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The Effects of Ubiquinol Intake and Sociophysical Training on the Activation of Psychological and Infrared Camera-Measured Body Temperature Physiology and Blood Molecular Markers: A Pilot Study among Healthy Female Older Adults

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Abstract: A combination of existing treatments with sensing technology may be the most appropriate approach for incurable neuropsychiatric disorders. Dietary antioxidant supplementation, exercise, and cognitive training are individually well-established treatments for neurodegeneration, Alzheimer's disease, and other dementias. Therefore, in a double-blind randomized controlled trial, we evaluated the response of normal healthy older female subjects to coenzyme Q10 supplementation and simultaneous sociophysical training that was undertaken in a non-contact environment using infrared cameras. The current pilot study reports the results from a multivariate analysis of blood biomarkers, body surface temperature measured with infrared thermal cameras, and psychological questionnaire scores from this trial, in which 100 mg/day of supplemental ubiquinol (the reduced form of coenzyme Q10) was administered daily for one month. We found a significant positive correlation between ubiquinol supplementation and positive mood scores in the State–Trait Anxiety Inventory test (STAI-positive) and a weak inverse correlation between ubiquinol supplementation and serum interleukin 4 (IL-4), a systemic inflammatory marker. We also found a significant positive correlation between the standard deviation of body surface temperatures, detected with non-contact infrared image sensors, and both STAI-positive and serum antidiuretic hormone (ADH). The results from this small pilot study indicate the potential synergistic effects of oral ubiquinol intake and sociophysical training on neuropsychiatric health in healthy female older adults.

Keywords: ubiquinol; infrared camera; social–physical training; psychological scores; blood mental markers; aging prevention; non-contact sensing

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1. Introduction

1.1. Background of Ubiquinol Supplementation and Exercise in Older Adults

Neuropsychiatric disorders such as Alzheimer's disease (AD) are known to progress chronically due to advancing age and lifestyle-related nutritional or psychological imbalances [1,2]. Systemic mitochondrial dysfunction and impaired energy production have been suggested as causal mechanisms for the chronic effects of various psychiatric disorders. The ratio of the reduced form (ubiquinol) of coenzyme Q10 (CoQ10), one of the molecules essential for mitochondrial energy production, decreases with age [3], suggesting an association between lower circulating CoQ10 levels and increases in age-related depression and fatigue [4]. Consequently, one focus for the development of AD diagnostic markers is the evaluation of mitochondrial function [5]. As CoQ10 has known protective effects

against amyloid [6], it is reasonable that supplemental CoQ10 (both reduced (ubiquinol) [7] and oxidized (ubiquinone) [8] forms) may prevent age-related cognitive decline in healthy older adults.

Exercise and participation in sports with its associated social interaction have also been shown to be effective against age-related neuropsychological decline [9], perhaps through the actions of the brain-derived neurotrophic factor (BDNF) [10]. The plasma levels of candidate molecular markers, namely progesterone and cortisol [11], glucose and 1,5-anhydroglucitol (1,5AG) [12], thyrotropin (thyroid-stimulating hormone; TSH) [13], tumor necrosis factor alpha [14], antidiuretic hormone (vasopressin; ADH) [15], interleukin 4 (IL-4) [16] and leptin [17], have also previously been related to neuropsychological decline. After preliminary trials and analyses of these candidate molecules, we focused on TSH, IL-4, and ADH in this report. We specifically focused on these three markers for the following reasons: We included TSH as one of our focus markers given the evidence from Polat and colleagues showing a positive effect of participating in sports in combination with CoQ10 supplementation on thyroid hormone metabolism [18]. We included an assessment of IL-4 in this study based on the evidence that exercise was able to induce the anti-inflammatory effect of IL-4 in a mouse model of muscle atrophy [19]. Finally, we included ADH as a key biomarker because, along with oxytocin, it is part of the ventral parasympathetic nervous system and has been considered a physiological indicator of psychological conditions and functions, including socialization [20].

1.2. Design

For the potential resolution of chronic neuropsychiatric disorders that may be attributable to lifestyle factors such as diet and exercise, we carried out a study of the effect of exercise with or without oral ubiquinol supplementation (Figure 1). The comprehensive evaluation method we designed for this study was a combined approach involving a psychological scale; plasma molecular markers; and body surface temperature measured by remote infrared sensing, which is insensitive to the psychological state.

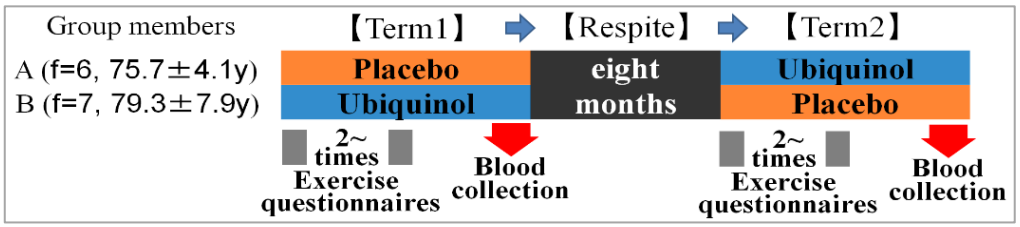

Figure 1. The schedule of the double-blind randomized trial.

The dose (100 mg/day) and duration (one month) of ubiquinol supplementation were chosen as the minimum dose and time expected to result in benefit based on several relevant reports of ubiquinol and ubiquinone [21–23].

The current double-blind randomized controlled crossover trial was designed to identify the synergistic psychological effects of exercise and oral ubiquinol (QH) supplementation on ubiquinone (QO), plasma biomarkers, and sociocognitive behavioral markers in older adults [24].

This study was designed based on the availability of facilities and research collaborators who were willing to participate without compensation. The exercises used were not designed specifically for this study but were chosen as ones that could be easily incorporated into the subjects' lives.

Twenty-five healthy older adults were initially enrolled, and thirteen participants completed the study. To visualize the structure of multivariate dynamics based on principal component analysis, we used our novel analysis technique, BOUQUET (Behavior Output analysis for Quantitative Emotional State Translation) [25–29]. In our previous animal model studies, we found synergism between training that promotes motivation and ubiquinol [30–35], leading to improvement in the activated state of socioemotional

psychology. In the analyses, the use of the BOUQUET method enabled the visualization of state transitions and presumed changes resulting from the formation of complex neural networks through comprehensive time-series changes in a variety of biological signal factors. The BOUQUET method helped us to visualize confounding time-series state transitions with variable types of factors (behavioral, psychological, physiological, and environmental). Our previous study of physical and psychological development in infants could be reported because the BOUQUET method allowed us to reduce the influence of non-target disturbance dynamics that made it difficult to detect patterns in a simple correlation analysis [36]. In this study, we utilized the BOUQUET method to estimate psychobiological mechanisms through computational theory based on multifactor data while hypothesizing the confounding of different complex biological mechanisms.

In addition to tracking the exercise-dependent dynamics of the aforementioned biomolecular markers, we further explored the possibility of capturing representative body temperature signals of these complex physiological systems via infrared image sensing technology as non-contact capturing in body temperature dynamics, which are expected to change in accordance with psychosomatic functional activities [36,37].

2. Materials and Methods

2.1. Analyzed Subjects

This study protocol was previously approved by the Human Research Review Board of the Tokyo University of Agriculture and Technology (TUAT.201103) and was conducted in accordance with the Helsinki Declaration.

This study was supported by the regional public nursing home managed by the social welfare corporation in an urban region of Tokyo. For this study, subjects were recruited from a group of older adults who had completed a previous study [38] exploring the impact of exercise on cognition. The exercise intervention used in the current study was the same as that used in the previous study. First, written consent was received from 25 (male = 2, female = 23) older adults (77.0 $\pm$ 5.3 years old). Of these, 13 (male = 1, female = 12, 76.5 $\pm$ 5.3 years old) were assigned to Group A, and 12 (male = 1, female = 11, 77.6 $\pm$ 6.5 years old) were assigned to Group B. The experiment was conducted in a double-blind fashion. The ubiquinol supplier labeled the ubiquinol and placebo capsules as either A or B prior to shipment, allowing the researchers to remain blinded throughout the experiment. The capsules were indistinguishable from one another. The capsules were then provided to the study subjects with only the A or B identifier. No further information regarding the capsules was provided to the subjects other than to request that they take one capsule per day. Experimenters were unblinded after all data were collected. A total of 13 individuals, 6 in Group A (male = 0, female = 6, 75.7 $\pm$ 4.1 years old) and 7 in Group B (male = 0, female = 7, 79.3 $\pm$ 7.9 years old), completed the entire protocol. These 13 females were analyzed.

