Chronic curcumin treatment improves spatial working memory but not recognition memory in middle-aged rhesus monkeys

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Abstract Studies of both humans and non-human primates have demonstrated that aging is typically characterized by a decline in cognition that can occur as early as the fifth decade of life. Age-related changes in working memory are particularly evident and mediated, in part, by the prefrontal cortex, an area known to evidence age-related changes in myelin that is attributed to inflammation. In recent years, several nutraceuticals, including curcumin, by virtue of their anti-inflammatory and antioxidant effects, have received considerable attention as potential treatments for age-related cognitive decline and inflammation. Accordingly, we assessed for the first time in a non-human primate model of normal aging the efficacy of dietary

intervention using the natural phenol curcumin to ameliorate the effects of aging on spatial working and recognition memory. Results revealed that monkeys receiving daily administration of curcumin over 14–18 months demonstrated a greater improvement in performance on repeated administration of a task of spatial working memory compared to monkeys that received a control substance.

Keywords Curcumin · Cognition · Aging · Rhesus monkey · Memory

Introduction

Studies of both humans and non-human primates have demonstrated that aging is typically characterized by a decline in cognition, with the earliest changes occurring in the domains of memory and executive function (Cahn-Weiner et al. 2000; Fristoe et al. 1997; Lai et al. 1995; Moore et al. 2003, 2006; M. B. Moss et al. 1997; Rabbitt and Lowe 2000; Souchay et al. 2000). In humans, changes within these two domains have been shown to begin as early as the fifth decade of life, i.e., in early middle age (Albert 1984; Chodosh et al. 2002; Drag and Bieliauskas 2010; Hara et al. 2012; Kwon et al. 2016; León et al. 2016; Light 1991; Simen et al. 2011; Zeamer et al. 2012; Zeamer et al. 2011). In rhesus monkeys, decreases in performance on tasks of executive function, short-term memory, and working memory also begin in middle age (Moore et al. 2003, 2006; M. Moss et al. 2007; Rapp and Amaral 1989, 1991;

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Sridharan et al. 2012; Voytko 1999). Of the age-related cognitive impairments reported in humans and monkeys, changes in short-term and working memory are particularly evident on spatial memory tasks, whereas performance on object memory are less affected (Arnsten and Goldman-Rakic 1990; Arnsten and Jentsch 1997; Bachevalier 1993; Bachevalier et al. 1991; Brown 2016; Darusman et al. 2014; Frick et al. 1995; Herndon et al. 1997; Johnson et al. 2016; Killiany et al. 2000; León et al. 2016; Rapp and Amaral 1989, 1991; Shamy et al. 2011; Zeamer et al. 2012).

It is well established that spatial working memory is mediated in part by the prefrontal cortex (PFC) in both humans and non-human primates (M. Arshad et al. 2016; Borella et al. 2014; Funahashi 2017; Johnson et al. 2016; Kwon et al. 2016; McEwen and Morrison 2013; Moore et al. 2005; Raz et al. 1997; Toepper et al. 2014; Wirt and Hyman 2017). Interestingly, there is also significant evidence for age-related changes in PFC

white matter and myelin (Bowley et al. 2010; Drag and Bieliauskas 2010; Guttmann et al. 1998; Makris et al. 2007; Peters and Sethares 2002; Wisco et al. 2008). Furthermore, there is evidence showing that inflammation may underlie this white matter pathology and myelin breakdown and therefore is a candidate target for interventions (Cornejo and von Bernhardt 2016; Robillard et al. 2016; Safaiyan et al. 2016; Xie et al. 2013).

In recent years, dietary nutraceuticals that are rich in polyphenols have received considerable attention as potential treatments to slow or perhaps even ameliorate age-related cognitive decline by virtue of their anti-inflammatory and antioxidant effects. Of these, curcumin, a natural phenol member of the ginger family and the principal curcuminoid of the spice turmeric, has been shown to produce significant anti-inflammatory effects in humans and rodents (L. Arshad et al. 2017; Begum et al. 2008; Cole et al. 2007; Hussain et al. 2017; Ma et al. 2017). Preliminary findings in both humans and rodents reveal that curcumin may slow or delay the processes of senescence including the onset or progression of age-related changes in cognitive functions such as spatial working memory (Cox et al. 2015; Grabowska et al. 2017; Nam et al. 2014; Rainey-Smith et al. 2016; Salvioli et al. 2007; Sikora et al. 2010a; Sikora et al. 2010b). Accordingly, using the rhesus monkey as a well-established model of normal aging, we assessed for the first time the efficacy of dietary intervention using the natural phenol curcumin as an intervention to slow or even ameliorate the effects of aging on spatial working memory and recognition memory. Oral doses of curcumin or a control substance were given to a total of 17 monkeys over an 18-month period during which they completed 2 rounds of cognitive testing on tasks of visual recognition and spatial working memory.

