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Nutraceutical Intervention Improves Older Adults' Cognitive Functioning

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Abstract

Interventions to improve the cognitive health of older adults are of critical importance. In the current study, we conducted a double-blind, placebo-controlled clinical trial using a pill-based nutraceutical (NT-020) that contained a proprietary formulation of blueberry, carnosine, green tea, vitamin D3, and Biovin to evaluate the impact on changes in multiple domains of cognitive functioning. One hundred and five cognitively intact adults aged 65–85 years of age (M = 73.6 years) were randomized to receive NT-020 ($n = 52$) or a placebo ($n = 53$). Participants were tested with a battery of cognitive performance tests that were classified into six broad domains—episodic memory, processing speed, verbal ability, working memory, executive functioning, and complex speed at baseline and 2 months later. The results indicated that persons taking NT-020 improved significantly on two measures of processing speed across the 2-month test period in contrast to persons on the placebo whose performance did not change. None of the other cognitive ability measures were related to intervention group. The results also indicated that the NT-020 was well tolerated by older adults, and the presence of adverse events or symptoms did not differ between the NT-020 and placebo groups. Overall, the results of the current study were promising and suggest the potential for interventions like these to improve the cognitive health of older adults.

Introduction

Approximately 87% of the population of the United States will experience normal age-related cognitive decline, as compared to the precipitous losses that are associated with dementing disorders.[1] In recent years, there has been considerable interest in interventions to lessen normative age-related declines in functioning, including those directed at physical activity,[2,3] gains through cognitive training efforts,[4,5] as well as changes in the extent to which older adults are cognitively stimulated throughout their lives.[6,7] In addition, there is considerable interest in the potential role of dietary supplements and other therapeutics in the cognitive performance of older adults.[8] In the current study, we examine the role of a pill-based nutraceutical on the cognitive performance of older adults.

The basis for the use of polyphenol-rich nutritional supplements as a moderator of age-related cognitive decline is the age-related increase in oxidative stress[9,10] and the potential benefit of non-vitamin polyphenols, which are the most abundant anti-oxidants in our diets. The benefits of these substances for the cognitive health of older adults have been reported in several studies.[11] For example, Shukitt-Hale's recent review[12] highlighted the potential benefits of blueberries as a compound to impact age-related changes in neuronal aging. Additionally, Devore and colleagues recently reported that greater self-reported intakes of blueberries and strawberries were associated with slower rates of cognitive decline.[13] Although a number of lines of evidence point toward the beneficial effects of these substances, limitations of this research include the use of correlational data as well as the lack of assessment of the bioavailability of these polyphenolic compounds from diets.[14]

In the current study, we conducted a clinical trial using a pill-based supplement or matched placebo control to evaluate the impact on the cognitive performance of older adults. The supplement (NT-020) is a proprietary formulation of blueberry, green tea extract (95% polyphenols), carnosine,

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VitaBlue® (40% polyphenolics, 12.5% anthocyanins from blueberries), and vitamin D_3 (2000 IU per serving) and also contains grape polyphenolics, including 5% resveratrol. In experimental animal models of aging, there is good support for a beneficial effect of polyphenolic components of fruits and vegetables as well as teas (green and black) for improvements in cognition.[15–17] For example, Bickford and colleagues examined the impact of NT-020 on Morris water maze performance among young animals ($n=10$), as well as older animals who received treatment of NT-020 ($n=13$) or a control diet ($n=13$) for 3 weeks prior to behavioral testing. The results showed that the NT-020 animals exhibited significantly lower cumulative distances on the Morris water maze test that is suggestive of better memory, as compared to the older control animals. Furthermore, there was much less variability among the treated old animals, as compared to the control animals.

In the current study, we conducted a short-term (2 months) randomized clinical trial to examine the influence of the nutraceutical NT-020 on the cognitive performance of older adults. Participants were tested with a battery of cognitive tasks at baseline and 2 months after being randomized to the interventional supplement or placebo.