2.2. Study Schedule

As shown in Figure 1, we followed a crossover design with the two periods separated by ~8 months. Period 1 lasted from March to May 2011, and period 2 lasted from February to March 2012. During each testing period, subjects took once-daily doses of 100 mg/day of supplemental ubiquinol (Kaneka) or placebo (in the same media; Kaneka) for one month. The typical dosing recommendation for oral ubiquinol is 90–200 mg/day. Since in our previous animal studies, we observed the effects of ubiquinol at lower intakes when it was accompanied by behavioral psychoactive intervention, in this initial study, we chose a dose on the low end of the standard dosing recommendation. During each testing period, subjects participated in two bouts of exercise at a 2-week interval using the same equipment and in the same training room that they were familiar with from their previous study experience. On the last day of each period, venous blood was collected (Figure 1).

2.3. Exercise Training Program and Behavioral Indices

The layout of the exercise training room is shown in Figure 2. During exercise bouts, subjects' behaviors were video-recorded with four wall-set web cameras (two meters high, Figure 2 (18)–(21)). After warm-up exercises were performed in the sitting position, subjects performed exercise training using four different air-pressure-based exercise machines (HURs) (Figure 2 (1) to (4)). Each exercise took approximately one minute and was performed to the beat of a metronome. Each exercise was performed a total of three times and in a cycle of one exercise followed by two breaks. The total exercise program took one hour from start to end. We identified two representative behaviors of the subjects while they rested between exercises in the waiting chairs (Figure 2 (5) to (17)): to record their exercise in a notebook ("writing") or to view participants performing exercise ("view forward"). The frequency per second of these behaviors was quantified and averaged. These behavioral measurement data were not directly analyzed in this study but were used for a foundational assessment that, in the background, confirmed sufficiently healthy cognitive levels in the participating older adults.

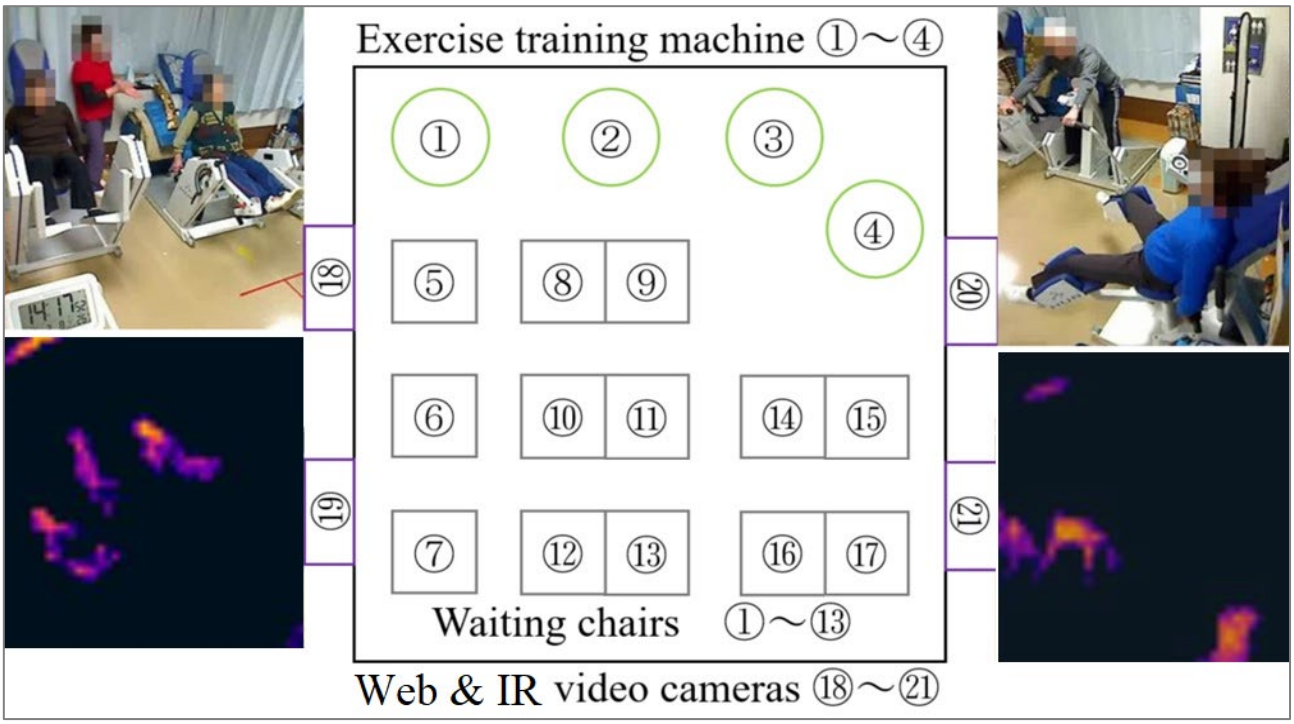

Figure 2. Exercise training room layout: machines (1–4), resting chairs (5–17), and Web and IR video cameras (18–21): (1) foot pedaling; (2) raising and lowering the knees; (3) rowing; (4) opening and closing the legs; (5) to (17) resting chairs during waiting; (18) to (21) four video cameras at the upper sidewalls.

2.4. Psychological Questionnaires

In the exercise room, the participants completed two psychological questionnaires before starting the exercise each day: the State–Trait Anxiety Inventory (STAI) translated into Japanese [39] and the Beck Depression Inventory-II (BDI-II) translated into Japanese [40]. The STAI scores were divided into either positive (calm, secure, ease, satisfied, comfortable, self-confident, relaxed, content, pleasant, satisfied with self, rested, cool and collected, happy, secure, decisions easily, and steady) or negative (tense, strained, upset, worrying over possible misfortunes, frightened, nervous, jittery, indecisive, worried, confused, restless, like a failure, cannot overcome, worry too much, disturbing thoughts, inadequate, unimportant thought bothers me, disappointments, and turmoil) and were summed for multivariate analysis.

2.5. Blood Collection and Molecular Measurement

Six milliliters of peripheral blood was drawn from the arm by clinicians at the nursing home at the end of each period on a different day than when exercise was performed to ensure that blood samples were collected while older participants were in a relaxed state. Blood was immediately centrifuged and separated into serum or plasma, temporarily kept on dry ice, and stored at −80 °C for approximately one week prior to shipment to outside laboratories for the measurement of blood analytes. Ubiquinol and ubiquinone levels were assessed by Kaneka Corp. Thyrotropin (TSH) [13], antidiuretic hormone (ADH), and interleukin 4 (IL-4) levels were measured by SRL Inc. According to the contract laboratories, storage of samples at −80 °C for one week does not affect the measurement results.

2.6. Body Surface Temperature with an Infrared Camera Installed on the Wall of the Room

The wall-installed infrared IR camera continuously acquired thermal images (48 × 47 = 2256 pixels) [36]. Images were saved as CSV files each second and into directories each hour, as controlled by the application software TP-L02 (Chino, Japan). The field angle of the sensor we used was able to be selected as either 25 or 60 degrees depending on the specifications of the objective lens used. We chose the wider field lens (60 degrees). Our sensing technology was originally designed for automobiles and used filtered far-infrared light at 8 to 14 μm for thermally unique object detection with an accuracy of 0.5 °C, and measurements were taken three times per second. In order to automatically detect the highest temperature of a participant's body, we developed a new image-processing algorithm using Microsoft Visual C++ (Microsoft, Tokyo, Japan) and OpenCV 2.2. IR-determined temperatures at each pixel of each image were converted into two-dimensional array variables. As a process to exclude the effects of ambient temperature and distance, the temperatures beside the exercise machine that participants were playing were acquired and referred to for normalization with adjustment using a standard room temperature gauge. The maximum temperatures were generally found around the participants' heads. In this study, instead of further processing for infrared intensity itself, fluctuations in surface temperature within each subject were focused on.

