Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial

Gary W. Small, M.D., Prabha Siddarth, Ph.D., Zhaoping Li, M.D., Ph.D., Karen J. Miller, Ph.D., Linda Ercoli, Ph.D., Natacha D. Emerson, M.A., Jacqueline Martinez, M.B.A., M.S., Koon-Pong Wong, Ph.D., Jie Liu, Ph.D., David A. Merrill, M.D., Ph.D., Stephen T. Chen, M.D., Susanne M. Henning, Ph.D., R.D., Nagichettiar Satyamurthy, Ph.D., Sung-Cheng Huang, D.Sc., David Heber, M.D., Ph.D., Jorge R. Barrio, Ph.D.

Objective: *Because curcumin's anti-inflammatory properties may protect the brain from neurodegeneration, we studied its effect on memory in non-demented adults and explored its impact on brain amyloid and tau accumulation using 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile positron emission tomography (FDDNP-PET).* **Methods:** *Forty subjects (age 51–84 years) were randomized to a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily [N = 21]) or placebo (N = 19) for 18 months. Primary outcomes were verbal (Buschke Selective Reminding Test [SRT]) and visual (Brief Visual Memory Test-Revised [BVMT-R]) memory, and attention (Trail Making A) was a secondary outcome. FDDNP-PET signals (15 curcumin, 15 placebo) were determined in amygdala, hypothalamus, medial and lateral temporal, posterior cingulate, parietal, frontal, and motor (reference) regions. Mixed effects general linear models controlling for age and education, and effect sizes (ES; Cohen's d) were estimated.* **Results:** *SRT Consistent Long-Term Retrieval improved with curcumin (ES = 0.63, p = 0.002) but not with placebo (ES = 0.06, p = 0.8; between-group: ES = 0.68, p = 0.05). Curcumin also improved SRT Total (ES = 0.53, p = 0.002), visual memory (BVMT-R Recall: ES = 0.50, p = 0.01; BVMT-R Delay: ES = 0.51, p = 0.006), and attention (ES = 0.96, p < 0.0001) compared with placebo (ES = 0.28, p = 0.1; between-group: ES = 0.67, p = 0.04). FDDNP binding decreased*

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significantly in the amygdala with curcumin (ES = −0.41, p = 0.04) compared with placebo (ES = 0.08, p = 0.6; between-group: ES = 0.48, p = 0.07). In the hypothalamus, FDDNP binding did not change with curcumin (ES = −0.30, p = 0.2), but increased with placebo (ES = 0.26, p = 0.05; between-group: ES = 0.55, p = 0.02). **Conclusions:** *Daily oral Theracurmin may lead to improved memory and attention in non-demented adults. The FDDNP-PET findings suggest that symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory.* (Am J Geriatr Psychiatry 2018; 26:266–277)

Key Words: Bioavailable curcumin, normal aging, memory, cognition, positron emission tomography

Highlights

- This is the first long-term (18 months) double-blind, placebo controlled trial of a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily) in non-demented adults.
- We found that daily oral Theracurmin led to significant memory and attention benefits.
- FDDNP-PET scans performed pre- and post-treatment suggested that behavioral and cognitive benefits are associated with decreases in plaque and tangle accumulation in brain regions modulating mood and memory.
- Curcumin's cognitive benefits may stem from its anti-inflammatory and/or anti-amyloid brain effects.

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-2,5-dione) is the Indian herb used in curry powder and is a polyphenolic compound derived from turmeric, the dried rhizome of *Curcuma longa L.* (Fam. Zingiberaceae).[1] Turmeric gives curry its yellow color and has been used as a food flavoring, preservative, and an herbal remedy for arthritis, cancer, and cardiac and other medical conditions.[1]

Curcumin's anti-inflammatory, antioxidant, anti-amyloid, and possible anti-tau properties may offer neuroprotective benefits.[2,3] Epidemiological studies indicate a lower prevalence of Alzheimer disease in Indian people who consume curcumin in curry and a link between dietary curry consumption and better cognitive performance in older adults, supporting the hypothesis that curcumin consumption may provide neuroprotective benefits.[4,5]

Despite such promising research on curcumin's potential brain health benefits, initial placebo-controlled trials in humans have yielded negative results,[6,7] perhaps because they used forms of curcumin with limited bioavailability.[8] Moreover, the neurodegeneration in patients who are already suffering from dementia may be too extensive for the treatment to be effective. Previous investigations indicate that the neuropathological and clinical decline of Alzheimer disease begins years before patients develop dementia symptoms (i.e., cognitive decline making them dependent on others).[9] Autopsy studies have demonstrated that the neuropathological hallmarks of Alzheimer disease, β-amyloid (in senile plaques) and tau (in neurofibrillary tangles), accumulate gradually in a predictable spatial pattern during aging decades before people develop dementia symptoms.[10,11]