Methods

Participants

Participants for the current study were recruited from the community using advertisements in local newspapers, booths at health fairs and memory screening events, as well as by postcards using commercially available mailing lists. Inclusion criteria for the study were ages 65–85 years, native English speaking, able to understand and sign the informed consent, and no evidence of dementia (Mini-Mental State Examination [MMSE] scores ≥ 24). Exclusion criteria for the study were history of known allergy to components of the study supplements, use of high dose anti-oxidant supplements other than what is provided in the trial, and depressed mood as assessed by the Center for Epidemiologic Studies–Depression scale (scores greater than 5).

Measures

In addition to the measures of cognitive performance described below, participants completed several descriptive instruments at the screening assessment. These included a questionnaire on basic demographic information, allergies, and personal medical history. Global cognitive performance was assessed using the MMSE[18] cognitive screening tool. Self-reported health status was evaluated using the SF-12 Health survey.[19] Finally, depressive symptoms were assessed using the 10-item Centers for Epidemiologic Studies Depression Scale (CES-D).[20]

Cognitive measures

The battery of cognitive tests included standard measures that were classified into six broad areas—episodic memory, processing speed, verbal ability, working memory, executive functioning, and complex speed. Episodic memory, or the ability to learn and remember a series of items, was measured using the Auditory Verbal Learning Test (AVLT),[21] which involves reading and remembering a list of 15 common English nouns. Two outcomes were examined here—immediate recall (average number of words recalled across five learning trials) and delayed recall (number of words recalled after a 20-min delay). Verbal ability was total number correct on a recognition vocabulary test[22] in which participants had to identify a synonym of a target word from one of five options. Processing speed provides an index of how rapidly a person can respond and was measured using the Identical Pictures Test,[22] the Number Comparison task,[22] and Trail Making A.[23] For Trail Making A, an inverse transformation was applied to scores before standardization to account for this measure recording latency, rather than number correct. Working memory provides an index of the ability to maintain some information in memory while simultaneously manipulating other information and was measured with the Forward and Backward Digit Span task.[24] Executive functioning includes skills that are involved in the planning and execution of cognitive tasks and was measured with Trail Making B,[23] Category Fluency,[25] and Controlled Oral Word Association.[26] For Trail Making B, an inverse transformation was applied in the same manner as Trail Making A. Finally, we assessed complex speed, which assesses the ability to do multiple mental tasks quickly using the number of correct items from the Digit Symbol Test.[24]

Interventional compound and randomization schedule

The study was double blinded. Participants were randomly assigned to receive NT-020 plus Biovin (900 mg proprietary formulation of blueberry, carnosine, green tea, plus 200 U vitamin D3, 40 mg Biovin) or a matched placebo control. Participants took one pill in the morning and one in the evening. Participants were encouraged to take the pills with food. Use of NT-020 and the placebo was covered by an Investigational New Drug application (IND 104287) from the Food and Drug Administration and the protocol was registered on clinicaltrials.gov (NCT01963767). For the randomization, the schedule was stratified on the basis of age (65–74 years and 75–85 years) and participants were randomized in blocks of ten.

Procedure

All procedures in the current study were approved by Western Institutional Review Board (IRB), and all persons who participated in the in-person assessments completed an informed consent. The first contact for potential participants was a telephone screen where basic inclusion and exclusion criteria were assessed (*e.g.*, aged 65–85 years). An in-person screening visit was then scheduled within the next 2 weeks during which the MMSE, CES-D, and SF-12 questionnaires were assessed. Persons who passed the screening were scheduled for a baseline visit during which participants were randomized to receive NT-020 or a placebo, the cognitive measures were administered, and participants received a blood draw for safety markers (*i.e.*, complete blood chemistry, comprehensive metabolic panel). In addition, participants received a 1-month supply of NT-020 or the placebo together with a pill diary to record when the pills were taken and any adverse events that occurred. One month later, participants returned any unused NT-020 or placebo along with the pill diary, received a blood draw, and received a

new month's supply of the supplement. One month later, participants returned to repeat the cognitive assessment battery and return any unused NT-020 or placebo, along with the pill diary. In addition to the scheduled assessments described above, participants were called 1 and 3 weeks after the baseline and 1-month assessment to assess adverse events and compliance with the supplement or placebo.

