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Effects of *N*-Acetylmannosamine (ManNAc) on Cognitive and Psychological Function in Middle-Aged and Older Healthy Adults: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: To delay the onset of dementia with age, it is important for healthy adults to take preventive measures before cognitive decline occurs. Cognitive function decline is often associated with mood disorders such as depression. *N*-acetylmannosamine (ManNAc) showed activity in a screening assay for components that induced the generation of orexin-producing neurons. Orexins are neuropeptides involved in the regulation of various bodily functions, such as cognitive and psychological function. Therefore, we aimed to examine the effects of ManNAc intake on cognitive and psychological function in middle-aged and older humans. **Methods:** A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the impact of ManNAc on cognitive and psychological functions in middle-aged and older healthy participants. Eighty participants were enrolled and randomly divided into active and placebo groups. The participants consumed either food containing ManNAc 8.8 mg or food without ManNAc for 12 weeks. As the main outcome, cognitive function was assessed before and after ingestion using the Cognitrax test. The secondary outcome, psychological function, was also examined using the POMS2. **Results:** The active group showed statistical significance in the "Neurocognitive Index", which is an assessment of overall cognitive function, in addition to the "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed" factors in the Cognitrax test compared to the placebo group ($P < 0.05$). Furthermore, the active group showed statis-

tically significant differences in "Vigor-Activity" and "Friendliness" in the POMS2 compared to the placebo group ($P < 0.05$). No adverse events attributable to the study foods were observed during the study period. **Conclusions:** Overall, ManNAc improved cognitive and psychological functions in middle-aged and older adults.

Keywords

Orexin, Epigenetics, Mild Cognitive Impairment, Aging, Clinical Trial

1. Introduction

Cognitive functions include memory, attention, language, information processing, and executive functions, most of which decline with age [1]. The world's elderly population continues to grow every year, and the number of people aged 60 and over is expected to increase from 1 billion in 2020 to 1.4 billion by 2030 [2]. At the same time, the number of people suffering from dementia is also on the rise, with more than 55 million people currently suffering from dementia worldwide, and it is estimated that nearly 10 million new cases of dementia are diagnosed each year [3]. Mild cognitive impairment (MCI) is a precursor to dementia, with 9.6% of people per year transitioning from MCI to dementia [4] [5], while approximately 30% of people with MCI are reported to return to their original healthy state [6]. Therefore, it is important to reduce cognitive decline to prevent the transition from healthy to MCI or the progression from MCI to dementia. MCI is often associated with mood disorders, such as depression, and both cognitive and psychological functioning are known to be related to health [7]. With cognitive decline, not only mood state but also social activities, such as interpersonal relationships, are known to be negatively affected [8]. In recent years, these effects have become indicators of mental and social frailty [9]. Therefore, early reduction of the risk of both cognitive decline and mood disorders through intervention is considered important in terms of preventing mental and social frailty and maintaining quality of life (QOL). In particular, several studies have recently verified the effects of functional food ingredients on cognitive decline and mood disorders [10] [11], and attention is being focused on reducing these risks through methods that allow for easy consumption, such as food.

Orexins are known to be among the factors that regulate cognitive and psychological function. Orexins are endogenous neuropeptides, classified into two independent groups: orexins A and B (also known as hypocretins 1 and 2). Their corresponding receptors are orexin type 1 and 2 receptors (also known as hypocretin type 1 and 2 receptors) [12] [13]. Although orexin production is restricted to neurons in the hypothalamus of the brain, orexin receptors are widely distributed throughout the brain, and orexin signaling governs a wide range of peripheral and central areas [14]-[17]. Due to this wide range of dominance, orexin signaling

regulates various important bodily functions, such as cognitive function, psychological function, the sleep-wake cycle, and energy balance [18]-[20]. It has also been reported that the number of orexin-producing neurons decreases with age in humans [21]. Furthermore, it has been reported that the concentration of orexin in the cerebral spinal fluid decreases in patients with Alzheimer's disease as cognitive function scores decline [22], and that the concentration of orexin in the cerebral spinal fluid is reduced in depressed patients compared to healthy controls [23]. Orexin signaling produced by orexin-producing neurons is, therefore, a promising therapeutic target in terms of its involvement in cognitive decline and mood disorders in general. Therefore, lifestyle interventions to increase or maintain orexin-producing neurons and preventive measures using functional foods may be useful as approaches to reduce the risk of age-related cognitive decline and mood disorders.

