Further Evidence of Benefits to Mood and Working Memory from Lipidated Curcumin in Healthy Older People: A 12-Week, Double-Blind, Placebo-Controlled, Partial Replication Study

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Abstract: Curcumin (a flavonoid isolated from turmeric) affects several processes involved in neurocognitive aging. We have previously reported that short term (4-weeks) administration of a highly bioavailable curcumin preparation (Longvida©) improved working memory and reduced fatigue and stress reactivity in a healthy older cohort. The present trial (ACTRN12616000484448) was a partial replication study, evaluating similar effects at 4 and 12-weeks Longvida© supplementation. A double-blind, placebo-controlled, parallel-groups trial was conducted. Eighty participants aged 50–80 years (mean = 68.1, SD = 6.34) were randomised to receive Longvida© (400 mg daily containing 80 mg curcumin) or a matching placebo. Assessment took place at baseline then following 4 and 12 weeks treatment. Outcome measures included cognitive performance, mood and biomarkers. Compared with placebo, curcumin was associated with several significant effects. These included better working memory performance at 12-weeks (Serial Threes, Serial Sevens and performance on a virtual Morris Water Maze), and lower fatigue scores on the Profile of Mood States (POMS) at both 4 and 12-weeks, and of tension, anger, confusion and total mood disturbance at 4-weeks only. The curcumin group had significantly elevated blood glucose. These results confirm that Longvida© improves aspects of mood and working memory in a healthy older cohort. The pattern of results is consistent with improvements in hippocampal function and may hold promise for alleviating cognitive decline in some populations.

Keywords: curcumin; working memory; mood; cognition

1. Introduction

The increase in the numbers of people living into old age brings with it substantial challenges to global healthcare. Perhaps the most critical is the growing number of people living with dementia, currently estimated at around 50 million, with a new case every 3.2 s, and projected to double every two decades [1]. The relative lack of success of 'single domain' approaches to the disorder have led to the search for strategies which reduce the risk of dementia by delaying its onset and offsetting age-related cognitive decline. In this context, a number of lifestyle factors, including components of diet, have been identified as potential candidates for improving cognitive function. These include whole dietary patterns such as the Mediterranean diet and components of food such as the flavonoids [2].

Curcumin is a flavonoid, from the spice turmeric, with many characteristics that make it a candidate to improve physiological measures related to systemic and central health. Preclinical studies indicate that curcumin has properties relevant to neurocognitive functioning [3].

Regarding human health, there are several systemic processes which represent modifiable risk factors for cognitive decline [4]. Evidence from clinical trials suggest that many of these are positively modulated by curcumin in (despite a recent, widely publicised paper claiming, "No double blinded, placebo controlled clinical trial of curcumin has been successful") [5]. For example a meta-analysis of randomised controlled trials (RCTs) of curcumin and tumour necrosis factor α (TNF α) levels, reported a significant reduction in this marker of inflammation across included studies [6]. Other RCTs have reported benefits to blood insulin (though not glucose) in healthy individuals [7], and improvements to several indices of glucoregulation in prediabetic and Type 2 diabetes [8]. Curcumin administration was associated with better cardiovascular function, increased central blood flow, decreased inflammation and oxidative stress, and qualitative changes to the gut microbiome.

Many of the same cardiometabolic processes are implicated in cognitive decline and dementia [4]. Thus, several placebo-controlled trials have investigated the potential for curcumin to improve cognitive function in both impaired and cognitively intact older cohorts. Small et al. [9] conducted an 18-month trial evaluating the efficacy of a bioavailable curcumin (180 mg of Theracurmin containing 10% curcumin). A cohort including both clinically intact individuals and those with Mild Cognitive Impairment were evaluated on standardised memory measures. A subset (15/arm) underwent [^{18}F]FDDNP positron emission tomography (FDDNP-PET) to reveal amyloid and tau load (two key central markers of Alzheimer's disease). Those in the curcumin group had significantly improved memory performance, along with reduced FDDNP-PET signal levels, indicating reduced amyloid and tau burden associated with curcumin treatment. This promising trial needs to be replicated with larger numbers.

Turning to effects of curcumin on cognition in healthy cohorts, Rainey-Smith and colleagues [10] conducted a 12-month trial of 1500 mg/day Biocurcumax™ in $n = 96$ healthy older adults (mean age, 66 years). Cognitive outcomes were measured at baseline, then at six and twelve months. Although there was a significant group x time interaction, the effects were not straightforward. Although the curcumin group outperformed placebo at six months, unfortunately the group scores were also significantly different at baseline, with an advantage for the placebo group, and statistically similar at the 12-month timepoint. This makes it difficult to disentangle the effects of the intervention from chance differences in performance.

Native curcumin has low bioavailability and likely has little efficacy unless large quantities are consumed daily. Several methods have been used to attempt to increase bioavailability. These include co-administering curcumin with piperine, or modifying the compound with lipidation. This is important since there appears to be a clear correspondence between curcumin bioavailability and its health benefits [11]. One solid-lipid curcumin preparation (SLCP), Longvida©, has been used in several preclinical and clinical trials. Primate studies indicate that Longvida© can protect against age-related cognitive decline [12].

Our previous RCT assessed the acute and chronic (28-day) mood and cognitive effects of 400 mg per day of Longvida© curcumin [13]. Compared with placebo, there were significant acute improvements to two measures of working memory, with one remaining significantly better at 28 days. Specifically, curcumin was associated with acutely improved Digit Vigilance and Serial Threes performance, and better Serial Threes performance following 28-day intervention. Additionally, there were a number of benefits to mood at 28 days. These included reduced self-rated fatigue as evaluated using the Chalder Fatigue Scale [14], a widely-used, 14-item scale gauging aspects of fatigue over the preceding week. At 28 days, there was also a significant attenuation of the negative effects of a cognitive challenge on alertness and contentment. Regarding biomarker assessment, curcumin was also associated with reduced total and low density lipoprotein [13].

These findings are supported by two recent systematic reviews (one including meta-analysis). The latter reported significant effects of curcumin over placebo, concluding that "curcumin is effective in improving memory performance in older adults" [15]. The other concluded that curcumin shows promise in improving cognitive function in both cognitively intact and compromised populations [16], but suggested more, well-designed studies are needed.

To summarise, there is accumulating evidence identifying curcumin as a candidate treatment to help prevent cognitive decline and dementia [17]. An obvious first step in evaluating this possibility is to test the efficacy to improve mood and cognition in healthy, older cohorts. In our previous study, this approach revealed significant improvements to mood and cognition in a 28-day intervention trial. Here we sought to extend the findings of that earlier trial by including a 12-week assessment in addition to a 28-day testing session.

The primary objective of this study was to evaluate whether the effects of our earlier 4-week trial could be replicated, and to extend the time course to evaluate if any effects were evident following 12-weeks curcumin supplementation. To this end, we conducted a double-blind RCT examining the effects of Longvida© curcumin on cognitive function, mood and wellbeing in healthy participants aged 50 to 85 years. We hypothesised that, compared with placebo, curcumin treatment would lead to reduced fatigue, improved working memory and attenuated stress reactivity.

2. Materials and Methods

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. Ethical approval was provided by the Swinburne University Human Research Ethics Committee (SHR2016-008). The trial was registered on the Australian New Zealand Clinical Trials Registry as ACTRN12616000484448.

2.1. Design

The trial used a double-blind, placebo-controlled, parallel-groups design to investigate the effects on mood and cognitive function of 12-weeks supplementation with a bioavailability-enhanced curcumin extract, Longvida©, in healthy older adults. Specific biomarkers were also measured. An interim assessment was completed at 4-weeks. A subset of participants (target 50%) took part in a neuroimaging sub-study (the results of which will be published elsewhere).

2.2. Participants

Figure 1 shows the recruitment pipeline. *n* = 79 participants completed the trial (from an initial target of 80). Participants who withdrew from the study prior to the final participant's baseline visit were replaced to optimise the chance of meeting the target number of 80 active or completed participants.

