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Oral Curcumin Supplementation Improves Fine Motor Function in the Middle-aged Rhesus Monkey.

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Abstract

Aged individuals experience decreased fine motor function of the hand and digits, which could result, in part, from the chronic, systemic state of inflammation that occurs with aging. Recent research for treating age-related inflammation has focused on the effects of nutraceuticals that have anti-inflammatory properties. One particular dietary polyphenol, curcumin, the principal curcuminoid of the spice turmeric, has been shown to have significant anti-inflammatory effects and there is mounting evidence that curcumin may serve to reduce systemic inflammation. Therefore it could be useful for alleviating age-related impairments in fine motor function. To test this hypothesis we assessed the efficacy of a dietary intervention with a commercially available optimized curcumin to ameliorate or delay the effects of aging on fine motor function of the hand of rhesus monkeys. We administered oral daily doses of curcumin or a control vehicle to eleven monkeys over a 14–18 month period in which they completed two rounds of fine motor function testing. The monkeys receiving curcumin were significantly faster at retrieving a food reward by round 2 of testing than monkeys receiving a control vehicle. Further, the monkeys receiving curcumin demonstrated a greater degree of improvement in performance on our fine motor task by the 2nd round of testing than monkeys receiving a control vehicle. These findings reveal that fine motor function of the hand and digits is improved in middle-aged monkeys receiving chronic daily administration of curcumin.

Keywords

Curcumin; Motor Function; Rhesus monkey; Inflammation

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Introduction:

Aged individuals experience decreased fine motor function of the hand and digits, including decreased dexterity, speed, strength, coordination and muscle mass (Hackel et al. 1992; Metter et al. 1997; Desrosiers et al. 1999; Ranganathan et al. 2001; Carmeli et al. 2002; Carmeli et al. 2003; Bowden and McNulty 2013a, 2013b; Sebastjan et al. 2017a, 2017b). Age-related motor dysfunction may be due in part to low-grade, chronic, systemic state of inflammation, referred to as “inflammaging”. Multiple studies have documented age-related inflammation in the brain and peripheral sites in humans and monkeys (Di Iorio et al. 2006; Deleidi et al. 2015; Oishi and Manabe 2016). In the rhesus monkey brain, age-related damage to myelin and loss of myelinated fibers occurs in frontal white matter regions in the monkey (Bowley et al. 2010), there is decreased fractional anisotropy in frontal white matter (Makris et al. 2007) and there is an overall decrease in the volume of white matter with age (Wisco et al. 2008). All of these changes are thought to be associated with inflammation (Xie et al. 2013; Cornejo and von Bernhardt 2016; Robillard et al. 2016; Safaiyan et al. 2016). In the peripheral nervous system there is reduced nerve conduction velocity in the median and ulnar nerves of the upper extremity, a reduction of the number of myelinated nerve fibers from cervical nerve roots, and decreased sensation in the hands in aged humans (LaFratta and Canestrari 1966; Dorfman and Bosley 1979; Mittal and Logmani 1987; Metter et al. 1997; Verdú et al. 2000; Carmeli et al. 2002; Carmeli et al. 2003). In rodent models of aging there is a decreased density of peripheral nerve fibers, demyelination and decreased myelin thickness of peripheral nerves (Chase et al. 1992; Bouche et al. 1993; Ceballos et al. 1999; Verdú et al. 2000). Similar to the changes in the central nervous system, these changes have also been linked to inflammation (Prolla and Mattson 2001; McGeer and McGeer 2004; Di Iorio et al. 2006).

In addition to the age-related changes to nerve fibers and myelin in the central and peripheral nervous systems, age-related changes in fine motor function may also result from arthritis which is characterized by loss of cartilage, decreased bone remodeling and osteophyte formation, bone sclerosis, joint mal-alignment and a maladaptive repair process of the cartilage (Pritzker et al. 2006; Kraus et al. 2015; Chin KY 2016). A significant underlying cause of arthritis is systemic inflammation that contributes to decreases in chondrocytes and reduced cartilage and is related to increased release of proteoglycans and metal metalloproteases and expression of prostaglandin E-2 and cytokines (Berenbaum 2013; Chin KY 2016; Loeser 2017). More specifically, analysis of synovial fluid from patients with osteoarthritis reveals significant increases in markers of inflammation such as TNF- α , IL-1B, NF-kB and COX-2 (Benito et al. 2005; Sohn et al. 2012; Kraus et al. 2015) that further supports the notion of that arthritis is an inflammatory disease.

