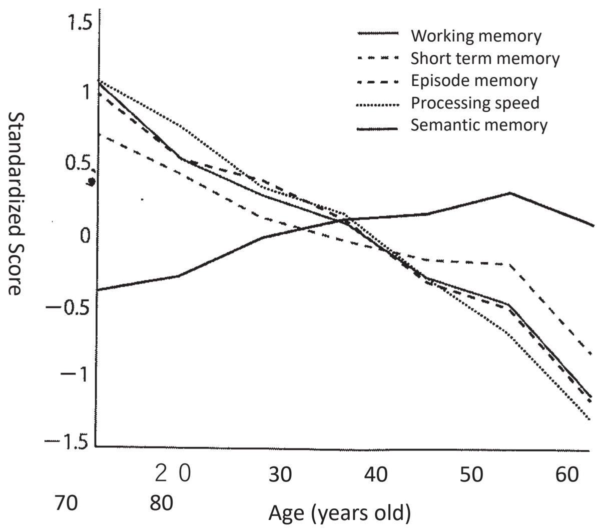
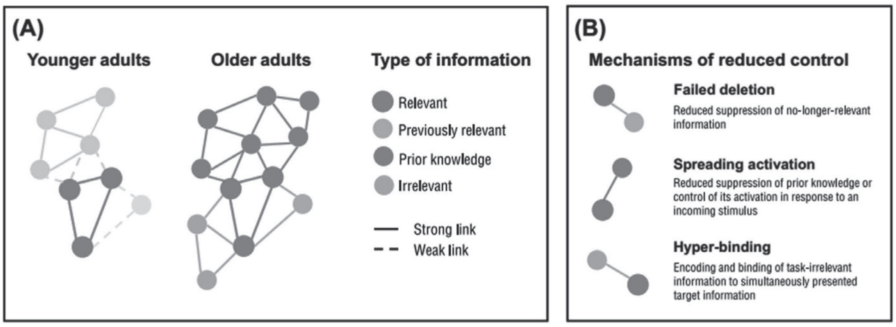


Figure 3. Decline of memory function by aging semantic memory is increasing even in the late life (up to 70s years old), while working-, short-term-, episode-memories decline in late life, as well as processing speed.



From; Amer T, Wynn JS, Hasher L: Cluttered memory representations shape cognition in old age(1)

Figure 4. Visualization of the nature of older adults' memory representations
(A) Relative to younger adults, whose memory representations predominantly contain relevant or target information, older adults' memories are cluttered with no-longer-relevant information that was never suppressed, prior knowledge representations cued by the target information, and irrelevant or distracting information from the current environment. Some of these elements might also be contained in the memory representations of younger adults, but, as pictured here, are less strongly activated and only weakly linked to target information. The additional information represented in older adults' memory representations can pose problems for retrieval of target information and (positively) impact other memory-dependent functions. (B) The cluttered nature of older adults' memory representations can be attributed to reduced inhibitory or cognitive control with age. Specifically, older adults show reduced suppression and/or deletion of information that is no longer relevant to the present task. Relative to younger adults, they also have difficulty suppressing, or controlling the spread of, prior knowledge that is cued by the incoming stimulus. Finally, older adults show increased encoding and binding of task-irrelevant information to simultaneously presented task-relevant target information.

geted information, and irrelevant information induced by the environment are more likely to be incorporated into memory. Furthermore, this extra information is tightly coupled to the target information, and this results in the formation of cluttered memory representations in elderly people compared with younger people (Figure 4).

However, although cluttered memory representations being difficult to retrieve can be a disadvantage, this is not always the case. In some cases, it may be more appropriate to describe them as 'enriched' rather than cluttered, because there may be cases in which memory representations seemingly unrelated to the target information are actually useful. Regardless of the terminology used, the extra information contained in the memory representations of these older adults is the content of previously relevant information, common sense, and current influences from the outside world, which are tightly bound to the target information and have a significant impact on the mental activity of the older adults. For example, the extra information can be used to solve a problem in a novel way. Integrating seemingly unrelated information from the surrounding area and presenting a new solution can be called a kind of creativity. This superior ability has been reported in a task in which older adults can come up with a fourth word that is related to each of the three unrelated words (remote associates task) and they tend to perform better than younger adults (Kim, 2007). Miscellaneous memory representations may also be useful in decision tasks. Older adults perform better than younger people in tasks in which past decisions are used as a reference, and on decision tasks in which they use stored information to resolve conflicts with others or to spend money appropriately. This ability, which can be described as so-called 'worldly wisdom,' observed in elderly people is thought to be derived from miscellaneous memory representations.

This rich, tightly coupled memory representation of elderly people could potentially be used to help them remember and learn. For example, in a face and name memory task, simply adding an occupation improves the memory performance of older adults more than that of younger ones (Weeks, 2016). Even if the memory representations of elderly people are miscellaneous information formed with irrelevant information, this property could be exploited to increase cognitive reserve, which could be useful in real life.

3-3. Cognitive mode switching with aging

When making decisions, there are two ways of thinking: one is to utilize existing knowledge, which is more certain, and the other is exploration, which is less certain but seeks new possibilities. People make decisions based on a combination of these two opposing modes of 'exploration' and 'exploitation'. For example, when making a purchase, do we choose from several products we have used before, or do we choose a new product we have never used before? Do we choose to spend our summer vacation in a place we have been to before, or do we opt to explore a new place? Do we choose among the modes of transportation previously used to get to a destination, or do we explore a new route you never used before? The trade-off balance between 'exploration' and 'utilization' is believed to change with age, and decisions are weighted toward 'utilization' as become older (Spreng, 2021). Looking at everyday life situations, we often experience that the actions of elderly people seem to be chosen from among the options they have experienced so far, and that they are perhaps unwilling or less willing to try something new.

