Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : December 1, 2017
Accepted : January 10, 2018
Published online : March 31, 2018

Original article

Let's aim at our healthy longevity with positive thinking (resilience)! : The results of 351 subjects enrolled in Anti-Aging Medical Survey

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Abstract

***Objectives*:** Wisconsin card sorting test (WCST) is known to be useful for evaluate prefrontal lobe function. 351 subjects were examined for their brain functional age by WCST, and were also examined for the correlation between brain functional age and mental stress symptoms. Here, we investigated rejuvenation of brain functional age for the effect of improvement of negative mental symptoms and resilience.

***Methods*:** 351 subjects participated in our Anti-Aging medical survey, 179 men, average age 63.5 year and 172 women, average age 65.7 year, between April 2006 and December 2016. We evaluated mental stress symptoms by use of Anti-Aging Common QOL Questionnaire.

***Results*:** The parameters of WCST were significant with aging. There is a gender difference for the correlation between mental stress symptoms and aging. Young women have a lot of mental stress symptoms, but they decrease with age. On the other hand, in men, mental stress symptoms increase with age. Increasing grip strength, quadriceps muscle, WBI, basal metabolism, preventing sarcopenia, frailty is important to keep young brain age. In multivariate analysis Diabetes, hypertension and obesity increased brain age, and decreased prefrontal function.

***Conclusions*:** Elderly women exhibited younger brain age than men, Elderly women with strong resilience showed few symptoms of mental stress and showed extended healthy life expectancy. To reduce symptoms of mental stress which accelerate brain aging, it is important to maintain and increase thigh muscle mass, and avoid fraily. Maintaining a young brain age prevents lifestyle diseases, and dementia, and increases healthy life expectancy.

***KEY WORDS*:** Wisconsin card sorting test, Brain functional age, Prefrontal lobe function, Lifestyle disease, Frailty, Dementia, Healthy life expectancy

Introduction

An Anti-Aging Medical Checkup (AAMC) is for the purpose of implementing guidance for lifestyle habit improvements in order to aim at healthy longevity by improving aging balance based upon the test results of vascular age, muscle age, bone age, hormone age and neural age [1-3)]. The Wisconsin card sorting test (WCST) is used for the measurement of neural age [4, 5)]. This is often used in clinical sites because it is said to be useful for the examination of functional disorders in the prefrontal cortex [6, 7)]. It is also possible to download it from the Japan Stroke Data Bank for free [8)]. In this research, we analyzed the data of the AAMC examinees conducted in their hospital and discussed the relationship of brain age and mental stress with other physical information.

Subjects and Method

The subjects were 179 males (average age: 63.5 years (95% confidence interval [CI]: 61.6～65.3)) and 172 females (average age: 65.7 (95% CI: 63.8 ～ 67.5)), 351 in total (including plural checkups), who received AAMC (called Anti-Aging Dock in this hospital) from June 2006 to December, 2016. The subjects received WCST for the purpose of age rating of neurological function.

The examinees received guidance for "positive thinking (resilience)." The main part of the resilience guidance in this hospital consisted of individual image trainings leading to positive thinking. For example, for a female examinee, a dinner party or window-shopping with a friend with whom she is at ease and can consult is arranged: and for a male examinee, events concerning music, sports or reading are

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arranged, where he can enjoy his habit and receive training.

The evaluations of the functional ages of muscles, vascular system, nerves, hormones and bones were conducted by AAMC, and the evaluation was carried out using an Anti-Aging Quality of Life Common Questionnaire (AAQOL) [9].

Muscles were measured using bioelectrical impedance muscle mass measurement (Phyion-MD: Nippon Shooter Ltd., Tokyo). The masses of upper and lower limbs, weight bearing index (WBI), body fat percentage (%), basal metabolism (kcal/day), water volume (kg), muscle rate (%) and bone mass (kg) were measured. WBI is defined as quadriceps muscle/body weight ratio. Muscle age was evaluated using these indexes.

Higher brain function was measured using WCST. WCST is a test to observe the reactions of an examinee by showing cards with graphics of triangles, stars, crosses and circles in red, green, yellow and blue, a kind of card game. The examinee analogizes to which category a new card should be classified to between color, figure and number.

The frontal cortex function and neural age (called "brain age" in this hospital) of the examinees were evaluated using the parameters of categories achieved (CA), numbers of response cards used until the first category achieved (NUCA), total errors (TE), percentage of perseverative errors of the Milner type (%PEM), percentage of perseverative errors of the Nelson type (%PEN) and reaction time which means card selection total time.

Dehydroepiandrosterone-sulfate (DHEA-s), insulin-like growth factor-I (IGF-I) and cortisol were measured for the evaluation of hormone age.

The relationships between neural age related indexes and other items were analyzed.