N-acetylmannosamine (ManNAc) is a naturally occurring uncharged monosaccharide and a component present in cells as an intermediate in the conversion of the glycolytic product fructose 6-phosphate to sialic acid via UDP-GlcNAc [24] [25]. ManNAc showed activity in a screening assay for components that induced the generation of orexin-producing neurons, marking the first reported successful induction of orexin-producing neurons from ES cells [26]. The induction of orexin-producing neurons was not observed with other metabolites of the sialic acid pathway, such as sialic acid or *N*-acetylglucosamine (GlcNAc), and the activity was specific to ManNAc treatment. This effect is considered to be an epigenetic mechanism, such as histone acetylation via the intracellular accumulation of UDP-GlcNAc, which is located upstream of ManNAc, following the addition of ManNAc [26]. It has also been reported that the number of orexin-producing neurons in the hypothalamus increased in old mice orally administered ManNAc [27]. Furthermore, the addition of ManNAc to human iPS cells has been reported to induce the generation of orexin-producing neurons [26]. Therefore, ManNAc is expected to induce the generation of orexin-producing neurons in humans [28].

Regarding the bioactivity of ManNAc on cognitive functions, there are reports that spatial and object discrimination abilities were improved in old mice orally administered ManNAc [29], and location learning ability was improved in old dogs orally administered ManNAc [30]. Regarding psychological function, there are reports that parasympathetic nerve activity is enhanced in old mice orally administered ManNAc. Based on these findings, ManNAc intake in humans is expected to improve cognitive and psychological function by inducing the generation of orexin-producing neurons; however, the effects in humans have not yet been demonstrated.

Therefore, we conducted a randomized, double-blind, placebo-controlled, parallel-group study to examine the effects of consumption of foods containing ManNAc, a bioactive nutrient, on cognitive and psychological function in healthy adult men and women aged 40 years or older and younger than 80 years, who were aware of forgetfulness and felt temporarily depressed in daily life.

2. Materials and Methods

2.1. Study Subjects and Setting

For this study, the principal investigator recruited paid volunteers according to inclusion/exclusion criteria. Subjects for this study had to be selected from healthy adults who did not have dementia but had mild age-related cognitive decline. Mini-Mental State Examination-Japanese version (MMSE-J) of the Dementia Screening Test was used as the criteria for determining dementia, with a score of 23 or below defined as the cut-off value for suspicion of dementia [4].

Healthy adults who met the following inclusion criteria and did not violate the exclusion criteria were included in the study. The study subjects were given a full explanation about the study before the start of the study, and their written consent was obtained.

The inclusion criteria were as follows: 1) males and females aged 40 to 79 years old; 2) subjects whose score on MMSE-J was 24 or more at screening tests; 3) subjects who were aware of forgetfulness, had had others point out forgetfulness, or were aware of memory decline; 4) subjects who felt temporal mood depression in daily life; 5) subjects who could make self-judgment and were voluntarily giving written informed consent. The exclusion criteria were as follows: 1) subjects who had been determined by a physician to have dementia; 2) those who were taking or had taken drugs related to dementia; 3) those who had a history of and/or contract serious diseases (e.g., diabetes, liver disease, kidney disease, heart disease, cerebrovascular disease); 4) those taking supplements that may improve cognitive function; 5) those who had a history and/or a surgical history of digestive disease affecting digestion and absorption; 6) those who were under treatment for or had a history of alcoholism; 7) those who had declared food allergies; 8) those who could not stop drinking a day before each measurement; 9) those who consumed more than approximately 20 g/day of pure alcohol and had a habit of drinking at least 4 days a week; 10) those with extremely irregular eating habits and lifestyle patterns; 11) those suffering from depression or other psychiatric disorders; 12) those who were pregnant or planning to become pregnant or breastfeed during the study period; 13) those who had donated over 200 mL of blood and/or blood components within the last one month prior to the current study or over 400 mL of blood and/or blood components within the last three months prior to the current study; 14) those who were planning to participate and/or had participated in other clinical studies within the last one month prior to the current study; and 15) those who were judged as unsuitable for the current study by the investigator for other reasons.

This study was subject to deliberation and approval (approval date: July 6, 2023) by the Ethical Committee of Kobuna Orthopedics Clinic (Chairman: Toshio Kawada) and was approved according to the "Declaration of Helsinki October 2013, WMA Fortaleza General Assembly (Brazil), as amended" and the "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects" (2021). This research study was conducted under the supervision of a physician at the

Nihonbashi Cardiology Clinic (Tokyo, Japan). The research plan for this study has been registered in the clinical trial registration system operated by the University Hospital Medical Information Network Research Center, with registration ID UMIN000051613 (trial registration name: A Study on the Effect of Test Food on Cognitive Function—A Randomized, Double-blind, Placebo-controlled, Parallel-group Study).