In situations where people make decisions, not only purely cognitive processes, but also emotions are involved. Older adults are known to place more emphasis than younger adults on emotional factors such as emotional satisfaction and importance to the individual in making decisions. Considering that the value of exploration of new relationships and connections (exploration) decreases and the value of relationships (exploitation) increases as people gain experience, exploitation understandably plays a more important role in exploration and exploitation in elderly people in terms of emotion (Scheibe, 2009).

When mental functions are divided into cognitive and emotional processes, emotional processes are known to play a greater role than cognitive processes in maintaining working memory in elderly people. Considering that working memories with emotion are more likely to be retained as long-term memories (Lieberman, 2019), it can be considered that a scheme to add information with emotion to existing information is active in elderly people, and such a scheme can explain the bias toward choice by emotion in elderly people. The scheme can explain the bias toward choice by emotion in elderly people.

The medial prefrontal cortex (mPFC) is believed to be involved in the schema that forms the interaction between emotion and cognition, and a neural circuit that receives noradrenergic projections originating in the nucleus accumbens is responsible for the reward system as emotion and cognition (Samanez-Larkin, 2015). In addition, the mPFC also forms circuits with the anterior insula, anterior cingulate cortex, and ectopia, all of which are involved in decisions that rely on 'utilization'. Neural circuits with the mPFC as their hub are thought to be responsible for decisions weighted toward 'utilization' as we age.

It is therefore understandable that the balance shifts toward utilization rather than exploration in elderly people, both in terms of cognition and emotion. Such network plasticity, a new neural circuit that can be acquired later in life, is an important clue when examining cognitive function in elderly people, and is also an important factor in explaining cognitive reserve.

4. Cognitive reserve

Normal aging changes in the brain and Alzheimer's (AD) pathology are continuous. Some people with AD pathology in the brain have normal cognitive function, and some people with positive biomarkers reflecting AD pathology have periods of normal cognitive function. The cognitive reserve hypothesis has been proposed as a concept to explain this situation (Stern, 2012), and it is assumed that people in the preclinical stage with AD pathology may maintain cognitive function by driving neural circuits to counteract the functional impairment that may be induced by the pathological findings. This ability to maintain normal cognitive function against aging and pathological processes has come to be referred to as 'cognitive reserve'. Cognitive reserve antagonizes aging changes and pathology in the brain and delays the onset of symptoms of dementia. Individuals with high cognitive reserve are more likely than those with low cognitive reserve to be antagonizing significant aging changes and pathology at the onset of symptoms once symptoms appear, so cognitive decline tends to be more rapid in those with high cognitive reserve (Figure 3). It is not fully known how cognitive reserve affects the overall course of dementia, i.e., mortality (Bruandet, 2008), but it has been speculated that people with high cognitive reserve may rather die earlier, considering that the entire course of dementia onset is compressed (Cheng, 2014). The extent to which high cognitive reserve delays the onset of dementia is unknown, but even if it can delay the onset of dementia by a year or two, it is expected to significantly reduce the prevalence of dementia from a public health perspective, which is why cognitive reserve has been studied.

As mentioned earlier, the most important characteristic to consider in treatment of elderly people as a whole is the wide heterogenicity. Individual differences in old age are greater as a result of different biological, psychological, and social factors up to the time when people reach old age. This is even more the case for mental and cognitive functions, which are more susceptible to the influence of psychosocial factors than physical functions.

Cognitive reserve refers to the ability to maintain cognitive function in antagonism to functional decline caused by brain aging or AD pathology. This is based on the idea that an individual's brain can develop sufficient reserve power through lifestyle. Cognitive decline in elderly people begins at some point and progresses slowly with age, but there are individual differences in the rate of decline. Individuals with high cognitive reserves can to some extent resist the pathological processes in the brain and protect themselves from functional decline. However, even those with high cognitive reserve can have rapid decline in cognitive function once functional decline begins. In other words, cognitive reserve delays the onset of cognitive decline.

The correlation between brain pathology and cognitive function is modest (Mungas, 2002), and there is a divergence between the two. For example, AD pathology is observed at autopsy in approximately 20% of elderly persons without cognitive decline before death (Schmitt, 2000; Bennett, 2006; Driscoll, 2006). Similarly, MRI shows cerebral infarction in up to 20% of elderly persons without cognitive decline (Longstreth, 1998).

Cognitive reserve is understood as the ability to maintain cognitive function in antagonism to aging and brain pathology, and its biological nature has not been elucidated, but structurally, extra neuron and synapse number and functionally, extra plasticity and compensatory capacity are assumed (Stern, 2009). Experiences that require function are considered to be important.

5. Conclusion

Brain function declines with aging, with some areas with marked aging and others with less aging. Human cognitive function is the brain function most affected by aging, but the mechanisms of cognitive aging are not well understood. Conversely, Alzheimer's disease can be viewed as a manifestation of extremely accelerated brain aging and is often characterized by amyloid deposition, neurofibrillary tangles, and neuronal loss. Pathological changes characteristic of Alzheimer's disease are observed in ageing, albeit to a lesser degree. Cognitive reserve explains the lack of cognitive decline while exhibiting the pathology of Alzheimer's disease. Research into the change in cognitive function with aging is useful in elucidation of the main body of cognitive reserve, and by increasing cognitive reserve, it may be possible to prevent the deterioration of human cognitive function due to aging.

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