Regardless of the underlying cause of decreased fine motor function in aged individuals, inflammation appears to be a common factor. An interesting avenue of research for treating age-related inflammation in the body as a whole has focused on the effects of nutraceuticals that have anti-inflammatory effects. While many studies have focused on their efficacy as treatments for age-related cognitive decline (Dong et al. 2012; Yu et al. 2012; Sun et al. 2013; Adamo 2014; Cox et al. 2015; Moore et al. 2017) other work has investigated the role of nutraceuticals in reducing inflammation related to age-related impairments in motor

function and the development of arthritis (Gupta SC et al. 2012; Peddada et al. 2015; Chin KY 2016; Daily et al. 2016; Kloesch et al. 2016; Zhang et al. 2016; Gupta S et al. 2017).

One particular dietary polyphenol, curcumin, a member of the ginger family and the principal curcuminoid of the spice turmeric, has been shown to have significant anti-inflammatory effects (Daily et al. 2016; Kloesch et al. 2016; Zhang et al. 2016). While there is evidence that curcumin can slow or delay the progression of age-related changes in cognitive processes (Salvioli et al. 2007; Sikora, Bielak-Zmijewska, et al. 2010; Sikora, Scapagnini, et al. 2010; Moore et al. 2017) there is also mounting evidence that curcumin may serve to reduce systemic inflammation by decreasing inflammatory mediators (eg. IL-6, IL-8, TNF-Alpha) and inhibiting proliferation of synoviocytes (Peddada et al. 2015; Chin KY 2016; Daily et al. 2016; Kloesch et al. 2016; Zhang et al. 2016; Gupta S et al. 2017). As a result curcumin may alleviate age-related impairments in fine motor function due to inflammation associated with normal aging and/or with arthritis. To test this hypothesis we assessed the efficacy of a dietary intervention with a commercially available optimized curcumin to ameliorate the effects of aging on fine motor function of the hand in middle-aged rhesus monkeys. We administered oral daily doses of curcumin or a control vehicle to eleven monkeys over a 14–18 month period in which they completed two rounds of fine motor function testing.

Materials and Methods:

Subjects:

The subjects were eleven, behaviorally naive, middle-aged adult (13–21 years of age), male and female rhesus monkeys (*Macaca mulatta*) (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, they 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 of the study. While on study, monkeys were individually housed in the Animal Science Center (ASC) of Boston University School of Medicine in colony rooms where they were in constant auditory and visual range of other monkeys. The ASC is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and all animal procedures 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* (2011). This study was also approved by the Boston University Institutional Animal Care and Use Committee. Diet consisted of Purina Monkey Chow (Purina Mills Inc, St. Louis, MO), 12–15 biscuits per day based on their weight supplemented by fruit with feeding taking place once per day, immediately following behavioral testing. During testing, small pieces of fruit or candy were used as rewards. Water was available continuously. The monkeys were housed under a 12-hour light/dark cycle with cycle changes occurring in a graded fashion over the course of an hour.

Curcumin Administration:

Following a quarantine period and acclimation to the colony room, monkeys were randomly assigned to either a vehicle control or curcumin treatment groups and began receiving a daily treatment (curcumin or control vehicle) each day for two weeks. The curcumin was Longvida® Optimized Curcumin that was manufactured and supplied by Verdure Sciences (Noblesville, IN). Their formulation is optimized natural curcumin for enhanced bioavailability. The curcumin dose was of 500 mg of curcumin and vehicle control was an equivalent measure of dextrin and tartrazine (to match color of active curcumin). The curcumin and vehicle 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 weekends and holidays. A technician observed the monkey until the treatment was eaten completely. If a monkey would not eat the treatment, and discarded it into the waste pan in their cage, a second treatment was given. Monkeys ate the treatments (curcumin or vehicle) on more than 98% of the days on study. All technicians and study personnel were blinded to the treatment type (curcumin or vehicle control) received by each monkey.