In recent years, investigators have begun testing more bioavailable forms of curcumin in non-demented adults. In a 12-month placebo-controlled trial, Rainey-Smith et al.[12] found no differences in all cognitive measures between curcumin- and placebo-treatment groups, except for a significant interaction between time and treatment group for the Montreal Cognitive Assessment test; this finding, however, resulted from a decline in general cognitive function of the placebo group at 6 months that was not observed in the curcumin group. A second trial demonstrated that another bioavailable form of curcumin improved working memory and sustained attention, compared with placebo, 1 hour after curcumin administration. After 1 month of treatment, working memory and mood improved in the curcumin-treated subjects, but no effects were observed for long-term memory.[13] These results were promising, but the brief trial duration limits conclusions regarding long-term use.

Although laboratory and animal studies indicate curcumin's potential effect on amyloid plaques and tau tangles,[2] previous human trials of curcumin have not monitored in vivo effects of this polyphenol on brain plaque and tangle accumulation. Our group developed 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile positron emission tomography (FDDNP-PET), which provides in vivo images of brain plaques and tangles.[14] We have shown that FDDNP binding values in selected brain areas are significantly higher in Alzheimer dementia than in healthy aging and mild cognitive impairment (MCI).[15] In non-demented individuals, lower cognitive performance is associated with higher FDDNP binding in brain regions that control thinking and memory.[16]

To address some of the limitations of previous human studies, we performed a randomized, double-blind, placebo-controlled, 18-month trial in middle-aged and older non-demented adults to determine the effects of daily oral use of a highly absorptive curcumin dispersed with colloidal nanoparticles (Theracurmin, Theravalues Corp., Tokyo, Japan)[8] on memory performance. We also explored its potential impact on neurodegeneration using FDDNP-PET to measure brain deposition of amyloid plaques and tau tangles.

METHODS

Study Design

The study used a randomized, double-blind, two-group parallel design comparing placebo to Theracurmin, a form of curcumin with increased intestinal endothelium penetrability.[17] Previous research has shown that healthy human volunteers consuming 30 mg of oral Theracurmin have a 27-fold higher area under the blood concentration-time curve values when compared with those consuming standard curcumin powder.[8]

Subjects were randomized to either placebo or Theracurmin (containing 90 mg of curcumin) twice daily (i.e., 180 mg curcumin/day). We chose a treatment period of 18 months to determine long-term cognitive effects of curcumin. Moreover, our previous studies suggested that this time period would be sufficient to detect significant changes in FDDNP-PET binding levels in non-demented middle-aged and older adults.[18]

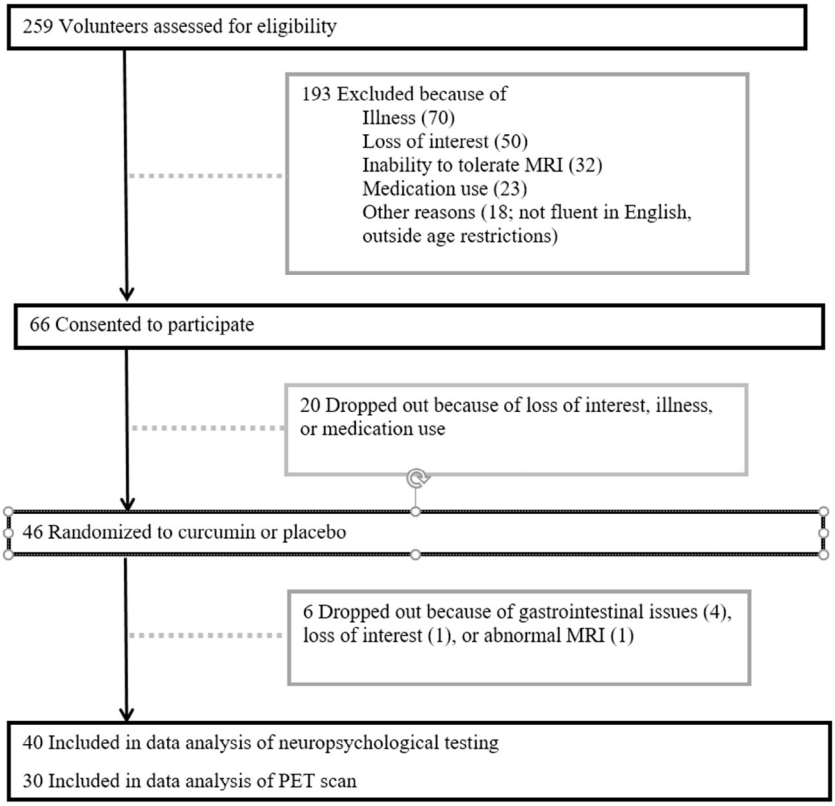
The medical center research pharmacy assigned subjects to treatment arms using a randomization table. The curcumin and placebo were encapsulated and the color of the active curcumin capsules did not differ from the placebo capsules. The capsules were tasteless, but curcumin can change the color of urine. However, change in urine color was never reported as an adverse event and unlikely to have led to un-blinding of the intervention. During baseline assessments, participants received vital signs, electrocardiograms, serum electrolytes, thyroid function, and complete blood counts, as well as a 3-month supply of placebo or Theracurmin, which they were instructed to begin the following morning. Subjects returned every 3 months for placebo or curcumin supplies. Potential adverse events and use of the supplement or placebo were checked every 3 months to monitor safety and compliance.