2.2. Research Methods

This study was conducted as a randomized, double-blind, placebo-controlled, parallel-group study (allocation ratio: 1:1) for a total of 13 weeks, consisting of a pre-observation period (1 week) and an intake period (12 weeks), with no methodological changes after study entry. The statistical analyst used computer-generated random numbers to allocate the subjects using a block randomization method (block size of 4) with age, gender, and MMSE-J and Cognitrax "Visual Memory" results as adjustment factors. The two allocated groups were assigned to the active group and the placebo group by study foods allocation manager who was not directly involved in the study. Furthermore, study foods allocation manager prepared and sealed a table with the allocation results (key code) and kept it in a sealed container until the key code was disclosed after the analysis subjects were determined, thereby ensuring blinding to persons other than the study food allocation manager. In addition, the study foods were distributed to the study subjects in one plain aluminum bag per grain to ensure blinding to the study subjects and intervention providers.

The sample size was calculated based on a report that showed that the intake of the food material plasmalogene maintained memory function in healthy adult men and women with an MMSE-J score of 24 or higher [31]. The target number of patients in this study was set at 40 per group (80 patients in total) based on the effect size calculated at the change from baseline at week 12 of Cognitrax "Visual Memory" intake at the two-sided 5% significance level to achieve 80% power. In addition, the study subjects were advised not to use supplements or health foods (including food for specified health uses, functional foods, and nutritional supplements such as amino acids and protein), to lead the same lifestyle as before the study, and not to drink alcohol excessively during the study period.

In addition, precautions were explained, such as avoiding alcohol consumption starting the day before all tests, going to bed early and not staying up late on the day before all tests, and not smoking on the day of all tests from the time of waking up until the end of the test. In addition, the study subjects were to use medicines only with the permission of the principal investigator or a research assistant, except in cases of emergency.

2.3. Intake of Study Food

During the intake period, the study food was consumed as an intervention. The active food was a mixture of ManNAc, reduced maltose, cellulose, calcium stearate,

silicon dioxide, and a tableted food. For the placebo food, ManNAc in the active food was replaced with reduced maltose and calcium stearate, and the amounts of the mixture were adjusted so that the placebo food was indistinguishable from the active food in appearance. The daily intake of both the active and placebo foods was designed at 250 mg × 1 tablet. During the intake period, the study subjects consumed one sachet (one grain) of the study food (active food for the active group and placebo food for the placebo group) once a day with water or lukewarm water.

The caloric and nutrient values per daily intake of the study foods are shown in Table 1. The amount of ManNAc in the active food was 8.8 mg per daily intake.

Table 1. Analysis of nutrient composition values of study food.

Table column subhead	Placebo	Active
Energy (kcal)[a]	1.0	1.0
Protein (g)[b]	0.0	0.0
Fat (g)	0.0	0.0
Carbohydrate (g)	0.2	0.2
Salt equivalent (g)	0.000	0.000

[a]Calorie conversion factor: protein, 4; fat, 9; carbohydrate, 4. [b]Nitrogen-to-protein conversion factor: 6.25.

2.4. Evaluation Items

The primary outcome was the Cognitrax score, which assesses cognitive function, and the secondary outcome was the POMS2 (shortened version), which assesses psychological function. These were assessed twice, before and 12 weeks after intake.

The Cognitrax test, which assesses cognitive function, is a computer-based cognitive function test developed as a Japanese version of CNS Vital Signs and consists of nine tests: a verbal memory test, a visual memory test, a finger-tapping test, the Symbol Digit Coding test, the Stroop test, an attention shift test, a sustained processing test, a logical thinking test, and a four-part sustained processing test [32]. The nine tests determined scores for the "Neurocognitive Index", "Composite Memory", "Verbal Memory", "Visual Memory", "Psychomotor Speed", "Reaction Time", "Complex Attention", "Cognitive Flexibility", "Processing Speed", "Executive Function", "Reasoning", "Working Memory", "Sustained Attention", "Simple Attention", and "Motor Speed". All tests and domain scores were assessed with standardized scores converted to a standard deviation of 15, with a mean value of 100 for the same age group.

The POMS2 was assessed as a measure of a wide range of psychological functions [33]. Using the Japanese version of the abbreviated version of the POMS2 for adults, the seven scales of "Anger-Hostility", "Confusion-Bewilderment", "Depression-Dejection", "Fatigue-Inertia", "Tension-Anxiety", "Vigor-Activity", and "Friendliness" and the Total Mood State were assessed using scores (T-scores)

standardized by age and gender, with a mean value of 50.