Table 1 Table of subjects, with sex and age when each monkey entered the study

Control group	Sex	Age entered study
AM033	Male	10.3
AM101	Male	17.4
AM263L	Female	16.3
AM267L	Female	16.1
AM269L	Female	15.4
AM311c	Male	16.8
AM342c	Female	16.2
AM347c	Female	11.2
AM350c	Female	14.2
Mean		14.88
SD		2.51
SE		0.84
Curcumin group	Sex	Age entered study
AM308c	Male	16.8
AM309c	Male	16.9
AM310c	Male	17.8
AM312c	Male	16.9
AM313c	Male	21.6
AM343c	Female	14.4
AM348c	Female	10.9
AM349c	Female	16.6
Mean		16.49
SD		3.02
SE		1.07

Methods

Subjects Seventeen, behaviorally naive, middle-aged adult (10–21 years of age), male and female rhesus monkeys (*Macaca mulatta*) were used in this study (Table 1). All of the monkeys were obtained from a national primate research facility or private vendor and had known birth dates and complete health records. Before entering the study, monkeys received medical examinations that included serum chemistry, hematology, urine analysis, and fecal analysis. In addition, all

monkeys underwent magnetic resonance imaging to ensure there was no occult neurological damage. Results of the medical exams and MRIs revealed that all monkeys were healthy at the time they were entered into the study. While on study, monkeys were individually housed in colony rooms where they were in constant auditory and visual range of other monkeys in the Animal Science Center (ASC) of Boston University Medical Campus. This facility is fully AAALAC approved and animal maintenance and research were conducted in accordance with the guidelines of the National Institutes of Health and the Institute of Laboratory Animal Resources Guide for the Care and Use of Laboratory Animals. All procedures were approved by the Institutional Animal Care and Use Committee of the Boston University Medical Campus. Diet consisted of Purina Monkey Chow (Purina Mills Inc., St. Louis, MO) supplemented by fruit with feeding taking place once per day, immediately following behavioral testing. All monkeys were fed 12–20 biscuits per day based on their weight. During testing, small pieces of fruit or candy were used as rewards. Water was available continuously. The monkeys were housed under a 12-h light/dark cycle with cycle changes occurring in a graded fashion over the course of an hour. Following a quarantine period, acclimation to the colony room and baseline testing, monkeys were randomly assigned to either a control or curcumin treatment group.

Baseline cognitive testing Prior to beginning daily control or curcumin administration, all monkeys were initially familiarized with behavioral testing in a Wisconsin General Testing Apparatus (WGTA) where they were trained to displace a single gray plaque on a wooden testing board to obtain a reward. On each trial, the plaque was placed pseudo-randomly over one of the three food wells, each 3.5 cm in diameter and 0.5 cm deep. Wells were spaced 1.5 cm apart in a single row across the middle of a testing board (Fig. 1). Small pieces of fruit or candy were used as rewards during testing. Monkeys were trained until they responded on 40 consecutive trials on each of 2 successive days.

Initial acquisition—delayed non-matching to sample The delayed non-matching to sample (DNMS) task is a benchmark recognition memory task that assesses the ability of subjects to identify a novel stimulus from a familiar stimulus following a 10-s delay interval. In the present study, all monkeys began the acquisition

phase of the DNMS test in the WGTA. The DNMS task assesses the subject's ability to identify a novel from a familiar stimulus. Using the same testing board as familiarization testing (Fig. 1), each trial began with a sample object presented over the central baited food well. The monkey was permitted to displace the object and obtain the reward. The WGTA door was then lowered, and the original, now familiar, sample object was placed over an unbaited lateral well and a novel, unfamiliar object was placed over the other lateral well that was baited. Ten seconds after the original sample trial, the choice trial was begun and the monkey was required to choose the unfamiliar, novel object in order to obtain the reward. Both testing objects were replaced after each trial so as not to reuse objects during the same testing period. Following a 10-s inter-trial interval, the next trial was initiated with a new, novel sample object presented over the baited central well. Ten seconds later, another recognition trial was given using that second sample object and another new novel object. The position of the two objects on successive recognition trials was varied from left to right lateral wells in a predetermined pseudorandom order. A non-correction procedure was used and 20 trials per day were given until the monkey reached a learning criterion of at least 90 correct responses in 100 consecutive trials or a maximum of 2000 trials. Objects were drawn from a pool of 600 “junk” objects, and paired so that in each daily session of 20 trials, 60 of the objects were used. Once all of the initial pairings were used (30 days of 20 trials per day), the 600 objects were randomly recombined to produce new pairs so that the pairings presented continued to be new and unique on each trial.