Ethical Standards

Before the start of this research, written letters of consent were obtained from the subjects and this research was conducted with the approval of the ethics committee of Doshisha University (Application Nos. #0832 and #14089).

Results

WCST and Aging

The results of WCST are shown in ***Fig. 1***. Significant relationships of real ages with categories achieved (CA), numbers of response cards used until the first category achieved (NUCA), total error (TE), percentage preservative errors of the Nelson type (%PEN) and reaction time were observed.

Mental Symptoms and Aging

The results of 21 factors of mental symptoms of the AAQOL recommended by the Japanese Society of Anti-Aging Medicine are shown. The relationships between the total score of mental symptoms and neural age were analyzed. The mental symptoms become severe with aging in males and, on the contrary, it was improved with aging in females (***Fig. 2***). It was at the age of 65, and when the total score of mental symptoms was 50, that the regression lines of males and females were crossed. There were many males who were older than 65 and had severe mental symptoms (total score > 50) and there were many young females who had severe mental symptoms (total score > 50).

The correlation analysis between mental symptom and real age is shown in ***Table 1***. In the case of males, the score of "Depressed," a mental symptom, increased with aging, and on the contrary, it decreased with aging (***Fig. 3***) in females. Similar differences between males and females can be recognized in other factors. The scores of "No feeling of happiness," "Nothing to look forward to in life," "Daily life is not enjoyable" and "Loss of confidence" increased with aging in males, and on the contrary, the scores of these symptoms decreased in females. The scores of "Lapse of memory," "Inability to sleep because of worries" and "Difficulty in falling asleep" increased with aging in both males and females.

Correlation between body composition changes and neural age

Table 2 shows the correlation analysis between body composition changes and neural age.

In the case of males, grip strength, muscle mass, basal metabolic rate, brachial muscle and femoral muscle showed negative correlations with neural age, and it was found that the amount of muscle mass greatly affected neural age. Increasing femoral muscle and brachial muscle mass, in particular, greatly related to the rejuvenation of neural age.

In the case of females, it was recognized that increases in BMI, body fat and waist circumference have a positive correlation with neural aging and that grip strength and WBI have negative correlations with neural aging. It can be said that increasing grip strength and WBI is important for maintaining a young neural age.

It was shown that increasing grip strength was recognized to relate to the rejuvenation of neural age for both males and females.

The relationships of neural age with cortisol, which is a stress hormone, and DHEA-s /Cortisol ratio (D/C ratio), which is an indicator of resistance, are shown in ***Fig. 4***. No significant relationship between cortisol and neural age was observed in males, but a very weak relationship (R^2 = 0.025) was observed in females. The D/C ratio showed very weak negative correlation with neural age in both males and females (male: R^2 = 0.116, female: R^2 = 0.070), and the more the D/C ratio rose, the more neural age was rejuvenated.

A multivariate analysis of the relationships between lifestyle diseases and neural age was conducted (***Table 3***). There were diabetes, hypertension and obesity as the risk factors involved in neural aging in males and only obesity was a risk factor involved in neural aging in females.

Factors affecting the changes in neural age

The repeat examinees who received AAMC multiple times were 64 males and 40 females, 104 in total. They received guidance in "positive thinking (resilience)". The change in the condition of mental symptoms before and after the guidance, and its effect on neural aging, were analyzed by a one-way analysis of variance (AVOVA)

In the case of males, the improvement of the score of "Depressed" was connected to the rejuvenation of neural age, and its exacerbation led to neural aging (***Fig. 5***). The exacerbation of the score for the symptom of "Nothing to