There were no changes in outcomes after the study began. In addition, the MMSE-J, which consists of a series of questions and tasks divided into 11 categories, including disorientation and memory, attention, and calculation, was administered during screening to allow doctors to exclude those with possible dementia.

The study subjects were given a food diary and a research logbook and asked to complete them daily throughout the intake period, beginning one week prior to the start of intake. The survey items included: 1) the intake of study foods, 2) the presence or absence of physical changes, 3) bedtime, 4) the presence or absence of changes in living conditions, 5) the use of medicines (medicines excluding nutritional drinks, new designated quasi-drugs, and new-range quasi-drugs), 6) the presence and frequency of exercise at sports clubs and at home, and 7) dietary contents (*i.e.*, the contents of meals (including meals, snacks, banned foods, supplements, health food supplements, drinks, alcohol, etc.)).

2.5. Statistical Analysis

The population analyzed was a per-protocol set (PPS). A repeated measures analysis of variance was performed to identify group and time point interactions. Group comparisons were also made by means of a t-test with no correspondence per test for the actual measured values and the change from before intake. Both tests were two-tailed with a significance level of 5%. Statistical analyses were performed using IBM SPSS Statistics 28. Study subject backgrounds are presented as the mean ± standard deviation, and other data as the mean ± standard error. No adjustments were made for multiple testing across multiple items and time points.

3. Results

3.1. Analysis Subjects

The number of subjects included in the study was 80 (31 males and 49 females). The study was initiated with 80 subjects with no drop-outs after randomization, and the allocated intervention was implemented for 40 subjects in each group. During the study period, one subject (male) in the active group and one subject (male) in the placebo group met the discontinuation criteria because the principal investigator considered it difficult for the subject to continue the study due to subjective symptoms. One subject (male) in the active group and one subject (male) in the placebo group dropped out due to withdrawal for reasons not related to the study food. At the end of the study, the number of study subjects was 76. In addition, five study subjects were found to meet the rejection criteria after completion of the study, so 71 subjects (men: 24, women: 47) were included in the analysis. The reason for the rejection criteria was that the precautions taken during the study period were found to have been violated (two subjects in the active group and three subjects in the placebo group). The analyses were performed as per the original allocation for each group.

The period from recruitment to the end of the follow-up for the study subjects was July 2023 to December 2023, and the study was terminated when all subjects had completed the follow-up. Table 2 shows the background of the study subjects for the analysis in this study, and Figure 1 shows a flowchart of the process from inclusion to analysis.

Table 2. Subject characteristics.

	Placebo	Active
	(n = 35)	(n = 36)
Age (years)	57.4 ± 6.3	57.2 ± 6.4
Sex (male/female)	12/23	12/24
Height (cm)	161.6 ± 7.6	160.9 ± 8.3
Weight (kg)	57.5 ± 12.6	55.0 ± 10.0
BMI (kg/m^2)	21.8 ± 3.5	21.1 ± 2.5
MMSE-J	28.6 ± 1.6	28.6 ± 1.1
Visual Memory in Cognitrax	92.8 ± 10.2	92.9 ± 10.3

Values are expressed as means ± SDs. No significant difference was observed.