Subject Selection and Assessment

We performed baseline cognitive assessments on 46 subjects who met study entry criteria from a pool of 259 potential volunteer, who were recruited through advertisements, media coverage, and referrals from physicians and families. Our study protocol detailed the methods and procedures and pre-specified inclusion and exclusion criteria (ClinicalTrials.gov Identifier: NCT01383161).

To be included, volunteers needed to have objective cognitive performance scores and clinical histories that were consistent with normal aging or MCI (i.e., mild neurocognitive disorder) and inconsistent with dementia (i.e., major neurocognitive disorder).[19,20] All subjects were aged between 50 and 90 years, agreed to participate for the entire 18 months, had adequate visual and auditory acuity for neuropsychological testing, and had screening laboratory tests and electrocardiograms that did not show significant medical abnormalities that might interfere with the study. Reasons for exclusion included significant cerebrovascular disease; probable Alzheimer disease or any other dementia;[20,21] neurological or physical illnesses that can produce cognitive deterioration; inability to undergo magnetic resonance imaging (MRI) or significant abnormality on brain MRI; history of myocardial infarction within the previous year or unstable cardiac disease; uncontrolled hypertension (systolic BP > 170 or diastolic BP > 100); significant

FIGURE 1. Volunteer flow chart.



liver or pulmonary disease, diabetes, or cancer; major depression or any major psychiatric disorder; history of alcoholism or substance addiction; use of vitamins other than a standard multivitamin supplement; use of any medication or supplement containing curcumin, cognitive enhancing supplements, or investigational drugs within the previous month or longer, depending on drug half-life; or evidence of vasogenic edema. Potential subjects who were regularly consuming curcumin and unwilling to discontinue it were excluded from the study. Because some nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen) can alter FDDNP binding, subjects taking such medication needed to be able to discontinue it for a week prior to PET scanning.[22] The most frequent reasons for exclusion were illness (N = 70), loss of interest in participating (N = 50), inability to tolerate MRI (N = 32), or medication use (N = 23; Figure 1).

At baseline, all subjects were screened to ensure they met inclusion criteria and received routine screening laboratory tests, and MRI scans to rule out reversible causes of cognitive impairment.[23] In addition, subjects were given the Montreal Cognitive Assessment[24] and the Beck Depression Inventory.[25] A neuropsychological test battery[15,26] was performed to assist in excluding subjects with dementia and to determine whether included subjects had normal aging or MCI. The battery assessed six cognitive domains: attention and psychomotor speed (Trail Making Test A, WAIS-III Digit Symbol Substitution); visuospatial functioning (WAIS-III Block Design Test, Rey-Osterrieth Complex Figure Test [copy]); executive functioning (Trail Making Test B, Stroop Interference [Kaplan version], F.A.S. Letter Fluency Test); learning (Buschke-Fuld Selective Reminding Test [SRT][total recall], Wechsler Memory Scale-3rd Edition [WMS-III] Verbal Paired Associations I, Benton Visual Retention Test); delayed recall (Buschke-Fuld SRT [Delayed Recall], Rey-Osterrieth Complex Figure Test [recall], WMS-III Verbal Paired Associations II); and language or

semantic memory (Boston Naming Test, Animal Naming Test). Subjects also received a memory functioning questionnaire, a standardized measure of memory self-awareness.[27] We used the following diagnostic criteria for MCI: 1) patient awareness of a memory problem, preferably confirmed by another person such as a family member; 2) cognitive impairment detected with standardized assessment tests; and 3) ability to perform normal daily activities. To increase specificity for detecting impairment, we included subjects who scored less than 1 standard deviation below the mean on at least two tests and whose diagnosis was corroborated by clinical assessment.