At the end of the two-week period of initial treatment, all monkeys began round 1 of testing on an extensive battery of cognitive and motor tasks (described in Moore et al, 2017) while continuing treatment. As described in Moore et al, 2017, the testing battery consisted of Delayed Non-matching to Sample task (basic task acquisition and with delays) and the Delayed Recognition Span Task (spatial working memory task). Following completion of these memory tasks, monkeys then completed our fine motor function task (described below). At the end of round 1 testing which took approximately 6–8 months to complete, the monkeys were not tested for 8 weeks, but continued to receive their daily dose of curcumin or vehicle control. At the end of the 8-week period, they began round 2 of testing (cognitive and motor tasks), again while continuing to receive daily curcumin or vehicle control.

Motor Testing:

As described in detail previously (Moore et al. 2010), monkeys were tested on our Hand Dexterity Task (HDT) that requires precise control of the digits, particularly apposition of the thumb and index finger, to retrieve a small, visible food reward from two different size round wells in a Plexiglas tray (Fig. 1). Food rewards (M&M's, Mars, Inc) are round candies and approximately 1cm in diameter. Both wells were 1 cm deep. The large diameter well is 25 mm wide and the smaller was 18 mm wide. Time to retrieve the food reward is recorded by a timer connected to photocells located in the openings on each side of the apparatus (Fig. 1). The timer starts when the monkey puts a hand through one of the openings, triggering the photocells to start the timer. The timer stops when the monkey removes its hand. An experimenter records whether or not the reward was successfully retrieved and the response time to retrieve is recorded. The HDT has been used to assess fine motor function of the hand and digits in adult monkeys with and without injury to the hand representation in the motor cortex as well as to compare the performance of middle-aged rhesus monkeys to young adult monkeys (Moore et al. 2010; Moore et al. 2012; Moore et al. 2013). Testing on the HDT in each round was conducted for 4 weeks with testing occurring on Monday,

Wednesday and Friday of each week. Each test day consisted of 32 trials, 16 trials for each hand. The order of trials for each hand and well follows a pseudorandom balanced sequence to eliminate any order effects. Monkeys are given 30 seconds to complete a trial. If they do not or would not complete a trial in 30 sec, the trial is terminated and the monkey is given one additional opportunity to complete that trial. After a second failed attempt, a non-response is recorded, the monkey's difficulties are noted in the study record and the next trial is initiated.

Hand Preference:

At the completion of testing on the HDT in each round, ten free choice trials with both sides of the apparatus baited and accessible are administered to determine which hand is "dominant". The hand that was used to retrieve the majority of food rewards during these free choice trials was designated as the dominant hand.

RESULTS:

Performance at Round 1 and 2:

For each round, the latency to retrieve the food reward with the dominant hand from the large wells and small wells on the HDT was averaged across the last 5 days of the 4-week testing period. The subject groups consisted of both male and female monkeys, however, it was determined that there was no effect of sex on any of the measurements and therefore the data for the males and females were grouped together.

Large Well

A two-way repeated measures ANOVA was used to compare the performance on the large well with round as the within subject variable and treatment group (curcumin vs. control vehicle) as a between-subject variable. This analysis revealed no significant overall effect of group [$F(1, 9) = 0.186, p = 0.676$] or round [$F(1, 9) = 2.16, p = 0.175$] but there was a significant group by round interaction [$F(1, 21) = 24.29, p = 0.0008$]. Follow-up analyses of the interaction with tests of simple main effects for each round revealed that, as illustrated in Figure 2, the monkeys treated with curcumin had significantly shorter latencies to retrieve rewards from the large well on round 2 ($F(1, 18) = 5.57, p < 0.05$) compared to vehicle treated monkeys.