Eligible participants were healthy men and women aged 50–85 years. Inclusion criteria included being free from medical conditions that may affect ability to participate in the study. That is no history of stroke, or neurological conditions (e.g., Parkinson's, epilepsy), depression, psychiatric disorders, cognitive impairment, present or past alcohol abuse, being free from dementia, fluent in written and spoken English, having normal or corrected vision and not colour blind. Exclusion criteria included any significant concurrent illness including auto-immune disorder, bleeding disorders, currently impaired cardiovascular function, Type I diabetes, glaucoma, uncontrolled high blood pressure or gallstones or any known or suspected food allergies. Smokers and users of recreational drugs (except alcohol and other food grade actives) were excluded. Individuals who had participated in any other study involving an investigational product in the preceding 4-weeks were excluded, as were those taking anti-coagulant drugs, cholinergic drugs or steroid medications. Taking vitamins or herbal supplements reasonably suspected to influence study outcomes was also an exclusion criterion.
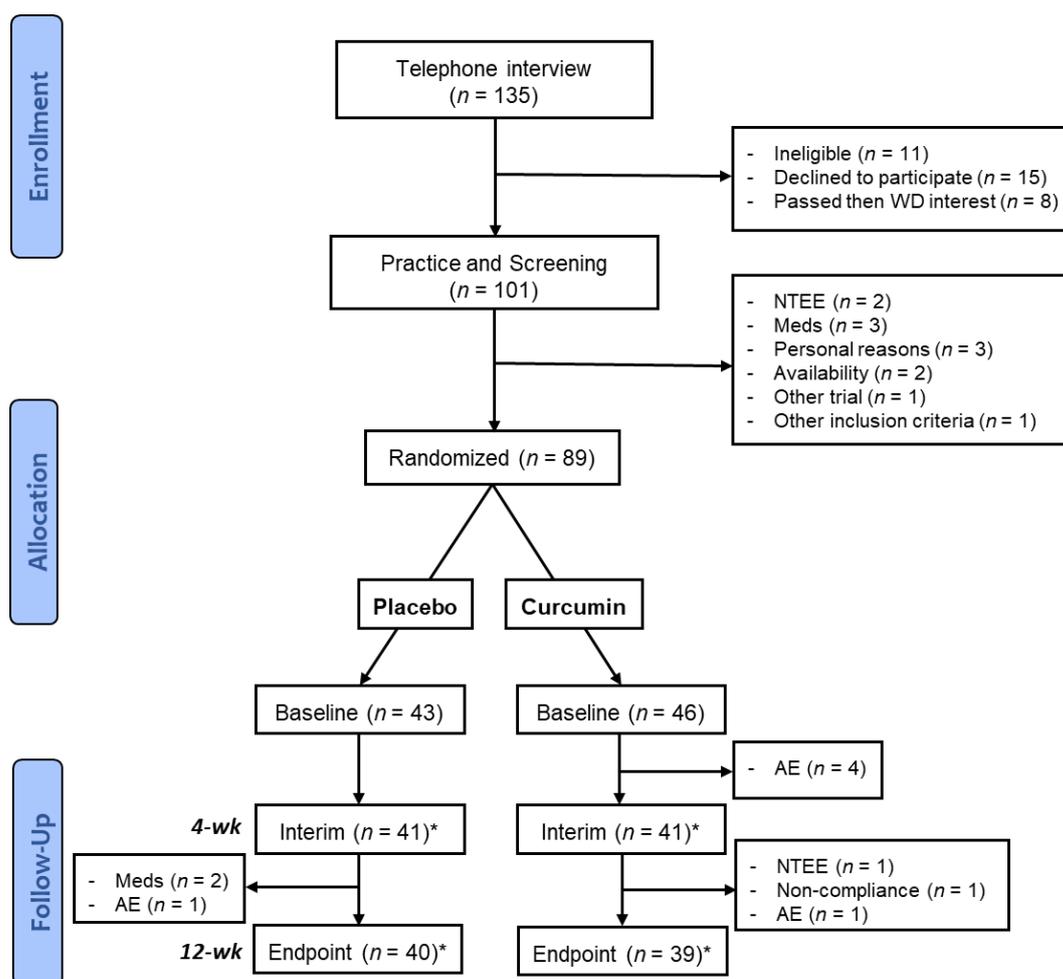
Figure 1. Modified Consort diagram showing participant recruitment and flow through the trial. Key: WD, withdrew; NTEE, Non-treatment emergent event (adverse event with onset prior to commencement of the trial intervention); Meds, use of medication listed in exclusion criteria; AE, adverse event; * Three participants (2 × Placebo, 1 × Curcumin) did not complete the Interim visit but did complete the Endpoint visit.

2.3. Treatment and Dosing Regime

The active treatment was 400 mg Longvida© Curcumin, consisting of approximately 80 mg curcumin in a SLCP formulation, with the remaining weight comprising of commonly used pharmaceutical excipients and small amounts of other curcuminoids present in turmeric extract. The placebo consisted of dextrin and a small amount of yellow food colouring, to match the appearance of curcumin supplements, smell and taste were also matched.

Treatment was administered orally as a single, once daily capsule taken between breakfast and lunch. The first dose was administered as part of the baseline visit with subsequent doses being self-administered by participants at home. The final dose was taken the day before the final assessment to ensure that follow-up assessments reflected the effects of chronic supplementation, rather than reflecting any superimposed, acute-on-chronic effects that may result from having curcumin or metabolites in circulation.

2.4. Randomisation and Treatment Allocation

In order to maintain blinding, randomisation and treatment allocation was carried out by a staff member external to the study. This individual was not involved in data collection or analysis.

Treatment IDs were randomised 1:1 to active and control treatment. Randomisation was stratified by sex and MRI sub-study participation (to be reported elsewhere). Upon enrolment, participants were assigned the next consecutive three-digit ID number corresponding to a Treatment ID. Treatments were pre-packaged and labelled with Treatment ID, administration instructions and trial contact details. Treatment allocation remained the same throughout duration of the trial.

2.5. Treatment Compliance

Two methods were applied to monitoring treatment compliance: a count of returned treatments and a treatment log that was completed by participants at home. The pre-packaged, take-home treatments contained more capsules than required to maintain daily supplementation to trial completion. Participants were instructed to bring all unused capsules to their follow up visit/s, these were counted and percentage compliance with treatment was calculated as (number of capsules dispensed − number of capsules returned)/number of doses that should have been consumed (i.e., days since prior visit) × 100). In the event of a participant forgetting to return or losing capsules, the daily treatment log was used to estimate the number of capsules consumed. Participants who forgot to return their study treatment were provided with a prepaid envelope and asked to return all unused capsules as soon as possible. These were then used to confirm compliance, 80–120% compliance with treatment constituted eligibility to be included in analyses.

2.6. Recruitment

Participants were free-living older Australians, recruited using a variety of methods. Some were on the Centre for Human Psychopharmacology database of individuals who had previously requested to be informed about trial participation opportunities. Additionally, advertisements were placed in Seniors' publications, at local clubs and organisations and on the University campus. All individuals who expressed interest in participation were provided with a copy of the Participant Information and Consent Form (PICF), which they were required to read before completing a formal Telephone Interview and being booked to enrol in the trial.

2.7. Procedure

Participants completed a telephone interview and four laboratory visits. The first of these was an enrolment, screening and practice visit. A baseline visit (Day 1) took place within 3 weeks of the practice visit, the 4-week visit at Day 28 (±4) and the 12-week visit at Day 84 (±4).

2.7.1. Telephone Screening Interview

Prior to enrolment in the study, a structured Telephone Interview was completed to provide a preliminary eligibility assessment and to ensure the understanding of participation requirements. To verify the absence of dementia, the modified Telephone Interview for Cognitive Status (TICS-M) was completed [18]. The TICS-M assesses four domains of cognitive function: orientation, memory, attention/calculation and language, with the greatest weight placed on memory. Total scores range from 0 to 39, with larger scores indicative of superior cognitive function. There are no established cut-off points for the differentiation of cognitively intact, impaired or demented individuals using the 13-item TICS-m. Based on previous findings using this specific version [18,19], participants scoring less than 21 on the TICS-m would be excluded from the study on the grounds that moderate to severe cognitive impairment was indicated, suggesting the possibility of dementia.

2.7.2. Enrolment, Screening and Practice Procedure

At this visit, written informed consent was obtained and eligibility was confirmed by a checklist and discussion of eligibility criteria. A medical history of any significant (i.e., lasting more than 2 weeks) illnesses or injuries occurring or treated within the past 5 years was taken and details of any

concomitant medication use was recorded. While satisfaction of eligibility criteria was, in most cases by self-report, the Mini Mental State Exam (MMSE) [20] and Beck Depression Inventory (BDI-II) [21] were completed in order to screen for the presence of dementia and depression.

Demographic data were collected including date of birth, gender, dominant hand, whether English was their primary language, smoking history, highest level and total years of formal education and current employments status. Characterisation questionnaires were also completed (see respective trial measures for details). They were familiarised with study measures and completed practice versions of all cognitive assessments to minimise practice effects.