Because previous animal[28,29] and human[13] research indicated memory effects of curcumin, we chose two memory tests as primary outcome measures after 6, 12, and 18 months of treatment. The Buschke SRT[30] was the primary outcome measure for verbal memory. The SRT is a standardized measure of verbal learning that presents 12 words to the subject who is asked to immediately recall as many words as possible. The examiner then presents words that the subject was unable to recall until the subject can recall all 12 words without prompting twice, or until the examiner has presented prompts up to 12 times. The Consistent Long Term Retrieval score is the number of words that the subject recalls without receiving prompts and indicates how well the subject consolidates the new information during the learning phase (encoding). We also used the Total Recall score (number of words recalled over the 12 trials), which reflects immediate recall (short-term memory) for new information. The Brief Visual Memory Test-Revised (BVMT-R)[31] was the primary outcome measure for visual memory. Because a previous human trial[13] showed a curcumin effect on sustained attention, we chose a measure of sustained attention, the Trail Making Test Part A, as a secondary outcome measure.[32] Curcumin may influence mood as well as cognition,[13,33] so we repeated the Beck Depression Inventory[25] to determine a possible effect of curcumin on symptoms of depression. To ensure that subjects were compliant in taking either curcumin or placebo and not consuming additional curcumin outside of the study, we performed plasma curcumin levels at baseline and after 18 months of treatment. Curcumin plasma bioavailability and total curcumin analysis studies were also performed (methods included in supplementary material). Subjects were also instructed to avoid consuming extra dietary curcumin.

Written informed consent was obtained from all subjects in accordance with the University of California, Los Angeles, human subjects protection committee procedures. The trial began in March 2012 and was completed in April 2016. Cumulative radiation dosimetry for all PET scans was below the mandated maximum annual dose and in compliance with state and federal regulations.

Genetic Analysis

DNA was obtained from blood samples. APOE genotypes were determined using standard techniques, as previously described.[16] Genetic data were available for 35 of the subjects completing the study.

Scanning Procedures

Data were available from FDDNP-PET scans performed on 30 subjects at baseline and after 18 months of curcumin supplementation or placebo. Ten subjects included in the study did not have baseline and post-treatment PET scans available for analysis because three dropped out before receiving the follow-up scan, three had technical issues with the scans that invalidated the data, and four did not receive scans due to lack of funding.

FDDNP methods are detailed in previous publications and the supplementary material.[15,16,34–37] In brief, all scans were performed with participants in a supine position and with the imaging plane parallel to the orbitomeatal line. A bolus of FDDNP (320–550 MBq) was injected via an indwelling venous catheter, and consecutive dynamic PET scans were performed for 1 hour. Bilateral regions of interest were manually traced on the early-summed images for the parietal, medial temporal (limbic regions, including hippocampus, parahippocampal areas, and entorhinal cortex), lateral temporal, posterior cingulate, anterior cingulate, amygdala, hypothalamus, occipital, motor, and frontal regions. The FDDNP binding data were quantified using Logan graphical analysis with the motor strip as the reference region. All PET scans were read and regions of interest drawn by individuals blinded to clinical assessments and treatment group.

General Statistical Analysis

Before statistical analyses, all data were inspected for outliers, skewness, kurtosis, and homogeneity of variance to ensure their appropriateness for parametric statistical tests. The curcumin and placebo groups were compared on baseline demographic and clinical characteristics with χ^2 statistics for categorical measures and t tests for continuous measures. All subjects with baseline data were used to examine all outcomes. Our primary and secondary outcome measures are continuous and were analyzed using a mixed-effects general linear model, as implemented in PROC MIXED in SAS v 9.4 (SAS Institute, Cary, NC). We included treatment group as the between-subject factor, time as the within-subject factor, and the interaction term between time and treatment group as predictors. Age and education level were used as covariates. We also examined using apolipoprotein E (APOE4) status and family history of dementia as additional covariates but findings were substantively similar, so we report results obtained with models with only age and education as covariates. Post hoc analyses determined the significance of between group differences and within-group changes. The significance threshold for each of the outcome measures was set at 0.05 (two-tailed).

RESULTS

Participant Flow and Follow-Up

A total of 46 subjects who met the study inclusion criteria were randomized; 6 withdrew from participation after randomization (Figure 1). Of the remaining 40 subjects, 21 belonged to the curcumin group and 19 to the placebo group. One subject randomized to curcumin dropped out after the 12-month visit (reported heartburn and bloating due to study material), and two placebo subjects dropped out after the 6-month visit (one due to loss of interest and the other due to inability to take the pills). Subjects who withdrew did not differ significantly from those who completed the study in mean age or baseline cognitive measures.