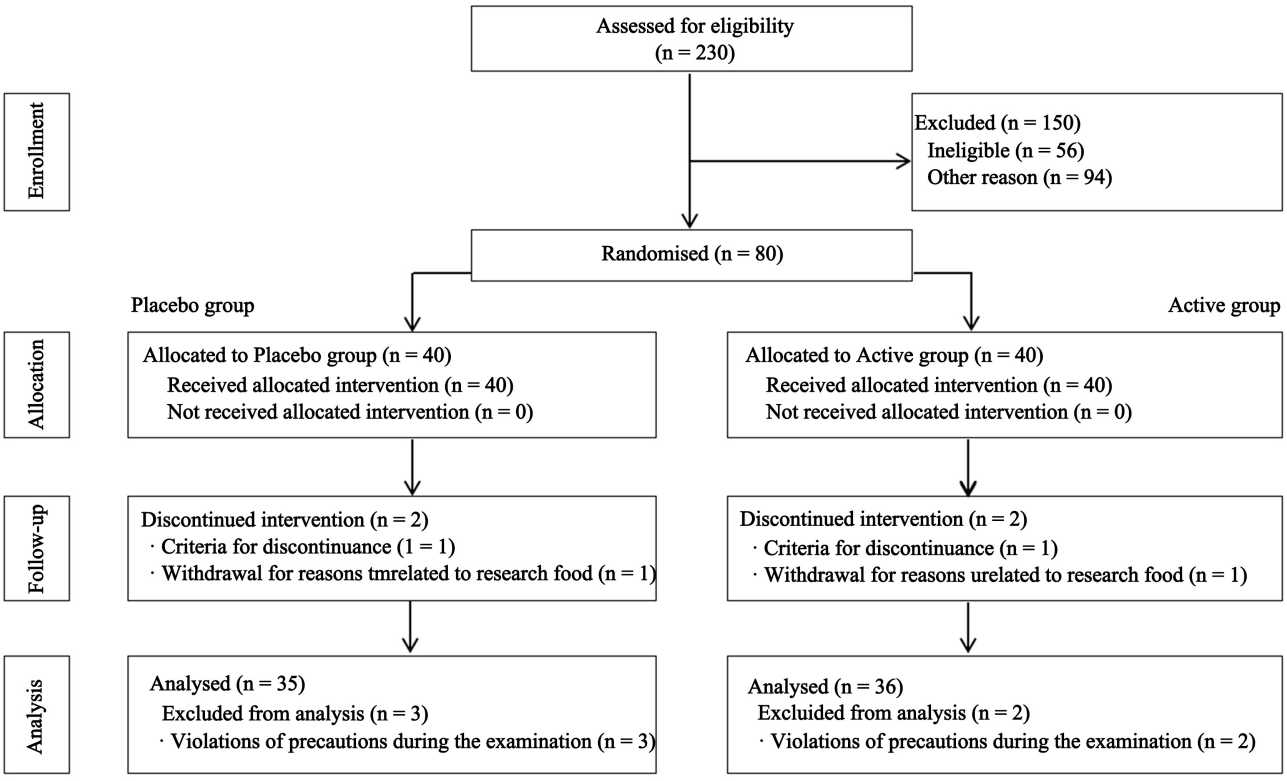

Figure 1. Flow diagram of progress through phases of a randomized, double-blind, placebo-controlled, parallel-group study.

3.2. Analysis Results

The results of the analysis of the Cognitrax test, which assesses cognitive function,

are shown in Table 3. Interaction effects were observed for "Neurocognitive Index", "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed". A comparison of the measured values of each test and the amount of change from before intake for each test between the groups showed significant differences in the measured values of the "Neurocognitive Index" and "Psychomotor Speed" after 12 weeks of intake ("Neurocognitive Index" P = 0.011, "Psychomotor Speed" P = 0.039). Significant differences were also found in the changes in the "Neurocognitive Index" (P = 0.015), "Psychomotor Speed" (P = 0.048), "Reaction Time" (P = 0.002), "Cognitive Flexibility" (P = 0.021), "Executive Function" (P = 0.017), and "Motor Speed" (P = 0.021) after 12 weeks of intake.

Table 3. Post-intervention changes in each cognitive function parameter.

Domain	Group		Baseline	12 Weeks	P-value (Interactions between Groups and Time Points)
Neurocognitive Index (NCI)	Placebo (n = 35)	Measured	98.8 ± 1.4	101.8 ± 1.4	P = 0.015
		Changes from baseline		3.0 ± 1.4	
	Active (n = 36)	Measured	97.3 ± 2.1	106.5 ± 1.1*	
		Changes from baseline		9.1 ± 2.0*	
Composite Memory	Placebo (n = 35)	Measured	89.9 ± 2.7	98.7 ± 2.9	P = 0.810
		Changes from baseline		8.8 ± 2.7	
	Active (n = 36)	Measured	92.5 ± 2.9	102.3 ± 2.7	
		Changes from baseline		9.8 ± 2.9	
Verbal Memory	Placebo (n = 35)	Measured	91.6 ± 3.5	98.9 ± 2.7	P = 0.923
		Changes from baseline		7.3 ± 2.9	
	Active (n = 36)	Measured	95.6 ± 3.2	103.3 ± 2.6	
		Changes from baseline		7.7 ± 3.1	
Visual Memory	Placebo (n = 35)	Measured	92.8 ± 1.7	99.3 ± 3.0	P = 0.725
		Changes from baseline		6.5 ± 3.1	
	Active (n = 36)	Measured	92.9 ± 1.7	100.7 ± 2.3	
		Changes from baseline		7.8 ± 2.3	
Psychomotor Speed	Placebo (n = 35)	Measured	103.2 ± 1.7	106.8 ± 1.7	P = 0.048
		Changes from baseline		3.5 ± 1.5	
	Active (n = 36)	Measured	103.4 ± 2.4	112.1 ± 1.9*	
		Changes from baseline		8.8 ± 2.1*	
Reaction Time	Placebo (n = 35)	Measured	94.4 ± 2.1	95.6 ± 2.1	P = 0.002
		Changes from baseline		1.3 ± 1.5	
	Active (n = 36)	Measured	86.3 ± 4.0	100.1 ± 1.4	
		Changes from baseline		13.8 ± 3.6**	