Volunteers were required to avoid significant changes to lifestyle factors such as habitual diet, exercise and medication (unless instructed by their doctor). In the event of such a change, they were asked to notify research staff to allow assessment of their ongoing trial eligibility.

2.7.3. Study Visits

Participants arrived at the Centre for Human Psychopharmacology (CHP) in the morning between 8:30 a.m. and 10:30 a.m. On arrival, their compliance with having fasted from 10:00 p.m. the night before (consuming only water) and avoiding vigorous exercise were confirmed. A blood sample was collected and cardiovascular assessments were performed. They were provided with their chosen breakfast and, following a brief break, completed the chronic mood questionnaires and the computerised cognitive battery.

After completion of all mood and cognitive tests, participants were provided with a take home pack containing 32 treatment capsules, which was sufficient to allow once daily supplementation for the period from the Baseline to 4-week visit, plus additional capsules, a treatment log with instructions for completion, reminders of lifestyle and pre-visit restrictions (e.g., diet and exercise). They were administered their first study capsule prior to leaving the laboratory.

The 4-week visit followed the same procedure as the baseline visit except that take-home packs included 65 capsules and participants completed the Survey of Subjective Experience. The 12-week visit followed the same procedure as the baseline visit, except that no take home pack or treatment capsules were provided. Participants completed the Survey of Subjective Experience and were asked to indicate whether they believed that the treatment capsules they had been receiving were placebo or curcumin. At the conclusion of the visit, participants completed a reimbursement form.

Participants received 120 AUD at the end of their participation in the study, in the form of a cheque posted to their designated mailing address. Participants who completed the MRI sub-study received an additional 30 AUD (150 AUD total).

Once the trial was unblinded, participants were notified of their treatment allocation and those who had been in the placebo group were offered a free 12-week supply of Longvida© Curcumin. This ensured that all participants had equal opportunity to benefit from any positive effects of the treatment. The following sections detail the measures utilised in the study.

2.7.4. Screening and Sample Characterisation

Mini Mental State Examination (MMSE)

The MMSE [20] was developed as a brief, quantitative assessment of cognitive function and is the most widely used measure for assessing cognitive status and detecting dementia in the elderly, both in research and clinical settings. The MMSE takes approximately 5–10 min to administer and assesses five domains of cognitive function: orientation, registration, attention/calculation memory and language. Participants scoring 20 or less, from a possible 30 were excluded from the study, as this is considered indicative of the presence of possible dementia.

Beck Depression Inventory-II (BDI-II)

The BDI-II [21] is one of the most widely used depression assessment tools in both clinical and research settings [22] and has been validated as measured for depression screening in community dwelling older adults [23]. It consists of 21 items to which participants respond according to how they have felt over the past two weeks. Each item is scored 0 to 3, resulting in possible total scores ranging from 0 to 63, with higher scores indicative of greater severity of depressive symptoms. A cut-off score of 20 was adopted for screening as this allows for the best detection of individuals with symptoms of moderate or severe depression [21].

Montreal Cognitive Assessment (MoCA)

The MoCA [24] measures global cognition and assesses cognitive domains of attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. The MoCA was selected for the in-person characterisation of global cognitive function, over the MMSE, as it is less susceptible to a ceiling effect and has demonstrated superior sensitivity in the detection of early or mild cognitive impairment [24–27].

National Adult Reading Test (NART)

The National Adult Reading Test (NART) [28] was used to characterise premorbid intelligence. It comprises an irregular word reading test that presents participants with 50 difficult or unusual words that they are required to read aloud. The number of words correctly pronounced is a widely-used estimate of premorbid Full-Scale IQ.

State-Trait Anxiety Inventory–Trait Scale (STAI-T)

The State-Trait Anxiety Inventory (STAI) [29] comprises two scales. The 'Trait' scale (STAI-T) consists of 20 self-descriptive statements (e.g., "I feel pleasant") to which participants respond by indicating how frequently each statement applies to how they "generally feel." Total scores range from 20 to 80 with higher scores indicating greater dispositional anxiety.

2.7.5. Chronic Mood and Wellbeing Questionnaires

The following questionnaires were completed at each assessment session (Baseline, 4-week and 12-week). They measured recent self-reported, state-non-specific feelings or experiences and were used to assess the effects of treatment on chronic mood and wellbeing. Items were administered in the following order.

Profile of Mood States (POMS)

The POMS [30] consists of 65 mood-related adjectives to which participants respond by indicting to what extent they have been feeling that way over the past week on a 5-point scale from 0 (not at all) to 4 (extremely). Items are summed into six factors: Tension-Anxiety, Confusion-Bewilderment, Vigor-Activity, Anger-Hostility, Depression-Dejection and Fatigue-Inertia. A Total Mood Disturbance (TMD) score is computed as the sum of the first five factors minus Vigor-Activity. On all scales, except Vigor-Activity, which is reversed, a high score indicates greater mood disturbance.

Chalder Fatigue Scale (CFS)

The CFS [14] assesses the severity of fatigue experienced during the preceding week as compared to how one "usually" feels. It comprises 14 statements, six regarding symptoms of mental fatigue and eight regarding symptoms of physical fatigue, to which participants respond on a four-point scale (0 to 3), ranging from "less than usual" to "much more than usual." Three resulting scores are calculated: Mental Fatigue, ranging from 0 to 18, Physical Fatigue ranging from 0 to 24 and Total Fatigue ranging from 0 to 42. Larger scores are indicative of greater fatigue.

Perceived Stress Scale (PSS)

The PSS [31] consists of 14 items designed to measure a respondent's perception of stress. Participants are asked to score on a scale from 0 to 4 how often they have felt a particular way over the past month. Total scores range from 0 to 56 with higher scores indicating a greater degree of perceived stress and lower scores indicating effective coping.

General Health Questionnaire (GHQ-28)

The GHQ-28 [32] screens for symptoms on four subscales, each comprising seven items: somatic symptoms, anxiety/insomnia, social dysfunction and severe depression. Each item relates to complaints participants may have had "over the past few weeks," to which they respond on a four point scale (0 to 3) indicating the extent to which they have been affected relative to how they usually feel, from "not at all" to "much more than usual." Resulting scores on each subscale range from 0 to 21, and a total score from 0 to 84 is calculated.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI [33] is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of scores for these seven components yields one global score.

Symptom Checklist

The symptom checklist comprised 28 items referring to possible mental or physical experiences such as "I have stomach pains," "I have a change in energy" or "I feel stressed more than usual". Participants were required to indicate to what extent the problem had distressed or bothered them in the past seven days, on a scale ranging from "not at all" to "very much so." Responses to these items were used to examine any change in distressing symptoms that participants may have had following treatment administration and to assist in the detection of adverse events.

State Mood and Workload Assessment

These items measured the current, state-specific mood and were completed at each assessment session (Baseline, 4-weeks and 12-week), immediately before and after the cognitive battery. They were used to assess the perceived challenge posed by the cognitive battery and its effect on mood, and whether this could be modified by treatment. Specific items were as follows.

Visual Analogue Scales

The Bond-Lader Visual Analogue Scales [34] present participants with 16, 100 mm lines anchored on either end by opposing adjectives, such as "Alert" and "Drowsy." For ease of use and improved accuracy over manual measurement, a computerised version of the Bond-Lader scale was used. Participants were presented with each line one at a time on the screen, and asked to use the mouse to place a repositionable X along the line according to how they felt at "this moment." Participants were verbally reminded that the ends of the lines represented the very extremes of the named emotions. Responses were scored as percentage distance along the line from the negative anchor, providing a score from 0 to 100. The 16 items load onto three factors: Alertness, Calmness and Contentedness, with larger scores indicating higher levels of these moods.

In addition to the Bond-Lader scale, custom visual analogue scales were used to measure state stress, fatigue, anxiety and self-perceived ability to concentrate. For these items, participants were presented with a line anchored by "not at all" and "extremely" and asked to respond by indicating how they felt "at this moment." The scales were scored as percentage distance from "Not at All" so

that larger scores indicated greater levels of stress, fatigue and anxiety (undesirable), and better ability to concentrate (desirable).

Subjective Effects Questionnaire

In order to capture information about participants' experiences, which may or may not have been detected by standardised questionnaires, three open ended questions were completed at the final study visit. These questions asked participants whether they had experienced any positive/negative/unusual (neither good nor bad) changes in their physical or mental health for which they did not know the cause or believed may be related to the study capsules. If yes, participants were asked to provide a brief written explanation.