For the curcumin group, mean (SD) follow-up was 18.7 (1.6) months; for the placebo group it was 18.5 (0.5) months. Treatment groups did not differ significantly in baseline demographic variables, age, sex ratio, proportion with MCI, APOE4 status, family history of dementia, or in Montreal Cognitive Assessment, Beck Depression Inventory, or Memory Functioning Questionnaire scores (Table 1). They did differ significantly in educational achievement (curcumin group: 17.5 [2.0] years; placebo group: 15.4 [2.7] years; Table 1). Baseline levels of free curcumin were 0 ng/mL for both groups; at 18 months the free curcumin mean (SD) level (measured randomly throughout the day) was 26.2 (20.1) ng/mL (range, 3.0 to 67.3), and the mean (SD) placebo group level was 0.1 (0.3) ng/ml (range, 0 to 1.2), confirming that subjects were compliant in taking either curcumin or placebo and not consuming additional curcumin outside of the study. The bioavailability study confirmed Theracurmin's more rapid absorption and peak concentration compared with two other curcumin forms (Figure 2).

TABLE 1. Baseline Characteristics of Subjects

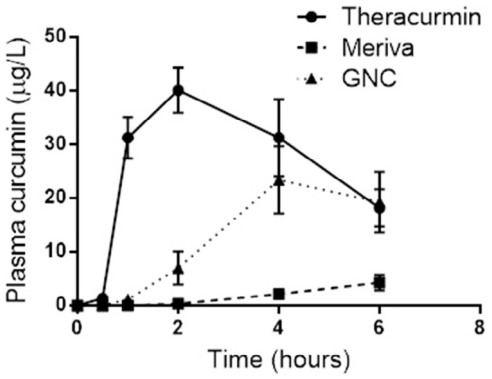
	Curcumin (N = 21)	Placebo (N = 19)
Age, years	63.1 (8.4)	62.9 (9.4)
Education, years[a]	17.5 (2.0)	15.4 (2.7)
Sex, female, N (%)	12 (57)	10 (53)
Mild cognitive impairment, N (%)	9 (43)	7 (37)
Montreal Cognitive Assessment	26.7 (2.6)	26.9 (2.5)
Wechsler Test of Adult Reading	41.1 (2.6)	41.9 (7.4)
Memory Functioning Questionnaire		
Frequency of Forgetting	164.7 (38.8)	158.8 (17.7)
Seriousness of Forgetting	89.8 (27.7)	80.3 (26.1)
Retrospective Functioning	16.2 (5.7)	17.5 (6.1)
Mnemonics Usage	22.5 (10.5)	24.5 (9.7)
Family history of dementia, N (%)	16 (76)	14 (74)
APOE4 carriers, N (%)	8 (38)	5 (26)

Notes: Values are means with standard deviations in parentheses, unless otherwise noted.
[a] $t_{(38)} = 2.9$, $p = 0.01$.

Cognitive Outcomes

For the primary verbal memory outcome measure (Buschke SRT, Consistent Long-Term Recall), the group by time interaction term was statistically significant ($F_{(1,37)} = 4.4$, $p = 0.05$): The curcumin group showed significant improvement from baseline after 18 months of treatment (change = 20.3, ES = 0.63, $t_{(37)} = 3.3$, $p = 0.002$), and the placebo group did not show significant change (change = 1.9, ES = 0.06, $t_{(37)} = 0.3$, $p = 0.8$). The between group effect size was determined to be 0.68 (Table 2; Figure 3). For the SRT Total score, the group by time interaction term did not

FIGURE 2. **Kinetics of curcumin absorption of blood collected at 0.5, 1, 2, 4, and 6 hours after capsule consumption. For the 10 healthy volunteers enrolled in the bioavailability study (see supplementary material), three forms of curcumin were compared. Theracurmin® was absorbed faster (T-max: 2 hours) than GNC Herbal Plus Standardized Turmeric® (4 hours; supplied by GNC [Pittsburgh, PA]) and Meriva® (6 hours; supplied by Indena SpA [Milan, Italy]). Theracurmin consumption also led to significantly higher peak concentrations (40.1 ± 13.3 μg/L) and areas under the curve (165 ± 64 μg × hour/L) compared with GNC Herbal Plus Turmeric (23.4 ± 18.8 μg/L, 74 ± 70 μg × hour/L), and Meriva (4.2 ± 4.6 μg/L, 9 ± 8 μg × hour/L).**



achieve statistical significance ($F_{(1,37)} = 3.0$, $p = 0.08$); however, the curcumin group showed significant improvement from baseline to 18 months (change = 8.0, ES = 0.53, $t_{(37)} = 3.3$, $p = 0.002$), whereas the placebo group did not show significant change (change = 1.6, ES = 0.02, $t_{(37)} = 0.6$, $p = 0.5$).

