Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population

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Abstract

Curcumin possesses many properties which may prevent or ameliorate pathological processes underlying age-related cognitive decline, dementia or mood disorders. These benefits in preclinical studies have not been established in humans. This randomized, double-blind, placebo-controlled trial examined the acute (1 and 3 h after a single dose), chronic (4 weeks) and acute-on-chronic (1 and 3 h after single dose following chronic treatment) effects of solid lipid curcumin formulation (400 mg as Longvida®) on cognitive function, mood and blood biomarkers in 60 healthy adults aged 60–85. One hour after administration curcumin significantly improved performance on sustained attention and working memory tasks, compared with placebo. Working memory and mood (general fatigue and change in state calmness, contentedness and fatigue induced by psychological stress) were significantly better following chronic treatment. A significant acute-on-chronic treatment effect on alertness and contentedness was also observed. Curcumin was associated with significantly reduced total and LDL cholesterol and had no effect on hematological safety measures. To our knowledge this is the first study to examine the effects of curcumin on cognition and mood in a healthy older population or to examine any acute behavioral effects in humans. Results highlight the need for further investigation of the potential psychological and cognitive benefits of curcumin in an older population.

Keywords

Curcumin, cognition, working memory, attention, mood, fatigue, cholesterol, elderly, older

Introduction

Curcumin, a polyphenol from the rhizome of turmeric (*Curcuma longa L.*) has been attributed with a range of beneficial properties which have led to the investigation of its therapeutic potential in numerous conditions. Many of these properties suggest that curcumin may prevent or ameliorate pathological processes underlying age-related cognitive decline and dementia. For example curcumin may inhibit amyloid pathology (Garcia-Alloza et al., 2007; Lim et al., 2001; Ono et al., 2004; Yang et al., 2005), protect against oxidative stress (Lim et al., 2001; Meng et al., 2013; Sood et al., 2011; Sun et al., 2013; Tiwari and Chopra, 2012; Wu et al., 2006; Yu et al., 2013), and reduce inflammation (Begum et al., 2008; Davis et al., 2007; Rinwa et al., 2013; Tiwari and Chopra, 2012). Curcumin has been reported to protect against neurodegeneration and promote neurogenesis and neuronal plasticity (Dong et al., 2012; Wu et al., 2006; Xu et al., 2007, 2009), and to beneficially influence various neurotransmitter systems (Ishrat et al., 2009; Kumar et al., 2010; Pyrzanowska et al., 2010; Rinwa and Kumar, 2012; Xu et al., 2007; Yadav et al., 2011).

Epidemiological studies suggest that dietary curcumin is associated with better cognitive function (Ng et al., 2006) and a lower prevalence of dementia (Chandra et al., 2001; Vas et al., 2001). Similarly, animal studies support the hypothesis that curcumin could assist cognitive function as they have demonstrated its ability to prevent or reverse deficits in memory and cognition associated with aging (Dong et al., 2012; Sun et al., 2013; Yu et al., 2013), stress (Xu et al., 2009), epilepsy (Choudhary et al., 2013), oxidative stress (Sun et al., 2013), anxiety (Chimakurthy and Talasila, 2010), traumatic brain injury (Wu et al., 2006), and dementia (Agrawal et al., 2010; Ishrat et al., 2009).

In addition to purported cognitive benefits, curcumin has demonstrated efficacy in reducing behavioral and neurotransmitter abnormalities in depression and anxiety (Bhutani et al., 2009; Hurley et al., 2013). In this context the magnitude of the effects of curcumin alone may be comparable with those of current pharmaceuticals (Chimakurthy and Talasila, 2010; Choudhary et al., 2013; Kulkarni et al., 2008; Wang et al., 2008; Xu et al., 2005; Zhang et al., 2012, 2013). Curcumin also appears to be capable of potentiating the effects of otherwise sub-therapeutic doses of mainstream pharmaceuticals (Kulkarni et al., 2008; Wang et al., 2008; Zhang et al., 2013), raising the possibility of its use as an adjunctive therapy. A recent trial by Sanmukhani and colleagues demonstrated the antidepressant benefits of curcumin in patients with major depressive disorder (Sanmukhani et al., 2014). Although less well studied, anti-fatigue effects of curcumin have

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been reported in an animal model of chronic fatigue (Gupta et al., 2009), in fatigue following exercise in rodents (Davis et al., 2007) and in surgical patients (Agarwal et al., 2011).

Despite the strong supporting rationale for the use of curcumin for the treatment and prevention of neurodegenerative disorders such as Alzheimer's disease (AD), previous clinical trials in AD patients have found no effects of curcumin. A 6 month randomized, placebo-controlled trial of 1 g or 4 g of curcumin daily found no effect on cognition in patients with probable or possible AD (Baum et al., 2008). Another randomized, placebo-controlled 24 week study of 2 g or 4 g of daily curcumin failed to show cognitive benefit in patients with mild to moderate AD (Ringman et al., 2012). In addition, the relatively high doses of curcumin utilized in these studies may have contributed to adverse events, with 10% ±1 of subjects in the curcumin group withdrawing due to gastrointestinal complaints in the two studies.