Curcumin administration The day after reaching criterion on the initial acquisition of the DNMS basic task, the monkeys were randomly assigned to either the curcumin treatment or control groups and began receiving their daily dose of 500 mg of dietary curcumin treatment or control for 2 weeks. An extensive literature search did not reveal any publications describing Curcumin administration to rhesus monkeys. Therefore, we chose a dose of 500 mg per day based on various doses in several on-going clinical trials with curcumin to treat cognitive decline in aging and Alzheimer's disease. The curcumin used in this study was Longvida® Optimized curcumin that was manufactured and supplied by Verdure Sciences (Noblesville, IN). Their formulation is optimized natural curcumin for enhanced

Fig. 1 A photograph of the testing board used for delayed non-matching to sample. Scale bar = 5.0 cm

bioavailability. The control was dextrin and tartrazine (to match the color of active curcumin). The curcumin and control were mixed with approximately 120–150 ml of yogurt or Prima-Burger™ (BioServ, Flemington, NJ) and frozen. One single treatment was given to each monkey each day following the completion of cognitive testing. Treatments were also administered on the week-ends and holidays. A technician observed the monkey to confirm the treatment was eaten completely. If a monkey would not eat the treatment (e.g., discarding or dropping it into the waste pan of their cage), a second treatment was given. Monkeys ate the treatments (both the control and curcumin) on more than 98% of the study days.

As shown in Fig. 2, at the end of the 2-week period of initial dosing with curcumin or control, the monkeys began the first round of cognitive testing, while continuing daily doses of curcumin or control. At the end of round 1 testing, the monkeys were not tested for 8 weeks, but continued to receive their daily dose of curcumin or control. At the end of the 8-week period, they began round 2 of testing, again while continuing to receive daily curcumin or control. During each round of cognitive testing (approximately 6–8 months in duration), monkeys completed the following cognitive tests: Re-acquisition of DNMS, DNMS delays (2-min delays), and Delayed Recognition Span Task (Spatial).

Delayed non-matching to sample re-acquisition The DNMS task was administered as described above and monkeys were re-tested until reaching a criterion level of at least 90 correct responses in 100 consecutive trials.

Delayed non-matching to sample 2-min delays Upon reaching criterion on the basic task, the 10-s delay between the presentation of the sample object and the recognition trial was increased, to 120 s. Ten trials a day for 10 days (for a total of 100 trials) at the delay interval were administered with the monkey remaining in the testing apparatus during the delay interval.

Delayed recognition span task—spatial The testing board for delayed recognition span task (DRST) was similar to the DNMS board (Fig. 3), but instead of a single row of three wells, this board had three rows of six wells each (3.5 cm wide, 0.5 cm deep) and the wells were spaced 6 cm mm apart within a row. The rows were spaced 1.5 cm apart. For this task, 15 identical plain brown discs (6 cm in diameter) were used as stimuli. During the first sequence of a trial, 1 disc was placed over 1 of the 18 wells, which was baited with a food reward. The WGTA door was then raised and the monkey was allowed to displace the disc to obtain the reward. The door was then lowered, the first disc was returned to its original position over the now unbaited well, and a second disc was placed on the board over a

*Continue Receiving Curcumin or Vehicle

Fig. 2 A flow chart showing the sequence of events in the present study.

Fig. 3 A photograph of the testing board used for delayed recognition span task. Scale bar = 5.0 cm

baited well in a different location. After 10 s, the door was once again raised, and the monkey was required to identify the new second disc in its novel spatial location in order to obtain the reward. Each successive correct response trial was followed by the addition of a new disc in a novel location on the testing board and this continued until the monkey made an error (i.e., chose a previously chosen disc). With the occurrence of the first error, the trial was terminated and the number of discs on the testing board minus one were counted to determine the recognition span score for that trial (i.e., number of correct consecutive responses). Five such trials were presented each day for 20 consecutive days (total 100 trials).

At the completion of these tasks, monkeys were placed on a break from testing for 8 weeks while continuing to receive daily administration of curcumin or control. At the end of the 8-week break, monkeys began round 2 of testing and completed DNMS Basic–re-acquisition, DNMS with 2-min delays, and DRST–spatial tasks.