Continued

Complex Attention	Placebo (n = 35)	Measured	106.4 ± 2.4	107.1 ± 2.5	P = 0.208
		Changes from baseline		0.6 ± 2.7	
	Active (n = 36)	Measured	106.1 ± 2.4	111.2 ± 1.1	
		Changes from baseline		5.1 ± 2.3	
Cognitive Flexibility	Placebo (n = 35)	Measured	100.2 ± 2.1	101.1 ± 2.7	P = 0.021
		Changes from baseline		0.9 ± 2.4	
	Active (n = 36)	Measured	98.3 ± 2.8	107.1 ± 1.6	
		Changes from baseline		8.8 ± 2.3*	
Processing Speed	Placebo (n = 35)	Measured	111.1 ± 1.9	114.7 ± 1.8	P = 0.228
		Changes from baseline		3.7 ± 1.9	
	Active (n = 36)	Measured	111.8 ± 2.0	118.9 ± 2.0	
		Changes from baseline		7.2 ± 2.1	
Executive Function	Placebo (n = 35)	Measured	100.1 ± 2.1	100.9 ± 2.8	P = 0.017
		Changes from baseline		0.7 ± 2.4	
	Active (n = 36)	Measured	97.9 ± 2.8	106.9 ± 1.6	
		Changes from baseline		8.9 ± 2.3*	
Reasoning	Placebo (n = 35)	Measured	95.5 ± 2.6	99.3 ± 2.7	P = 0.580
		Changes from baseline		3.8 ± 3.0	
	Active (n = 36)	Measured	97.1 ± 2.5	98.6 ± 2.8	
		Changes from baseline		1.5 ± 2.8	
Working Memory	Placebo (n = 35)	Measured	103.6 ± 2.3	105.0 ± 2.4	P = 0.997
		Changes from baseline		1.4 ± 2.0	
	Active (n = 36)	Measured	102.7 ± 1.6	104.1 ± 2.3	
		Changes from baseline		1.4 ± 2.1	
Sustained Attention	Placebo (n = 35)	Measured	105.6 ± 1.6	108.1 ± 1.6	P = 0.676
		Changes from baseline		2.5 ± 1.3	
	Active (n = 36)	Measured	106.4 ± 1.5	107.9 ± 1.8	
		Changes from baseline		1.6 ± 1.8	
Simple Attention	Placebo (n = 35)	Measured	100.0 ± 3.4	104.2 ± 1.1	P = 0.971
		Changes from baseline		4.2 ± 3.7	
	Active (n = 36)	Measured	101.7 ± 3.0	106.1 ± 0.9	
		Changes from baseline		4.3 ± 2.4	
Motor Speed	Placebo (n = 35)	Measured	97.4 ± 2.1	99.2 ± 2.0	P = 0.021
		Changes from baseline		1.7 ± 1.3	
	Active (n = 36)	Measured	97.5 ± 2.4	104.6 ± 1.9	
		Changes from baseline		7.0 ± 1.8*	

Values are expressed as means ± SEs. *Significantly different from the placebo group ($P < 0.05$). **Significantly different from the placebo group ($P < 0.01$).

Table 4. Post-intervention changes in each psychological function parameter.