A major challenge to the therapeutic potential of curcumin, which was identified as a potential limitation in both of these AD trials (Baum et al., 2008; Ringman et al., 2012), is its poor bioavailability (Anand et al., 2007; Witkin and Li, 2013). Orally administered curcumin is poorly absorbed and undergoes rapid glucuronidation and sulfation in the intestine and liver. Studies of various curcumin products have reported measurable curcumin glucuronide and sulfate levels but few have detected curcumin in its free (unconjugated) form, which crosses the blood–brain barrier more readily (e.g. Baum et al., 2008; Ringman et al., 2012; Witkin et al., 2013), which it must do in order to achieve therapeutic benefits via any of the central mechanisms discussed. Animal studies have shown that it is able to do so; however, the majority of these have administered curcumin via injection, and in doing so circumvented the biotransformations which the compound undergoes during digestion (Garcia-Alloza et al., 2007; Tsai et al., 2011; Yanagisawa et al., 2011; Yang et al., 2005). As such, successful use of curcumin for cognitive or affective enhancement will likely require the use of a formulation with increased absorption and/or reduced conversion of free curcumin to conjugates. Differences in the preparation and the diversity of methods of bioavailability enhancement have led to substantial variation in the potency of curcumin products (Anand et al., 2007). Consequently, the present study selected to investigate a curcumin formulation with demonstrated superior bioavailability and biological effect. Gota and colleagues showed that in healthy individuals the solid lipid curcumin particle formulation used here was able to achieve peak plasma concentrations of free (unglucuronidated) curcumin which were at least 65 times greater than that of unformulated curcumin (Gota et al., 2010). The ability of this formulation to cross the blood–brain barrier when orally administered has been confirmed in mice, where it was reported to reach concentrations four times greater than that of unformulated curcumin (Begum et al., 2008). Finally the potential of this formulation to reach thresholds required for biological activity in humans is supported by studies which have previously demonstrated effects on important biomarkers in healthy adults (DiSilvestro et al., 2012; Gota et al., 2010).

The present study sought to investigate the effects of acute, chronic and acute-on-chronic (single dose following chronic treatment) curcumin administration in healthy older adults. It is, to our knowledge, the first study to examine the effects of curcumin on cognition in a healthy elderly population or to examine any acute behavioral effects of curcumin in humans. It was anticipated that the utilization of a curcumin formulation with enhanced bioavailability and of sensitive computerized cognitive tasks would provide the best opportunity to detect cognitive enhancement by curcumin, which has been demonstrated in animal studies but not yet achieved in human trials. It was hypothesized that curcumin would produce improvements in cognitive task performance and state non-specific mood. Curcumin was also predicted to reduce the effect that completing cognitively demanding tasks had on state mood. Blood biomarkers were also explored as potential mechanisms of action.

Materials and methods

Design

This was a randomized, double-blind, placebo-controlled, parallel-groups design trial investigating the acute (1 h and 3 h after single dose a single dose), chronic (4 weeks) and acute-on-chronic (1 h and 3 h after single dose a single dose following 4-week treatment) effects of curcumin treatment. The trial was registered as ACTRN12612001027808.

This study received ethical approval from the Swinburne University Human Research Ethics Committee. It was carried out in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Informed consent was obtained from all participants prior to their enrolment.

Participants

Participants were required to satisfy the following inclusion/exclusion criteria: aged 60–85 years; fluent in written and spoken English; normal or corrected to normal vision; free from any significant current illness including any auto-immune disorder, bleeding disorders, heart conditions, diabetes, glaucoma, high blood pressure, osteoporosis and dementia; free from a history of neurological conditions or psychiatric disorders; not currently taking anti-coagulant drugs, anti-cholinergics or acetylcholinesterase inhibitors or steroid medications; not regularly taking herbal or vitamin supplements that may influence study measures; no past or present drug or alcohol abuse; not a smoker or user of recreational drugs; free from known or suspected food allergies. The modified Telephone Interview for Cognitive Status (TICS-M; de Jager et al., 2003) was completed prior to enrolment to confirm the absence of dementia. Results were also used as a measure of global cognitive function for participants who later enrolled in the study.

A total of 61 participants were enrolled; however, one withdrew prior to Baseline assessment. All participants who received treatment completed the study. The final sample consisted of 22 males and 38 females, with a mean age of 68.5 years (SD = 5.7). Participants were financially reimbursed for their time and travel costs.

Treatment

Participants were randomly assigned to either the curcumin (n = 30) or placebo (n = 30) treatment groups. The curcumin group received 400 mg Longvida® Optimized Curcumin, containing approximately 80 mg curcumin in a solid lipid formulation (remaining weight comprised commonly used pharmaceutical

excipients and small amounts of other curcuminoids present in turmeric extract). Placebo capsules contained dextrin and a small amount (approximately 4 mg/capsule) of tartrazine (E102) for coloring to visually match the active treatment.

Treatments were taken as a once daily capsule between breakfast and lunch, for 4 weeks. The first and last doses were administered during the Baseline and Follow-Up session, respectively. Participants received more than the required number of capsules and a count of remaining tablets at Follow-Up was used to assess treatment compliance. Participants were required to be 80–120% compliant with treatment in order to be included in data analysis. All participants satisfied this requirement (M = 99.07%, SD = 4.89).