2.7. Multivariate Analysis

In preliminary analyses across the entire dataset, we did not identify any effect of the repetition of the exercises. Therefore, to reduce the number of factors and improve multivariate reliability, the data were analyzed as an exploration of the chronic effects, including psychological scores and IR values obtained at the time of the last exercise along with the measures of related serum analytes collected during the same period. Each marker shown in Table 1 was first compared individually between the groups, i.e., ubiquinol and placebo, by one-way ANOVA. Since this study was designed with comparisons between the ubiquinol and placebo intake condition groups, one-way ANOVA together with the Tukey post hoc test were used to confirm the statistical differences in blood ubiquinol concentrations first. Next, the multivariate correlation structures of all data were visualized using our previously reported method, BOUQUET, based on principal component analysis using a correlation matrix. The coordinates presented by the first (horizontal axis) and second (vertical axis) components were calculated in a data-driven manner from different kinds of indices, such as behavior, analyses, and psychological intensity [27,41]. In the coordinates, each participant's dot was included in a group cluster represented by a variance ellipse whose long and short diameters were calculated via another principal component analysis with a variance–covariance matrix in the abovementioned coordinates. The eigenvectors multiplied by the eigenvalue were superimposed in the coordinate to explain the contribution of each index. The comparison between the two clusters was analyzed by Wilk's lambda using R. In the BOUQUET analysis, which evaluates the state of variance of data reduced to a representative two-dimensional coordinate via principal component analysis assuming confounding among multivariates, the contribution of each factor based on the factor loading vectors was reviewed after confirming the success of the

test implementation condition by checking the statistical difference between the two groups using Wilks' lambda (multivariate analysis of variance: MANOVA) [42]. To confirm the correlational structure of the factors suggested by BOUQUET, Pearson's product–moment correlation analysis in the statistical software R was utilized to search for explanatory factors for the main condition design, and ubiquinol in serum, the sub-focused novel variable, and the infrared image sensor index were inferred as different mechanisms from each other.

Table 1. The correlation analyses between sUbiquinol and markers of biomolecules, body surface temperatures, and psychological scores. R is Pearson's product–moment correlation coefficient. The t-value is the t-distribution size of the difference relative to the variation in sample data. p value is the probability ((*): $p < 0.1$, **: $p < 0.01$, and ***: $p < 0.001$).

Marker	Molecule in Blood Serum	Pearson's Product–Moment Correlation with sUbiquinol		
		R	t	p
sUbiquinol	Ubiquinol: reduced coenzyme Q10	-	-	-
sUbiquinone	Ubiquinone: oxidized coenzyme Q10	**0.798**	**6.492**	**0.000 *** **
TSH	Thyrotropin	−0.180	0.898	0.378
IL-4	Interleukin 4	**−0.347**	**−1.811**	**0.0827 (*)**
ADH	Antidiuretic hormone (vasopressin)	−0.015	0.073	0.942
Marker	**Infrared intensity**			
IR_sd	Body surface temperature: standard deviation	0.256	1.295	0.208
IR_ave	Body surface temperature: average	0.329	1.7056	0.101
Marker	**Psychological questionnaire**			
STAI-positive	State–Trait Anxiety Inventory (positive mood)	**0.502**	**2.844**	**0.00897 ****
STAI-negative	State–Trait Anxiety Inventory (negative mood)	−0.226	1.137	0.267
BDI-II	Beck Depression Inventory-II	−0.277	1.410	0.171

3. Results

3.1. Each Index Comparison between Two Group Conditions, Ubiquinol and Placebo

The measured molecular concentrations in blood, psychological questionnaire scores, and IR signals detected on the body surface in Group A (Term 1: placebo and Term 2: ubiquinol), Group B (Term 1: ubiquinol and Term 2: placebo), and total (the sum of Group A and Group B) are shown in Figure 3. It was confirmed that the participants were compliant with the treatment (ubiquinol or placebo) in each condition, which was confirmed by the difference ($p < 0.05$) in sUbiquinol (ubiquinol in serum; sQH) between study conditions. No other parameter was significantly different when comparing the two conditions ubiquinol (QH: blue) and placebo (P: orange).

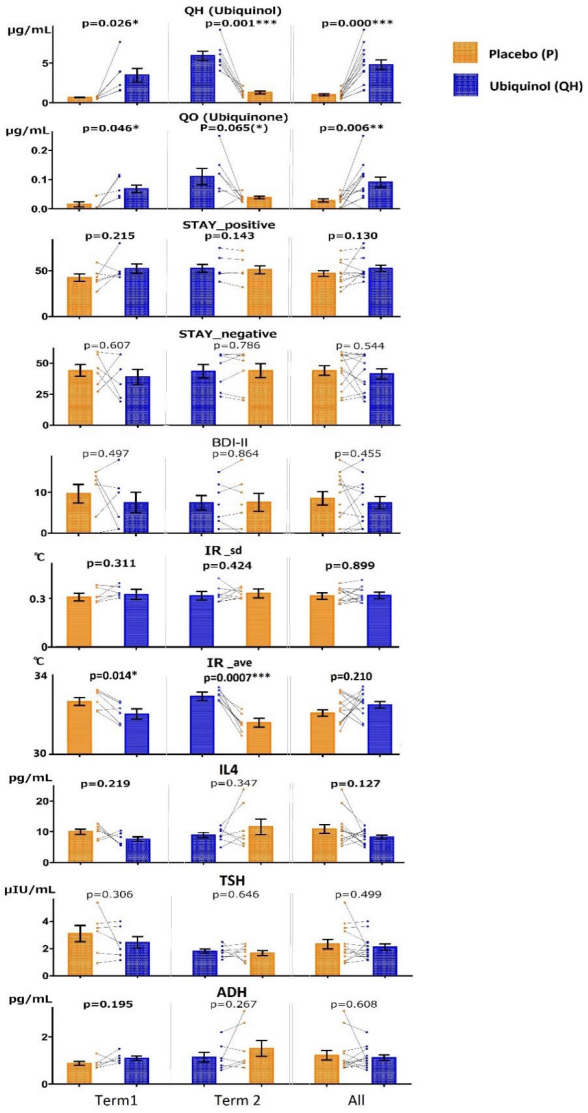

Figure 3. Single-pair comparisons in all the collected data. In Group A, Term 1 is placebo (T1(P)), and Term 2 is ubiquinol (T2(QH)). Group B is reversed; Term 1 is ubiquinol (T1(QH)), and Term 2 is placebo (T2(P)). The final panel in the grouping is the summarized comparison between P and QH intake conditions combining Groups A and B. The statistical results by one-way ANOVA are marked with asterisks ((*): $p < 0.1$, *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$) and thick values ($p < 0.25$).

3.2. BOUQUET Reveals a Moderate Association of Ubiquinol Intake with "STAI-Positive" and a "BDI-II" Reveals a Weak Association with "IL-4"

The multivariate analysis of the collected indices revealed that the coordinates of the first and second components for Group A (shifting from placebo to ubiquinol) were not significant, as shown in Figure 4b (Wilks' lambda; $p = 0.2407$), nor were the first and second components for Group B (shifting from ubiquinol to placebo), as shown in Figure 4c. However, Figure 4a indicates that when considering the total, the data were finally significant (* $p = 0.04926$). These coordinates and the distribution of Groups A and B are summarized as each total variance ellipse for either Group A or B consistently. It is worth noting that the eigenvector of "STAI-positive" is pointed in a similar direction to "sUbiquinol", and the shorter eigenvectors of "BDI-II" and "IL-4" are pointed in opposite directions. "IR_sd" was a shorter eigenvector positioned near "STAI-positive" and "sUbiquinol", in an opposite direction to "BDI-II".

