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## Pyrroloquinoline quinone disodium salt improves brain function in both younger and older adults†

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Brain function is important for a good quality of life. Pyrroloquinoline quinone disodium salt (PQQ) has been proven to improve brain function and cognition in older adults (above 45 years). In this double-blind, placebo-controlled study, we investigated the effects of PQQ on cognitive function in adults aged between 20 and 65 years. PQQ (20 mg per day) was administered for 12 weeks to the participants. After 12 weeks, the participants showed improvements in composite memory and verbal memory. A further age-stratified analysis was performed. In younger adults (aged 20–40 years), PQQ improved cognitive function (cognitive flexibility, processing speed, and execution speed) after 8 weeks. Only older adults (aged 41–65 years) showed improvements in complex and verbal memory after 12 weeks. In the logistic regression analysis that included the results of all cognitive tests, the changes due to PQQ intake were observed at 8 and 12 weeks in the young and old groups, respectively.

### 1. Introduction

The brain has advanced functions that are essential for life support. Cognitive function includes a variety of processes such as perception, attention, memory, decision-making, and language comprehension. It is a higher-order brain function. However, cognitive function must be maintained and improved as it deteriorates with age. Improvement of cognitive function is also essential in young people with conditions such as attention deficit hyperactivity disorder, to improve their quality of life. Various food items have been shown to improve cognitive function.<sup>1</sup> One of them, discussed herein, is pyrroloquinoline quinone disodium salt (disodium 9-carboxy-4,5-dioxo-4,5-dihydro-1*H*-pyrrolo[2,3-*f*]quinoline-2,7-dicarboxylate: PQQ), which is a water-soluble salt of the coenzyme pyrroloquinoline quinone.<sup>2,3</sup> Products with PQQ have been registered for use in the USA, the EU, and Japan (BioPQQ in Japan and the USA; MGCPQQ in the EU).<sup>4</sup> Pyrroloquinoline quinone disodium salt is obtained using fermentation and purification.

It has been subjected to multiple safety tests. Various functions of PQQ have been reported, including mitochondrial biogenesis, promoting longevity, antioxidant activity, and improving skin texture.<sup>5–8</sup> *In vitro* studies have reported that PQQ has a strong neuroprotective effect against neurotoxicity and enhances the expression of nerve growth factor (NGF).<sup>9,10</sup> In addition, water maze tests in rats have shown that oral ingestion of PQQ promotes memory learning and suppresses memory loss caused by oxidative stress.<sup>11</sup> These studies indicate that PQQ could be used as a brain food, and clinical trials related to brain function have been conducted. In healthy adults, PQQ reportedly improves attention, information identification and processing, language memory, immediate memory, working memory, and sleep as well as reduces stress and fatigue.<sup>12–16</sup> However, most studies involved older individuals, and very few studies included young adults. Furthermore, only a few studies have evaluated the effects of PQQ in a wide range of age groups. In recent years, data analysis technologies are being extensively used and machine learning is widely applied. Several clinical trials have been conducted using newly developed technologies, including logistic regression.<sup>17,18</sup> This technique can be used to classify groups based on highly variable data. Wide age groups are expected to have variability scores in brain function tests. We used all data from the Cognitrix test to determine whether we could distinguish between placebo and PQQ recipients, that is, to determine whether there were changes in cognitive function with PQQ intake. Herein, we report the effects of PQQ on brain function in individuals aged between 20 and 65 years.

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Cognitive function improvement is necessary for all individuals irrespective of sex. We conducted this research without considering sex as a factor.

## 2. Materials and methods

### 2.1 Clinical test

This study has been registered at the UMIN Clinical Trials Registry System under UMIN ID UMIN000034459 (<https://www.umin.ac.jp/icdr/index.html>). The study was performed with a double-blind placebo control. Informed consent was obtained from all participants. Mitsubishi Gas Chemical Company Inc. commissioned a contractor of Huma R & D Co., Ltd to perform this clinical test. The pyrroloquinoline quinone disodium salt used in this study was BioPQQ, manufactured by Mitsubishi Gas Chemical Company (Tokyo, Japan). The capsules used in the test group contained 20 mg PQQ, 224 mg starch, and 5 mg Ca stearate. The capsules used in the placebo group contained 224 mg starch and 5 mg Ca stearate. One capsule was taken with water after breakfast, every day.