Results

Delayed non-matching to sample re-acquisition The total number of trials and errors to criterion were analyzed for each monkey for the reacquisition of the delayed non-matching to sample (DNMS) basic task for both round 1 and round 2 (Table 2). Since the subject groups consisted of both male and female monkeys, one-way ANOVAs were used to determine whether there was an effect of sex on performance. This analysis revealed no effect of sex on performance on the DNMS task in round 1 in terms of trials ($[F(1, 15) = 2.96, p = 0.106]$) and errors ($[F(1, 15) = 1.77, p = 0.203]$) or in round 2 in terms of trials ($[F(1, 15) = 0.332,$

$p = 0.572]$) and errors ($[F(1, 15) = 0.747, p = 0.400]$). Therefore, sex was not included as a factor in the following analyses.

Separate two-way repeated measures analyses of variance (ANOVA) were conducted, one for trials and the other for errors with treatment group as the between subject variable and round as the within subject variable. For total number of trials to criterion, there was no significant overall effect of treatment group $[F(1, 15) = 1.53, p = 0.235]$ and no group by round interaction $[F(1, 33) = 0.0005, p = 0.982]$ but there was a significant overall effect of round $[F(1, 15) = 38.23, p = 0.0001]$. Similar results were found for total errors to criterion with no significant overall effect of group $[F(1, 15) = 0.947, p = 0.346]$ and no group by round interaction $[F(1, 33) = 0.115, p = 0.739]$ but a significant overall effect of round $[F(1, 15) = 34.87, p = 0.0001]$. This data reveals that there was no group difference on the DNMS task suggesting that curcumin did not effect performance on this task.

We next followed-up by calculating a difference score between performance on the two rounds to determine whether there were systematic differences in performance on the DNMS task between round 1 to round 2 (Table 2). On the DNMS basic task, a lower score at round 2 represents an improved performance (e.g., Fewer trials or errors to reach criterion) and therefore to calculate the difference score, we the used the following formula: $((\text{round 1} - \text{round 2}) / \text{round 1}) \times 100$. This calculation gives a percent difference from round 1 to round 2 and therefore a higher positive difference score indicates a greater level of improvement. Separate one-way ANOVAs revealed that there were no significant group differences in performance for trials $[F(1, 15) = 0.851, p = 0.371]$ or errors $[F(1, 15) = 1.81, p = 0.198]$ between round 1 and 2. Overall, these results suggest that there was no effect of curcumin on

Table 2 Table of individual monkey data for trials and errors on the DNMS task on round 1 and round 2. The difference in performance for trials and errors between round 1 and round 2 for each monkey is also listed. On the DNMS task, a lower score at round 2 represents an improved performance (e.g., fewer trials

or errors to reach criterion) and therefore to calculate the difference score, we the used the following formula: $((\text{round 1} - \text{round 2}) / \text{round 1}) \times 100$. This calculation gives a percent difference from round 1 to round 2 and therefore a higher positive difference score indicates a greater level of improvement

Control group	Sex	1st DNMS (trials to criterion)	1st DNMS (errors to criterion)	2nd DNMS (trials to criterion)	2nd DNMS (errors to criterion)	% Difference DNMS trials	% Difference DNMS errors
AM033	M	240	91	100	21	58.33	76.92
AM101	M	460	114	0	0	100.00	100.00
AM263L	F	664	178	120	31	81.93	82.58
AM267L	F	256	41	100	8	60.94	80.49
AM269L	F	970	244	120	14	87.63	94.26
AM311c	M	500	174	0	0	100.00	100.00
AM342c	F	977	218	0	0	100.00	100.00
AM347c	F	1833	542	20	2	98.91	99.63
AM350c	F	583	182	220	45	62.26	75.27
Mean		720.33	198.22	75.56	13.44	83.33	89.91
SD		493.83	143.72	76.01	16.06	18.26	10.86
SE		164.61	47.91	25.34	5.35	6.09	3.62
Curcumin group	Sex	1st DNMS (trials to criterion)	1st DNMS (errors to criterion)	2nd DNMS (trials to criterion)	2nd DNMS (errors to criterion)	% Difference DNMS trials	% Difference DNMS errors
AM308c	M	440	107	20	4	95.45	96.26
AM309c	M	620	178	240	64	61.29	64.04
AM310c	M	640	140	0	0	100.00	100.00
AM312c	M	1060	323	300	58	71.70	82.04
AM313c	M	959	233	688	200	28.26	14.16
AM343c	F	1379	263	234	53	62.26	75.27
AM348c	F	859	231	250	50	70.90	78.35
AM349c	F	896	272	0	0	100.00	100.00
Mean		856.63	218.38	216.50	53.63	73.73	76.27
SD		293.44	72.08	227.92	65.22	24.55	28.21
SE		103.75	25.48	80.58	23.06	8.68	9.97

performance on the DNMS task. However, there is typically no decline in performance on this task in monkeys in the age-range that was used in this study and the monkeys in both groups were already performing at a high level, perhaps even at ceiling levels. Therefore, any improvements in performance may have been very small in magnitude and not large enough to reach significance. It would be of interest to repeat this study with older monkeys, who do typically show deficits on the DNMS task to determine whether curcumin would improve their performance.