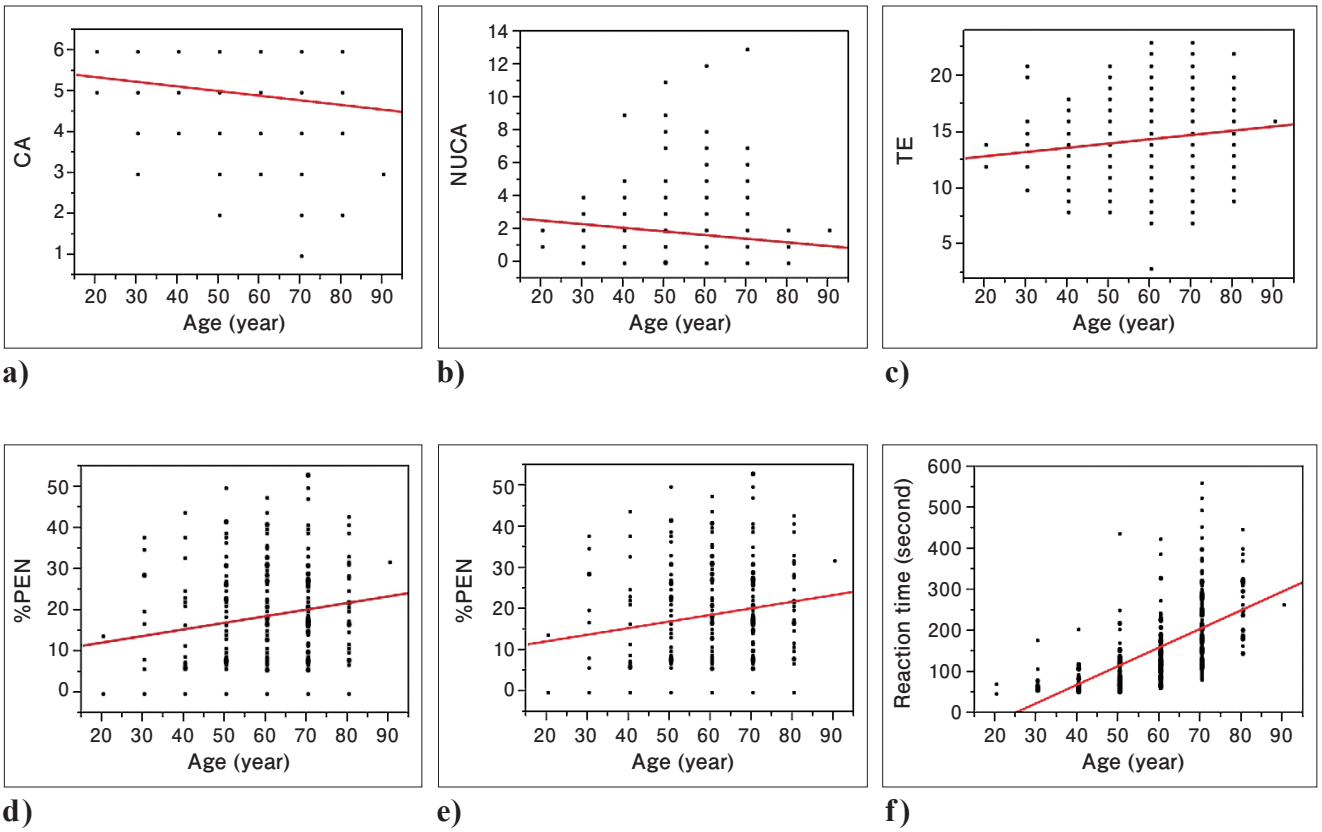

Fig. 1. **Relationship between WCST parameter and aging.**

a) CA, y = −0.01x + 5.59, R^2 = 0.027, p = 0.002. **b)** NUCA, y = −0.02x + 3.02, R^2 = 0.019, p = 0.009. **c)** TE, y = 0.04x + 12.17, R^2 = 0.079, p = 0.010. **d)** %PEM, y = 0.04x + 7.18, R^2 = 0.002, p = 0.391. **e)** %PEN, y = 0.16x + 9.19, R^2 = 0.024, p = 0.004. **f)** Reaction time, y = 4.54x −109.18, R^2 = 0.357, p < 0.001. n = 351. WCST, Wisconsin Card Sorting Test; CA, categories achieved; NUCA, numbers of response cards used until the first category achieved; TE, total errors; %PEM, percentage perseverative errors of Milner; %PEN, percentage perseverative errors of Nelson.