**Safety.** There were no adverse events associated with the test food. There were no serious adverse events or adverse events leading to the discontinuation of the test food. As preliminary tests, blood tests (ESI excel file<sup>†</sup>); mini-mental state examination (MMSE); and height, weight, and comprehensive body composition measurements were performed. The selection criteria were as follows: healthy volunteers with no serious illness, aged between 20 and 65 years, with no abnormalities in cognitive function with an MMSE score of 24 or higher, and those who could maintain a constant lifestyle during the test period. Participants were chosen regardless of sex after obtaining written informed consent. Participants who were being treated for mild chronic diseases (*e.g.*, hypertension and hyperlipidemia) were selected at the discretion of the investigator.

**Cognitive test.** The test developed by CNS Vital Signs (Health solution, Inc., Tokyo, Japan) called Cognitrix was used.<sup>19</sup> This test is conducted online. The following 15 kinds of brain functions were assessed: composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive speed, social acuity, reasoning, working memory, sustained attention, simple attention, and motor speed.

The exclusion criteria were individuals with serious liver/kidney disease, heart disease, respiratory disorder, an endocrine disorder, diabetes, food allergy, drug allergy, cancer, dementia and mental illness, and allergy to gelatin; pregnant women/nursing women; those who wished to become pregnant during the test period; those who had taken PQQ within 3 months before the study; and those who were deemed unsuitable by the physician for participation. Blood and urine tests were performed in advance at weeks 8 and 12.

### 2.2 Software

All software used Python (<https://www.python.org/>). Statistical analyses were performed using the “stats” module in the

library scipy1.5.2 of python3.8.5. Machine learning used the library scikit-learn 0.23.2.

### 2.3 Ethics review

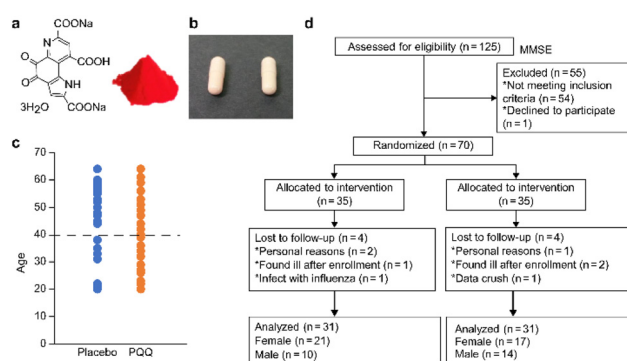
Yoga Allergy Clinic Clinical Research Ethics Review Board (Installation location: 4-32-16 Yoga, Setagaya-ku, Tokyo Establisher: Tadao Kawamura) and Nihonbashi Egawa Clinic Clinical Research Ethics Review Board reviewed and approved the study; approval number RD10010TS04. This study complied with the ethical principles of the Declaration of Helsinki (adopted in 1964, and revised in October 2013). Furthermore, the study was based on the Japanese law “Ethical Guidelines for Medical Research for Humans (2014 Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor and Welfare Notification No. 3)” and “Law Concerning the Protection of Personal Information (May 30, 2003, Japanese Law No. 57)”.

**Participant privacy and protection of human rights.** All aspects related to this study were handled in accordance with the “Act on the Protection of Personal Information (May 30, 2003, Law No. 57)”.