NASA Task Load Index (NASA-TLX)

The NASA TLX [35] is a self-report measure of subjective workload. Participants are asked to rate the perceived mental, physical and temporal demands of a task from low to high, as well as how much effort was required (low to high), how they think they performed (good to bad) and how much frustration was caused (low to high). Participants are provided with the brief explanation of each scale, which ensures consistency of understanding and interpretation. As with the Visual Analogue Scales, the NASA-TLX items were each presented as single on-screen lines that were scored from 0 to 100.

2.7.6. Computerised Cognitive Assessment

Standard cognitive tasks, with known psychometric properties, were presented using E-Prime 2.0 (PST Net) and Python 2.7.9. The battery took approximately 60 min to complete, and parallel versions of each task allowed a novel version for each testing session. Participants were provided with written instructions for each task and, during assessment, were monitored by a researcher who answered any questions and provided verbal explanation of the tasks if required.

Divided Attention Tracking Task (DATT)

The DATT task, a slight modification of that used by Scholey et al. [36], assessed the interfering effects of divided attention at the time of encoding on subsequent verbal recognition.

Participants were presented with 20 recordings of spoken words via headphones and asked to remember them. Each word was augmented to have a duration of exactly 1000 ms. In the Divided Attention Encoding condition, participants simultaneously used the computer mouse to track a moving on-screen dot. The dot moved in a random path at a rate of approximately 6 cm/sec. During Focused Attention Encoding, there was a tracking task.

In the subsequent Recognition phase, participants were presented with 80 spoken words via headphones: 40 new decoy words and 20 target words from each of the focused and divided attention conditions providing a 1:1 target to decoy ratio. Participants were asked to indicate whether they recognised each word as being one they heard earlier using keypad buttons labelled "Yes" and "No." Participants were not required to distinguish the condition under which a word has been presented. A delay of approximately 30 min separated the encoding and recognition phases. In order to avoid differences in retention time being erroneously attributed to differences in encoding condition effects, the order of the Focused Attention Encoding and Divided Attention Encoding was counterbalanced across participants.

The task was scored for accuracy and speed of correct responses during the Recognition phase overall (correct recognition and correct rejection), correct recognition irrespective of encoding phase and separately for divided and focused encoding words. The key comparison was the difference between recognition accuracy for words presented in the divided and focused attention conditions.

Virtual Morris Water Maze (vMWM)

The Morris Water Maze (MWM) is a prototypical task for assessing spatial learning and memory in rodents [37]. Successful completion of the task requires that the subject learn the location of an escape platform submerged in a pool of cloudy water. In its original form, the animal uses distal cues to navigate to the previously learnt platform location.

In this virtual analogue of the task, participants are placed in a virtual room. They are required to navigate as quickly as possible to reach a platform hidden below the surface of the water and "escape from the pool." The platform is in a fixed location, relative to environmental cues. The participant starts each trial at one of a number of different points around the outside of the pool. Outcome measures include time and length of path taken to reach the target; the initial heading errors are recorded for each trial, as well as time in target quadrant.

Participants began with four familiarisation trials in which the platform was visible and no cues were positioned in the room, and they were told that the visible platform location was no indication of where the hidden platform would be. Sixteen learning trials were then completed in which the platform was hidden below the surface of the water at the same location (no visible indication of its location was given). Participants started each trial facing the wall in 1 of 4 starting positions, trials were completed in 4 blocks, each comprising 1 trial at each of the starting locations, and outcomes were average within each block. They were instructed to make an active effort to find the platform even if they had no idea where it was (i.e., in the initial trials). If the platform was not found within 45 s, it became visible.

At the end of the 16 learning trials, a single immediate memory probe trial was completed in which, unbeknown to participants, the platform was absent. Participants started in a previously unused starting location, in the centre of a non-target quadrant, but were given no indication that this trial differed from the preceding 16. Successful learning would result in disproportionately greater time in the target quadrant. After a delay of approximately 30 min (during which other cognitive tasks were completed) participants were presented with a single delayed memory trial that was identical to the immediate memory probe. Again, time spent in the target quadrant was indicative of better spatial memory.

Serial Subtractions

A starting number between 800 and 999 was presented on screen. Participants were required to subtract three or seven (serial Threes and Serial Sevens, respectively) from this number and enter the three-digit response using the computer keyboard numeric keys. Each of the three-digit keystrokes was represented on-screen by an asterisk to ensure all calculations were performed mentally. After the first response was entered, the initial display was cleared from the screen and participants were required to continue subtracting three/seven from their previous answer. In case of an error, the accuracy of each response was scored with respect to the preceding response only. Participants were told to respond as quickly and accurately as possible and the total number of correct responses provided within three minutes was used as the measure of performance.

Arrow Flankers Task

This Go/No-Go modification of the Erikson Flanker Task [38] provided a measure of executive function and cognitive control, in particular interference suppression (the ability to ignore irrelevant or conflicting information) and response inhibition (the ability to refrain from providing an undesirable response). Similar modifications have demonstrated behavioural and neurological differences associated with cognitive maturation [39], cognitive impairment and dementia [40] and medication use in ADHD [41].

The task comprised four trial conditions. All conditions involved participants being presented with five on screen symbols in a horizontal line. The central "target" symbol was always an arrow pointing

left or right, and participants were instructed to press the keyboard arrow key that corresponded to the direction of this target as quickly as possible. The "flanking" symbols varied by condition, but were always four of the same symbols: two on the left and two on the right of the target. Flanking symbols were either 'facilitating' (arrows pointing in the same direction as the target), 'interfering' (arrows pointing in the opposite direction to the target), 'neutral' (circles) or 'no-go' (Xs), where participants were instructed not to respond to the target as a measure of response inhibition.

2.7.7. Biochemical Measures

All blood samples were collected via venipuncture. A range of analyses were performed to assess treatment safety and bioavailability and possible mechanisms of action. These included:

Potassium (mmol/L serum), Chloride (mmol/L serum), Bicarbonate (mmol/L serum), Urea (mmol/L serum), Creatinine (umol/L serum), eGFR (mL/min/1.73 m^2), Urate (mmol/L serum), Calcium (mmol/L serum) and Phosphate (mmol/L serum).

Tests of liver function included total protein (g/L serum), Albumin (g/L serum), ALP (U/L serum), Bilirubin (umol/L serum), GGT (U/L serum), AST (U/L serum), ALT (U/L serum) and Glucose (mmol/L serum). Lipid profile measures included triglycerides (mmol/L serum), Total cholesterol (mmol/L serum), High density lipoprotein (HDL) (mmol/L serum), Low density lipoprotein (LDL) (mmol/L serum), LDL:HDL and Cholesterol:HDL.

Inflammatory markers, including highly sensitive C-reactive protein (hsCRP, mg/L serum), Estimated sedimentation rate (mm/h), Interleukin 1 Beta (IL-1β, pg/mL serum), Interleukin 6 (IL-6, pg/mL serum), Tumour necrosis factor alpha (TNFα, pg/mL serum), 8-hydroxy-2' -deoxyguanosine (8-OHdG, ng/mL serum) and protein carbonyls (nmol/mg), were measured in house using commercially purchased ELISA kits as markers of oxidative stress.

2.7.8. Statistical Analyses

Analyses were performed using IBM SPSS v25. Group characteristics were compared using one-way ANOVA or a non-parametric alternative according to data distribution. The planned method of analysis for investigation of treatment effects was Analysis of Covariance (ANCOVA) with post-treatment outcome as the dependent variable, baseline as a covariate and treatment as a between subjects factor. The 4-week and 12-week outcomes were assessed separately. Where the nature of the data did not permit the planned analyses, appropriate alternatives were used as indicated. Analyses of cognitive task performance, perceived demands and the effect of cognitive battery on state mood were repeated additionally, including the demographics variables age, years of education and cognitive status as measured by the TICS-M [18]. These variables were selected as covariates as they may have influenced how challenging participants found the cognitive battery. The TICS-M was chosen for inclusion as the measure of cognitive status, instead on the MoCA, for consistency with our previous study [13].

3. Results

In addition to the results presented below, detailed summary statistics of each outcome can be found in online Supplementary Material Tables S1–S7. Details of data transformations and statistical analyses are contained in online Supplementary Material Tables S8–S13.

3.1. Recruitment and Retention

A flow chart of participant recruitment and retention is shown in Figure 1 and detailed in Supplementary Material. Sample characteristics are presented in Table 1.

Table 1. Baseline Group Demographics. Except for gender, numbers are mean with standard deviation (SD) in brackets.