Domain	Group		Baseline	12 Weeks	P-value (Interactions between Groups and Time Points)
Anger-Hostility	Placebo (n = 35)	Measured	43.5 ± 0.8	43.4 ± 0.9	P = 0.229
		Changes from baseline		−0.1 ± 0.8	
	Active (n = 36)	Measured	45.9 ± 1.0	47.2 ± 1.3*	
		Changes from baseline		1.3 ± 0.9	
Confusion-Bewilderment	Placebo (n = 35)	Measured	43.7 ± 0.9	43.9 ± 1.0	P = 0.695
		Changes from baseline		0.1 ± 0.8	
	Active (n = 36)	Measured	45.9 ± 1.2	45.5 ± 1.4	
		Changes from baseline		−0.4 ± 1.1	
Depression-Dejection	Placebo (n = 35)	Measured	44.6 ± 0.7	45.3 ± 1.2	P = 0.813
		Changes from baseline		0.7 ± 1.0	
	Active (n = 36)	Measured	45.7 ± 0.9	46.1 ± 1.2	
		Changes from baseline		0.4 ± 1.1	
Fatigue-Inertia	Placebo (n = 35)	Measured	43.4 ± 0.9	43.0 ± 1.2	P = 0.679
		Changes from baseline		−0.4 ± 1.1	
	Active (n = 36)	Measured	45.9 ± 1.3	46.1 ± 1.4	
		Changes from baseline		0.3 ± 1.2	
Tension-Anxiety	Placebo (n = 35)	Measured	43.3 ± 0.9	42.4 ± 1.0	P = 0.561
		Changes from baseline		−0.9 ± 0.8	
	Active (n = 36)	Measured	45.4 ± 1.1	45.3 ± 1.3	
		Changes from baseline		−0.1 ± 1.2	
Vigor-Activity	Placebo (n = 35)	Measured	48.9 ± 1.6	49.0 ± 1.6	P = 0.049
		Changes from baseline		0.1 ± 1.1	
	Active (n = 36)	Measured	50.1 ± 1.4	53.6 ± 1.8	
		Changes from baseline		3.5 ± 1.3*	
Friendliness	Placebo (n = 35)	Measured	52.9 ± 1.7	51.2 ± 1.6	P = 0.002
		Changes from baseline		−1.7 ± 0.9	
	Active (n = 36)	Measured	49.5 ± 1.7	52.7 ± 2.0	
		Changes from baseline		3.2 ± 1.2**	
Total Mood State	Placebo (n = 35)	Measured	43.6 ± 0.8	43.4 ± 1.1	P = 0.784
		Changes from baseline		−0.2 ± 0.8	
	Active (n = 36)	Measured	45.6 ± 1.0	45.1 ± 1.4	
		Changes from baseline		−0.6 ± 1.1	

Values are expressed as means ± SEs. *Significantly different from the placebo group ($P < 0.05$). **Significantly different from the placebo group ($P < 0.01$).

The results of the T-score analysis for each scale of the POMS2 (short version) assessing psychological function are shown in Table 4. Interaction effects were found for "Vigor-Activity" and "Friendliness". A between-group comparison of the measured values of each test and the change from before intake showed significant differences in the changes in "Vigor-Activity" (P = 0.049) and "Friendliness" (P = 0.002) after 12 weeks of intake.

3.3. Adverse Events

Adverse events that occurred during the study period included colds, headaches, and back pain in the placebo group, as well as dizziness, dry eyes, and colds in the active group, with similar frequency of occurrence. All confirmed events were ruled out as causally related to the study foods by the investigators.

4. Discussion

We conducted a randomized, double-blind, placebo-controlled, parallel-group study to examine the effects of the consumption of foods containing ManNAc on cognitive and psychological function in healthy adult men and women aged 40 years or older and younger than 80 years, who were aware of forgetfulness and felt temporarily depressed in daily life. The results show that there were significant differences in the amount of change from before intake in the "Neurocognitive Index", "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed" factors in the cognitive function test (Cognitrax). Additionally, the active group showed higher values than the placebo group. In the psychological function test (POMS2), significant differences were observed in the amount of change from before intake in "Vigor-Activity" and "Friendliness", with the active group showing higher values than the placebo group. Higher values for the "Neurocognitive Index", "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed" of the Cognitrax test and "Vigor-Activity" and "Friendliness" of POMS2 are considered to indicate a better condition.

The Cognitrax "Neurocognitive Index" test, which showed significant improvement in this study, is calculated by averaging the domain scores for "Composite Memory", "Psychomotor Speed", "Reaction Time", "Complex Attention", and "Cognitive Flexibility". It is used to assess an individual's overall neurocognitive status. Therefore, the improvement in the "Neurocognitive Index" observed with ManNAc intake is considered to indicate an improvement in overall cognitive function. Furthermore, ManNAc intake significantly improved the domain scores for "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed". "Psychomotor Speed" reflects how well an individual perceives, attends to, and reacts to visual perceptual information and executes motor speed and fine motor coordination [34]. "Motor Speed" is a part of "Psychomotor Speed". Reduced psychomotor speed in older adults is associated with an increased risk of developing brain diseases, such as dementia [35]. "Reac-

tion Time" reflects how quickly subjects can respond to instructions that increase in complexity, and is also considered to be an indicator of information processing speed [32] [34]. "Cognitive Flexibility" refers to the ability to respond to and process changes in instructions, while "Executive Function" refers to the ability to make quick decisions based on an understanding of background rules and concepts. Age-related decline in information processing speed is associated with the progression from MCI to dementia [36] [37], and declines in cognitive flexibility and executive function are considered hallmarks of MCI [38]. Therefore, the fact that ManNAc intake was found to improve "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed" may be beneficial for the transition from healthy to MCI or for arresting the progression from MCI to dementia.