## 3. Results and discussion

### 3.1 Clinical study

Pyrroloquinoline quinone (4,5-dihydro-4,5-dioxo-1*H*-pyrrolo [2,3-*f*]quinoline-2,7,9-tricarboxylic acid) was fermented by bacteria and purified under good manufacturing practice (GMP, food grade). Currently (2022), only MGCPQQ (BioPQQ in the US and Japan), which was used in this study, is permitted as a food in the EU. The product is highly pure as determined using HPLC analysis (ESI Fig. S1 and S2<sup>†</sup>). The commercial product of PQQ is a red trihydrate crystal (Fig. 1 and Fig. S3<sup>†</sup>).<sup>20</sup> This product is safe, as it involves the use of a non-genetically modified organism (non-GMO), and is usable by



**Fig. 1** Materials used and age distribution. (a) Chemical structure and image of pyrroloquinoline quinone (PQQ). PQQ disodium trihydrate is a red powder. (b) Capsules for a clinical study. The left capsule is the placebo and the right capsule contains PQQ. (c) Age distribution of participants. The line indicates the two age groups. Groups: All: age 20–64 years; Old: age 41–64 years; and young: age 20–40 years. (d) Flow diagram of this study. Cognitrix test at 0 W, 8 W, and 12 w.



vegetarians. Hard capsules made of cellulose contained 20 mg PQQ, and they were ingested daily by the participants. The placebo group received capsules without PQQ (Fig. 1). The placebo and PQQ capsules were similar in terms of appearance.

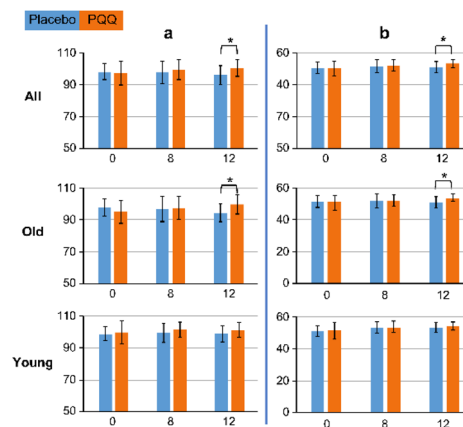
This study was conducted in a double-blind manner to assess cognitive and brain functions in healthy Japanese adults aged between 20 and 65 years. The Cognitrix test is used for various kinds of cognitive functions.<sup>21</sup> This is a computerized neurocognitive test. The measurement of brain function of a food component using the Cognitrix test has also been reported.<sup>22</sup> We analyzed 15 kinds of brain function. Each participant visited a medical institution (testing institution) and underwent the tests and diagnoses prescribed. With respect to the schedule, inspections were carried out at 0 weeks (0 w: first inspection day), 8 weeks (8 w), and 12 weeks (12 w) of ingestion.

The person responsible for test food allocation adopted the Cognitrix task as a comprehensive cognitive function assessment, because the original cognitive function may be a confounding factor, and used the standardized score results and age structure of the Cognitrix Neurocognitive Index task. Randomization was performed *via* dynamic allocation, and the participants were assigned to the following two groups: a test food group and a control food group.

The test food allocation manager supervised the food allocation table and ensured that blinding was maintained for all other parties involved. The test period was 12 weeks. No adverse events were observed after the ingestion of the test food. Of the 70 participants, 66 completed the test, and 4 dropped out. In addition, the data of one participant were corrupted. The age distribution of the participants is shown in Fig. 1 and Table 1, and the data were found to be continuous.

Three types of analysis were performed. The group named "All" included participants of all ages. The "Old" group included individuals aged 41–65 years. The "Young" group included individuals aged 20–40 years. The mean, standard deviation, and *P*-value of the changes before and after ingestion of the test food were calculated in the PQQ and placebo groups.