Procedure

Participants attended one Practice/Screening session and two testing sessions, Baseline and Follow-Up, which were separated by 28 days.

At Practice/Screening, eligibility was confirmed which included in-person screening for dementia using the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and for clinically significant depression or excessive anxiety through use of the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and trait scale of the State-Trait Anxiety Inventory (Spielberger et al., 1969) respectively. The National Adult Reading Test (Nelson, 1991) was completed to gauge pre-morbid intellect, prior to any cognitive decline which may have been present. Participants were familiarized with all study measures and completed four abbreviated versions of the assessment battery in order to minimize practice effects and errors at Baseline due to misunderstanding of tasks.

At the Baseline and Follow-Up sessions a fasting blood sample was collected by venipuncture before a standardized breakfast was provided and participants completed questionnaires assessing recent, state non-specific mood. Participants then undertook the first of three performances of the assessment battery, which consisted of an array of computerized cognitive tasks that was preceded and followed by evaluation of state mood. Change in mood following the cognitive array was taken as a measure of the impact of undertaking a mental challenge on mood.

Immediately after completion of the first assessment battery performance a single treatment dose was administered. The assessment battery was repeated at 1 h and 3 h after dose administration. A standardized lunch was provided in the break between the 1 h and 3 h assessments. Participants were prohibited from eating or drinking anything other than the provided meals and water, for the duration of the testing session. This was done to ensure that variation in food intake at the two sessions did not produce variation in task performance.

Mood measures

Recent, state-non-specific mood was assessed by the 21-item version of the Depression, Anxiety and Stress Scales (DASS21; Lovibond and Lovibond, 1995) and the Chalder Fatigue Scale (CFS; Chalder et al., 1993) which includes subscales specific to mental fatigue and physical fatigue. Both questionnaires addressed mood in the week preceding the testing session.

The state mood evaluation included computerized versions of the Bond-Lader Visual Analogue Scales (Bond and Lader, 1974), which measure alertness, contentedness and calmness. Two additional visual analogue scales measured stress and fatigue, and anxiety was measured by the state scale of the State-Trait Anxiety Inventory (Spielberger et al., 1969). Each of these mood measures asked participants to respond according to how they currently felt. Change in mood following the cognitive array was taken as a measure of the impact of undertaking a mental challenge on mood.

Cognitive array

The cognitive array comprised parallel versions of the following tasks from the Computerised Mental Performance Assessment System (Northumbria University).

Immediate word recall task – Fifteen single words were presented on screen for 1500 ms with an inter-stimulus interval of 1000 ms. Immediately following the final word participants were given 60 s to write down as many words as could be recalled.

Simple reaction time task – Participants responded with a button press to the presentation of 50 identical stimuli. Stimuli were presented at random intervals of 1000–3000 ms.

Two choice reaction time task – Participants responded with the press of either of two buttons to the presentation of either of two corresponding stimuli. A total of 50 stimuli (25 of each type in random order) were presented at random intervals of 1000–3000 ms.

Rapid visual information processing task – Single-digit numbers were presented at a rate of 100 stimuli per minute for 5 min. Participants responded with a button press when they detected that three odd numbers or three even numbers had been presented in succession.

Digit vigilance task – Two single-digit numbers were presented on screen. The "target number" remained steady while the other changed at a rate of 80 numbers per minute for 2 min. Participants responded with a button press when the changing number matched the target number.

Serial three and serial seven subtraction tasks – A starting number between 800 and 999 was presented on screen. Participants mentally subtract three/seven and provided their answer using the keyboard number keys. They continued subtracting three/seven from the previously entered answer for 2 min. Each digit entered was represented on screen by an asterisk, thus requiring all subtractions to be done mentally, without visual assistance.

Delayed word recall task – Participants were again given 60 s to write down as many of the 15 words presented earlier, as they could recall. A delay of approximately 25 min separated word presentation and the delayed word recall task.

Delayed word recognition task – Participants were presented with 30 single words, 15 of which were from the original presentation list. They were required to indicate whether or not they recognized each word as having been presented earlier. Each word remained on screen until a response was recorded. A delay of approximately 25 min separated word presentation and the delayed word recognition task.

Delayed picture recognition task – Following the immediate word recall task, 20 monochrome line-drawings of common objects were presented one at a time for 3000 ms each, with inter-stimulus interval of 1000 ms. In the delayed picture recognition task 40 monochrome line-drawings of common objects were presented, 20 of which were from the original presentation list. Participants were required to indicate whether or not they recognized each picture as having been presented earlier. Each picture

remained on screen until a response was recorded. A delay of approximately 25 min separated picture presentation and the delayed picture recognition task.

Biochemical measures

The collected blood sample was used for the measurement of lipid profile (triglycerides, total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL)), fibrinogen, inflammatory markers (high sensitivity C-reactive protein, interleukin 1β, interleukin 6 and tumor necrosis factor α) and amyloid-β40 and -β42. Hematological safety measures of liver and renal health/function were also measured (sodium, potassium, chloride, bicarbonate, urea creatinine, urate, calcium, phosphate, total protein, albumin, alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase, aspartate aminotransferase and alanine aminotransferase).