The POMS2 "Vigor-Activity", which showed significant improvement in this study, reflects high levels of energy, dynamism, and vitality, while "Friendliness" assesses positive feelings toward others and positive interpersonal orientation. Aging is associated with cognitive decline, mood swings, and adverse effects on social activities, such as interpersonal relationships, which are known to be problematic as mental and social frailty [8] [9]. The fact that the intake of ManNAc improved cognitive function and significantly improved two items of the POMS2 scale, "Vigor-Activity" and "Friendliness", which evaluate vitality, positive emotions, and human relationships, indicates that it is beneficial for improving mental and social frailty in middle-aged and older people.

The mechanism by which ManNAc improves cognitive and psychological function may be the direct action of ManNAc on brain neurons. ManNAc taken orally is absorbed through the small intestine, enters the bloodstream, passes through the blood-brain barrier, and reaches the brain [24] [39]. Furthermore, the addition of ManNAc to human iPS cells induces the generation of orexin neurons. ManNAc has also been reported to have effects under the conditions of orexin gene expression silencing in orexin neurons [26]. Furthermore, it has been reported that the number of orexin neurons in the hypothalamus increases in aged mice after oral administration of ManNAc [27]. These findings suggest that orally ingested ManNAc acts directly on the brain neurons and promotes the generation or reactivation of orexin neurons. Orexin is produced in the hypothalamus, and orexin receptors are distributed over a wide area of the brain, including the prefrontal cortex and amygdala [13] [17]. The prefrontal cortex is associated with higher cognitive functions, such as cognitive flexibility and executive function, while the amygdala is a region associated with psychological function, such as anxiety [40]-[43]. Therefore, the effects on overall cognitive function and multiple cognitive domains, as well as positive mood states, identified in this study may reflect orexin-mediated effects on a broad range of brain regions. The number of orexin neurons decreases with age in humans [21]. It has also been reported that the concentration of orexin in the cerebral spinal fluid decreases in Alzheimer's disease patients as their cognitive function declines [22]. Additionally, the concentration of orexin in the cerebral spinal fluid is lower in depressed patients than in healthy controls,

suggesting that there is a relationship between reduced cognitive and psychological function and reduced orexin levels [23]. Therefore, the improvement in cognitive and psychological function in middle-aged and older adults with ManNAc intake may be due to an increase in orexin levels via an increase or reactivation in orexin neurons, which decrease with aging.

In this study, the safety of ManNAc was also confirmed. As a result, no adverse events attributable to the intake of foods containing ManNAc were observed, suggesting that there are no safety issues with the long-term intake of foods containing ManNAc.

However, several research limitations exist in this study. The duration of intervention in this study was only 12 weeks, meaning that long-term effects were not considered. In terms of dementia and mental and social frailty prevention, it is necessary to examine whether the intervention effects on cognitive and psychological function persist over time. It is also not clear whether the intervention effects persist after intake is discontinued. Future research should examine the effects of ManNAc on cognitive and psychological function over a longer intervention period to confirm the effects.

5. Conclusion

This is the first randomized controlled trial to demonstrate the efficacy of ManNAc on cognitive and psychological function in middle-aged or older healthy adults. The subjects who consumed ManNAc for 12 weeks showed significant improvements in the "Neurocognitive Index", which assesses overall cognitive function, in addition to "Psychomotor Speed", "Reaction Time", "Cognitive Flexibility", "Executive Function", and "Motor Speed". Furthermore, the "Vigor-Activity" and "Friendliness" factors, which measure positive mood, improved significantly. For middle-aged and older adults who need to cope not only with age-related cognitive decline but also with the associated mental and social frailty, maintaining quality of life through easily accessible methods, such as dietary supplements, may be useful.

Authors' Contributions

Conceptualization: T.K. and K.T.; methodology: Y.H. and N.M.; validation: S.M.; formal analysis: Y.U. and S.M.; investigation: Y.H.; writing—original draft preparation: Y.H. and Y.U.; writing—review and editing: K.F.; visualization: Y.U.; supervision: K.T. and Y.I.; project administration: T.O. and T.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and ap-

proved by the Ethical Committee of Kobuna Orthopedics Clinic (approval date: 6 July 2023; approval number: MK-2307-01).

Informed Consent Statement

Informed consent was obtained from all participants involved in the study.

Data Availability Statement

The data used in this manuscript are not publicly available because of commercial restriction, but are available on reasonable request.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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