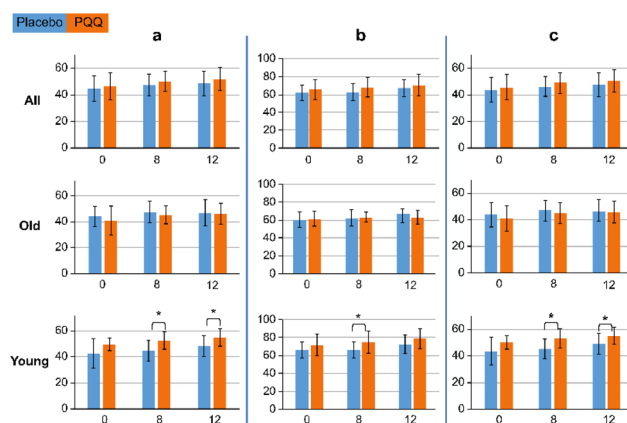
Data analysis was performed using Python statistical software. All results are shown in ESI Tables S1–S3.† The cognitive function showed an improvement in score with the administration of PQQ and an overall significant difference in composite memory ( $P = 0.003$ ) and verbal memory ( $P = 0.001$ ). Fig. 2 (ESI Fig. S4†) shows the results, along with an age-specific ana-



**Fig. 2** Composite memory and verbal memory scores of the placebo and pyrroloquinoline quinone (PQQ) groups. The blue bar indicates the placebo. The red bar indicates PQQ. (a) Composite memory scores increased significantly in the PQQ group after 12 weeks for all ages and old age. (b) Verbal memory scores increased significantly in the PQQ group after 12 weeks for all ages and old age. No significant change was observed in the young age group. \*:  $P < 0.05$ .

lysis, of this function. In the Old group, composite memory ( $P = 0.011$ ) and verbal memory ( $P = 0.002$ ) improved at 12 weeks of PQQ ingestion. No differences were observed in the Young group in terms of verbal memory and composite memory.

In the age-specific analysis, some functions improved upon PQQ ingestion, whereas some functions did not show a significant difference among the groups. There was a significant difference in cognitive flexibility, processing speed, and executive speed in the Young group at 8 weeks. The results are shown in Fig. 3 (ESI Fig. S5†). There was no significant difference in these functions between the other two groups.



**Fig. 3** Characteristic cognitive function scores for the Young group. The blue bar indicates the placebo. The red bar indicates PQQ; (a) indicates the cognitive flexibility scores. The scores increased significantly in the PQQ group after 8 and 12 weeks. (b) Scores for processing speed increased significantly in the PQQ group after 8 weeks. (c) Scores for executive speed increased in the PQQ group after 8 and 12 weeks. \*:  $P < 0.05$ .

**Table 1** Age distribution of the placebo and pyrroloquinoline quinone (PQQ) groups

	Age (years)		Number		
	Average	SD	Placebo	PQQ	
Total (age 20–65 years)	41.5	13.7	62	31	31
Old (age 41–65 years)	52.9	6.6	33	18	15
Young (age 20–40 years)	28.8	6.7	29	13	16