Statistical analyses

Considerations of sample size were based upon statistical power analysis.[27] Specifically, the study was originally powered to detect a medium-sized effect ($d=0.5$) with a total sample size of 50 per group. The cognitive outcome analyses were conducted using analysis of co-variance (ANCOVA) values whereby scores from the final assessment point were used as the outcomes and baseline scores were co-varied. For randomized experiments with pre-test (baseline) and post-test (follow-up) measurements, usually ANCOVA should be preferred with pre-test score as a co-variate. The reason for preferring ANCOVA over repeated-measures ANOVA is that the latter has lower power and some assumptions (most prominently homogeneity of variances) that are unlikely to be met. Group status (NT-020, placebo) was the between-subjects variable. A one-tailed p value of 0.05 was used for the analyses.

Results

Sample characteristics

Figure 1 displays the breakdown of the sample across the longitudinal follow-up period. Of the 139 who participated in the in-person screening session, 113 (81%) were randomized to the NT-020 or the placebo groups. Across the 2-month follow-up period, 2 persons dropped out of the placebo group and 6 dropped from the NT-020 group. The majority of persons who left the study indicated that they no longer had time to participate. Calculation of the differences in attrition between the groups using a Fisher exact test revealed no significant differences ($p=0.273$). The demographic characteristics of the sample that completed the 2-month follow-up are shown in Table 1. The sample was approximately 73 years of age, almost two-thirds were women, the majority of the sample was white, and the average MMSE score was over 29. A comparison of the two groups using independent groups t-tests or chi-squared tests revealed no statistically significant group differences.

Cognitive performance

Table 2 displays the means and standard errors for each of the cognitive outcomes at baseline and follow-up. The results of the ANCOVA indicated that group status was statistically significant for Identical Pictures ($F\ [1, 103]=3.55$, $p=0.03$; $d=0.37$) and there was a trend toward significance for Number Comparison ($F\ [1, 103]=2.43$, $p=0.06$; $d=0.31$). In both cases, the NT-020 group exhibited better performance than the placebo group. None of the other group effects were close to statistical significance (p values >0.10). To better understand the effects on Identical Pictures and Number comparison, we plotted the values in Fig. 2 and computed within-groups paired t-tests on the scores from baseline and follow-up. For Identical Pictures, the NT-020 group exhibited statistically significant increases in performance ($t\ [51]=2.38$, $p=0.021$), whereas the placebo group remained stable ($t\ [52]=-1.27$, $p=0.211$). Similarly, the NT-020 group exhibited significant gains across the follow-up period on Number Comparison ($t\ [51]=-2.62$, $p=0.012$), whereas the placebo group experienced slight, but not statistically significant, declines ($t\ [52]=0.51$, $p=0.611$).

Compliance and adverse events

Participants completed pill and symptom diaries across the course of the follow-up period. Between the baseline and the mid-point assessment, participants averaged 1.93 doses per day out of a maximum of 2 and this did not vary as a