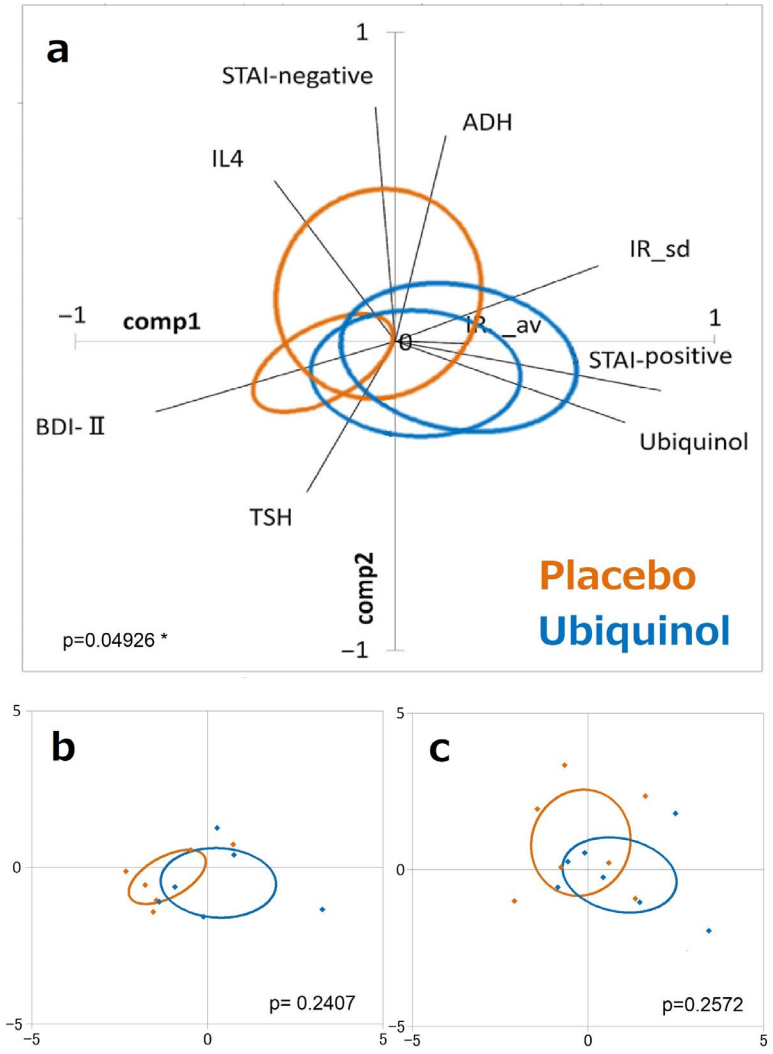

Figure 4. The principal component analysis of all collected indices was visualized in the same coordinates of the first (horizontal) and second (vertical) components: (**a**) The total distribution of Groups A and B was determined on each of the factors' loading plus vectors projecting from the average center. (**b**) The distribution ellipses of Group A shifted from left in Term 1 (placebo, orange) to right in Term 2 (ubiquinol, blue). (**c**) Group B (ubiquinol, blue in Term 1 and placebo, orange in Term 2) appeared to shift in an opposite direction to Group A consistently. The statistical result by Wilks' lambda is marked with a asterisk * ($p < 0.05$).

3.3. Pearson's Product–Moment Correlations with sUbiquinol Indicate a Significant Positive Relationship with STAI-Positive and a Weak Inverse Relationship with IL-4

The multivariate analysis results were further evaluated by Pearson's product–moment correlation coefficients first with sUbiquinol. The results confirmed a positive correlation between STAI-positive and sUbiquinol (Figure 5A, $p = 0.0089$ **) and a tendency toward a weak negative correlation between IL-4 and sUbiquinol (Figure 5B, $p = 0.0827$ (*)). The results for all indices are shown in Table 1.

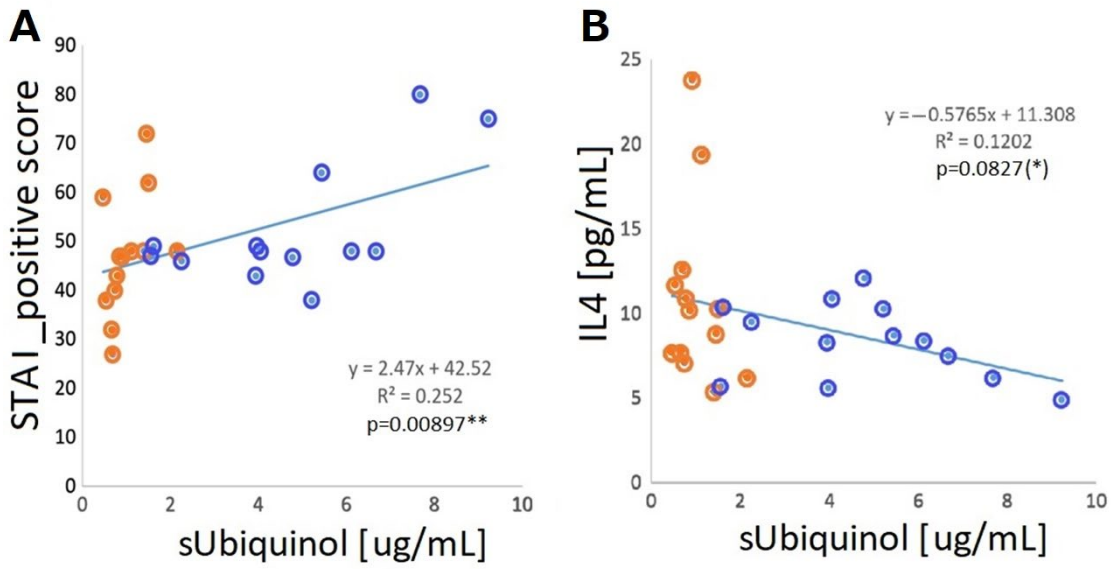

Figure 5. The Pearson correlation coefficient in the dataset between serum ubiquinol density (sUbiquinol) and representative markers. The statistical results were marked with asterisks ((*): $p < 0.1$, and **: $p < 0.01$).

3.4. Pearson's Product–Moment Correlations with the Standard Deviation of IR Body Surface Temperatures Indicate a Significant Positive Relationship between Ubiquinol Intake and STAI-Positive and ADH

Finally, the results of the possible effects of non-contact human sensing using IR thermal detection technology are summarized in Table 2. The same psychological marker previously found to be associated with sUbiquinol, i.e., STAI-positive ($p = 0.036$), was also found to be significantly associated with serum vasopressin density ($p = 0.006$ **).

Table 2. The correlation analyses between the standard deviation of IR-detected body surface temperature and physiological markers and psychological scores. The statistical results are marked with asterisks (*: $p < 0.05$ and **: $p < 0.01$).

Marker	Molecule in Blood Serum	Pearson's Product–Moment Correlation with IR-sd		
		R	t	*p*
sUbiquinol	Ubiquinol	-	-	-
sUbiquinone	Ubiquinone	0.186	0.930	0.362
TSH	Thyrotropin	0.0454	0.223	0.825
IL-4	Interleukin 4	−0.207	−1.036	0.310
ADH	Antidiuretic hormone (vasopressin)	**0.524**	**3.014**	**0.006** **
Marker	**Infrared intensity**			
IR_sd	**Standard Deviation**	-	-	-
IR_ave	Average	0.0985	0.485	0.632
Marker	**Psychological questionnaire**			
STAI-positive	State–Trait Anxiety Inventory (positive mood)	**0.412**	**2.221**	**0.036** *
STAI-negative	State–Trait Anxiety Inventory (negative mood)	0.00601	0.0295	0.977
BDI-II	Beck Depression Inventory-II	−0.321	−1.666	0.109

4. Discussion

In this double-blind randomized study, we evaluated the potential benefit of ubiquinol supplementation [43] and sociophysical exercise [44] for neuroprotection in healthy older adults. Five young, healthy university students piloted the use of the study exercise machines prior to the start of this study and concluded that the exercise was harder than they had imagined. Therefore, our study participants should be regarded as generally healthy enough to participate in the study. In the preliminary simple comparison of ubiquinol and placebo, we found no significant difference in our measured behaviors,

psychological questionnaire scores, or blood biomarkers (Figure 3). Since the body surface temperature index (TR_ave) was significantly different between the two groups, the body temperature differences between groups were likely preserved across test conditions, as it was not affected by ubiquinol intake. Although not statistically significant, a slight inverse trend was seen in ADH. As seen in previous studies, this may be related to the increased expression of vasopressin in thermoregulatory centers of the hypothalamus such as the paraventricular nucleus (PVN) and the suprachiasmatic nucleus (SON) during physical training [45].