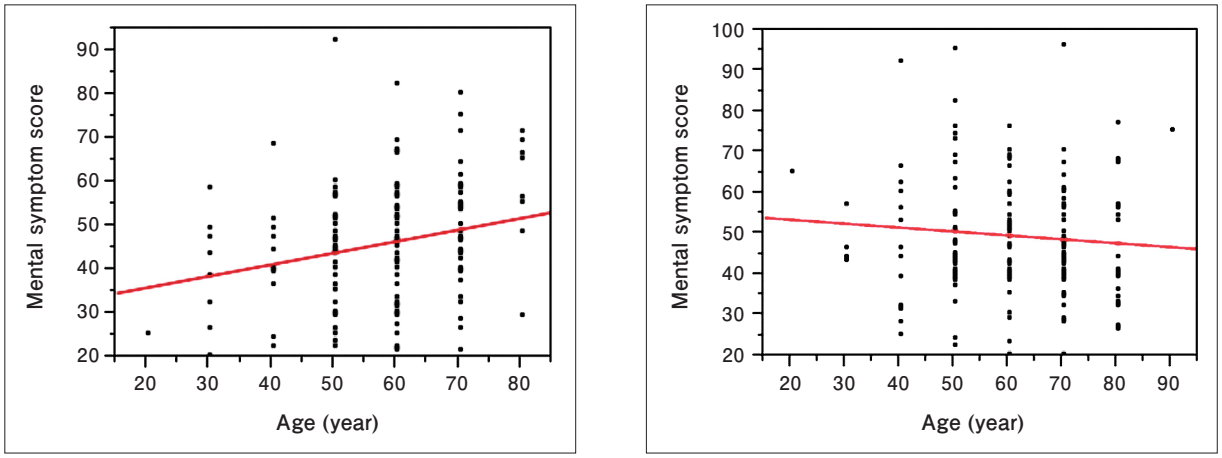

Fig. 2. **Relationship between mental symptoms in AAQOL and aging.**

a) Male, y = 0.26x + 30.75, R^2 = 0.059, p = 0.001, n = 179. **b)** Female, y = −0.10x + 55.6, R^2 = 0.008, p = 0.245, n = 172. Y axis shows the total score of mental symptoms in AAQOL. AAQOL, Anti-Aging Quality of Life Common Questionnaire; AAQOL; CI, confidence interval.

Table 1. Correlation analysis between neural age and "Mental symptom" score in AAQOL.

Mental symptoms	Male	R^2	p value	Female	R^2	p value
Depressed	0.01x + 1.13	0.032	0.017	− 0.01x + 2.77	0.037	0.011
Lapse of memory	0.02x + 2.32	0.036	0.011	0.02x + 2.17	0.046	0.005
No feeling of happiness	0.02x + 0.96	0.028	0.006	− 0.01x + 2.77	0.025	0.040
Feeling of uselessness	0.01x + 1.09	0.048	0.026	− 0.01x + 2.56	0.014	0.127
Nothing to look forward to in life	0.02x + 0.81	0.034	0.006	− 0.01x + 2.58	0.005	0.198
Loss of motivation	0.01x + 1.41	0.034	0.013	− 0.01x + 2.30	0.001	0.090
Daily life is not enjoyable	0.02x + 0.74	0.080	<0.001	− 0.01x + 2.74	0.001	0.073
Loss of confidence	0.01x + 1.35	0.023	0.045	− 0.01x + 2.91	0.021	0.056
Inability to sleep because of worries	0.02x + 0.94	0.083	<0.001	0.003x + 2.35	0.001	0.616
Difficulty in falling asleep	0.03x + 0.85	0.069	<0.001	0.01x + 1.95	0.023	0.045

Male; 63.5 years (95% CI: 61.6 ～ 65.3), n = 179. Female; 65.7 years (95% CI：63.8 ～ 67.5), n = 172. AAQOL, Anti-Aging Quality of Life Common Questionnaire; AAQOL; CI, confidence interval.

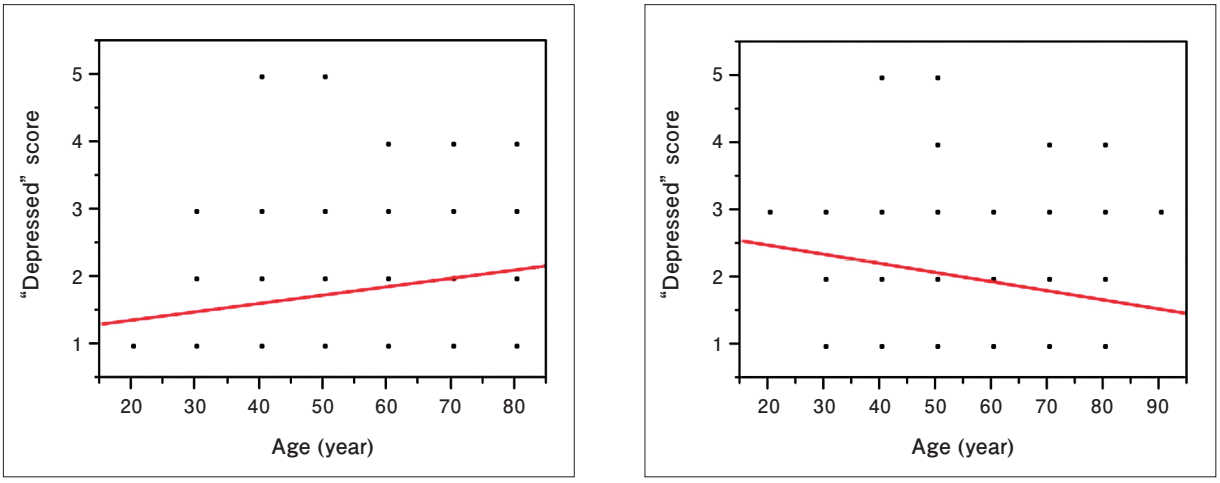

Fig. 3. **Relationship between mental symptom "depression" and aging.**

a) Male, y = 0.01x + 1.13, R^2 = 0.032, p = 0.017, n = 179. **b)** Female, y = −0.01x + 2.77, R^2 = 0.037, p = 0.011, n = 172. Y axis shows scores of mental symptom "depression" in AAQOL. AAQOL, Anti-Aging Quality of Life Common Questionnaire; AAQOL; CI, confidence interval.