Variables	Placebo (n = 43)	Curcumin (n = 42)
% Male	48.84	50
Age (years)	68.38 (6.71)	67.81 (6.00)
TICS-M	28.09 (3.146)	27.79 (2.90)
MMSE	29.35 (0.94)	29.143 (1.095)
Years education	16.56 (3.048)	16.162 (2.879)
STAI-T	29.63 (7.41)	27.57 (5.739)
BDI	3.79 (4.29)	2.98 (3.37)
NART	40.465 (5.00)	40.48 (4.63)

Key. TICS-M = Telephone Interview for Cognitive Status, MMSE = Mini Mental State Exam, STAI-T = State-Trait Anxiety Inventory–Trait Scale, BDI = Beck Depression Inventory-II, NART = National Adult Reading Test.

3.2. Treatment Compliance and Assessment Timing

All participants attending the 4-week visit satisfied the 80–120% compliance requirement for inclusion in analyses (mean 98.43%, ±4.06%). At the 12-week visit one participant reported having not taken their study capsules for 11 days, so was excluded from end-point analyses. The remaining participants all satisfied the compliance requirements (mean = 97.96%, SD = 3.61%). There was an average of 27.98 (±SD 1.28) days between baseline and 4-week assessment, and 83.78 (±1.47) between baseline and final assessment.

3.3. Description of Analysis Sample

The dataset used for analyses comprised of the participants for whom any post-treatment data were available and as a follow-up point of interest. This resulted in a total Baseline sample size of 85. These participants were aged 55.10 to 83.41 years (mean 68.10, SD 6.34 years), 49.4% were male and 90.6% were right-handed. Of the sample, 85.9% had undertaken tertiary or post-graduate education and an average of 16.36 years (SD 2.95 years) of formal education. A total of 57.6% of the sample were retired, 25.9% were working part time or casually and 14.1% were working full time. One participant reported that they were studying, and one classed themselves as unemployed. No participant was a current smoker, but 45.9% of participants reported that they had previously been a smoker. Time since quitting ranged from 2 to 60 years (mean 28.23, SD 14.06 years).

The baseline characteristics of the two treatment groups did not significantly differ in any demographic measured, nor in global cognitive function (MMSE, MoCA or TICS-M), estimate of "pre-morbid IQ" (NART), depressive symptoms (BDI-II) or trait anxiety (STAI-T). Further characteristics of the cohort can be found in the online Supplementary Material (Table 1 and Table S1).

Note that other effects, including on cognitive performance related to hippocampal function, which was also undertaken during neuroimaging, will be reported elsewhere.

3.4. Treatment Effects: Mood (See Also Supplementary Material Tables S2 and S3)

Significant effects and notable patterns in the data are presented below. Unless specified, these effects include adjustment for age, education and cognitive status. Details of relevant data transformations and more details on statistical analyses of each outcome can be found in the online Supplementary Material Table S2.

3.4.1. Profile of Mood States (POMS)

Compared with placebo, the Fatigue-Inertia scale of the POMS was significantly improved in the curcumin group at both 4-week ($F_{(1,79)}$ = 6.795, p = 0.01) and 12-week ($F_{(1,75)}$ = 8.120, p = 0.006). Examination of the other subscales revealed significant beneficial effects of curcumin at 4-weeks only for Tension-Anxiety ($F_{(1,77)}$ = 8.073, p = 0.006), Confusion-Bewilderment ($F_{(1,79)}$ = 5.364, p = 0.023)

and Anger-Hostility (F(1,78) = 8.952, p = 0.004). For Total Mood Disturbance (TMD) there was a significant beneficial effect of curcumin at 4-weeks (F(1,77) = 8.073, p = 0.006), but not 12-weeks. Effects on Depression-Dejection did not reach significance (p = 0.054), and Vigor-Activity did not show any evidence of a treatment effect (see Figure 2).
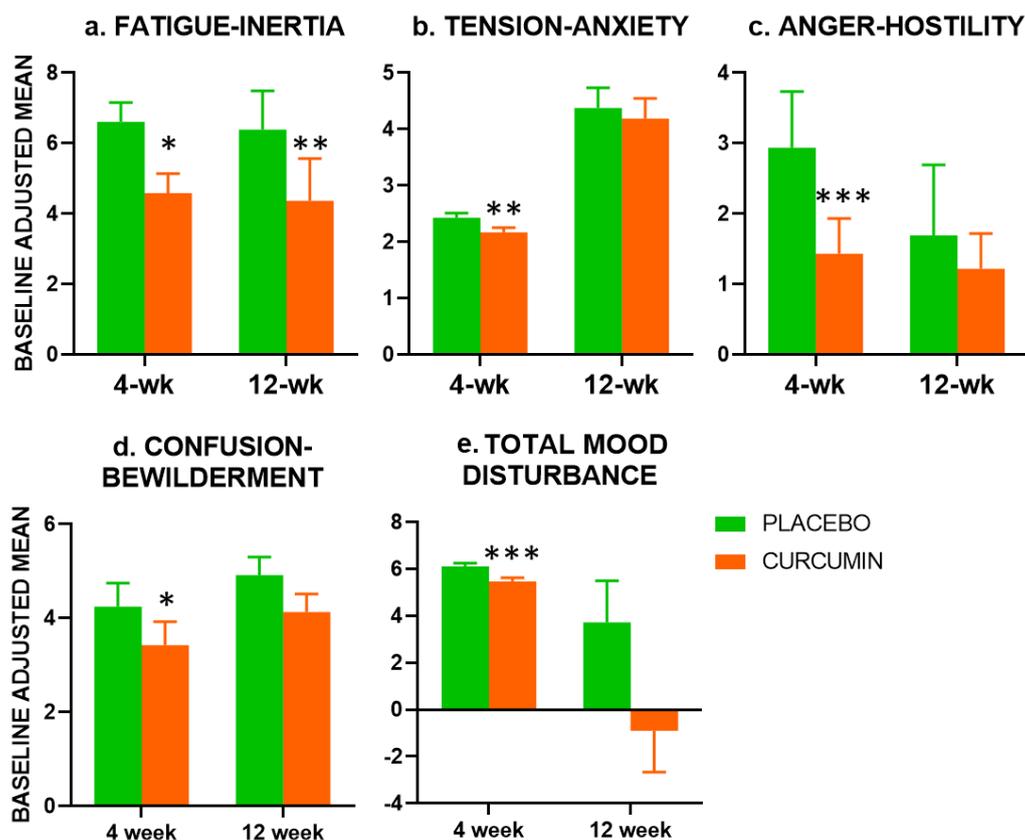
Figure 2. Effects of Longvida© curcumin on mood. Graphs depict baseline adjusted means with SEM (or 95% confidence intervals due to back transformation for a. 12-week, c. both, d. 4-week; see Supplementary Table S3 for unadjusted means and standard deviations). *, p < 0.05; **, p < 0.01; ***, p < 0.005.

3.4.2. NASA Task Load Index (NASA-TLX)

There were no significant differences between curcumin and placebo groups in the mental, physical or temporal demands of the cognitive battery perceived by participants in the at 4-week or 12-week assessments. At the 4-week assessment, participant in the curcumin group reported significantly lower ratings of their own performance (both with and without adjustment for age, education and cognitive status) (p < 0.05). At the same time, there were trends for the curcumin group to report lower levels of effort and frustration during the battery (p = 0.089 and p = 0.065, respectively). These differences did not survive adjustment for demographics.

At the 12-week analysis, there were no significant effects of treatment on perceived battery demands, or ratings of own performance, effort or frustration with or without adjustment for age, education and cognitive status.

3.4.3. GHQ-28

There was no significant effect of treatment on scores on the Depression, Somatic Symptoms or Social Dysfunction subscales at either 4-week or 12-week assessments. There was a trend towards a benefit of curcumin treatment on change in Anxiety-Insomnia scale scores at the 4-week assessment (p = 0.056), but not at 12-week (p = 0.717).

3.4.4. PSQI

There were no significant treatment effects on PSQI from analyses of variance. However, when data were analysed by chi-squared examining the direction of change, the curcumin group performed significantly better on the 'daytime dysfunction' subscale at 12-weeks (χ^2 (n76, df2) = 8.019, p = 0.018).

There were no significant treatment effects on the CFS, or the PSS. Nor were there significant treatment effects at 4-week or 12-week on the change in calmness, alertness, contentedness, fatigue, stress, anxiety or ability to concentrate, induced by the performance of the cognitive battery.