Statistics and calculations

Characteristics of the two treatment groups were compared using independent Student's *t*, Mann–Whitney *U* and chi-square tests. The effects of acute, chronic and acute-on-chronic treatment were examined using analysis of covariance (ANCOVA), with assessment prior to the treatment duration of interests as a covariate. Where violations of statistical assumptions prevented this, the analysis method used is explained with its results.

Analyses of cognitive task performance and state mood were repeated additionally including the demographics variables age, years of education and cognitive status as measured by the TICS-M. These variables were selected as covariates as they may have influenced how challenging participants found the cognitive array. The TICS-M was chosen over the MMSE for inclusion as the measure of cognitive status as it showed greater variation of scores and better differentiation of cognitive abilities.

All analyses were performed using IBM SPSS Statistics software (version 20; IBM Corp). A p-value of 0.05 or less was considered significant. All graphs are presented as estimated marginal mean after adjustment for covariates ± standard error of mean.

Results

Demographic data for the two treatment groups is shown in Table 1. The groups did not significantly differ in age, gender frequency, body mass index, years of education, highest level of education obtained, occupational status, cognitive status (MMSE and TICS-M scores), pre-morbid intellect (National Adult Reading Test (NART) score), trait anxiety (STAI-T) or depressive symptoms (BDI-II) at screening.

The cohort was not impaired as measured by the MMSE and TICS-M, nor were they classified as having mild cognitive impairment. There are no established population means for this age group for the cognitive battery used. However, their performance was significantly slower and their memory performance was significantly worse when compared with scores from a database of healthy young adults (Simple Reaction Time speed $t_{(57)} = 4.569$, $p < 0.001$; Choice Reaction Time speed $t_{(58)} = 13.486$, $p < 0.001$; Immediate recall number correct $t_{(59)} = -12.796$, $p < 0.001$; Delayed Recall number correct $t_{(59)} = -11.913$, $p < 0.001$; Word recognition speed $t_{(59)} = 7.339$, $p < 0.001$, and accuracy $t_{(59)} = -3.607$, $p = 0.001$; Picture Recognition speed $t_{(58)} = 5.598$, $p < 0.001$, and accuracy $t_{(58)} = -2.506$, $p = 0.015$).

Table 1. Demographic and characteristic data of placebo and curcumin groups.

	Placebo	Curcumin
Age	69.43 (6.579)	67.56 (4.479)
Males	40.0%	33.3%
Body mass index	27.23 (4.818)	25.54 (3.481)
Education years	14.93 (3.685)	14.33 (4.816)
Education level		
Primary	3.3%	3.3%
Secondary	30.0%	26.7%
Tertiary	46.7%	46.7%
Postgraduate	20.0%	23.3%
Occupational status		
Full time	3.3%	0.0%
Part time / casual	46.7%	56.7%
Studying	0.0%	3.3%
Retired	50%	40.0%
MMSE	28.90 (1.398)	28.93 (1.048)
TICS-M	28.30 (4.284)	27.87 (3.910)
BDI-II	4.27 (3.352)	4.20 (3.899)
STAI-T	32.23 (7.040)	30.47 (7.403)
NART	38.13 (7.357)	39.97 (5.881)

Mean (standard error) or percentage. BDI-II: Beck Depression Inventory-II; MMSE: Mini-Mental Sate Exam; NART: National Adult Reading Test; STAI-T: State-Trait Anxiety Inventory trait scale; TICS-M: Modified Telephone Interview for Cognitive Status.

Cognitive results

One hour after dose administration there was a significant beneficial effect of acute curcumin treatment on number of correct responses during serial three subtraction task ($F_{(1,57)} = 4.962$, $p = 0.030$). The number of correct responses provided by participants in the curcumin group increased by 16% from pre-dose performance, compared with an increase of just 2% in the placebo group. This effect remained significant when the analysis was adjusted for demographics ($F_{(1,54)} = 4.792$, $p = 0.033$). Accuracy on the digit vigilance task was square root transformed to comply with statistical assumptions and also showed a significant benefit of curcumin over placebo at the One-Hour Post-Dose assessment ($F_{(1,55)} = 4.159$, $p = 0.046$, with demographics $F_{(1,53)} = 1.955$, $p = 0.168$). These effects of treatment were no longer apparent 3 h after acute dose administration.

Following 4 weeks of treatment there was a trend towards the same beneficial effect of curcumin on number of correct serial three subtraction task responses ($F_{(1,57)} = 2.792$, $p = 0.100$), with the number of correct responses provided by participants in the curcumin group increasing by 17% from Baseline pre-dose performance, compared with an increase of just 3% in the placebo group. This effect reached significance when demographic variables were adjusted for ($F_{(1,54)} = 4.247$, $p = 0.044$).

These significant effects of treatment on cognitive function are shown in Figure 1. There were no further acute, chronic or acute-on-chronic effects of treatment on cognitive task performance.