For the primary visual memory outcome measure (BVMT-R), the group by time interaction was not significant ($F_{(1,37)} = 0.3$, $p = 0.5$), even though the curcumin group showed significant improvement from baseline to 18 months (change = 3.7, ES = 0.50, $t_{(37)} = 2.7$, $p = 0.01$) and the placebo group did not (change = 2.0, ES = 0.26, $t_{(37)} = 1.3$, $p = 0.2$). For the BVMT-R Delay score, the group by time interaction term did not achieve statistical significance ($F_{(1,37)} = 0.2$, $p = 0.08$); the curcumin group showed significant improvement from baseline to 18 months (change = 1.4, ES = 0.51, $t_{(37)} = 2.9$, $p = 0.006$), whereas the placebo group did not (change = 0.2, ES = 0.02, $t_{(37)} = 0.3$, $p = 0.8$).

For the secondary outcome measure of attention (Trail Making Test Part A), the interaction term ($F_{(1,37)} = 4.8$, $p = 0.04$) indicated that the change for the curcumin group was significantly greater compared with the change for the placebo group (ES = 0.67). The curcumin group improved significantly from baseline to 18 months (change = 8.0, ES = 0.96, $t_{(37)} = 4.9$, $p < 0.0001$), and the placebo group did not show significant change (change = 2.8, ES = 0.28, $t_{(37)} = 1.7$, $p = 0.1$). At 18 months, the curcumin group also showed significant improvements in Beck Depression Inventory scores (change = –1.9, ES = 0.55, $t_{(37)} = –2.2$, $p = 0.04$), and the placebo group did not (change = –0.4, ES = 0.07, $t_{(37)} = –0.5$, $p = 0.6$). Between group changes were not significantly different ($F_{(1,37)} = 1.2$, $p = 0.3$).

FDDNP-PET Scan Results

At baseline, regional FDDNP binding values did not differ significantly between the curcumin and placebo treatment groups (Table 3). After 18 months of treatment, we found significant changes in mean FDDNP binding in two regions of interest. In the amygdala, between group changes did not reach significance ($F_{(1,27)} = 3.7$, $p = 0.07$); however, FDDNP binding levels declined significantly in the curcumin group (ES = –0.41, $t_{(27)} = –2.1$, $p = 0.04$) whereas in the placebo group there was no significant change (ES = 0.08, $t_{(27)} = 0.5$, $p = 0.6$). Further, changes in amygdala binding values were significantly correlated with changes in Beck Depression Inventory scores in the curcumin group: Spearman r = 0.62, p = 0.02. Changes in hypothalamic binding values were significantly different between the curcumin and placebo groups ($F_{(1,27)} = 5.8$, $p = 0.02$; ES = 0.55): The change in the curcumin group was not significant whereas the placebo group showed a significant increase after 18 months (ES = –0.30, $t_{(27)} = –1.3$, $p = 0.2$ versus ES = 0.26, $t_{(27)} = 2.0$, $p = 0.05$).

Adverse Events

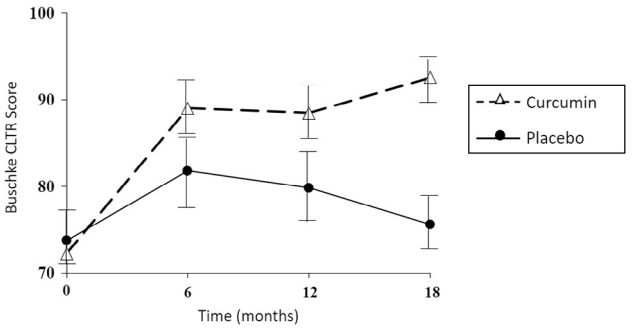
Four curcumin-treated subjects and two placebo-treated subjects experienced gastrointestinal side effects (transient abdominal pain, gastritis, or nausea). One subject receiving curcumin reported a temporary feeling of heat and pressure in the chest after FDDNP-PET scanning at baseline.

TABLE 2. Baseline and 18-Month Cognitive and Mood Scores, Percent Changes, and Effect Sizes

	Curcumin			Placebo			Effect Size		
Measures	Baseline	18-Month	% Change	Baseline	18-Month	% Change	Within Curcumin	Within Placebo	Between Group
Buschke Selective Reminding Test									
Consistent Long Term Recall	72.3 (31.6)	92.6 (30.9)	28.1	73.7 (31.8)	75.6 (36.4)	2.6	0.63	0.06	0.68
Total	113.7 (13.9)	121.7 (13.2)	7.9	111.3 (15.6)	112.9 (18.4)	1.4	0.53	0.02	0.51
Long-Term Storage	112.1 (18.7)	119.9 (15.5)	7.0	108.0 (20.0)	111.2 (23.8)	3.0	0.40	0.08	0.33
Brief Visual Memory Test									
Recall	19.2 (6.9)	22.4 (6.4)	16.7	20.3 (6.0)	22.5 (7.8)	10.8	0.50	0.26	0.24
Delay	7.3 (2.7)	8.5 (2.1)	16.4	8.3 (2.5)	8.5 (2.8)	2.4	0.51	0.02	0.48
Trail Making Test Part A	32.6 (9.3)	24.9 (5.3)	23.6	30.5 (8.3)	28.4 (10.8)	7.4	0.96	0.28	0.67
Beck Depression Inventory	4.6 (4.5)	2.7 (2.5)	41.3	4.4 (3.4)	4.0 (5.0)	10.0	0.55	0.07	0.48

Notes: Values are provided as mean (standard deviation).