Small Well

A two-way repeated measures ANOVA was used to compare the performance on the small well with round as the within subject variable and treatment group (curcumin vs. control vehicle) as a between-subject variable. This analysis revealed a no significant overall effect of group [$F(1, 9) = 1.76, p = 0.217$], round [$F(1, 9) = 0.899, p = 0.368$] or group by round interaction [$F(1, 21) = 0.169, p = 0.691$]. This is an interesting finding based on our extensive data using the HDT to assess the performance of older monkeys and monkeys with cortical injury to the hand area of motor cortex. In both groups of monkeys faster times to retrieve were observed for the smaller well. Extensive reviews of performance topography revealed that the monkeys with poorer performance impaired either from age or cortical injury learned to pin the food reward against the side of the either well and slide it out rather

than grasp it with the normal finger-thumb apposition. This action, a compensatory strategy, is more successful in the smaller well. In contrast, in the larger well, where there is more space, this action is less successful because there is more room for the food reward to slide along the side of the well and away from the fingers. Hence, retrieval from the smaller well appears to be easier and may create a “floor effect” masking group differences on this well.

Difference in Performance at Round 2

In order to determine if there was improved performance at round 2 compared to round 1, the above analyses were followed by calculating the difference in time to retrieve the food reward in both wells for all trials in the last five days of testing from round 1 to round 2 for the dominant hand of each monkey. As shown in table 1, a higher difference score represents a faster time to retrieve at round 2 than at round 1. Separate one-way ANOVAs with group (curcumin vs. vehicle) as the between subject variable revealed a significant group difference for the large well ($[F(1, 9) = 23.577, p = 0.0009]$) but not for the small well ($[F(1, 21) = 0.003, p = 0.956]$) as shown in Figure 3. Therefore, monkeys that received daily doses of curcumin significantly improved their performance over time. In fact, when the individual performance of each monkey was examined, five of the six monkeys receiving curcumin improved their performance from round 1 to round 2 on the large well while none of the five monkeys in the vehicle group improved their performance.

DISCUSSION

Summary of Results:

In the present study, monkeys receiving daily oral administration of curcumin were significantly faster at retrieving a food reward during round 2 than monkeys receiving vehicle control. Further, the monkeys receiving curcumin demonstrated a greater degree of improvement in performance on our fine motor task in round 2 of testing compared to round 1. In fact, five of the six monkeys receiving curcumin improved their performance from the 1st round to the 2nd round while none of the monkeys in the control vehicle group improved in their performance. These findings reveal that fine motor function of the hand and digits is improved in middle-aged monkeys receiving daily administration of curcumin for 14–18 months. In fact, the time to retrieve the food reward in the last five days of testing in round 2 by the middle-aged monkeys receiving curcumin fell into the range of performance of young monkeys on this task (data published in (Moore et al. 2010)).

Age-Related Changes in Motor Function in Humans and Rhesus Monkeys

Our findings are of particular interest given the extensive data showing that motor functions of the hand decrease during the normal aging process in humans (Desrosiers et al. 1999) and monkeys (Zhang et al. 2000; Lacreuse and Herndon 2003; Lacreuse et al. 2005; Walton et al. 2006; Lacreuse et al. 2007; Moore et al. 2010). More specifically, several studies have demonstrated the effects of age on upper extremity abilities and reported significant declines in manual dexterity, motor coordination, grip strength of the hand and speed of movements in community-dwelling individuals over the age of 60 years (Mathiowetz et al. 1984; Mathiowetz et al. 1985; Shiffman 1992; Desrosiers et al. 1999; Carmeli et al. 2003). These age-related changes in the motor function of the hand become notable in the 60s and 70s and

occur in the absence of significant neurological disease or cortical damage (Desrosiers et al. 1999; Ranganathan et al. 2001; Carmeli et al. 2003).

In aged non-human primates, overall age-related motor slowing of fine motor function, impaired ability for complex movements and increased bradykinetic movements of the hand have been documented (Zhang et al. 2000; Lacreuse and Herndon 2003; Lacreuse et al. 2005; Walton et al. 2006; Lacreuse et al. 2007; Moore et al. 2010). Investigators have also found age-related decreases in bimanual motor function, fine motor dexterity and movement speed of the hand (Zhang et al. 2000; Lacreuse and Herndon 2003; Lacreuse et al. 2005; Walton et al. 2006; Lacreuse et al. 2007; Moore et al. 2010). In addition, male rhesus monkeys appear to have greater declines in motor function of the hand than females while hormone status does not appear to affect performance (Lacreuse and Herndon 2003; Lacreuse et al. 2005; Lacreuse et al. 2007).