Delayed non-matching to sample delays The percent of correct responses on the DNMS basic task with 2-min

delays was determined for each monkey in both round 1 and round 2 (Table 3). Similar to the DNMS basic task, there was also no effect of sex on performance on the DNMS delay task in round 1 ($[F(1, 15) = 1.89, p = 0.188]$) and round 2 ($[F(1, 15) = 1.41, p = 0.254]$) and therefore sex was not included as a factor in the following analyzes.

A two-way repeated measures analysis of variance (ANOVA) with group as the between subject variable and round as the within subject variable revealed no significant effect of group [$F(1, 15) = 0.669, p = 0.421$], round [$F(1, 15) = 0.384, p = 0.541$] or group by round interaction [$F(1, 33) = 2.98, p = 0.09$]. This was followed-up with examining a difference score

Table 3 Table of individual monkey data for performance on the DNMS delay task and the difference in performance between round 1 and round 2 for each monkey is also listed. On DNMS delays, a lower score at round 2 represents a decrease in performance (e.g., fewer correct responses) and therefore to calculate the

difference score, we the used the following formula: $((\text{round 1} - \text{round 2}) / \text{round 1}) \times 100 \times -1$. This calculation gives a percent difference from round 1 to round 2 and therefore a higher positive difference score indicates a greater level of improvement

Control group	Sex	1st DNMS 2-min delay (% correct)	2nd DNMS 2-min delay (% correct)	% Difference
AM033	M	89	89	0.00
AM101	M	74	67	-9.46
AM263L	F	73	76	4.11
AM267L	F	72	76	5.56
AM269L	F	72	71	-1.39
AM311c	M	80	93	16.25
AM342c	F	81	86	6.17
AM347c	F	81	83	2.47
AM350c	F	73	83	13.70
Mean		77.22	80.44	4.16
SD		5.87	8.55	7.74
SE		1.96	2.85	2.58
Curcumin group	Sex	1st DNMS 2-min delay (% correct)	2nd DNMS 2-min delay (% correct)	% Difference
AM308c	M	87	74	-14.94
AM309c	M	84	76	-9.52
AM310c	M	93	95	2.15
AM312c	M	89	80	-10.11
AM313c	M	83	82	-1.20
AM343c	F	80	74	-7.50
AM348c	F	86	76	-11.63
AM349c	F	73	88	20.55
Mean		84.38	80.63	-4.03
SD		6.05	7.50	11.38
SE		2.14	2.65	4.02

that was calculated for the performance of each monkey to determine their change in performance from round 1 to round 2 (Table 3). On DNMS delays, a lower score at round 2 represents a decrease in performance (e.g., fewer correct responses) and therefore to calculate the difference score, we the used the following formula: $((\text{round 1} - \text{round 2}) / \text{round 1}) \times 100 \times -1$. This calculation gives a percent difference from round 1 to round 2 and therefore a higher positive difference score indicates a greater level of improvement. A one-way ANOVA revealed that were no significant differences between the two treatment groups in their performance from round 1 to round 2 [$F(1, 15) = 3.07, p = 0.100$]. These results, taken together with the results from the DNMS basic task, suggests that daily administration of curcumin over an 18-

month period does not have a significant effect on recognition memory following either a relatively short (10 s) or longer (120 s) delay.

Delayed recognition span task—spatial The mean total span achieved by each monkey was determined across the 20 days of testing on the delayed recognition span task—spatial (DRSTsp) (Table 4). As with the DNMS task, we had both male and female monkeys complete the DRST task. One-way ANOVAs were used to determine whether there was an effect of sex on DRST performance. This analysis revealed no effect of sex on performance on the DRST task in round 1 [$F(1, 15) = 0.766, p = 0.395$] and round 2 [$F(1, 15) = 0.00067, p = 0.979$] and therefore sex was not included as a factor in the following analyzes.