FIGURE 3. For the primary verbal memory outcome measure (Buschke SRT, Consistent Long-Term Recall), the curcumin group showed significant improvement from baseline after 18 months of treatment (change = 20.3, ES = 0.63, $t_{(37)}$ = 3.3, p = 0.002); the placebo group did not show significant change (change = 1.9, ES = 0.06, $t_{(37)}$ = 0.3, p = 0.8), and between group differences were significant ($t_{(37)}$ = 2.1, ES = 0.68, p = 0.05).



DISCUSSION

These findings suggest that daily oral ingestion of a bioavailable and safe form of curcumin improves memory performance over an 18-month period in middle-aged and older non-demented adults. Moreover, such daily oral curcumin consumption may lead to less neuropathological accumulation in the amygdala and hypothalamus.

Volunteers taking Theracurmin demonstrated significant memory improvement after 18 months as measured by the Buschke SRT, and the Consistent Long-Term Retrieval score showed significant curcumin–placebo between-group differences,with an effect size of 0.68. The Consistent Long-Term Retrieval score reflects the subject's ability to consolidate new information (short-term memory) and continuously recall the target information over time. Previous research has shown that the Buschke SRT is a sensitive cognitive measure that can predict future cognitive decline and intervention response[38–41] in people with age-associated memory complaints as well as those with dementia. The observation that the secondary attention outcome measure (Trail Making Test Part A) also demonstrated significant between-group differences further supports the conclusion that long-term Theracurmin consumption offers benefits to cognitive functioning over an 18-month period.

The finding that curcumin compared with placebo consumption may lead to less FDDNP binding in the amygdala and the hypothalamus—brain regions that are part of the limbic system—further supports these cognitive findings. The amygdala performs a role in memory processing, decision-making, and emotional responses. In addition to linking the nervous system to the endocrine system, the hypothalamus plays a role in processing emotional responses, and neurofibrillary degeneration in the hypothalamus affects neurons that innervate cortical regions involved in Alzheimer disease.[42]

TABLE 3. Baseline and 18-Month Regional FDDNP Binding Levels, Percent Changes, and Effect Sizes

	Curcumin			Placebo			Effect Size		
Regions	Baseline	18-Month	% Change	Baseline	18-Month	% Change	Within Curcumin	Within Placebo	Between Group
Frontal	1.11 (0.05)	1.10 (0.06)	−0.63	1.15 (0.08)	1.13 (0.08)	−1.52	−0.13	−0.22	−0.10
Parietal	1.04 (0.06)	1.06 (0.06)	1.38	1.07 (0.05)	1.07 (0.05)	−0.51	0.24	−0.11	−0.35
Lat Temp	1.11 (0.05)	1.12 (0.05)	0.64	1.13 (0.08)	1.14 (0.07)	0.50	0.14	0.08	−0.06
Med Temp	1.16 (0.06)	1.17 (0.07)	0.52	1.18 (0.07)	1.19 (0.06)	1.31	0.09	0.23	0.14
Post Cingul	1.13 (0.06)	1.12 (0.05)	−0.88	1.14 (0.08)	1.14 (0.06)	−0.17	−0.19	−0.03	0.16
Ant Cingul	1.18 (0.06)	1.18 (0.05)	−0.16	1.22 (0.09)	1.20 (0.08)	−1.50	−0.04	−0.21	−0.17
Amygdala[a]	1.29 (0.06)	1.26 (0.06)	−2.05	1.31 (0.11)	1.32 (0.10)	0.62	−0.41	0.08	0.48
Hypothalamus[b]	1.42 (0.06)	1.40 (0.06)	−1.31	1.42 (0.14)	1.46 (0.13)	2.52	−0.30	0.26	0.55

Notes: Values are provided as mean (standard deviation). Ant Cingul: anterior cingulate; Lat Temp: lateral temporal; Med Temp: medial temporal; Post Cingul: posterior cingulate.
[a]Trend in between group difference ($p = 0.07$); significant decrease within the curcumin group ($p = 0.04$).
[b]Significant between group difference ($p = 0.02$); significant increase within the placebo group ($p = 0.05$).