With the HDT used here to assess fine motor function of the hand, monkeys use the thumb and one finger to retrieve a small food reward from a well. Successful completion of this task requires coordination of reaching, precise manipulation of the digits and manual dexterity. We have previously demonstrated an age-related decrease in fine motor function using the HDT (Moore et al. 2010). Specifically, our previous study revealed that the HDT was sensitive to detect age-related impairments in performance (Moore et al. 2010). These findings were consistent with other researchers using a similar testing apparatus (Lacreuse et al. 2005) and therefore it is likely that the performance of the monkeys on this apparatus in the current study reflects a valid measure of improvement in fine motor function of the hand.

White Matter and Motor Function:

While it is well established that motor function changes with age, the underlying cause has not been fully determined. However, several studies have demonstrated that changes in white matter, particularly in frontal brain regions, correlate with decreased motor function (Gunning-Dixon et al. 2009; Seidler et al. 2010; Sullivan et al. 2010; Xiong and Mok 2011; Raj et al. 2017). Specifically, Salat (2005) demonstrated age-related declines in fractional anisotropy in frontal white matter and Sullivan et al, 2010 noted that performance on tasks of fine motor function of the fingers correlated with fractional anisotropy in both the internal and external capsules. Further, in aged adults, smaller fractional anisotropy values were found in the anterior aspect of the corpus callosum, a structure involved in bimanual coordination of fine motor function (Pfefferbaum et al. 2000; Kennerley et al. 2002; Salat et al. 2005; Ota et al. 2006; Sullivan et al. 2010).

In the rhesus monkey brain, there is also considerable evidence of age-related damage to myelin and loss of myelinated fibers in frontal white matter (Bowley et al. 2010), loss of myelin integrity in frontal white matter as measured by decreased fractional anisotropy (Makris et al. 2007) and an overall decrease in the volume of white matter with age (Wisco et al. 2008). All of these changes in white matter and myelin are thought to be associated with inflammation (Xie et al. 2013; Cornejo and von Bernhardi 2016; Robillard et al. 2016; Safaiyan et al. 2016).

Aging, White Matter and Inflammation:

A low-grade, chronic, systemic state of inflammation in aging, referred to as “inflammaging” has been well established and is known to be related to myelin degeneration (Tracy 2003; Franceschi et al. 2007; Giunta and Sergio 2008; Chung et al. 2009; Franceschi and Campisi 2014; Loeser 2017; Raj et al. 2017). Specifically, neuroinflammation appears to be increased in frontal white matter regions (Sloane et al. 1999; Hart et al. 2012; Shobin et al. 2017). Several interlinked mechanisms of chronic inflammation have been proposed to explain age-related inflammation including pro- and anti-inflammatory cytokine imbalances, immunosenescence, DNA damage, a decline in autophagic function, and oxidation (Xia et al. 2016). Regardless of the underlying cause, levels of inflammatory cytokines increase with age (Singh and Newman 2011) and are associated with age-related myelin degeneration. Thus, promoting an anti-inflammatory environment through drug or diet could be beneficial in reducing inflammaging (Marchal, Dal-Pan, et al. 2013; Marchal, Pifferi, et al. 2013).

Curcumin and Inflammation:

Curcumin is a powerful anti-inflammatory agent (Lee et al. 2007; Tegenge et al. 2014; Yang Z et al. 2014; Nahar et al. 2015; Parada et al. 2015) that acts directly as an inhibitor of the activity of the transcription factor NF- κ B that regulates inflammation by increasing the expression of many pro-inflammatory cytokines, such as TNF- α , IL-1 β and IL-6. NF- κ B signaling integrates and regulates innate and adaptive immune responses in both aging and age-related diseases (Miagkov et al. 1998; Roman-Blas and Jimenez 2006; Salminen et al. 2008; Tegenge et al. 2014; Yang Z et al. 2014; Ghosh et al. 2015; Peddada et al. 2015; Chin KY 2016; Saito and Tanaka 2017). 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; Lee et al. 2007; Chin KY 2016; Kure et al. 2017) and therefore likely has some therapeutic benefit to reduce age-related inflammation.