Table 4 Table of individual monkey data for performance on the DRSTsp task on round 1 and round 2. The difference in performance on the DRSTsp between round 1 and round 2 for each monkey is also listed. On the DRST task, a lower score at round 2 represents a decrease in performance (e.g., decreased memory

span) and therefore to calculate the difference score, we use the following formula: $((\text{round 1} - \text{round 2}) / \text{round 1}) \times 100 \times -1$. This calculation gives a percent difference from round 1 to round 2 and therefore a higher positive difference score indicates a greater level of improvement

Control group	Sex	1st DRSTsp total	2nd DRSTsp total	% Difference
AM033L	M	2.52	2.06	-18.25
AM101L	M	1.82	1.77	-2.75
AM263L	F	2.02	1.97	-2.48
AM267L	F	2.15	2.12	-1.40
AM269L	F	1.99	2.03	2.01
AM311c	M	2.41	2.59	7.47
AM342c	F	2.19	2.83	29.22
AM347c	F	3.80	2.49	-34.47
AM350c	F	1.72	2.12	23.26
Mean		2.29	2.22	0.29
SD		0.62	0.34	19.34
SE		0.21	0.11	6.45
Curcumin group	Sex	1st DRSTsp total	2nd DRSTsp total	% Difference
AM308c	M	1.97	2.34	18.78
AM309c	M	1.81	2.21	22.10
AM310c	M	2.09	2.42	15.79
AM312c	M	1.89	2.31	22.22
AM313c	M	2.01	2.91	44.78
AM343c	F	2.24	2.13	-4.91
AM348c	F	2.17	2.10	-3.23
AM349c	F	2.11	3.19	51.18
Mean		2.04	2.45	20.84
SD		0.14	0.39	19.89
SE		0.05	0.14	7.03

Fig. 4 Graph of mean total span on the delayed recognition span task (spatial) for the curcumin and control groups in round 1 and round 2 of testing. Error bars=standard error

Fig. 5 Graph of the mean difference in total span between round 1 and round 2 of testing for the delayed recognition span task (spatial) for the subjects in the curcumin and control groups. Error bars=standard error. * $p < 0.048$

A two-way repeated measures analysis of variance (ANOVA) with treatment group as the between subject variable and round as the within subject variable revealed no significant overall effect of treatment group [$F(1, 15) = 0.005, p = 0.943$], round [$F(1, 15) = 2.04, p = 0.174$], or group by round interaction [$F(1, 33) = 4.06, p = 0.06$] as shown in Fig. 4.

This analysis was followed by a one-way ANOVA to determine if there was a significant difference in performance from round 1 to round 2 using a difference score. As with DNMS delays, on the DRST task, a lower score at round 2 represents a decrease in performance (e.g., decreased memory span) and therefore to calculate the difference score, we use the following formula: $((\text{round 1} - \text{round 2}) / \text{round 1}) \times 100 \times -1$. This calculation gives a percent difference from round 1 to round 2 and therefore a higher positive difference score indicates a greater level of improvement. As shown in Fig. 5, monkeys in the curcumin group evidenced a greater improvement in performance between round 1 and 2 when compared to the control monkeys [$F(1, 15) = 4.66, p = 0.048$] (Table 4 and Fig. 5).

These results suggest that the monkeys that received daily doses of curcumin demonstrated a greater improvement in performance from round 1 to round 2 than the control monkeys on the DRSTsp task, a task of spatial working memory.

Discussion

Summary of results The present study demonstrates that monkeys receiving daily oral doses of curcumin evidenced a greater improvement in performance on a task of spatial working memory, DRSTsp, as compared with monkeys that received a control substance. In contrast, there was no difference between the curcumin and control group on a benchmark task of visual recognition memory, DNMS, even when a 120-s delay was employed. These findings are of particular interest given our previous data showing that middle-aged monkeys are not typically impaired on the DNMS task but that spatial working memory begins to decline in middle-age and that aged monkeys are impaired on the DRSTsp task relative to young monkeys (Herndon et al. 1997; Moore et al. 2006; Moss et al. 1997).

Delayed non-matching to sample and delayed recognition span test The DNMS task is a task of visual recognition memory and has been used extensively to document changes in memory with age in non-human primates. Specifically, monkeys of advanced age are frequently impaired on this task and require significantly more trials to reach criterion than young and middle-aged monkeys. However, this impairment is typically not evident in rhesus monkeys until after the age of 20–25 years (Herndon et al. 1997; M. B. Moss et al. 1988). Therefore, it is not surprising that in the present study we do not see a significant difference in performance between control and curcumin monkeys because the all monkeys were younger than 25 years of age. Follow-up studies with monkeys 25 years of age or older would be of interest to determine if curcumin may reverse performance decline on the DNMS in older monkeys.