### 3.2 Logistic regression

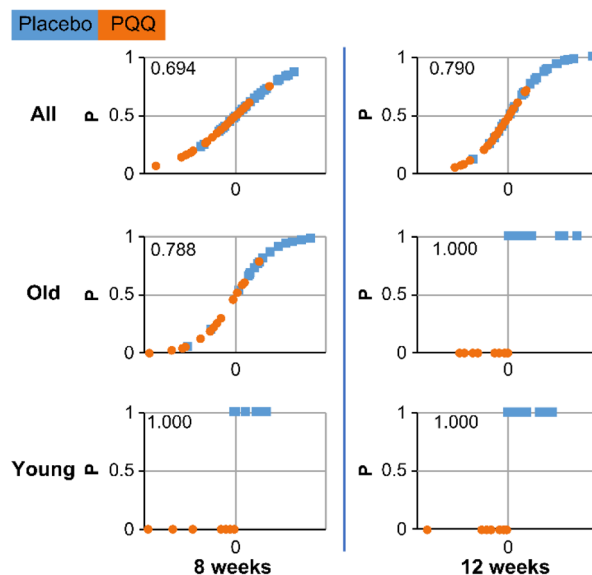
Logistic regression was used for distinguishing the PQQ and placebo groups. This analysis differentiates between placebo and PQQ intake groups across all data, rather than individual trial items. In other words, it determines whether the two groups can be separated from the overall cognitive function test results. It is a method to determine the effect of PQQ intake with high sensitivity. PQQ was considered to affect cognitive function if the effects of its intake and non-intake could be distinguished. Data from the 15 cognitive functions, divided into training and testing data, were used in the analysis (ESI Scheme S1†), and the results are presented in Table 2. The correct answer rate indicated differences between the groups. The logistic regression analysis was based on the premise that unavoidable errors and mistakes are mixed in any measurement. In other words, we determined whether the results were valid probabilistically; if the probability is  $\leq 0.5$ , it is difficult to conclude, but if it is  $> 0.5$ , a conclusion can be drawn. Furthermore, as the period of ingesting PQQ increased from 8 weeks to 12 weeks, the differences between the groups, as determined using a double-blind test, increased. This showed that the efficacy increased as a function of the ingestion time. The correct answer rate for 8 weeks was slightly more than 0.5, and it increased to 0.67 at 12 weeks. At 12 weeks, PQQ intake affected cognitive function. There was a difference in the duration of PQQ intake. Thus, the results of the double-blind study showed that the effectiveness of PQQ increased as a function of time. Here, the logistic regression analysis showed the distribution of the two groups, placebo, and PQQ, and this finding is consistent with the above results. Cognitive function improves after 12 weeks of PQQ intake.

Fig. 4 shows the results of assessing the distinction between the placebo and PQQ groups by machine learning after training all data (ESI Scheme S2†). In the case of logistic regression, the correct answer rate of the result of learning with data (100%) and testing with the same data (100%) is shown as a score. The age-specific analysis showed improvements in the Young group in 8 weeks, with a score of 1.00. Thus, the cognitive function test results show that PQQ is effective compared with the placebo. At 12 weeks, the correct answer rate of both age groups was 0.67, whereas the score of the Old group was 1.00. The analysis of data by age strongly showed the effect of PQQ. Additionally, the results of the logistic regression analysis demonstrated that as the age distribution of the group becomes smaller, the effect of PQQ becomes clearer.

**Table 2** Correct answer rates in the placebo and pyrroloquinoline quinone (PQQ) groups at 8 and 12 weeks<sup>a</sup>

Results Correct rate		Analysis condition	
8 weeks	12 weeks	Learning data number	Test data number
0.57	0.67	50	12

<sup>a</sup> 5-fold stratified cross-validation.



**Fig. 4** Logical function scores. Each dot represents an individual participant. The score indicates the probability of being able to determine placebo or PQQ intake. A score of 1 can be completely determined from the Cognitrix score. The score for all ages was 0.694 at 8 weeks and 0.790 at 12 weeks. The scores improved during the test period. In the Young group, the score reached 1.000 in 8 weeks. In the Old group, the score improved from 0.788 to 1.000 from 8 weeks to 12 weeks.

### 3.3 Effect of PQQ

In the present study, the effects of PQQ on the cognitive function of old and young adults were evaluated. A wide range of age (20–65 years) was considered in the present study, in contrast to that in previous studies on PQQ cognitive function.<sup>12–15</sup> The average age group of  $41.5 \pm 13.7$  years comprised several age groups. This average age is close to the average age of individuals in most stable countries, but less than that in Japan.<sup>23</sup> We have tabulated the cognition-related studies using PQQ (Table 3).

These trials involved only elderly individuals, targeting people over 45 years of age. This group comprises individuals older than normal citizens. Therefore, the effects of PQQ on young people remained largely elusive until the present study was conducted.

In our research, the functions that were related by PQQ are as follows: verbal memory is the memory of words. Complex memory is the sum of verbal and visual memories. Cognitive flexibility is the ability to respond to changes in instructions. Processing speed is the ability to process information quickly. Executive speed is understanding and making decisions about rules and concepts. These functions are necessary for leading a social life.