When the analyses were repeated adjusting for participant age, education and cognitive status, the results were unchanged except that there was a non-significant trend (p = 0.083) for participants receiving placebo to have a lower increase in stress following the cognitive battery, at the 4-week assessment only.

3.5. Treatment Effects: Cognitive Function (See also Supplementary Material Tables S4 and S7)

3.5.1. Divided Attention Tracking Task (DATT)

Analysis of task performance at baseline showed a highly significant ($p < 0.001$) effect of the secondary tasks on performance. Recognition accuracy for words presented during the divided attention (tracking) condition was significantly worse than during the focused condition. This demonstrates that the task manipulation had the planned effect with greater attentional load during encoding impairing later recognition.

There was no significant effect of treatment on overall recognition accuracy, recognition of words from either the divided attention or focused condition. For attentional load deficit (i.e., the difference in recognition of words presented in the divided and focused attention conditions), there was a marginal advantage for the curcumin group (F(1,78) = 3.982, p = 0.050) at the 12-week assessment only. This did not survive adjustment for age, education and cognitive status (F(1,72) = 3.640, p = 0.060).

3.5.2. Virtual Morris Water Maze (vMWM)

At the 12-week assessment, there was a significant beneficial effect of treatment during learning probe performance, with participants in the curcumin group spending a higher proportion of time spent in the target quadrant (F(1,71) = 5.408, p = 0.023), suggesting greater learning and awareness of previous platform location (Figure 3c).
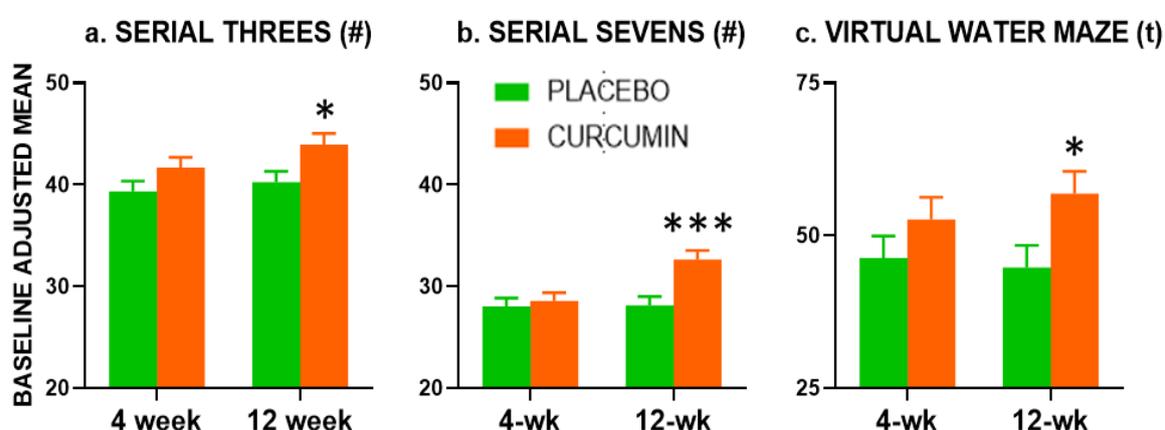

Figure 3. Positive effects of Longvida© on major cognitive outcomes. Graphs depict baseline adjusted means with Standard Error. Outcomes are number (#) correct for (**a**) Serial Threes and (**b**) Serial Sevens and time (t) in the target quadrant during the learning probe for (**c**) the virtual Morris Maze. *, $p < 0.05$; ***, $p < 0.005$.

There was also a significant Trial × Treatment interaction that favoured the curcumin group ($p = 0.019$) at week 12. Further analyses of the block-by-block data revealed that from block 2 to block 3, participants in the placebo group showed an average decrease in performance, while participants in the curcumin group continued to improve. Participants in the curcumin group tended to spend more time in the target quadrant across all blocks. During block three, participants in the curcumin group spent significantly more time in the target quadrant ($p = 0.007$).

There was no significant effect of treatment on time spent in the target quadrant during the memory trial, at either the 4-week or 12-week assessments. These results were unchanged when age, education and cognitive status were included in the analyses.

3.5.3. Serial Subtractions

Serial Subtractions results are presented in Figure 2a,b. At the 4-week assessment of the Serial Threes performance, there was a trend ($p = 0.074$) for participants receiving curcumin to provide a greater number of correct responses than those receiving placebo. This was no longer seen when controlling for age, education and cognitive status ($p = 0.109$). At the 12-week assessment, there was a significant beneficial effect of curcumin on the number of Serial Threes correct responses (F(1,72) = 5.764, $p = 0.019$).

At the 12-week assessment only, there was a significant ($p = 0.001$) beneficial effect of curcumin treatment on the Serial Sevens correct responses which remained significant when adjusting for age, education and cognitive status (F(1,72) = 12.837, $p = 0.001$).

3.5.4. Arrow Flankers Tasks

Analysis of task performance at baseline showed a significant effect of congruence on Arrow Flankers reaction time. Response times in the congruent condition were significantly faster than in the neutral condition, which, in turn, were significantly faster than in the incongruent condition. This demonstrates that task manipulations had the planned effect, with the congruent condition facilitating responses and the incongruent condition causing interference.

At both the 4-week and 12-week assessments, there was no significant effect of treatment on overall reaction time across all conditions, or during the congruent, incongruent or neutral conditions. Nor was there any direct treatment effect on the interference effect of incongruent flankers (incongruent RT–neutral RT), or the faciliatory effect of congruent flankers (neutral RT–congruent RT).

Analysis of accuracy in no-go trials was not possible due to a ceiling effect in performance. A score of 90% or more was obtained by 74% of participants at baseline, 78% at the 4-week and 90.9% at the 12-week assessment. Instead, analysis was performed on the change in accuracy from baseline comparing the two treatment groups, and the two treatment groups were compared on the frequency of the direction of change, i.e., decline in accuracy, no change or improvements (Chi square). No significant effects of treatment were found.

The same Chi square analysis of accuracy across all conditions and within conditions found no significant effect of treatment at the 4-week analysis. There was a trend for a between groups difference of change in incongruent condition accuracy ($p = 0.063$).

At the 12-week analysis, the two groups showed a significantly different pattern of change in the faciliatory effect of congruent flankers, with the curcumin group being more likely to have an increase in faciliatory effect from the baseline to follow-up (χ^2 (2, $n = 73$) = 7.612, $p = 0.022$).

3.6. Biochemical Measures

At the 12-week assessment, only participants in the curcumin arm had significantly higher levels of fasting glucose (mmol/L serum), with F(1,71) = 6.342, $p = 0.014$. The adjusted means for Placebo = 5.328 (Standard Error (SE) = 0.059), and the curcumin group = 5.542 (SE = 0.061).

There was no significant effect of treatment on any other tissue measure, i.e., renal function or electrolytes, liver function, lipid profile, cytokines, estimated sedimentation rate, c-reactive protein, DNA (8-OHdG) or protein (protein carbonyls) oxidative stress.

4. Discussion

As with our previous study [13], curcumin administration resulted in significant improvements to working memory and reductions in fatigue. These results support our hypothesis that the highly bioavailable curcumin preparation Longvida© can improve mood and cognition in older, cognitively intact people.

Our previous 4-week trial found improvements resulting from curcumin administration in Serial Threes performance at the 4-week endpoint [13]. In the study reported here, treatment effects on Serial Threes did not reach significance at 4-weeks ($p = 0.074$, 2-tailed), but were significant at 12-weeks. Similarly, significantly improved Serial Sevens performance emerged at the 12-week assessment only (see Figure 2). There were also benefits to vMWM performance at the 4-week timepoint.

There were no significant treatment effects on the Divided Attention task. Independent of condition, however, we did find the predicted differences in performance with respect to presence/absence of a secondary task during encoding. This suggests that participants were engaging with the task. Further research might usefully examine the effects of titrating cognitive load during multi-tasking to further explore the possibility of curcumin benefitting divided attention tasks.

Regarding the Arrow Flankers task, there were no significant direct effects of curcumin on performance. However, there did appear to be differential treatment effects with respect to congruence. Specifically, those in the curcumin arm appeared more sensitive to the facilitatory effect of congruent flankers. While it is difficult to draw conclusions from this single finding, it may reflect more cognitive resources being allocated to the learning of task strategies, an effect which is consistent with known physiological effects of curcumin.