Previous research has shown that FDDNP binding levels in non-demented middle-aged and older people vary according to symptoms of anxiety and depression,[43] and patients with major depression in late life show elevated FDDNP binding values.[44]Moreover, both preclinical and clinical trials suggest possible antidepressant and antianxiety effects of curcumin.[45,46] Such findings suggest that curcumin's cognitive benefits could be mediated through effects on brain regions such as the amygdala and hypothalamus that control both mood and memory. Consistent with this hypothesis was our finding that the curcumin group showed significant improvements in Beck Depression Inventory scores, whereas the placebo group did not, and further, increases in amygdala FDDNP binding levels were significantly associated with mood changes in the curcumin treated group. Subjects with significant symptoms of depression or anxiety were excluded from this study. If curcumin's putative effects are mediated in part through its mood stabilizing impact, these results may have been greater had we not excluded subjects with more severe symptoms of depression and anxiety.

Exactly how curcumin may exert cognitive and mood effects is not certain, but several potential mechanisms could explain our findings. Curcumin reduces inflammation,[47] and heightened brain inflammation has been linked to both Alzheimer disease and major depression.[48–50] Curcumin also has powerful antioxidant properties, and oxidative stress is central in the early pathogenesis of Alzheimer disease.[51] Curcumin's possible brain health benefits also may result from its disruption of the formation, accumulation, and toxicity of amyloid plaques; facilitation of macrophage uptake and ingestion of plaques; anti-proliferative actions on microglia; interaction with such neurotoxic heavy metals as cadmium and lead; inhibition of cholesterol formation; and decreases in serum peroxides.[2,3,52–57]

As in any study, methodological issues deserve comment. Only approximately 15% of the screened volunteers were included in the study, and our recruitment method yielded a sample of motivated, educated, physically healthy subjects concerned about age-related memory problems. The sample, therefore, was not representative of the general population. As for all PET imaging studies, several factors can influence results, including use of concomitant medications and head motion during imaging.[15] In addition, curcumin has the potential to interfere with FDDNP binding to amyloid[58] and tau,[59] and it is important to consider whether curcumin consumption may have affected FDDNP binding to plaques and tangles at the 18-month follow-up scans. This is unlikely, however, for multiple reasons. Amyloid and tau curcumin binding experiments reported in the literature have been performed in vitro with brain slices[60] or such methods as X-ray crystallography,[61] which do not take into consideration the intestinal or blood–brain barrier transport properties of curcumin. Moreover, curcumin's low intestinal absorption, rapid metabolism, and systemic elimination severely limit its central bioavailability.[62] In addition, curcumin penetrability through the blood–brain barrier has been shown to be negligible.[63]

The use of adjuvants that block curcumin metabolism, or nanoparticles, liposomes, phospholipid

complexes, and other strategies have improved its bioavailability somewhat, but only as defined as increased curcumin blood levels[8,64–66] with minimum effects on curcumin availability to the brain. Thus, factors other than direct brain amyloid or tau aggregate binding are more likely to explain curcumin's brain health effects. Abundant evidence indicates that curcumin's in vivo central effect of reducing amyloid accumulation might derive from multiple activities beyond direct binding inhibition of aggregate formation.[66] These curcumin effects may be mediated through the gut-controlled inflammatory processes in the body, involving multiple pathways, including metal chelation, limitation of oxidative damage, and reduction of cholesterol, proinflammatory cytokines, and lipids.[2,3,52–54,56,57,62]

The relatively small sample size in this study warrants caution in interpreting our results and limits their generalizability. Another limitation was that we did not correct for multiple tests in the analyses as this was a pilot trial. Further, the FDDNP-PET results were on a subset of the total sample, should be considered exploratory, and require replication in a larger sample. We controlled for education in all the analyses, but we cannot rule out the possibility that the relatively small but significant difference in educational level between the two treatment groups may have had an effect. Forty percent of the sample (N = 16) was diagnosed with MCI. Although the proportion of MCI subjects did not differ between the two treatment groups, the number of subjects with MCI was too small to determine whether the findings were being driven by those with or without MCI. We intend to examine MCI and normal aging subjects separately in a future trial with a larger sample size.

Despite such limitations, this study has several strengths, including the relatively long treatment duration with a bioavailable form of curcumin; the focus on non-demented middle-aged and older adults rather than subjects with more advanced neurodegeneration; the use of sensitive cognitive measures to track memory effects; and exploration of possible concurrent effects of curcumin on brain plaque and tangle burden. Our positive findings that daily use of Theracurmin, a bioavailable form of curcumin, improves memory and decreases amyloid and tau binding in the amygdala and hypothalamus are encouraging that this relatively inexpensive and nontoxic treatment may have a potential for not only improving age-related memory decline but also preventing or possibly staving off progression of neurodegeneration and eventually future symptoms of Alzheimer disease. These results warrant further study in similar populations to confirm the observed cognitive benefits of curcumin and elucidate the underlying mechanisms responsible for such effects.

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APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2017.10.010.

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