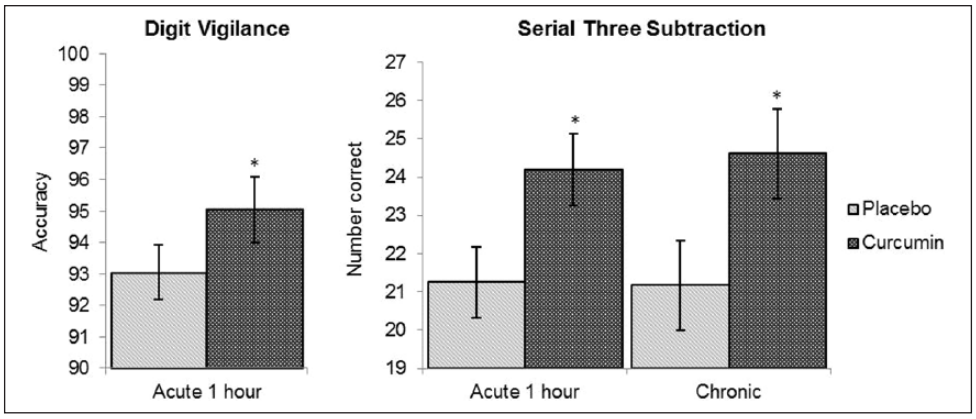

Figure 1. Cognitive measures significantly affected by treatment; digit vigilance task accuracy 1 h after acute dose, and number of correct responses in serial three subtraction task 1 h after acute dose and after 4 weeks of chronic treatment (the latter additionally adjusted for demographics). *$p < 0.05$.

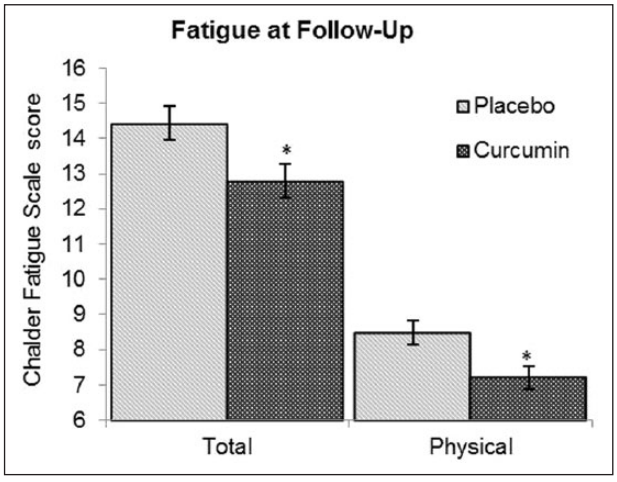

Figure 2. Significant effect of four weeks of chronic curcumin treatment on state-non-specific fatigue. *$p < 0.05$.

Mood results

State non-specific mood

Chronic curcumin treatment was associated with significantly lower levels fatigue compared with placebo ($F_{(1,56)} = 5.775$, $p = 0.020$) (Figure 2). At Follow-Up the curcumin group showed an average 11% reduction in fatigue from Baseline compared with a decrease of just 2% in the placebo group. Examination of the CFS subscales revealed that this effect was specific to physical fatigue ($F_{(1,57)} = 7.443$, $p = 0.008$) where the curcumin group showed an average 11% decrease and the placebo group a 4%. Treatment did not significantly influence mental fatigue at Follow-Up.

A floor effect was observed in scores on each of the DASS scales, the majority of participants scoring zero on each scale at both assessments. The resulting lack of variation prevented analysis of these measures.

State mood

At Baseline pre-dose assessment the cognitive array had a significant detrimental effect on mood. It increased anxiety ($t_{(59)} = 2.134$, $p = 0.024$), stress ($z = 3.977$, $p < 0.001$), and fatigue ($z = 3.892$, $p < 0.001$) and decreased alertness ($t_{(59)} = 4.630$, $p < 0.001$), calmness ($t_{(59)} = 4.746$, $p < 0.001$) and contentedness ($t_{(58)} = 4.746$, $p < 0.001$). While mood did recover in the break between assessments, the recovery was not complete and, with the exception of calmness and anxiety, there was a pattern for degeneration in mood over the course of the testing session (data not shown).

Acute treatment did not significantly effect change in mood following mental challenge.

Four weeks of chronic curcumin treatment had a significant beneficial effect on the change in mood induced by the mental challenge (Figure 3). Participants in the curcumin group showed an average 1.82% decrease in fatigue after the Follow-Up Pre-Dose performance of the cognitive array, while the fatigue rating of the placebo group increased by 17% ($F_{(1,54)} = 4.412$, $p = 0.040$, with demographics: $F_{(1,52)} = 0.5905$, $p = 0.019$). Compared with placebo, the curcumin treatment was also associated with a significantly smaller reduction in calmness ($F_{(1,55)} = 5.540$, $p = 0.022$, with demographics: $F_{(1,52)} = 5.092$, $p = 0.028$) (placebo –15%, curcumin –4%) and contentedness ($F_{(1,56)} = 4.109$, $p = 0.047$, with demographics: $F_{(1,53)} = 3.337$, $p = 0.073$) (placebo –7%, curcumin –2%).

At the Follow-Up session, there was a trend for the curcumin group to show a lesser reduction in alertness following mental challenge, 1 h after acute-on-chronic dose administration ($p = 0.061$). Participants in the curcumin group showed an average 5% reduction in alertness while the placebo group showed an average 9% reduction. This effect became significant when demographic variables were adjusted for ($F_{(1,51)} = 6.190$, $p = 0.016$).