Turning to mood effects, as in our previous study, curcumin administration led to reductions in fatigue at both 4 and 12-weeks. It should be noted that in this study, the reduction was in the POMS subscale of Fatigue-Inertia rather than the Chalder Fatigue Scale in our previous study [13]. Nevertheless, the results are broadly consistent across the two trials. Fatigue was a primary outcome in this trial (albeit measured using the CFS rather than the POMS). It is worth noting that in the current study, the 65-item POMS preceded the CFS. It may simply be that the first scale encountered is better placed to capture mood effects simply because participants engage more with earlier measures. The reduction in fatigue at both the 4-week and 12-week timepoints and in the (single post treatment) 4-week assessment in our previous study suggests that it is a robust effect of Longvida© curcumin in this population. This is also supported by the possibility of significant improvements in the 'daytime dysfunction' subscale of the PSQI, suggesting that the reductions in fatigue may have ramifications for everyday function. This finding should be explored in more detail, including utilising actigraphy to assess if fatigue reductions were manifesting in greater levels of activity.

Unlike our previous study, there were no effects of treatment on stress reactivity. That is, there were no treatment-related effects on mood changes occurring in response to completing the cognitive battery. The reasons for the slightly different pattern of the results may reflect methodological differences across the two studies. As an example, different mood scales were used. In study one, the Depression Anxiety and Stress Scale (DASS) was utilised [13,42]. In that study, the majority of participants scored zero on all three DASS scales, so here we instead opted to use the POMS. This revealed significant effects on a number of mood items. As well as reduced Fatigue-Inertia at both post-treatment assessments, the curcumin group had significant improvements in Tension-Anxiety, Confusion-Bewilderment and Anger-Hostility, as well as the overall Total Mood Disturbance scale at the 4-week assessment only. This suggests that a more comprehensive mood instrument may have higher utility in this kind of study.

Another methodological difference is that in our previous study [13], as well as at a 4-week assessment, participants were tested acutely 1 and 3 h following their first dose of curcumin.

Acute-on-chronic effects were also evaluated by examining the same 1 and 3 h timepoints following the day-28 dose. Thus, the effects of treatment may have interacted with practice or repetition effects of cognitive testing. Significant benefits at 4-weeks in the previous study coincided with the third period of cognitive testing. Benefits seen here at 12-weeks would also represent the third testing event. This notion is supported to some extent by the modest facilitatory effect of congruent flankers in the curcumin group only, raising the possibility that curcumin facilitates learning. This possibility is also supported by the improvements to learning in the vMWM task. Future studies should also examine inter-individual differences in the bioavailability of curcumin (both the parent compound and its metabolites) and their relationship with changes in mood and cognition.

At the 12-week assessment only, participants in the curcumin arm had significantly higher blood glucose. It should be noted that this effect did not approach the levels to signal diabetes risk. In fact slightly elevated glucose levels are known to facilitate aspects of cognitive function including working memory and specifically Serial Sevens [43]. This suggests that this slight elevation in circulating glucose may contribute to the mechanisms of cognitive enhancement seen in the curcumin group. This possibility requires further exploration. On the other hand, it should be noted that the cholesterol reduction observed in our previous study was not replicated here, so the extent to which fluctuations in biomarkers are robust remains unknown.

The mechanisms by which the extract confers these mood and cognitive benefits are not known. They likely include multiple systemic and central mechanisms which have been ascribed to other nutrients [4], including flavonoids. Interestingly, the effects of other, more widely-researched compounds, e.g., cocoa flavanols, may be restricted to acute effects on mood and cognition [44], with longer term effects on mood alone [45].

While many tasks were not differentially significantly affected by treatment, it is worth noting that the vast majority of outcomes were numerically superior in the curcumin arm at both timepoints.

5. Conclusions

In conclusion, these data further support previous findings that Longvida© curcumin improves working memory and mood as well as the possibility of learning in healthy individuals. It is noteworthy that memory and fatigue are widely reported as the two more concerning non-physiological aspects of ageing [46]. This has potential promise to offset these effects and may also be relevant to conditions where mood and cognition are fragile.

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SUPPLEMENTARY TABLES: notes

- Numbers vary between visits and measures due to missing data or outliers that have been removed.
- For variables highlighted in blue the data for placebo and/or curcumin were skewed. Medians and IQRs for these measures are presented in Table S7.
- Summary statistics for all visits are included, even if only one visit's data were skewed to allow meaningful comparison.

Table S1. Extended Baseline Group Demographics

	Placebo (n = 43)		Curcumin (n = 42)	
	Mean	sd	Mean	sd
Age	68.38	6.712	67.811	6.002
TICS-M	28.093	3.146	27.786	2.901
MMSE	29.349	0.948	29.143	1.095
EduYears	16.558	3.048	16.162	2.879
STAI-T	29.628	7.41	27.571	5.739
BDI	3.791	4.285	2.976	3.368
NART	40.465	4.997	40.476	4.629
Male	48.84%		50.00%	
English primary Language	100.00%		97.62%	
Right handed	90.70%		90.48%	
Previous smoker	48.84%		42.86%	
Education level				
Primary	0.00%		2.38%	
Secondary	13.95%		11.90%	
Tertiary	58.14%		64.29%	
Postgraduate	27.91%		21.43%	
Employment				
Retired	58.14%		57.14%	
Unemployed	2.33%		0.00%	
Part Time/Casual	30.23%		21.43%	
Studying	0.00%		2.38%	
Full Time	9.30%		19.05%	

Table S2. Change in state mood induced by performance of cognitive battery

		Placebo			Curcumin	
	n	Mean	sd	n	Mean	sd
Calmness						
Baseline	43	-6.953	12.587	41	-4.256	12.110
Interim (4 weeks)	41	-6.683	14.854	40	-7.588	14.496
Endpoint (12 weeks)	40	-5.863	12.261	37	-7.230	14.129
Alertness						
Baseline	43	-12.424	8.407	42	-13.130	11.285
Interim (4 weeks)	41	-12.222	11.231	41	-10.089	13.012
Endpoint (12 weeks)	40	-11.133	11.052	37	-9.937	10.006
Contentedness						
Baseline	43	-6.674	10.563	42	-5.529	9.270
Interim (4 weeks)	41	-5.473	11.082	41	-6.195	14.132
Endpoint (12 weeks)	40	-5.830	9.691	38	-2.921	10.612
Stress						
Baseline	43	28.465	33.452	42	32.952	34.233
Interim (4 weeks)	41	30.707	30.112	41	40.073	30.828
Endpoint (12 weeks)	40	36.700	27.535	38	36.158	30.603
Anxiety						
Baseline	43	8.907	16.064	42	5.714	20.977
Interim (4 weeks)	41	4.390	15.328	41	7.000	18.473
Endpoint (12 weeks)	39	6.897	14.549	38	3.868	17.802
Fatigue						
Baseline	43	10.744	15.189	41	15.829	17.832
Interim (4 weeks)	41	9.024	20.597	41	3.268	19.320
Endpoint (12 weeks)	40	5.650	18.777	38	3.000	24.787
Ability to concentrate						
Baseline	43	-34.488	29.427	42	-45.571	28.910
Interim (4 weeks)	41	-30.683	32.545	41	-38.951	32.778
Endpoint (12 weeks)	40	-40.300	29.480	38	-39.684	28.887

Table S3. Chronic mood and wellbeing questionnaire scores

			Placebo			Curcumin	
		n	Mean	sd	n	Mean	sd
CHALDER FATIGUE SCALE							
Total Fatigue							
	Baseline	42	14.262	3.575	42	14.595	2.846
	Interim (4 weeks)	41	14.317	3.350	41	14.122	3.763
	Endpoint (12 weeks)	39	15.256	4.140	39	14.308	4.420
Physical Fatigue							
	Baseline	42	8.214	2.203	42	8.476	2.051
	Interim (4 weeks)	41	8.341	2.287	41	8.122	2.451
	Endpoint (12 weeks)	39	8.974	2.870	39	8.359	2.861
Mental Fatigue							
	Baseline	42	6.048	1.780	42	6.119	1.087
	Interim (4 weeks)	41	5.976	1.508	41	6.000	1.517
	Endpoint (12 weeks)	39	6.282	1.806	39	5.949	1.835
PROFILE OF MOOD STATES (POMS)							
Total Mood Disturbance (TMD)							
	Baseline	43	4.395	19.786	41	2.146	19.351
	Interim (4 weeks)	40	7.725	19.049	41	-0.659	18.578
	Endpoint (12 weeks)	39	4.077	14.414	39	-0.538	14.807
Tension-Anxiety							
	Baseline	43	5.442	3.354	41	4.902	3.338
	Interim (4 weeks)	40	5.575	3.587	41	4.122	3.219
	Endpoint (12 weeks)	39	4.513	2.553	39	4.051	2.733
Depression-Dejection							
	Baseline	43	3.256	4.271	41	3.098	5.142
	Interim (4 weeks)	40	3.950	3.883	41	2.976	3.725
	Endpoint (12 weeks)	39	2.692	2.939	39	2.564	3.455
Anger-Hostility							
	Baseline	43	3.884	4.119	41	3.220	3.029
	Interim (4 weeks)	41	4.585	4.582	41	2.659	3.832
	Endpoint (12 weeks)	39	2.564	2.808	39	2.051	2.575
Confusion-Bewilderment							
	Baseline	43	5.093	3.753	42	4.833	3.378
	Interim (4 weeks)	41	5.415	3.808	41	4.049	2.792
	Endpoint (12 weeks)	39	5.000	3.253	39	4.051	2.762
Fatigue-Inertia							
	Baseline	43	5.535	5.404	42	5.667	3.874
	Interim (4 weeks)	41	6.585	5.277	41	4.610	4.030