However, multivariate analysis revealed a complex correlative structure. Eigenvectors and eigenvalues calculated by principal component analysis and then clustered by conditional group were significantly different. We interpreted this to mean that ubiquinol intake and physical exercise mutually contribute to positive psychological outcomes (presented by STAI-positive) in healthy older adults (Figure 4). We utilized the BOUQUET [46,47] method to comprehensively describe how to relate multiple types of information from different domains with one another and visualize the general structure with the inclusion of confounding factors. The general structure consisted of two axes, one featuring ubiquinol with STAI positivity in a similar direction and BDI-II with IL-4 in the opposite direction. These relationships were statistically confirmed by Pearson bivariate correlation analysis, as shown in Figure 5. BOUQUET analysis considering the interplay between multiple factors revealed a shift in the distribution ellipses of both groups, especially in the relationship between ubiquinol intake and psychological markers such as feeling secure and comfortable, considered STAI-positive features. These results are consistent with reports of response to ubiquinol intake in healthy older adults in Australia and New Zealand [7]. Concerning IL-4, aging leads to an increase in pro-inflammatory cytokines and a decrease in T-cell repertoire and pro-regenerative functions in the central nervous system (CNS) as regenerative functions. The T-lymphocyte secretion of IL-4 suppresses microglial activation, inducing the astrocytic production of glial cell-derived neurotrophic factor (GDNF), contributing to neuroprotection [48]. Ubiquinol has a presumed antioxidant function [49], and our research using animal models described an additional psychological impact of oral ubiquinol intake on socialization [33].

Furthermore, the magnitude of fluctuations in the body surface temperature within each individual that could be captured with a non-contact infrared camera is predicted to have different mechanisms. It may be attributed to both antidiuretic hormones and positive psychological indicators, which makes sense since these hormones have been actively reported to have psycho-dependent regulatory properties in recent years [50,51]. However, further statistical evaluation is needed to examine the reliability of these hypotheses, taking into account the number of replications and confounding among multiple types of factors.

In 2011, during the study, we experienced the Great East Japan Earthquake, which impacted Tokyo and surrounding prefectures [52]. This earthquake and the accompanying Fukushima power plant issues could reasonably be considered the worst experience in our regional history. We did not provide any scientific evidence of how traumatic this background was for four of our participants; however, we could not ignore the effect of this unexpected disaster on our everyday lives. Given the amount and frequency of the discussion we observed about the earthquake and Fukushima during exercise periods, it is reasonable to assume that the participants were in an unusual state of stress that might impact the molecular and psychological testing results. Any unfocused fear or vague anxiety might have led to a depression- and recovery-like response in the BDI-II scores in the placebo phase shown in Figure 4. The first phase of this study (Term 1) was performed just after the earthquake, and the second phase (Term 2) was carried out several months later. It is possible that the participants were experiencing different psychological responses during the immediate (Term 1) and aftermath (Term 2) of the disaster. This may explain the larger difference in distribution (Wilks' lambda $p = 0.263$) between the first-term placebo Group A (Figure 4b, orange) and the second-term placebo Group B (Figure 4c, orange) than between the distributions for the two ubiquinol groups ($p = 0.399$; first-term ubiquinol

in Figure 4c, blue; second-term ubiquinol in Figure 4b, blue). This distribution difference between the placebo and ubiquinol groups might suggest that ubiquinol intake led to a more prolonged response to the disaster, whereas the response in the placebo group was modulated over time, suggesting that memory faded more rapidly in the placebo group. The impact of ubiquinol intake on interleukins has been reported [53]. In this study of ubiquinol intake, IL-4 decreased, suggesting a possible mechanism. The Th2-type cytokine IL-4 is relevant to Alzheimer's disorders and protective against depression due to its ability to counter-regulate inflammation [54] and contribute to acquired stress resilience through BDNF-dependent neurogenesis [55]. Since the relationship between ubiquinol and IL-4 we uncovered suggests the relevance of the immune system in this feasibility step, further experiments should be performed using flow cytometry to identify the involvement of immune cell types in peripheral blood mononuclear cells (PBMCs) [56].

The exercise intervention used in the current study was the same as that used in the previous study. In the current study, 13 participants (male = 1, female = 12, 76.5 $\pm$ 5.3 years old) were assigned to Group A, and 12 (male = 1, female = 11, 77.6 $\pm$ 6.5 years old) were assigned to Group B. The experiment was conducted in a double-blind fashion. Experimenters were unblinded after all data were collected. A total of 13 individuals, 6 in Group A (male = 0, female = 6, 75.7 $\pm$ 4.1 years old) and 7 in Group B (male = 0, female = 7, 79.3 $\pm$ 7.9 years old), completed the entire protocol. All 25 participants completed the ubiquinol intake and exercise trials, but for 12 of the subjects, at least one of the various measurements required for this study was unavailable due to human error (either on the part of the researchers or the subjects). This resulted in only 13 subjects being included in the analyses. All subjects with complete data were included. No bias was involved in removing subjects with missing data.

Males were not specifically excluded from this study. Although we expected approximately equal numbers of male and female participants, only females chose to or were able to fully participate in our study. The population of Japan has the longest life expectancy of any country worldwide. According to the Statistics Bureau of Japan, in 2011, there were 1707 million females and 1268 million males aged 65 years and older. Consistent with the trend of more females than males, in 2021, there were 2057 million females and 1583 million males 65 years of age and older. The older adults who used this service, provided by a city home for the elderly in a Tokyo suburb, were originally approximately ten times more likely to be female. Beyond addressing the experimental question, our study also provided an avenue to communicate with older adults in the community and provide them with a healthy experience while also providing field training for our students. In another study, ubiquinol supplementation, as assessed by the SF-36 subjective quality of life score, resulted in genotype-dependent (single-nucleotide polymorphisms) physical and mental health benefits, but this study also only included females [57]. In order to generalize these results to a broader population, additional, larger studies will need to be performed involving females and males.

The development of wearable sensor systems that track and record human physiological states has been actively underway [58,59], but given the limitations unique to wearables, infrared imaging sensors, which are non-contact, with less stress and thus physiological recording is available with low basic influence on the target person [36,60], were used in this trial. Although it was difficult to address significant effects given the presence of disturbing artifacts associated with the infrared light, the integrated results were consistent with the results indicating that ADH and positive psychological indicators were related to body surface temperature fluctuation [61], suggesting the possibility of successful validation based on previous reports. The mean (IR_ave) and standard deviation (IR_sd) of infrared intensity, i.e., the body surface temperature, were not related to ubiquinol intake (Figures 3 and 4, and Table 1), whereas IR_sd was significantly associated with plasma ADH levels and positive mood scores (STAY-positive) (Table 2). The relationship between alterations in body temperature rhythm and psychological states [36] might be explained by the reported mechanism linking vasopressin and oxytocin with adrenocorticotropin (ACTH)

regulated in the suprachiasmatic nucleus (SCN) and the corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) that are involved in the hypothalamic–pituitary–adrenal (HPA) system [62]. Because we used low-resolution infrared image sensors to detect the temperature on the same body part, usually the head, there were some potential limitations associated with measuring body surface temperatures.

In this study, subtle differences between anxiety states, as determined by STAI-positive and -negative indicators, and depression as determined by BDI-II, which is induced by antioxidant supplementation [63], may be observed in multivariate analysis using our BOUQUET method and multiple regression analysis. The relevant molecular mechanism that may explain the significant relationship between ubiquinol and STAI-positive indicators (Figure 4 and Table 1) could include the increase in IL-4 levels, which has been shown to accompany decreases in catalase activity, ROS, and neuron-specific enolase levels when physical training was studied in individuals with Alzheimer's disease [64]. Although not measured in this study, ubiquinol supplementation in our subjects may also lead to the suppression of these important factors.

Regarding the potential relationship between CoQ10 supplementation and inflammation, in addition to the correlation we found between sUbiquinol and IL-4, the literature includes reports of relationships with IL-6 and other cytokines [65]. Further study is required to appreciate the potential effects of CoQ10 supplementation on systemic inflammatory state.

As for a mechanism that may include the other representative axis, IR-sd, ADH, STAI-positive, and BDI-II (Figure 4, Table 2), we examined the potential role of ADH (vasopressin). Vasopressin regulates water and electrolyte balance and has a diagnostic role in cardiorenal dysfunction. Regarding the vasopressin pathway, the cytokine IL-4, and exercise, Toschi et al. showed that the expression of the vasopressin receptor V1aR is regulated during skeletal muscle regeneration and that vasopressin signaling is a powerful enhancer of muscle regeneration through a mechanism involving IL-4 [66]. In addition, vasopressin and its receptors are expressed in the brain, and evidence points to their role as stress biomarkers of anxiety disorders and depression that may be related to alterations in body temperature [67,68].