Due to a violation of statistical assumptions that could not be overcome, the planned ANCOVA could not be performed on the effect of acute-on-chronic treatment on change in contentedness at the One-Hour Post-Dose assessment. At this performance of the assessment the curcumin group showed an average 1% reduction in contentedness following the cognitive array, while contentedness was reduced by 5% in the placebo group. Analysis of variance performed on magnitude of the change in contentedness at the Follow-Up 1 h assessment revealed a beneficial effect of curcumin ($F_{(1,53)} = 10.111$, $p = 0.002$). These acute-on-chronic results are displayed in Figure 4.

An examination of the change in mood before each performance of the cognitive array at the Follow-Up session revealed a

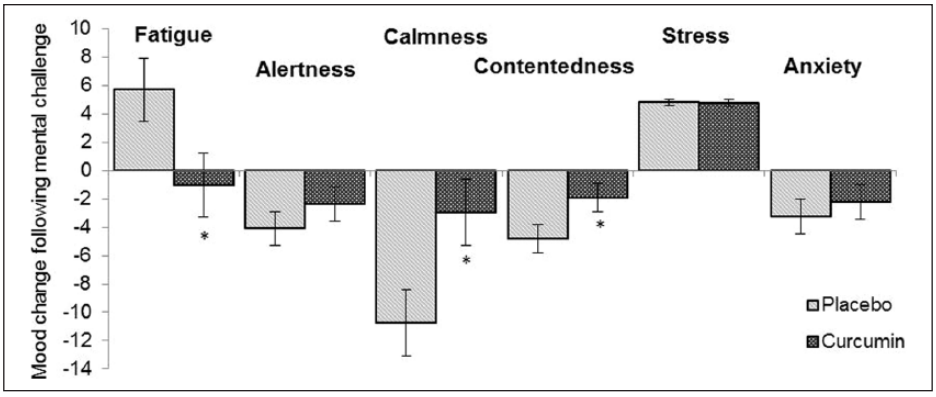

Figure 3. Effect of chronic treatment on change in mood following mental challenge at Follow-Up, Pre-Dose assessment. *$p < 0.05$.

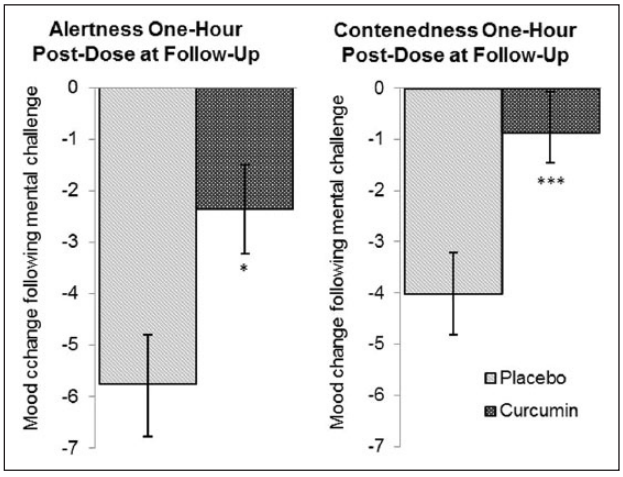

Figure 4. Significant effects of acute-on-chronic treatment on change in alertness (additionally adjusted for demographic variables) and contentedness following mental challenge 1 h after dose administration at Follow-Up. *$p < 0.05$, ***$p < 0.005$.

significant benefit of treatment. The curcumin group showed an average 2% increase in contentedness from the pre-dose to 1 h assessment while the placebo group showed an average 2% decrease ($F_{(1,55)} = 5.80$, $p = 0.023$, with demographics: $F_{(1,52)} = 6.038$, $p = 0.017$). However, the difference between groups was no longer significant at the 3 h assessment. At the 3 h assessment, treatment had a significant effect on pre-battery calmness (calmness: $F_{(1,56)} = 5.406$, $p = 0.024$, with demographics: $F_{(1,53)} = 5.948$, $p = 0.018$) and fatigue ($F_{(1,55)} = 5.107$, $p = 0.028$, with demographics: $F_{(1,52)} = 3.793$, $p = 0.057$). The curcumin group showed an average 5% increase in calmness and no notable change in fatigue (<1%) while the placebo group showed an average 7% decrease in calmness and a dramatic 44% increase in fatigue. These significant group differences are depicted in Figure 5.

Blood biomarkers

Curcumin treatment was associated with significantly lower levels of total cholesterol ($F_{(1,50)} = 4.841$, $p = 0.032$) and LDL ($F_{(1,49)} = 6.827$, $p = 0.012$) at Follow-Up (Figure 6).

Curcumin treatment was well tolerated and did not significantly impact of any of the examined hematological safety measures.

No other significant effects of treatment on blood biomarkers were observed, although the effects on interleukin 1β, interleukin 6 and tumor necrosis factor α could not be assessed as the majority of participants had serum levels below the limits of quantification.

Discussion

This randomized, double-blind, placebo-controlled, parallel-groups trial sought to investigate the effects of acute, chronic and acute-on-chronic curcumin treatment on cognition, mood and ability to cope with mental challenge in healthy older adults. The study had an excellent retention rate, with 100% of participants who received treatment completing the trial. However, it was not without limitations; the low levels of depression, anxiety, stress and inflammatory cytokines exhibited by participants at both testing sessions prevented the planned examinations of these measures.