Curcumin and the Central Nervous System:

Several studies in humans and rodents have reported benefits of curcumin supplementation. Bala et al. 2006 demonstrated that a month of dietary supplementation of curcumin was sufficient to attenuate lipid peroxidation as well as reducing lipofuscin concentration within the cortex, hippocampus, cerebellum, and medulla. In rodents, Yu et al, 2016 found that curcumin has a protective effect on demyelination after injury. Additionally, curcumin can protect neurons against lipopolysaccharide-induced neurodegeneration by inhibiting NF- κ B and cytokine expression. (Sharma et al. 2017) Finally, in a transgenic mouse model of Alzheimer’s disease, curcumin blocks the accumulation of amyloid plaques (Yang F et al. 2005).

The mechanisms by which curcumin is protective against myelin damage are not completely understood, but several rodent studies have focused on the anti-inflammatory action of curcumin. As mentioned above, curcumin inhibits the transcription factors NF- κ B and the JAK-STAT pathway to reduce the expression and production of pro-inflammatory mediators (Kim et al. 2003; Kang et al. 2004; Jung et al. 2006). Another possible mechanism of action of curcumin in the brain is the regulation of iron accumulation and its effect on myelin.

While iron is a necessary component for oligodendrocytes to generate myelin and accumulation of iron within the aged brain has been associated with decreases in myelination (Steiger et al. 2016). Oligodendrocytes cannot generate iron and thus must take up iron that is then sequestered by ferritin protein. Inflammation is known to alter iron status and in aging increased inflammation is associated with an increase in ferritin expression (Connor et al. 1992). Importantly, iron mediated oxidative stress can result in iron release from ferritin resulting in a positive feedback loop leading to increased injury. While curcumin supplementation has been shown to decrease ferritin protein, it attenuates iron deposition in liver and spleen culture by acting as a potent chelator of iron and therefore may act to restore age-related iron deposition (Jiao et al. 2009; Chin D et al. 2014). This is of particular importance as motor regions of the brain contain more iron than non-motor regions and regulation of iron by curcumin may mitigate age-related changes in these motor areas (Koeppen 1995; Zecca et al. 2004).

Osteoarthritis, Inflammation, and Motor Function in Aging:

While there is considerable evidence to support the notion that curcumin may reduce inflammation in the brain and alter age-related changes in myelin, it is also likely that curcumin also reduces inflammation in the periphery and may therefore impact symptoms of joint degeneration or osteoarthritis. While we were unable to clinically assess the presence of arthritis in our monkeys, osteoarthritis is common in laboratory bred and raised rhesus and cynomolgus monkeys and chimpanzees (Stone et al, 2015; Videan et al, 2011; Ham et al, 2002; Loeser et al, 2000; Colman et al, 1999a;b; Carlson et al, 1996; Grynepas et al, 1993; DeRousseau, 1985).

Based on the well-established anti-inflammatory properties of curcumin and the occurrence of age-related systemic inflammation and its relationship to osteoarthritis, several studies have investigated the efficacy of curcumin to treat osteoarthritis (Chin KY 2016; Akuri et al. 2017; Onakpoya et al. 2017). Chin (2016) reviewed fifteen clinical studies that compared treatment with curcumin and either control vehicle, NSAID, chondroitin sulfate or glucosamine. These studies administered 180–2000mg of curcumin daily and used various arthritis indices or physical activity assessments to rate the effectiveness of each treatment. They demonstrated that daily administration of curcumin resulted in significant improvements in pain-free walking, degree of pain before and after passive and active movement, joint pain and tenderness and degree of joint motion. Four studies in this review also determined that both circulating inflammatory cytokines levels (Badria et al. 2002; Belcaro et al. 2010a, 2010b; Henrotin et al. 2014; Rahimnia et al. 2015) and markers of oxidative stress were decreased with curcumin administration (Badria et al. 2002; Panahi et al. 2016). Additionally, patients receiving daily doses of curcumin had reduced CD4+ T cells, CD45RO+ memory T cells, serum Fas ligand and decreased indicators of oxidative stress including serum nitrite/nitrate and superoxide dismutase. Finally, it has also been shown that curcumin prevents a loss of cartilage in joints due to osteoarthritis by enhancing the proliferation of chondrocytes and limits IL-1 β induced suppression of chondrogenesis and apoptosis of chondrocytes. (Shakibaei et al. 2005; Buhrmann et al. 2010) Curcumin suppresses mRNA expression of pro-inflammatory mediators, including IL-1 β and TNF- α and significantly reduced the progression of osteoarthritis as evidenced by less cartilage