In order to corroborate and further our results, additional studies of longer duration, with more subjects, including both males and females, need to be performed. In these studies, additional potential confounding factors such as nutritional status, diet, habitual and acute exercise status, and more in-depth evaluations of psychological and physiological state should be evaluated to determine the potential of more subtle age-related changes that may exist. Given the success of our small pilot program in promoting motivation and enhancing health in older adults, we feel that a longer study is warranted and will potentially allow for the dissemination of this intervention for broader use.

5. Conclusions

While the number of subjects was relatively small, all crossover trial data, including questionnaires and blood markers, were carefully analyzed for common hypothetical mechanisms of psychological improvement with ubiquinol supplementation and sociophysical exercise. We found a significant positive correlation between ubiquinol supplementation and positive mood scores in the State–Trait Anxiety Inventory test (STAI-positive) and a weak inverse correlation between ubiquinol supplementation and serum IL-4, a systemic inflammatory marker. We also found a significant positive correlation between the standard deviation of body surface temperatures, detected with non-contact infrared image sensors, and both STAI-positive and serum ADH. The results from this small pilot study indicate the potential synergistic effects of oral ubiquinol intake and sociophysical training on neuropsychiatric health in healthy female older adults.

The relative reproducibility of our findings is supported by statistically screening multiple factors simultaneously and may suggest a new approach to visualizing complex psychological modulation in quantitative terms. This study is still at an early stage, and

further investigation in basic and clinical fields is needed to better describe the synergistic effects of oral ubiquinol intake and sociophysical training on neuropsychiatric health in healthy older adults.

Author Contributions: M.K. performed the study, and M.O., M.H. and M.K. analyzed the study. M.O., M.H., R.C. and M.K. also contributed to the research design, analysis, and manuscript organization. M.K. is the representative researcher. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study protocol was approved by the Human Research Review Board of Tokyo University of Agriculture and Technology (TUAT.2011-03) and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from the participants for the publication of this report and the accompanying images.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy.

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Lauretani, F.; Longobucco, Y.; Ferrari Pellegrini, F.; De Iorio, A.M.; Fazio, C.; Federici, R.; Gallini, E.; La Porta, U.; Ravazzoni, G.; Roberti, M.F.; et al. Comprehensive Model for Physical and Cognitive Frailty: Current Organization and Unmet Needs. *Front. Psychol.* **2020**, *11*, 569629. [CrossRef] [PubMed]
2. Gu, Y.; Nieves, J.W.; Stern, Y.; Luchsinger, J.A.; Scarmeas, N. Combinación de Alimentos y Riesgo de Enfermedad de Alzheimer. Una Dieta Protectora. *Arch. Neurol.* **2010**, *67*, 699–706. [CrossRef] [PubMed]
3. Wada, H.; Goto, H.; Hagiwara, S.I.; Yamamoto, Y. Redox Status of Coenzyme Q10 Is Associated with Chronological Age. *J. Am. Geriatr. Soc.* **2007**, *55*, 1141–1142. [CrossRef] [PubMed]
4. Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Lower Plasma Coenzyme Q10 in Depression: A Marker for Treatment Resistance and Chronic Fatigue in Depression and a Risk Factor to Cardiovascular Disorder in That Illness. *Neuroendocrinol. Lett.* **2009**, *30*, 462–469. [PubMed]
5. Mantzavinos, V.; Alexiou, A. Biomarkers for Alzheimer's Disease Diagnosis. *Curr. Alzheimer Res.* **2017**, *14*, 1149–1154. [CrossRef]
6. Frontiñán-Rubio, J.; Rabanal-Ruiz, Y.; Durán-Prado, M.; Alcain, F.J. The Protective Effect of Ubiquinone against the Amyloid Peptide in Endothelial Cells Is Isoprenoid Chain Length-Dependent. *Antioxidants* **2021**, *10*, 1806. [CrossRef]
7. Stough, C.; Nankivell, M.; Camfield, D.A.; Perry, N.L.; Pipingas, A.; Macpherson, H.; Wesnes, K.; Ou, R.; Hare, D.; De Haan, J.; et al. COQ10 and Cognition a Review and Study Protocol for a 90-Day Randomized Controlled Trial Investigating the Cognitive Effects of Ubiquinol in the Healthy Elderly. *Front. Aging Neurosci.* **2019**, *11*, 103. [CrossRef] [PubMed]
8. Shetty, R.A.; Forster, M.J.; Sumien, N. Coenzyme Q10 Supplementation Reverses Age-Related Impairments in Spatial Learning and Lowers Protein Oxidation. *Age* **2013**, *35*, 1821–1834. [CrossRef]
9. Ali, A.A.; Abo El-Ella, D.M.; El-Emam, S.Z.; Shahat, A.S.; El-Sayed, R.M. Physical & Mental Activities Enhance the Neuroprotective Effect of Vinpocetine & Coenzyme Q10 Combination against Alzheimer & Bone Remodeling in Rats. *Life Sci.* **2019**, *229*, 21–35. [CrossRef]
10. Quan, H.; Koltai, E.; Suzuki, K.; Aguiar, A.S.; Pinho, R.; Boldogh, I.; Berkes, I.; Radak, Z. Exercise, Redox System and Neurodegenerative Diseases. *Biochim. Biophys. Acta Mol. Basis Dis.* **2020**, *1866*, 165778. [CrossRef]
11. Pluchino, N.; Russo, M.; Santoro, A.N.; Litta, P.; Cela, V.; Genazzani, A.R. Steroid Hormones and BDNF. *Neuroscience* **2013**, *239*, 271–279. [CrossRef] [PubMed]
12. Rawlings, A.M.; Sharrett, A.R.; Albert, M.S.; Coresh, J.; Windham, B.G.; Power, M.C.; Knopman, D.S.; Walker, K.; Burgard, S.; Mosley, T.H.; et al. The Association of Late-Life Diabetes Status and Hyperglycemia with Incident Mild Cognitive Impairment and Dementia: The ARIC Study. *Diabetes Care* **2019**, *42*, 1248–1264. [CrossRef] [PubMed]
13. Tan, Z.S.; Beiser, A.; Vasan, R.S.; Au, R.; Auerbach, S.; Kiel, D.P.; Wolf, P.A.; Seshadri, S. Thyroid Function and the Risk of Alzheimer Disease: The Framingham Study. *Arch. Intern. Med.* **2008**, *168*, 1514–1520. [CrossRef] [PubMed]