Compared with placebo, a single curcumin dose acutely improved performance on the digit vigilance task, a measure of sustained attention, and the serial three subtraction task, a measure of working memory. Performance of the serial three subtraction task was also improved by 4 weeks of curcumin treatment. As reported in previous nutraceuticals trials (Kennedy et al., 2010; Scholey et al., 2010) the serial seven subtraction task did not show the same enhancement. This dissimilarity in treatment effects on serial three and serial seven performance has been attributed to the two tasks not simply representing different levels of difficulty but requiring the engagement of differing cognitive processes. Performance of the serial three subtraction tasks primarily relies on working memory and also reflects psychomotor speed and attention but places little demand on executive function, while the serial seven subtraction task places little demand on psychomotor speed but requires substantial engagement of executive function (Scholey and Kennedy, 2002). These results suggest that working memory and sustained attention were the cognitive processes most enhanced by curcumin.

Working memory is a particularly important target for potential cognitive enhancers in the elderly as it is known to decline in normal healthy aging and may underlie age-related changes in

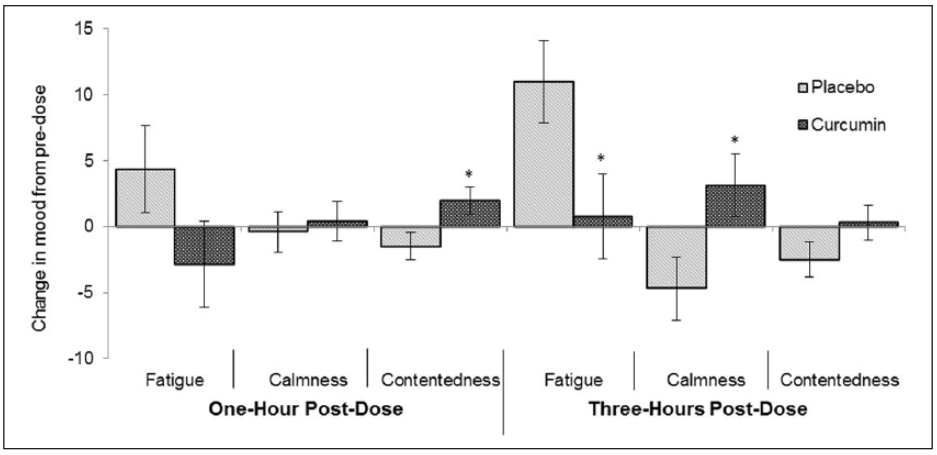

Figure 5. Significant effects of treatment change in mood prior to mental challenge from Pre-Dose assessment, at Follow-Up. *$p < 0.05$.

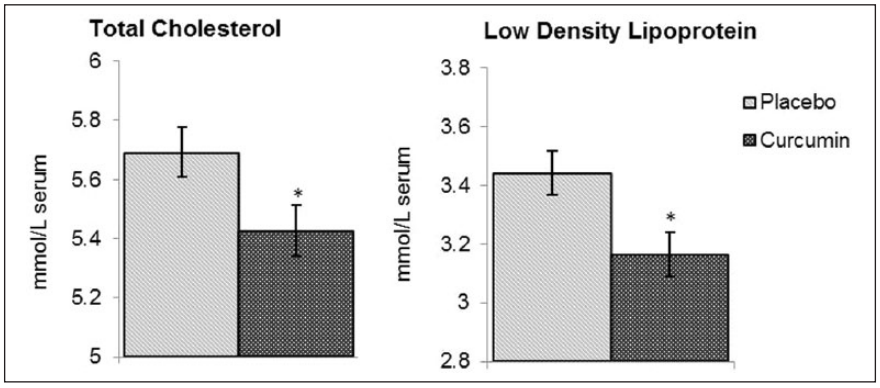

Figure 6. Lipid measures significantly affected by chronic treatment. *$p < 0.05$.

other cognitive functions (Park et al., 1996). Further deficits in working memory are seen in multiple types of dementia (Calderon et al., 2001; Kensinger et al., 2003). Therefore the preservation or enhancement of working memory may aid in preventing or reversing age-related memory impairments or dementia risk. Evidence of the relationship between attention and aging is less consistent (for review see Staub et al., 2013); however, ability to sustain focus on any task is essential to its successful completion, and improvements to sustained attention could have wide-reaching benefits.

While mechanistic data on the cognitive effects of curcumin in healthy humans is lacking, animal studies indicate that curcumin is able to inhibit monoamine oxidase (MAO) and increase serotonin and dopamine levels 1 h after administration (Kulkarni et al., 2008). Similar enhancement of these neurotransmitter systems has also been reported 24 h after the cessation of chronic curcumin treatment (Kumar et al., 2010; Pyrzanowska et al., 2010). Monoamines, dopamine in particular, are known to be involved in working memory (Ellis and Nathan, 2001). Dopamine release is increased during working memory and attention tasks in healthy adults and correlates with task performance (Aalto et al., 2005). It could therefore be hypothesized that the observed improvements in cognitive task performance following acute and chronic treatment were due to the effect of curcumin on monoaminergic neurotransmission. However, further studies of the effects of curcumin on neurotransmitters (and other biomarkers) in humans and the time course of these effects are required to verify this.