Table 2. Correlation analysis between neural age and physical information.

	Male	R^2	p value	Female	R^2	p value
BMI [kg/m²]	− 0.61x + 73.56	0.011	0.160	1.64x + 23.73	0.083	<0.001
Body Fat [%]	0.45x + 47.70	0.017	0.081	1.30x + 24.78	0.166	<0.001
Waist [cm]	0.04x + 55.20	0.000	0.828	0.64x + 11.57	0.133	<0.001
Grip strength (right) [kg]	− 0.88x + 88.48	0.122	<0.001	− 0.69x + 75.22	0.066	<0.001
WBI	− 5.45x + 62.82	0.000	0.688	− 44.6x + 93.25	0.046	0.005
Muscle mass [%]	0.69x + 31.90	0.019	0.036	− 0.67x + 81.99	0.014	0.122
Basal metaboric rate [kcal]	− 0.03x + 96.53	0.083	<0.001	− 0.02x + 82.46	0.017	0.093
Brachial muscle [kg]	−16.97x + 71.63	0.032	0.017	11.37x + 56.50	0.004	0.428
Femoral muscle [kg]	− 5.42x + 78.80	0.049	0.003	− 5.36x + 75.31	0.017	0.088

Male; 63.5 years (95% CI: 61.6 ～ 65.3), n = 179. Female; 65.7 years (95% CI：63.8 ～ 67.5), n = 172. BMI, body mass index; WBI, weight bearing index = leg extension strength ÷ body weight; CI, confidence interval.