14. Decourt, B.; Lahiri, D.K.; Sabbagh, M.N. Targeting Tumor Necrosis Factor Alpha for Alzheimer's Disease. *Curr. Alzheimer Res.* **2017**, *14*, 412–425. [CrossRef] [PubMed]
15. Swaab, D.F.; Bao, A.M.; Lucassen, P.J. The Stress System in the Human Brain in Depression and Neurodegeneration. *Ageing Res. Rev.* **2005**, *4*, 141–194. [CrossRef] [PubMed]
16. Moussa, C.; Hebron, M.; Huang, X.; Ahn, J.; Rissman, R.A.; Aisen, P.S.; Turner, R.S. Resveratrol Regulates Neuro-Inflammation and Induces Adaptive Immunity in Alzheimer's Disease. *J. Neuroinflamm.* **2017**, *14*, 1. [CrossRef] [PubMed]
17. Hamilton, K.; Harvey, J. The Neuronal Actions of Leptin and the Implications for Treating Alzheimer's Disease. *Pharmaceuticals* **2021**, *14*, 52. [CrossRef]
18. Polat, M.; Polat, Y.; Akbulut, T.; Cinar, V.; Marangoz, I. The Effects of Trainings Applied with CoQ10 and Zinc Supplementation on the Thyroid Hormone Metabolism in Soccer Players. *Biomed. Res. India* **2017**, *28*, 7070–7075.
19. Maruoka, H.; Tanaka, K.-I.; Takayanagi, M.; Zenda, M.; Ogawa, A. The Influence of the Different Exercise Length on Alveolar and Cytokine The Analysis of Chronic Obstructive Pulmonary Disease (COPD) and Skeletal Muscle Atrophy Model Mice. *J. Clin.Physiol.* **2021**, *51*, 23–34.
20. Drury, R.; Matos, M.; Lee, K.H.; Kirby, J.N.; Doty, J.R.; Petrocchi, N.; Gilbert, P. The Current and Future Role of Heart Rate Variability for Assessing and Training Compassion. *Front. Public Health* **2017**, *5*, 40. [CrossRef]
21. Abdollahzad, H.; Aghdashi, M.A.; Asghari Jafarabadi, M.; Alipour, B. Effects of Coenzyme Q10 Supplementation on Inflammatory Cytokines (TNF-α, IL-6) and Oxidative Stress in Rheumatoid Arthritis Patients: A Randomized Controlled Trial. *Arch. Med. Res.* **2015**, *46*, 527–533. [CrossRef] [PubMed]
22. Hosoe, K.; Kitano, M.; Kishida, H.; Kubo, H.; Fujii, K.; Kitahara, M. Study on Safety and Bioavailability of Ubiquinol (Kaneka QH^{TM}) after Single and 4-Week Multiple Oral Administration to Healthy Volunteers. *Regul. Toxicol. Pharmacol.* **2007**, *47*, 19–28. [CrossRef] [PubMed]
23. Martucci, A.; Reurean-Pintilei, D.; Manole, A. Bioavailability and Sustained Plasma Concentrations of CoQ10 in Healthy Volunteers by a Novel Oral Timed-Release Preparation. *Nutrients* **2019**, *11*, 527. [CrossRef] [PubMed]
24. Peixoto De Barcelos, I.; Haas, R.H. Biology CoQ10 and Aging. *Biology* **2019**, *8*, 28. [CrossRef]
25. Koshiba, M.; Mimura, K.; Sugiura, Y.; Okuya, T.; Senoo, A.; Ishibashi, H.; Nakamura, S. Reading Marmoset Behavior "semantics" under Particular Social Context by Multi-Parameters Correlation Analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 1499–1504. [CrossRef] [PubMed]
26. Koshiba, M.; Shirakawa, Y.; Mimura, K.; Senoo, A.; Karino, G.; Nakamura, S. Familiarity Perception Call Elicited under Restricted Sensory Cues in Peer-Social Interactions of the Domestic Chick. *PLoS ONE* **2013**, *8*, 58847. [CrossRef] [PubMed]
27. Koshiba, M.; Karino, G.; Mimura, K.; Nakamura, S.; Yui, K.; Kunikata, T.; Yamanouchi, H. Psycho-Cognitive Intervention for ASD from Cross-Species Behavioral Analyses of Infants, Chicks and Common Marmosets. *CNS Neurol. Disord. Drug Targets* **2016**, *15*, 578–586. [CrossRef]
28. Koshiba, M.; Senoo, A.; Mimura, K.; Shirakawa, Y.; Karino, G.; Obara, S.; Ozawa, S.; Sekihara, H.; Fukushima, Y.; Ueda, T.; et al. A Cross-Species Socio-Emotional Behaviour Development Revealed by a Multivariate Analysis. *Sci. Rep.* **2013**, *3*, 2630. [CrossRef]
29. Koshiba, M.; Watarai-Senoo, A.; Karino, G.; Ozawa, S.; Kamei, Y.; Honda, Y.; Tanaka, I.; Kodama, T.; Usui, S.; Tokuno, H. A Susceptible Period of Photic Day-Night Rhythm Loss in Common Marmoset Social Behavior Development. *Front. Behav. Neurosci.* **2021**, *14*, 539411. [CrossRef]
30. Mimura, K.; Senoo, A.; Fujii, K.; Shimizu, T.; Saga, T.; Tanaka, I.; Honda, Y.; Tokuno, H.; Usui, S.; Kodama, T.; et al. Multivariate Correlation Analysis Suggested High Ubiquinol and Low Ubiquinone in Plasma Promoted Primate's Social Motivation and IR Detected Lower Body Temperature. *J. Clin. Toxicol.* **2013**, *3*, 160. [CrossRef]
31. Mimura, K. A Sensitive Period of Peer-Social Learning. *J. Clin. Toxicol.* **2013**, *3*, 1000158. [CrossRef]
32. Mimura, K.; Nakamura, S.; Koshiba, M. A Flexion Period for Attachment Formation in Isolated Chicks to Unfamiliar Peers Visualized in a Developmental Trajectory Space through Behavioral Multivariate Correlation Analysis. *Neurosci. Lett.* **2013**, *547*, 70–75. [CrossRef] [PubMed]
33. Koshiba, M.; Karino, G.; Senoo, A.; Mimura, K.; Shirakawa, Y.; Fukushima, Y.; Obara, S.; Sekihara, H.; Ozawa, S.; Ikegami, K.; et al. Peer Attachment Formation by Systemic Redox Regulation with Social Training after a Sensitive Period. *Sci. Rep.* **2013**, *3*, 2503. [CrossRef]
34. Karino, G.; Shukuya, M.; Nakamura, S.; Murakoshi, T.; Kunikata, T.; Yamanouchi, H.; Koshiba, M. Common Marmosets Develop Age-Specific Peer Social Experiences That May Affect Their Adult Body Weight Adaptation to Climate. *Stress Brain Behavior.* **2015**, *3*, e019001.
35. Koshiba, M.; Senoo, A.; Karino, G.; Shirakawa, Y.; Mimura, K.; Sagawa, T.; Tsugawa, W.; Sode, K.; Nakamura, S. Blood Glucose Dependence on Emotional Behaviors and Body Surface Temperatures in Common Marmoset's Socio-Psychological Learning with Peers for "development of Human-Environment Interface by Sensing and Multivariate Analysis of Bio-Ecosystem". *ECS Trans.* **2012**, *50*, 9. [CrossRef]
36. Karino, G.; Senoo, A.; Kunikata, T.; Kamei, Y.; Yamanouchi, H.; Nakamura, S.; Shukuya, M.; Colman, R.J.; Koshiba, M. Inexpensive Home Infrared Living/Environment Sensor with Regional Thermal Information for Infant Physical and Psychological Development. *Int. J. Environ. Res. Public Health* **2020**, *17*, 6844. [CrossRef] [PubMed]
37. Stephanos Ioannou, V.G. and A.M. Thermal Infrared Imaging in Psychophysiology Potentialities and Limits Enhanced Reader. *Psychophysiology* **2014**, *51*, 951–963. [CrossRef]