We believe that composite and verbal memories are functions that are strongly affected by PQQ intake in ALL groups. As our study covers a wide age range, it is anticipated that the effect of PQQ intake is unlikely to appear. However, in fact, PQQ intake at a sharp age ( $72.10 \pm 3.77$ ) reportedly improves various brain functions, including attention, information





**Table 3** Clinical studies on the effects of pyrroloquinoline quinone (PQQ) on cognition

	Cognitive function	Age	Ref.
1	Composite memory, verbal memory (cognitive flexibility, processing speed, executive speed)	41.5 ± 13.7 (20–40)	Present study
2	Attention, information identification, processing ability	45–65	12
3	Immediate memory	50–70	Lower score is strong effect 14
4	Attention, working memory	58.6 ± 5.1	Lower score is strong effect (attention) 15
5	Language memory	50–71	13
6	Composite memory, verbal memory cognitive flexibility, processing speed, executive speed reaction time, complex attention, motor speed	72.10 ± 3.77	24

identification, processing ability, immediate memory, working memory, language memory, composite memory, verbal memory, cognitive flexibility, processing speed, executive speed, reaction time, complex attention, and motor speed.<sup>24</sup> Furthermore, composite and verbal memories are effective in older adults. In contrast, the young group did not show a significant difference plausibly because this group's composite memory was good from the beginning.

Age-based analysis indicated that the improvements in cognitive flexibility and executive speed are more effective in the young group. The processing speed showed a significant difference at 8 weeks and no effect at 12 weeks because of the weak function. The improvements in the young group were unexpected and significant. In previous studies, cognitive function was found to be high in groups with low scores after the intake of PQQ.<sup>14,15</sup> Therefore, it was speculated that the effect of PQQ would be small because the brain functions in young adults were high. In fact, the score was not low for younger individuals. These features are unique to young people, unlike the old group. Cognitive function changed faster in the young group than in the old group, as determined by the logistic regression analysis. In this study, we were able to observe differences in the effects of PQQ by age.

Our hypothesis is as follows: cognitive function improves faster in the young group than in the old group. It is consistent with the fact that aging is known to lower basal metabolism. Moreover, the effect of PQQ is closely related to the metabolism of mitochondrial neoplasia and activation. Therefore, active metabolism in young individuals could contribute to the differential improvement in cognitive function by age. It is expected that young people with a high metabolism will show improved brain function early by mitochondrial activation. Increased metabolism results in an increase in the production of reactive oxygen species. Thus, the high antioxidant activity of PQQ could contribute to improved cognitive function, especially in younger individuals. Additionally, the cognitive areas differ between young and elderly individuals. The characteristic cognitive area of young people is focused on processing speed, and not memory. Thus, PQQ may also improve functions that have not declined with age.

Cognitive flexibility scores are associated with ADHD.<sup>25</sup> Cognitive flexibility is improved by training.<sup>26</sup> Sports have a positive influence on cognitive function.<sup>27</sup> PQQ increases the expression of PGC-1 $\alpha$ , whose levels are elevated during sports

activities.<sup>3</sup> In the future, determining the influence on learning and sports activities is a challenge in PQQ studies.

## 4. Conclusions

In summary, PQQ improves cognitive functions of cognitive flexibility and executive speed within 8 weeks in young adults aged 20–40 years. Cognitive functions of composite and verbal memories are improved after 12 weeks in adults aged 20–65 years. In the logistic regression analysis, 100% of learning data could determine PQQ intake from the cognitive test results. It was observed that cognitive function improved after 8 weeks in the younger generation. It was found that younger people are more likely to be effective even if different analysis methods are used. The areas of cognitive function are also different. PQQ is a functional food that improves brain function at any age. Our research is expected to expand the area where PQQ is used as a functional food from the elderly to all generations.

## Author contributions

T. S. developed the clinical plan; M. T. analyzed the study results; K. I. wrote the article; and E. N. and S. N. conducted the statistical analysis.

## Conflicts of interest

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