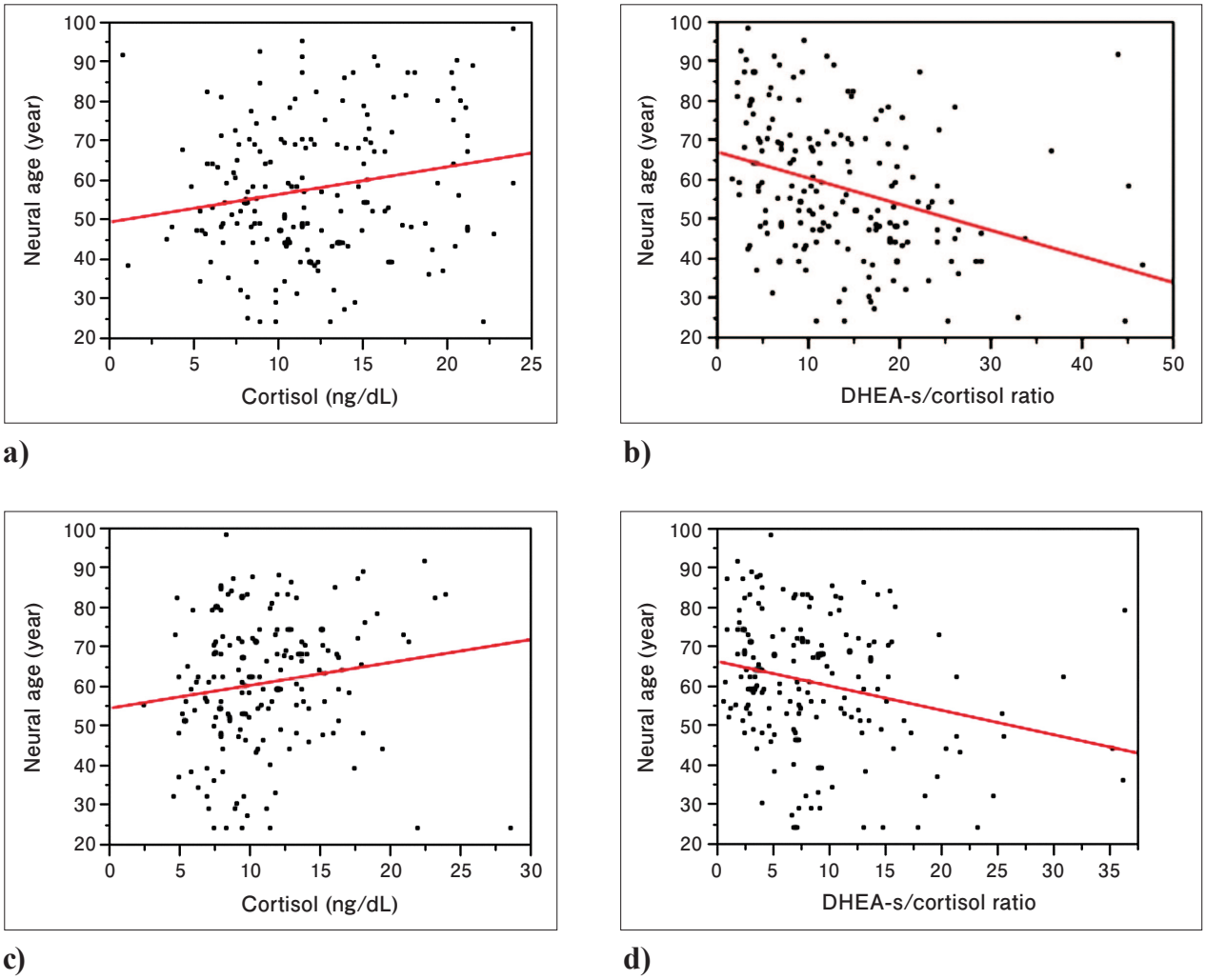

Fig. 4. **Stress-related hormones and neural age.**

a) Cortisol in male, **b)** DHEA-s/Cortisol ratio in male, **c)** Cortisol in female, **d)** DHEA-s/Cortisol ratio in female. Y axis shows neural age. Serum cortisol concentration shows positive correlation to neural age in male **(a)**; $y = 0.70x + 5.04$, $R^2 = 0.037$, $p = 0.091$, $n = 179$ and in female **(c)**; $y = 0.60x + 54.74$, $R^2 = 0.025$, $p = 0.039$, $n = 172$. DHEA-s/Cortisol ratio shows negative correlation in male **(b)**; $y = -0.66x + 67.43$, $R^2 = 0.116$, $p < 0.001$, $n = 179$ and in female **(d)**; $y = -0.64x + 66.82$, $R^2 = 0.070$, $p < 0.001$, $n = 172$. DHEA-s, dehydroepiandrosterone-sulfate.

Table 3. Multiple logistic regression analysis by using the neurological age as the target variable.

	Male				Female			
	Odds ratio	95% CI		p value	Odds ratio	95% CI		p value
Hypertension	1.02	1.00	1.05	<0.05	1.01	0.99	1.04	0.21
Diabetes	1.03	1.01	1.06	<0.05	1.03	0.99	1.07	0.12
Dyslipidemia	0.99	0.97	1.01	0.52	0.99	0.97	1.01	0.52
Metabolic syndrome	1.00	0.95	1.05	0.90	1.00	0.95	1.05	0.90
Obesity	1.04	1.01	1.07	<0.05	1.04	1.01	1.07	<0.05

Male; 63.5 years (95% CI: 61.6 ~ 65.3), n = 179. Female; 65.7 years (95% CI：63.8 ~ 67.5), n = 172. CI, confidence interval.

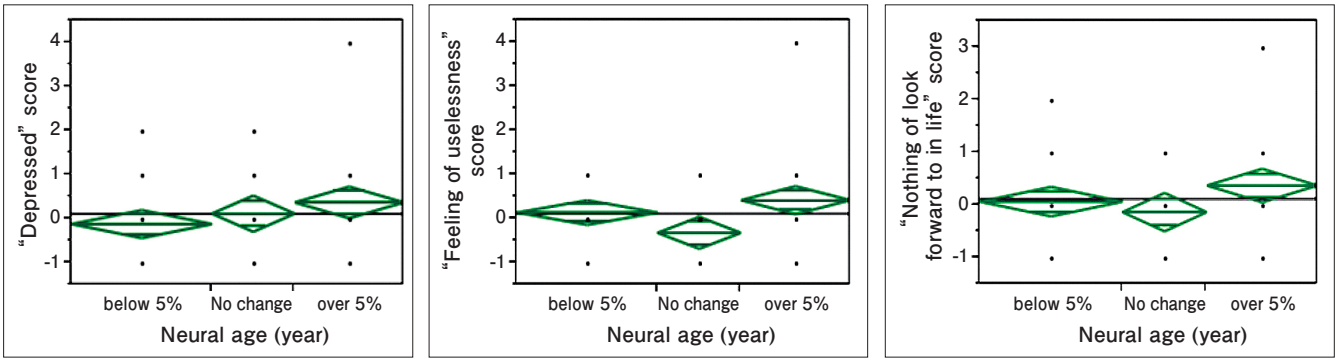

Fig. 5. **Mental symptoms and neural age in male.**

a) "Depressed", **b)** "Feeling of uselessness", **c)** "Nothing to look forward to in life". Y axis shows the Score change of mental symptoms in AAQOL (n = 351). Improvement in "Depressed" tends to rejuvenate neural age (Difference 0.38, 95% CI: −0.10 ~ 0.87, p = 0.09). Deterioration in "Depressed" proceed ageing neural age (Difference 0.39, 95% CI: 0.002 ~ 0.78, p < 0.05). Deterioration in "Feeling of uselessness" ages neural age (Difference 0.39, 95% CI: 63.8 ~ 67.5, p < 0.05). Deterioration in "Nothing to look forward to in life" ages neural age (Difference 0.56, 95% CI: 0.13 ~ 0.99, p < 0.01). AAQOL, Anti-Aging QOL Common Questionnaire; Difference, different values from "No change"; CI, confident interval.

look forward to in life" was recognized to relate to neural aging. The exacerbation of the score for the symptom of "Feeling of uselessness" was recognized to relate to neural aging.