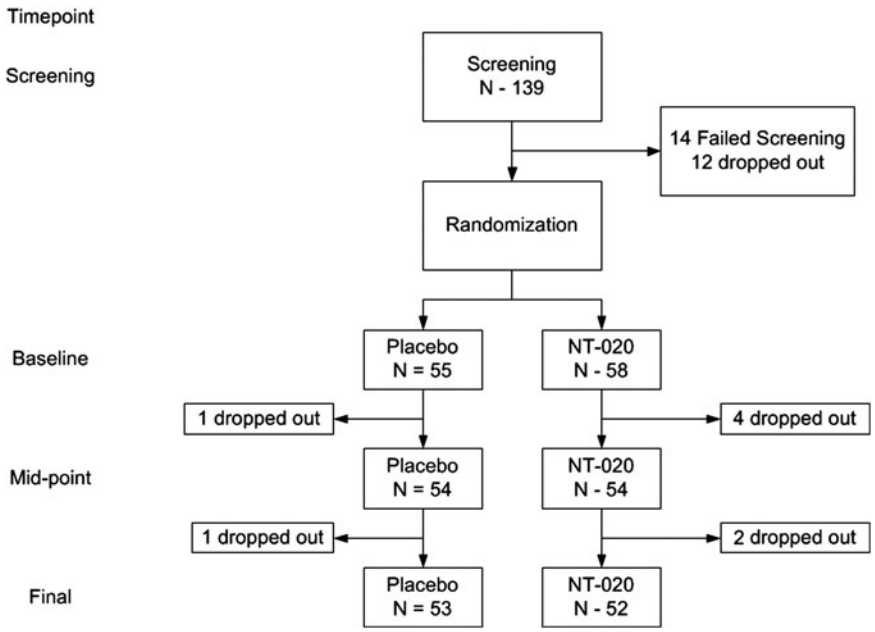

FIG. 1. Breakdown of the sample.

Table 1. Demographic Characteristics of the Sample

		Placebo (n = *53*)	*NT-020* (n = *52*)
Years of age	M	74.34	72.82
	SD	5.48	5.54
Gender	% Female	60.4	63.5
Race/ethnicity	% White	100	92.3
Years of education	M	15.61	15.88
	SD	2.93	2.41
MMSE	M	29.21	29.37
	SD	1.03	1.07
CES-D	M	2.75	2.85
	SD	1.31	1.13
SF-12	M	29.89	29.38
	SD	2.36	3.09

function of intervention group ($M_{placebo} = 1.93$, $M_{NT\text{-}020} = 1.92$; F [1, 103] = 0.06, $p = 0.799$). Between the mid-point and the final measurement point, participants averaged 1.91 doses per day out of a maximum of 2 and this did not vary as a function of intervention group ($M_{placebo} = 1.91$, $M_{NT\text{-}020} = 1.90$; F [1, 103] = 0.24, $p = 0.625$). The most commonly reported reasons for why participants missed a dose was that they forgot or had an unrelated health issue (*e.g.*, cold, fever) and decided not to take a dose that day.

Between baseline and the 1-month assessment point, participants reported an average of four adverse events per person across the follow-up period, but this did not differ between intervention groups ($M_{placebo} = 4.38$, $M_{NT\text{-}020} = 4.59$; F [1, 103] = 0.03, $p = 0.866$). Similarly, the groups did not differ in the number of adverse events between the 1-month and 2-month follow-up points ($M_{placebo} = 1.64$, $M_{NT\text{-}020} = 1.86$; F [1, 103] = 0.30, $p = 0.584$). The most commonly reported symptoms were changes in activity (*e.g.*, lethargy, nervousness) or gastrointestinal symptoms (*e.g.*, upset stomach, diarrhea). One participant exhibited a significant cardiac adverse event during the course of the study during her first month of participation. This event was reported to Western IRB and it was determined to be unrelated to her participation in the study. The study was unblinded for this participant and she was found to be in the NT-020 arm. This participant was removed from the study.

Discussion

The results of the current study indicate modest improvements in two measures of processing speed after 2 months of taking NT-020, as compared to persons on the placebo who showed no such improvement. None of the other cognitive measures exhibited significant gains across the follow-up period. The results of this randomized trial indicate that cognitive performance can be improved by a pill-based nutraceutical. The results of the current study are noteworthy in that the domain of processing speed that was improved here is most often affected early on in the course of cognitive aging, and successful performance on these tasks often underlies more complex cognitive outcomes, such as memory and verbal ability.[28]

The small, but statistically significant, improvements in processing speed observed here are consistent with other nutraceutical interventions on cognitive performance. For example, Krikorian and colleagues examined the consumption of blueberry juice[29] or Concord Grape juice[30] on the cognitive performance of older adults. They reported that participants who consumed blueberry juice had better performance on tests of memory as compared to their baseline performance, as well as when compared to a matched group who consumed a placebo beverage. Moreover, the magnitude of pre-test to post-test improvements in the blueberry juice group was quite substantial and amounted to an over 1 standard deviation increase in performance. The results for Concord Grape juice, which was tested using a randomized, placebo-controlled, double-blind trial, were not as strong because it failed to improve memory performance at the aggregate, although there were improvements in distractibility.