Four weeks of chronic curcumin treatment was found to significantly reduce fatigue during the week preceding the Follow-Up session compared with placebo. It also improved resilience to the detrimental impact of cognitive stress on mood. Compared with placebo, curcumin was associated with a lesser reduction in calmness and contentedness and an inhibition of increased fatigue following mental challenge. This benefit was observed both immediately following mental challenge and over the duration of the testing session. A single acute-on-chronic dose of curcumin further protected against reductions in alertness and contentedness induced by performance of the cognitive array.

Fatigue in the elderly may too be due a greater vulnerability to physical and psychological stressors as a result of diminishing physical and psychological reserves (Avlund, 2010). As such, the reduced fatigue in participants who received curcumin treatment may have been at least in part due to their observed improvements in resilience to psychological stress. However, as the anti-fatigue effect of curcumin treatment was associated primarily with physical rather than mental fatigue, it likely also reflected benefits to physical health or function.

The effects of curcumin on fatigue have not been well investigated but it is known to possess a number of health-promoting properties which could have produced the observed reduction in fatigue. For example, in the present study curcumin was associated with lower levels of total and LDL cholesterol; anti-fatigue effects have previously been reported for other hypolipidemic supplements (Pistone et al., 2003). Also though not examined here, curcumin is able to reduce oxidative stress (Meng et al., 2013; Scapagnini et al., 2006; Sood et al., 2011; Sun et al., 2013; Tiwari and Chopra, 2012; Wu et al., 2006; Yu et al., 2013), which has been associated with symptoms of fatigue (Kennedy et al., 2005; Shichiri et al., 2013). Alternatively, curcumin may help to combat fatigue by improving the maintenance of energy levels and ability to meet energy demands through its effects on mitochondrial function, AMP-activated protein kinase and glucose uptake and regulation (Eckert et al., 2013; Kang and Kim, 2010; Kim et al., 2010; Sharma et al., 2009; Sood et al., 2011).

Greater negative reactivity to stressors has been linked with depression and anxiety symptoms, risk and disorders (de Rooij et al., 2010; Myin-Germeys et al., 2003). It follows that interventions such as curcumin that can lessen the affective impact of psychological stress on mood may have the potential to reduce vulnerability to depression and anxiety disorders. This is consistent with animal studies which have demonstrated antidepressant and neurotransmitter-enhancing effects of curcumin in stress-induced models of depression (Bhutani et al., 2009; Gao et al., 2009; Jiang et al., 2013).

However the observed mood-enhancing effects of curcumin were achieved, they support its potential for the prevention of fatigue and affective disorders, such as depression and anxiety, which is particularly important in an older cohort where these conditions may have serious detrimental consequences. Fatigue, anxiety and depression (disorders or subsyndromal symptoms) among older adults have each been associated with decline in physical function and ability to perform activities of daily living (Kazama et al., 2011; Moreh et al., 2010; Norton et al., 2012; Schultz-Larsen and Avlund, 2007), poorer cognitive function and dementia (Byers et al., 2012; Han et al., 2008; Gallacher et al., 2009; Ohayon and Vecchierini, 2002; Sinoff and Werner, 2003), greater cost and utilization of health services, including home care and hospitalization (Avlund et al., 2001; Vasiliadis et al., 2013), and mortality (Byers et al., 2012; Carriere et al., 2013; Moreh et al., 2010; Schultz-Larsen and Avlund, 2007). Fatigue is additionally associated with poorer self-rated health, and greater loneliness (Moreh et al., 2010). Depression predicts poorer medical compliance (DiMatteo et al., 2000), and depression and anxiety are both associated with suicidal ideation and suicide (Chopra et al., 2005; Kang et al., 2014; Waern et al., 2002).

The mechanisms underlying the above effects are not currently known. Future research might usefully include measurement of the curcumin parent molecule or its metabolites to allow examination of the relationship between absorption/bioavailability and behavioral changes. Similarly, as blood samples were collected only once per visit, the biochemical results reflect the overall effects of 4 weeks of chronic treatment. We therefore cannot discern when during the intervention period the behavioral or biochemical changes (cholesterol reduction) emerged or indeed whether there were acute biochemical changes that were not measured.

Conclusion

Cognitive decline, dementia, fatigue, depression and anxiety in the elderly can have a serious detrimental impact on welfare and self-sufficiency. Interventions that prevent or reduce any of these conditions may improve quality of life of our growing elderly demographic and reduce the increasing pressure placed on heath, social and financial support systems when these conditions limit the ability of the elderly to care for themselves. To our knowledge this is the first study to examine the effects of curcumin on cognition in a healthy elderly population or to examine any acute behavioral effects of curcumin in humans. Hematological safety measures confirmed that 4 weeks of daily treatment with 400 mg of Longvida® curcumin was safe and well tolerated in an elderly population. Behavioral measures showed that even at the low dose implemented here (approximately 80 mg) curcumin has the potential to improve important cognitive functions, reduce fatigue and improve resilience to the detrimental effects of psychological stress on mood. In doing so it highlights the need for further investigation of the potential psychological benefits of curcumin older populations.

Conflict of interest

None declared.

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