In the case of females, no significant relationship between the changes of these scores and neural aging was recognized.

Discussion

Based on a paper "Happy People Live Longer" by Frey BS, Professor Kazuo Tsubota, Department of Ophthalmology, Keio University, and former chief of the Japanese Society of Anti-Aging Medicine, advocates the concept of "positive thinking." The things relating to "food," "exercise" and "healthy longevity" are being acknowledged among the people who are concerned about anti-aging, but the effects that mental symptoms bring about such as such "positive thinking" and "happy" have not been well known.

In the area of psychology, resilience is defined as the individual's ability to adapt their own life tasks to social disadvantageous and hostile conditions. Both concepts of "in a good mood" and "resilience" can be positioned as measures against mental stress. The measures against mental stress are very important for healthy longevity as well as "food" and "exercise." The clinic, which we belong to, also focuses on measures against mental stress and is giving guidance of "positive thinking (resilience)" to examinees in a positive way.

For excess calories causing glycative stress [11-15] and oxidative stress, there is much evidence indicating they are aging promoting factors. Furthermore, mental stress also affects the endocrine system, autonomic nervous system and immune system through the functions of hypothalamus, pituitary and adrenal systems, and as a result, it promotes aging. A strong mental stress load for a long period of time becomes a factor of depression. It is reported that in the condition of depression, it is possible that hypercortisolemia exists at higher rate and that neurotrophic factors decrease

which harms hippocampal neurons [16]. Furthermore, the study on mental stress by brain function analysis using functional MRI, and the study on neural circuit for emotion control are progressing. Recently, Konishi *et al*. pointed out that brain aging and cognitive impairment are related to the prefrontal cortex ventral [6], and Monchi *et al*. noted that these are related to the caudate nuclei [7]. There are reports that the left prefrontal cortex is involved with agreeable stimuli [17, 18].

WCST that was used for the evaluation of neural age is said mainly to reflect the degree of functional impairment of the prefrontal cortex [4, 5]. Each index of WCST has a strong correlation with aging and it is recognized to be clinically useful as the index of neural age. It was also shown that there is a difference in the correlation between mental symptom and aging between the sexes. Young females' total score of mental symptoms was high, and it was suggested that young females need mental health care. This is matched with the results of recent research by Foster [19]. Even though social participation by women has been progressing recently in Japan, the problem of difference in the terms and conditions of employment between males and females still remain. The above result probably reflects the situation where females are in need of mental elbowroom or they are under a lot of emotional pressure.

In the scattering diagram of real ages and total scores of mental symptoms, it was approximately at the age of 65 and when the total score of mental symptom was 50 that the regression lines of males and females were crossed. Depressed symptoms, in particular, increased with aging in males and on the contrary, it decreased in females. There were many other males with the symptoms of "Nothing to look forward to in life" and "Feeling of uselessness." From the analysis of stress-related hormones in the blood, it was shown that the level of cortisol rises with aging and the D/C ratio lowers in males. If they are exposed to stress, corticotropin-releasing hormone: (CRH) is released from hypothalamus and acts on the pituitary gland, and then adrenocorticotropic hormone (ACTH) is released from the pituitary gland and it stimulates the adrenal cortex, and as a result, cortisol and DHEA are released. However, the release of cortisol is predominant. From these facts, it is assumed that mental stress affected the heart-brain interaction and hypothalamus-pituitary-adrenal axis (HPA-axis), increased cortisol and decreased DHEA and, as a result, it acted in the direction of neural aging.

As a result of the analysis of the conditions before and after the guidance of resilience in males, the rejuvenation of neural age was observed as a result of the improvement of the symptoms of "Nothing to look forward to in life," "Depressed" and "Feeling of uselessness" that had been exacerbated. Cortisol is involved with resilience and, in the case of depression, the concentration of cortisol in the blood increase. Meanwhile, DHEA is involved with the response to stress and mental diseases, and it was shown that the D/C ratio can be an important parameter showing the vulnerability to stress. The prevention of aging is said to be a measure against mental stress, oxidative stress and glycative stress. The results obtained in this research do not contradict these concepts.