In contrast, performance on the DRSTsp task is more sensitive to aging than performance on recognition tasks such as DNMS, and indeed the monkeys in both the control and experimental groups in the present study scored below that of young adult monkeys we had previously tested on the DRST (Killiany et al. 2000; M. B. Moss et al. 1997). The finding that the group of monkeys receiving curcumin evidenced improvement only on the DRST raises the question of whether the effect of curcumin is limited to spatial working memory loading tasks, or has a more general effect on memory and cognition per se. This could be better assessed with an older cohort of monkeys (e.g., 25 years of age) in whom we would expect more significant baseline deficits in recognition memory that then could exhibit an even greater level of improvement with curcumin treatment. Improvement on the DNMS task as well as DRSTsp would support this latter notion that curcumin has a more general effect on cognition and memory.

Prefrontal cortex and the DRSTsp task Performance on the delayed recognition span task (spatial) is mediated, at least in part, by the dorsolateral prefrontal cortex (DLPFC), a cortical area associated with age-related decreases in gray and white matter volume, degenerative changes in myelin, and decreased level of monoamines and their receptors (Arnsten et al. 1994; Arnsten and Goldman-Rakic 1990; Arnsten and Jentsch 1997; Grady 1998; Makris et al. 2007; Moore et al. 2005; Peters et al. 1994; Raz et al. 1997; Sawaguchi et al. 1990; R. West 2000; R. L. West 1996). In addition, there

is an increase in phagocytic and activated microglial in frontal white matter (Shobin et al. 2017), a loss of myelin integrity in area 46 as measured by decreased fractional anisotropy in PFC white matter (Makris et al. 2007), and an overall decrease in the volume of white matter with age (Wisco et al. 2008). Taken together, these findings show a particular vulnerability of area 46 to age-related alterations in morphology that are related to declines in cognitive function and therefore is an area that is likely to be susceptible to the anti-inflammatory effects of curcumin. If in fact curcumin is altering age-related changes in the PFC, this may be the underlying cause of the improved performance on the DRST by monkeys receiving curcumin.

Hippocampus and the DNMS task In earlier studies, we have also shown that the hippocampus (HC) plays a significant role in mediating performance on both the DNMS and DRSTsp tasks, though more prominently on the DNMS task (Beason-Held et al. 1999). However, unlike the PFC, there is less evidence of age-related changes in the HC and as a result, the ameliorative effects of curcumin may be disproportionately greater on the PFC. This would explain why the effects of curcumin in the present study were selective to performance in the DRSTsp task. Regardless, these two areas, hippocampus and PFC, are likely targets for an anti-inflammatory therapeutic, such as curcumin, and therefore should be carefully analyzed in the brains of the monkeys in this study.

Cognition and curcumin in human studies Currently, there are two clinical trials in progress investigating the effects of curcumin in older humans. Specifically, these trials are measuring the effects of curcumin on memory, attention, motor function, and biomarkers for inflammation ([ClinicalTrial.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT01383161) Identifier NCT01383161) and cognitive impairment and the amount of abnormal amyloid protein evident in the brain ([ClinicalTrial.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT03085680) Identifier NCT03085680). In addition, three other studies have been reported recently in the literature describing the effects of curcumin on cognition in human populations. A study of Asian subjects (ages 60–93 years) demonstrated significantly higher scores on the Mini-Mental Status Exam by individuals who regularly consumed curry as a part of their daily diets (Ng et al. 2006). Similarly, a study using the Longvida® formulation of curcumin that was used in the present study revealed improved

performance on tests of attention, working memory, and mood by participants receiving acute and chronic doses of curcumin (Cox et al. 2015). Finally, a study with community dwelling older individuals (mean age 65–67 years) revealed a significant effect of curcumin on repeated performance on the Montreal Cognitive Assessment. However, the group difference in this study was driven by a decline in function by subjects in the control group, while the performance by the participants receiving curcumin did not decline (Rainey-Smith et al. 2016). Therefore, while the individuals receiving curcumin did not necessarily improve, their cognitive abilities did not decline over a 12-month period suggesting that curcumin may play a role in slowing or arresting age-related cognitive decline, at least in late middle-age individuals.