38. Kimura, K.; Obuchi, S.; Arai, T.; Nagasawa, H.; Shiba, Y.; Watanabe, S.; Kojima, M. The Influence of Short-Term Strength Training on Health-Related Quality of Life and Executive Cognitive Function. *J. Physiol. Anthropol.* **2010**, *29*, 95–101. [CrossRef]
39. Spielberger, C.D.; Gorsuch, R.L.; Lushene, R.; Vagg, P.R.; Jacobs, G.A. *State-Trait-Anxiety-Inventory for Adults Self-Evaluation Questionnaire STAI Form Y-1 Nad Form Y-2 1968*; Mind Garden: Redwood City, CA, USA, 1977; Volume 5.
40. Steer, R.A.; Rissmiller, D.J.; Beck, A.T. Use of the Beck Depression Inventory-II with Depressed Geriatric Inpatients. *Behav. Res. Ther.* **2000**, *38*, 311–318. [CrossRef]
41. Shirakawa, Y. Peer-Social Network Development Revealed by the Brain Multivariate Correlation Map with 10 Monoamines and 11 Behaviors. *J. Clin. Toxicol.* **2013**, *3*, 1000161. [CrossRef]
42. Duignan, J. *A Dictionary of Business Research Methods*; Oxford University Press: Oxford, UK, 2016; ISBN 9780191792236.
43. Hernández-Camacho, J.D.; Bernier, M.; López-Lluch, G.; Navas, P. Coenzyme Q10 Supplementation in Aging and Disease. *Front. Physiol.* **2018**, *9*, 44. [CrossRef] [PubMed]
44. Mcphee, J.S.; French, D.P.; Jackson, D.; Nazroo, J.; Pendleton, N.; Degens, H. Physical Activity in Older Age: Perspectives for Healthy Ageing and Frailty. *Biogerontology* **2016**, *17*, 567–580. [CrossRef] [PubMed]
45. Santiago, H.P.; Leite, L.H.R.; Lima, P.M.A.; Fóscolo, D.R.C.; Natali, A.J.; Prímola-Gomes, T.N.; Szawka, R.E.; Coimbra, C.C. Effects of Physical Training on Hypothalamic Neuronal Activation and Expressions of Vasopressin and Oxytocin in SHR after Running until Fatigue. *Pflugers Arch.* **2024**, *476*, 365–377. [CrossRef] [PubMed]
46. Koshiba, M.; Nakamura, S.; Mimura, K.; Senoo, A.; Karino, G.; Amemiya, S.; Miyaji, T.; Kunikata, T.; Yamanouchi, H. Socio-Emotional Development Evaluated by Behaviour Output Analysis for Quantitative Emotional State Translation (BOUQUET): Towards Early Diagnosis of Individuals with Developmental Disorders. *OA Autism.* **2013**, *1*, 18. [CrossRef]
47. Senoo, A.; Okuya, T.; Sugiura, Y.; Mimura, K.; Honda, Y.; Tanaka, I.; Kodama, T.; Tokuno, H.; Yui, K.; Nakamura, S.; et al. Effects of Constant Daylight Exposure during Early Development on Marmoset Psychosocial Behavior. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 1493–1498. [CrossRef] [PubMed]
48. Kaushik, D.K.; Pasetto, L.; Colangelo, A.M.; De La Fuente, A.G.; Mayne, K.; White, J.A.; Mcmurran, C.E.; Rivera, F.J. Aging and Neurodegenerative Disease: Is the Adaptive Immune System a Friend or Foe? *Front. Aging Neurosci.* **2020**, *12*, 572090. [CrossRef]
49. Kelso, G.F.; Porteous, C.M.; Coulter, C.V.; Hughes, G.; Porteous, W.K.; Ledgerwood, E.C.; Smith, R.A.J.; Murphy, M.P. Selective Targeting of a Redox-Active Ubiquinone to Mitochondria within Cells: Antioxidant and Antiapoptotic Properties. *J. Biol. Chem.* **2001**, *276*, 4588–4596. [CrossRef]
50. Mavani, G.P.; DeVita, M.V.; Michelis, M.F. A Review of the Nonpressor and Nonantidiuretic Actions of the Hormone Vasopressin. *Front. Med.* **2015**, *2*, 19. [CrossRef]
51. Todd Pearson, J.; Ramchandra, R.; Simões Colombari, D.A.; Allen Crone, S.; Proczka, M.; Przybylski, J.; Cudnoch-Jędrzejewska, A.; Szczepan, E.; Żera, T. Vasopressin and Breathing: Review of Evidence for Respiratory Effects of the Antidiuretic Hormone. *Physiol* **2021**, *12*, 744177. [CrossRef]
52. Harada, N.; Shigemura, J.; Tanichi, M.; Kawaida, K.; Takahashi, S. Mental Health and Psychological Impacts from the 2011 Great East Japan Earthquake Disaster: A Systematic Literature Review. *Disaster Mil. Med.* **2015**, *1*, 17. [CrossRef]
53. Diaz-castro, J.; Moreno-fernandez, J.; Chirosa, I.; Chirosa, L.J.; Guisado, R.; Ochoa, J.J. Beneficial E Ff Ect of Ubiquinol on Hematological and Inflammatory Signaling during Exercise. *Nutrients* **2020**, *12*, 424. [CrossRef] [PubMed]
54. Frodl, T.; Amico, F. Is There an Association between Peripheral Immune Markers and Structural/Functional Neuroimaging Findings? *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2014**, *48*, 295–303. [CrossRef] [PubMed]
55. Zhang, J.; Rong, P.; Zhang, L.; He, H.; Zhou, T.; Fan, Y.; Mo, L.; Zhao, Q.; Han, Y.; Li, S.; et al. IL4-Driven Microglia Modulate Stress Resilience through BDNF-Dependent Neurogenesis. *Sci. Adv.* **2021**, *7*, eabb9888. [CrossRef] [PubMed]
56. Talukdar, A.; Sharma, K.A.; Rai, R.; Deka, D.; Rao, D.N. Effect of Coenzyme Q10 on Th1/Th2 Paradigm in Females with Idiopathic Recurrent Pregnancy Loss. *Am. J. Reprod. Immunol.* **2015**, *74*, 169–180. [CrossRef]
57. Moran, J.M.; Takahashi, M.; Kinoshita, T.; Maruyama, K.; Suzuki, T. CYP7A1, NPC1L1, ABCB1, and CD36 Polymorphisms Associated with Coenzyme Q 10 Availability Affect the Subjective Quality of Life Score (SF-36) after Long-Term CoQ 10 Supplementation in Women. *Nutrients* **2022**, *14*, 2579. [CrossRef]
58. Deng, Z.; Guo, L.; Chen, X.; Wu, W. Smart Wearable Systems for Health Monitoring. *Sensors* **2023**, *23*, 2479. [CrossRef] [PubMed]
59. Vaghasiya, J.V.; Mayorga-Martinez, C.C.; Pumera, M. Wearable Sensors for Telehealth Based on Emerging Materials and Nanoarchitectonics. *npj Flex. Electron.* **2023**, *7*, 26. [CrossRef]
60. Zhao, Y.; Bergmann, J.H.M. Non-Contact Infrared Thermometers and Thermal Scanners for Human Body Temperature Monitoring: A Systematic Review. *Sensors* **2023**, *23*, 7439. [CrossRef]
61. Jerem, P.; Jenni-Eiermann, S.; McKeegan, D.; McCafferty, D.J.; Nager, R.G. Eye Region Surface Temperature Dynamics during Acute Stress Relate to Baseline Glucocorticoids Independently of Environmental Conditions. *Physiol. Behav.* **2019**, *210*, 112627. [CrossRef]
62. Bao, A.M.; Meynen, G.; Swaab, D.F. The Stress System in Depression and Neurodegeneration: Focus on the Human Hypothalamus. *Brain Res. Rev.* **2008**, *57*, 531–553. [CrossRef]
63. Grases, G.; Colom, M.A.; Fernandez, R.A.; Costa-Bauzá, A.; Grases, F. Evidence of Higher Oxidative Status in Depression and Anxiety. *Oxidative Med. Cell. Longev.* **2014**, *2014*, 430216. [CrossRef] [PubMed]
64. Johri, A. Molecular Sciences Disentangling Mitochondria in Alzheimer's Disease. *Int. J. Mol. Sci.* **2021**, *22*, 11520. [CrossRef] [PubMed]

65. Testai, L.; Martelli, A.; Flori, L.; Cicero, A.F.G.; Colletti, A. Coenzyme Q 10: Clinical Applications beyond Cardiovascular Diseases. *Nutrients* **2021**, *13*, 1697. [CrossRef] [PubMed]
66. Toschi, A.; Severi, A.; Coletti, D.; Catizone, A.; Musarò, A.; Molinaro, M.; Nervi, C.; Adamo, S.; Scicchitano, B.M.; Sciences, O. Skeletal Muscle Regeneration in Mice Is Stimulated by Local Overexpression of V1a-Vasopressin Receptor. *Mol. Endocrinol.* **2011**, *25*, 1661–1673. [CrossRef] [PubMed]
67. Gorlova, A.; Svirin, E.; Pavlov, D.; Cespuglio, R.; Proshin, A.; Schroeter, C.A.; Lesch, K.-P.; Strekalova, T.; Anokhin, P.K. Understanding the Role of Oxidative Stress, Neuroinflammation and Abnormal Myelination in Excessive Aggression Associated with Depression: Recent Input from Mechanistic Studies. *Int. J. Mol. Sci.* **2023**, *24*, 915. [CrossRef] [PubMed]
68. Luis García-Giménez, J.; Chandra Tripathi, S.; John Percy, A.; Dhama, K.; Munjal, A.; Hmn, I.; Latheef, S.K.; Dadar, M.; Abdul Samad, H.; Khandia, R.; et al. Biomarkers in Stress Related Diseases/Disorders: Diagnostic, Prognostic, and Therapeutic Values. *Front. Mol. Biosci.* **2019**, *6*, 91. [CrossRef]