Although the results of the current study were generally consistent with those reported by Krikorian, there are a number of differences between their work and the current findings. First, no statistically significant effects on word recall were observed because the results here indicated improvements in processing speed only. Second, the effects that were present here were somewhat smaller, amounting to approximately 1/3 of a standard deviation of a difference. There are a number of possible reasons for the differences in the findings. First, the Krikorian studies used participants who either exhibited ''early memory changes''[29] or had mild cognitive impairment.[30] By contrast, the participants in

Table 2. Cognitive Test Scores (Mean ± SE) from Baseline and Follow-Up for Placebo and NT-020 Groups

	Placebo (n = *53*)		*NT-020* (n = *52*)	
Measure	*Baseline*	*Follow-up*	*Baseline*	*Follow-up*
Identical Pictures	21.15 ± .68	21.72 ± .61	23.06 ± .68	24.12 ± .65
Number Comparison	21.85 ± .63	21.60 ± .65	21.35 ± .64	21.99 ± .65
Trailmaking A	40.91 ± 1.52	39.09 ± 1.70	37.58 ± 1.54	35.11 ± 1.72
Trailmaking B	92.98 ± 6.05	84.60 ± 4.95	84.80 ± 6.16	78.71 ± 5.04
Digit Span Forward	10.39 ± .29	10.55 ± .31	10.69 ± .29	10.57 ± .31
Digit Span Backward	6.39 ± .33	7.11 ± .34	7.82 ± .34	7.73 ± .34
Category Fluency	15.39 ± .64	16.13 ± .61	17.21 ± .65	16.61 ± .62
COWA	38.98 ± 1.64	41.07 ± 1.49	40.84 ± 1.66	41.74 ± 1.51
Vocabulary	38.00 ± .97	38.64 ± 1.02	40.44 ± .97	40.71 ± 1.02
AVLT-Immediate	8.67 ± .27	9.10 ± .29	8.70 ± .27	9.23 ± .29
AVLT-Delayed	8.51 ± .44	8.73 ± .48	8.13 ± .44	8.98 ± .49

SE, standard error; COWA, Controlled Oral Word Association Test; AVLT, Auditory Verbal Learning Test.