Possible mechanisms of the effects of curcumin on cognition In considering where the effects of curcumin may have the greatest ameliorative effects, white matter emerges as the most likely candidate as it has been demonstrated that such changes are strongly correlated with declines in cognitive performance (Bowley et al. 2010; Makris et al. 2007; Peters et al. 1994; Peters and Sethares 2002). One hypothesis that has been advanced to account for changes in white matter and myelin is the age-related immunosenescence contributing to a chronic state of neuroinflammation (Di Benedetto et al. 2017; Ownby 2010). For example, it has been demonstrated that the distribution of inflammatory glial cells are particularly prominent in white matter where there is also an age-related increase in microglial activation and phagocytosis (Shobin et al. 2017). Further support for this notion comes from recent evidence of increased circulating pro-inflammatory cytokines that negatively impact the CNS and it is likely that increased inflammatory processes are related to changes in myelin and white matter (Cornejo and von Bernhardi 2016; Robillard et al. 2016; Safaiyan et al. 2016; Xie et al. 2013). Finally, changes in myelin, increased microglial activation, and increased markers of inflammation are all strongly correlated with age-related cognitive decline and therefore are potential targets for therapeutics (Simen et al. 2011).

There is compelling evidence of changes in myelin and increased inflammatory markers as major determining factors of age-related cognitive decline

(Di Benedetto et al. 2017; Ownby 2010; Salvioli et al. 2007; Sikora et al. 2010a; Sikora et al. 2010b). Recently, many lines of evidence indicate that curcumin is a potent anti-inflammatory agent (Lee et al. 2007; Nahar et al. 2015; Parada et al. 2015; Tegenge et al. 2014; Yang et al. 2014) and therefore a suitable candidate to act upon the inflammatory process that occurs in the aging brain and hence could slow or arrest changes in myelin and cognitive decline (Lee et al. 2007; Parada et al. 2015; Salvioli et al. 2007; Sikora et al. 2010a; Sikora et al. 2010b; Tegenge et al. 2014; Yang et al. 2014). In this role, the action of curcumin appears to be as an inhibitor of the activity of the transcription factor NF- κ B that is a regulator of the inflammatory process where it activates the expression of many pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6. Some of the NF- κ B-induced proteins, such as TNF- α , are also its activators, which is particularly important in the chronic inflammatory state. NF- κ B seems to be the culprit of inflammation during aging, since this signaling system integrates the intracellular regulation of immune responses in both aging and age-related diseases (Salminen et al. 2008; Tegenge et al. 2014; Yang et al. 2014). Further, it has been demonstrated that curcumin blocks the production of pro-inflammatory and cytotoxic mediators such as TNF- α , IL-1 α , and IL-6 (Jin et al. 2007; Kure et al. 2017; Lee et al. 2007). Taken together, these actions by curcumin may be the underlying cause of improved performance on the DRST task by monkeys in this study receiving long-term administration of curcumin. Future studies, examining brain tissue and CSF from these monkeys, will help to elucidate the potential mechanisms of curcumin in these monkeys.

Curcumin and the brain

The curcumin used in this study was Longvida® Optimized curcumin that is formulated as a solid lipid to allow for greater absorption following ingestion. While there is evidence that this formulation of curcumin does enter the brain (Begum et al. 2008; Ryu et al. 2006), it remains unclear at this time the extent to which the lipidated curcumin used in this study was absorbed into the blood stream and/or

crossed into the brain. While future studies will analyze serum, CSF, and brain samples from these monkeys to determine the extent that the curcumin was absorbed from the GI system into the circulation and/or brain, it is important to note that peripheral inflammation, a common age co-morbidity, has also been shown to be related to cognitive impairment and relevant to this study, peripheral cytokines have been associated with lower cognitive performance in humans (Hilsabeck et al. 2010; Lim et al. 2013). While peripheral inflammation is usually associated with an acute infection, it is not unlikely that age-related peripheral inflammation may also impact cognitive performance. Therefore, regardless of whether curcumin in fact enters the CNS, its potential effect on peripheral inflammation could also be related to improved cognitive performance observed in our monkeys. Most certainly, these promising findings highlight the importance of continued investigation of the effects of curcumin on markers of inflammation, and in turn, in behavioral and cognitive function.

Conclusions and future directions

While we have demonstrated that chronic treatment with curcumin improved cognitive performance in middle-aged monkeys on a task of spatial working memory, the monkeys in this study were at an age when cognitive declines are in the earliest stages and are often only minor in severity. It would be of interest to further investigate the effects of curcumin using older monkeys in an age range where greater than 30% demonstrate moderate to severe cognitive impairment (Herndon et al. 1997; M. Moss et al. 2007). Monkeys in this advanced age range also have the most severe myelin pathology and increases in inflammatory markers (Peters et al. 2000; Peters and Sethares 2002; Peters et al. 2001). If myelin pathology is related to cognitive deficits and if curcumin does possess potent anti-inflammatory properties, we would predict that it could slow or even ameliorate the cognitive decline in impaired aged monkeys.

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