Frailty is defined as the conditions showing the physiological reserve lowered with aging and the vulnerability against stress to the body [20]. Frailty is reversible and the prevention against a state requiring long-term care, lack of independence, tumbling, fractures, and death is possible through early and appropriate intervention. Sarcopenia is diagnosed by decreases of grip strength, walking speed and muscle mass. The decreases of grip strength and walking speed are overlapped in both diagnostic criterions of frailty and sarcopenia, so that frailty and sarcopenia are overlapping concepts.

Frailty and sarcopenia have a significant impact on the independence of the elderly. In a report analyzing the relationship between the level of independence and the neural age of the elderly, the differences in neural age among the elderly living an independent life [21], those requiring support attending daycare [22] and those requiring long-term care admitted in a medical care facility for the elderly [23] are discussed. As a result, neural aging had an impact on the degree of independence more remarkably than the muscle age directly related to frailty and sarcopenia had [24].

In this research, the indexes relating to frailty and sarcopenia were also focused on, and the relationships between each index and neural age were analyzed. As the results of body composition tests, in the case of males, the lower BMI was, the higher neural age was and the higher grip strength, quadriceps muscles, WBI and basal metabolic rate were. This suggests that in order to keep neural age young, it is important to prevent frailty and sarcopenia [25]. It is interesting that, in the case of females, the higher BMI was, the higher neural age was; the higher body fat percentage and waist circumference were, the higher neural age was; and the higher grip strength, quadriceps muscle and WBI are, the lower neural age was. In this research, obesity made neural age high in both males and females. However, the differences between the sexes in BMI became salient with age: a lower BMI caused higher neural age in males, but it caused a lower neural age in females. It is reported that the higher obesity and BMI are, the lower the mortality rate from heart failure is. This is discussed as the "obesity paradox," and it is interesting that males become physically weaker than females through age and their incidence rates of cancer and lifestyle diseases become higher [26-28].

It was found that diabetes, hypertension and obesity caused aging in the nervous system and prefrontal cortex functions through a multivariate analysis between lifestyle diseases and neural ages. There are several papers concerning the relationship between diabetes and dementia [29-31] and it has been discussed that insulin resistance, high insulin level and insulin-degrading enzymes are also involved in the degradation of amyloid-beta, and that high blood glucose accumulates amyloid-beta [32, 33]. Diabetes and obesity are typical diseases involved in strong glycative stress. Glycative stress is a series of reactions where blood glucose, triglyceride and the rise of triglyceride form the intermediates of glycation reaction having aldehyde group (3-deoxyglucosone: 3DG, glyoxal, methylglyoxal, glyceraldehyde, etc.), they Amadori-modify protein in vivo, and it causes carbonyl modification and forms advanced glycation end products (AGEs). The increase of toxicity caused by glycation of amyloid-beta and the acceleration of neurodegenerative fibril change are involved in the progression of Alzheimer's type dementia [34, 35]. Diabetes and obesity were identified as risk factors involved in the aging of the nervous system by multivariate analysis. Therefore, it is supported that glycative stress is an aging risk factor of the nervous system. The relationship between hypertension and cerebrovascular disorders also is discussed [36, 37].

It was presumed that females have more "positive thinking" and are younger in neural age than males due to their strength of resilience, and they are preventing diseases and extending their healthy longevity.

Summary

1) WCST can examine the functional disorder of prefrontal cortex and each index is clinically significant as an index of neural age.
2) Mental stress affected heart-brain interaction and HPA-axis and was involved in the aging of the nervous system by increasing cortisol and decreasing DHEA.
3) The cases of mental symptoms including "Depressed" increased with age in males, and on the contrary, they decreased in females. There were many males, in particular, who were suffering exacerbated metal symptoms such as "Nothing to look forward to in life," "Depressed" and "Feeling of uselessness" and the improvement of these symptoms was effective in the prevention of the aging of the nervous system.
4) In order to maintain a young neural age, it was important to prevent frailty and sarcopenia by increasing grip strength, quadriceps muscle, WBI and basal metabolic rate.
5) Diabetes, hypertension and obesity were extracted as the factors lowering the functions of the prefrontal cortex.
6) It was shown that elderly females have better "positive thinking," are younger in neural age and stronger in resilience than elderly males and it was suggested that these characteristics of the elderly females possibly prevent diseases and extend their healthy longevity.

Conclusion

Elderly females were younger in neural age and had better "positive thinking" than elderly males. It is important to improve mental symptoms, increase and maintain the quadriceps muscle mass, prevent frailty and aging of nervous system and improve "positive thinking" in order to prevent lifestyle diseases and dementia and extend healthy longevity. Let's aim at our healthy longevity!

Conflict of interest

The authors declare no conflict of interest in this study.

Acknowledgement

The outline of this research was presented at the 17th meeting of Japanese Society of Anti-Aging Medicine on June 2nd-4th, 2017 (Tokyo) and the 31st meeting of Japan Physicians Association on October 8, 2017 (Osaka).

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