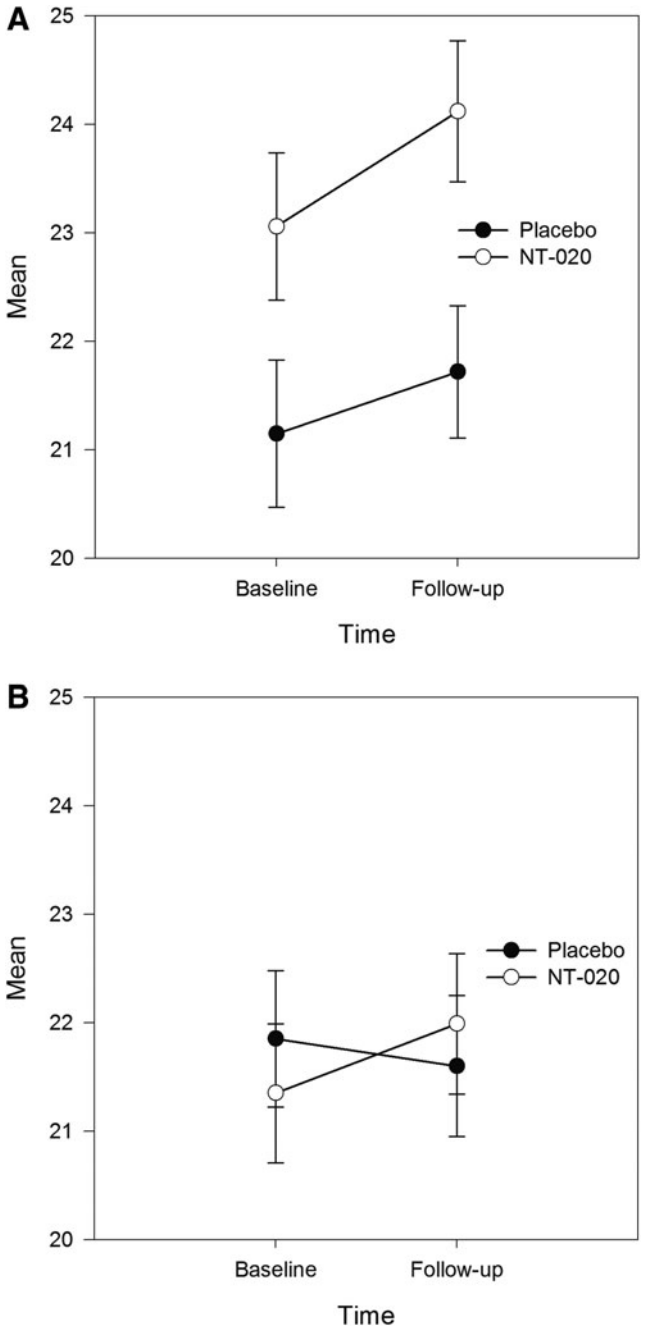

FIG. 2. Identical pictures (**A**) and number completion (**B**) performance as a function of time and group.

the current study were very high functioning, as evidenced by the nearly perfect MMSE scores, as well as the high level of educational attainment. It may be the case that because the participants in the Krikorian studies were selected on the basis of having memory deficits this was a domain that had the most potential to improve.

In the current study, we saw improvements in processing speed, which is a domain that typically exhibits significant changes with advancing age.[31,32] Among persons who are cognitively intact, the domain of processing speed may be one that is most malleable on account of the normative declines that appear. Indeed, a recent cognitive training intervention showed that gains to processing speed were the most robust among a group of older adults, as compared to other cognitive ability domains that were evaluated.[4] Second, the length of the intervention period used here was relatively modest, up to 60 days, whereas the work by Krikorian spanned 12 weeks[29] or up to 16 weeks.[30] In some respects, the presence of statistically significant improvements in processing speed among a cognitively healthy and highly educated sample of older adults speaks to the robustness of these findings. Nevertheless, future studies using NT-020 may include persons with cognitive impairment and may also extend the intervention period.

The results of the analysis of adverse events and compliance to pill counts indicated that the study was well tolerated by the older adult participants. Dietary interventions, such as the one described here, were recently highlighted as a ''new opportunity'' for clinical interventions designed to address cognitive decline in old age.[33] Indeed, the work described here demonstrated modest improvements in one domain of cognitive performance among a high-functioning group of older adults.

Although the results of the current study are informative, there are several limitations to note. First, the participants examined here were very high functioning in terms of their overall level of cognitive performance as well as health and educational attainment. Had we included persons who were less healthy cognitively or those with identifiable cognitive impairments, we may have observed more robust findings. Second, the 2-month follow-up period may have been too short to observe widespread benefits to cognitive performance. Future studies should lengthen the intervention period to evaluate the optimal time of intervention so that maximal results can be observed. The decision upon which this optimal time of intervention is based may be understood by examining the biological markers of oxidative stress and inflammation to determine how and when they change across the intervention period. Similarly, we are unable to draw conclusions regarding the mechanism of action for the effects that we have observed. In the future, having markers of oxidative stress and inflammation, as well as brain-based measures of functioning, may allow us to identify the manner by which this compound, as well as others, may influence functioning.

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Author Disclosure Statement

Drs. Small, Rawson, and McEvoy as well as Ms. Eisel and Ms. Martin have no conflicts to report. Dr. Bickford and Dr. Paul Sanberg are co-founders of Natura Therapeutics, the company that developed and markets NT-020. As co-Principal Investigator of the current study, Dr. Bickford's conflict of interest was managed by Western IRB, as the University of South Florida has intellectual property associated with NT-020. Dr. Cyndy Sanberg is President and COO of Natura Therapeutics. Drs. Shytle and Tan are inventors of NT-020 and share Intellectual Property rights. Neither Drs. Bickford, Shytle, or Tan nor Dr. Cyndy Sanberg or Dr. Paul Sanberg had direct contact with any study data. They were involved in the preparation of the manuscript, but not in the collection or analysis of any study data.

Finally, Natura Therapeutics provided NT-020 and the matched placebos for use in the study at no cost.

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