erosion, reduced synovitis and degradation of type II collagen (Peddada et al. 2015; Zhang et al. 2016; Gupta S et al. 2017). The findings from these studies support the hypothesis that curcumin plays a role in decreasing the inflammation associated with osteoarthritis and in relieving many of the symptoms of this disease process. Since it is likely that monkeys in the present study had some degree of joint inflammation or osteoarthritis which could contribute to their motor impairments, it is possible that these were mitigated by curcumin administration and contribute to the observed improvement in performance.

Conclusions:

We have demonstrated that chronic oral administration of curcumin improves fine motor function of the hand and digits in middle-aged rhesus monkeys. This finding is of particular interest from a clinical perspective given the well documented evidence showing that motor functions of the hand, such as manual dexterity and digit strength, decrease during the normal aging process and there are currently no treatments to alleviate motor changes with age. Curcumin appears to be a good candidate therapy, not only due to its effect on the inflammation that occurs with age and the underlying changes in motor function, but it is also known to be well tolerated and is readily available. Further studies of the effects of curcumin on motor function are needed, in particular in older monkeys to determine if curcumin will also alleviate motor deficits in much older monkeys. In addition, the precise mechanisms of curcumin underlying improved motor function remains unclear though evidence from human and rodent studies point towards curcumin reducing age-associated inflammation, either in the brain or periphery, as the most likely cause. Study of cortical tissue from the monkeys in this study is currently planned and may provide further insights into the mechanisms of curcumin in the brain.

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Figure 1.

A photograph of the Plexiglas testing apparatus used to administer the Hand Dexterity Task (HDT). The arrows indicate the right and left openings that the monkey must put the appropriate hand through in order to retrieve the food reward from the wells in each tray.

Figure 2.

Graph of total time to retrieve the food reward on the HDT over the last 5 days of testing for the control vehicle and curcumin groups for rounds 1 and 2 of testing. There were no significant group differences on the performance of this task in round 1 but by round 2 the monkeys receiving curcumin demonstrated significant faster times to retrieve than monkeys receiving a control vehicle (* $p < 0.05$). Error bars = standard error.

Figure 3.

Graph of the difference in the total time to retrieve the food reward on the HDT over the last 5 days of testing for the control vehicle and curcumin groups between rounds 1 and 2 of testing. This analysis revealed a significant group difference in performance between rounds 1 and 2 with the monkeys receiving curcumin demonstrating greater improvement in performance from round 1 to round 2 than monkeys receiving a control vehicle (* $p < 0.0009$). Error bars = standard error.

Table 1.

Table of subjects, with sex, age, and dominant hand for each monkey and the difference in time to retrieve between rounds 1 and 2 of testing.

Subject	Group	Sex	Age	Dominant Hand	Difference in Time to Retrieve from Round 1 to Round 2 (secs)
AM321c	Control Vehicle	Male	13.33	Right	-0.56
AM311c	Control Vehicle	Male	20.10	Left	-0.18
AM350c	Control Vehicle	Female	16.00	Left	-0.26
AM342c	Control Vehicle	Female	18.10	Left	-0.34
AM347c	Control Vehicle	Female	13.00	Left	-0.46
AM308c	Curcumin	Male	20.10	Left	-0.08
AM309c	Curcumin	Male	20.10	Left	0.12
AM310c	Curcumin	Male	21.10	Left	0.38
AM312c	Curcumin	Male	20.10	Left	0.22
AM348c	Curcumin	Female	13.10	Left	0.45
AM349c	Curcumin	Female	18.10	Left	0.01