Endpoint (12 weeks)	39	7.026	4.374	39	5.000	3.811

Vigor-Activity

Baseline	43	18.814	4.742	42	19.167	6.378
Interim (4 weeks)	41	17.610	4.852	41	19.073	5.561
Endpoint (12 weeks)	39	17.718	4.039	39	18.256	4.935

PERCEIVED STRESS SCALE (PSS)

Baseline	42	10.857	4.657	42	11.310	5.106
Interim (4 weeks)	41	11.268	5.613	41	11.634	5.634
Endpoint (12 weeks)	39	10.231	4.445	39	11.718	5.341

GENERAL HEALTH QUESTIONNAIRE (GHQ-28)
Total

Baseline	43	15.419	5.687	42	16.048	7.054
Interim (4 weeks)	41	15.732	6.637	41	15.146	8.104
Endpoint (12 weeks)	39	15.436	5.661	39	15.872	10.222

Somatic Symptoms

Baseline	43	4.186	2.822	42	4.214	3.041
Interim (4 weeks)	41	4.220	3.103	41	4.463	3.302
Endpoint (12 weeks)	39	4.769	3.391	39	4.615	3.603

Anxiety-Insomnia

Baseline	43	3.907	2.724	42	4.167	2.775
Interim (4 weeks)	41	4.537	3.279	41	3.366	2.809
Endpoint (12 weeks)	39	3.410	2.161	39	3.667	3.223

Social Dysfunction

Baseline	43	6.837	1.526	42	7.048	1.937
Interim (4 weeks)	41	6.659	1.811	41	6.561	1.845
Endpoint (12 weeks)	39	6.872	1.542	39	6.615	2.347

Depression

Baseline	43	0.488	0.736	42	0.619	1.324
Interim (4 weeks)	41	0.317	0.850	40	0.475	1.062
Endpoint (12 weeks)	39	0.385	0.907	39	0.974	2.758

PITTSBURGH SLEEP QUALITY INDEX (PSQI)
Global Score

Baseline	41	6.146	3.403	40	5.350	2.694
Interim (4 weeks)	40	6.025	3.230	41	5.073	2.659
Endpoint (12 weeks)	39	6.179	2.981	39	5.667	2.629

Subjective Sleep Quality

Baseline	43	0.907	0.570	41	0.829	0.667
Interim (4 weeks)	40	0.900	0.632	41	0.780	0.652
Endpoint (12 weeks)	39	0.821	0.644	39	0.897	0.641

Sleep Latency

Baseline	43	1.000	0.976	41	0.683	0.722
Interim (4 weeks)	41	0.951	0.865	41	0.537	0.674
Endpoint (12 weeks)	39	0.923	0.870	39	0.795	0.732

Sleep Duration

Baseline	43	0.395	0.695	41	0.293	0.559
Interim (4 weeks)	41	0.366	0.623	41	0.293	0.559
Endpoint (12 weeks)	39	0.385	0.590	39	0.282	0.510

Sleep Efficacy

Baseline	43	1.256	1.311	42	0.881	1.173
Interim (4 weeks)	41	1.220	1.314	41	0.902	1.020
Endpoint (12 weeks)	39	1.179	1.144	39	0.974	1.135

Sleep Disturbance

Baseline	43	1.326	0.474	41	1.293	0.461
Interim (4 weeks)	41	1.268	0.549	41	1.317	0.471
Endpoint (12 weeks)	39	1.308	0.468	39	1.385	0.544

Use of Medication

Baseline	43	0.256	0.759	41	0.146	0.478
Interim (4 weeks)	41	0.195	0.641	41	0.098	0.374
Endpoint (12 weeks)	39	0.282	0.759	39	0.154	0.432

Daytime Dysfunction

Baseline	41	1.122	0.331	40	1.175	0.446
Interim (4 weeks)	41	1.268	0.549	41	1.146	0.422
Endpoint (12 weeks)	39	1.282	0.456	39	1.179	0.389

Table S4. Cognitive Battery Results

		Placebo			Curcumin	
	n	Mean	sd	n	Mean	sd
VIRTUAL MORRIS WATER MAZE						
Time in Target Quadrant During Learning Trials						
Baseline						
Block 1	42	44.475	15.733	42	43.722	15.460
Block 2	42	49.435	19.605	42	55.885	19.691
Block 3	42	51.651	15.735	42	55.004	19.210
Block 4	42	48.656	17.155	42	56.584	18.118
Interim (4 weeks)						
Block 1	41	43.604	13.021	41	46.324	12.896
Block 2	41	53.337	19.015	41	53.029	16.879
Block 3	41	44.486	18.593	41	55.356	16.880
Block 4	41	47.586	18.699	41	54.106	17.504
Endpoint (12 weeks)						
Block 1	40	46.959	14.555	38	52.081	13.891
Block 2	40	55.237	20.294	38	61.771	19.055
Block 3	40	51.509	16.196	38	58.304	18.443
Block 4	40	52.619	17.184	38	56.807	17.523
Time in Target Quadrant During Immediate Learning Probe						
Baseline	42	45.702	29.317	42	43.728	26.017
Interim (4 weeks)	41	47.367	24.587	41	51.662	27.418
Endpoint (12 weeks)	40	44.323	27.018	38	57.222	22.374
Time in Target Quadrant During Delayed Memory Probe						
Baseline	42	52.029	25.220	42	48.841	26.880
Interim (4 weeks)	41	43.660	23.441	41	50.246	26.723
Endpoint (12 weeks)	40	46.643	28.287	38	54.062	24.064
DIVIDED ATTENTION TASK						
Overall Recognition Accuracy						
Baseline	43	69.126	8.741	42	68.148	7.853
Interim (4 weeks)	41	71.032	7.687	41	69.902	7.625
Endpoint (12 weeks)	40	70.870	8.723	38	70.747	7.899
Focused Attention Encoding Recognition Accuracy						
Baseline	43	63.372	17.584	42	59.762	17.142
Interim (4 weeks)	41	69.146	16.121	41	63.537	19.819
Endpoint (12 weeks)	40	69.875	17.227	38	61.842	18.651

	N	Mean	SD	N	Mean	SD
Divided Attention Encoding Recognition Accuracy						
Baseline	43	57.907	19.525	42	52.381	16.463
Interim (4 weeks)	41	56.341	17.784	41	53.537	17.827
Endpoint (12 weeks)	40	53.500	18.852	38	55.000	18.744
Divided Attention Accuracy Deficit[1]						
Baseline	43	-5.465	14.426	42	-7.381	17.188
Interim (4 weeks)	41	-12.805	16.585	41	-10.000	22.333
Endpoint (12 weeks)	40	-16.375	21.779	38	-6.842	19.879
Overall Correct Response Time						
Baseline	43	1562.000	267.757	42	1537.976	201.178
Interim (4 weeks)	41	1557.488	254.225	41	1508.683	208.614
Endpoint (12 weeks)	40	1543.850	223.727	38	1527.105	205.992
Focused Attention Encoding Recognition Response Time						
Baseline	43	1522.070	251.766	42	1502.357	194.459
Interim (4 weeks)	41	1518.171	240.522	41	1462.024	179.152
Endpoint (12 weeks)	40	1481.275	203.691	38	1492.500	188.378
Divided Attention Encoding Recognition Response Time						
Baseline	43	1563.070	263.827	42	1585.143	248.372
Interim (4 weeks)	41	1562.829	247.423	40	1529.425	224.407
Endpoint (12 weeks)	40	1582.900	275.147	38	1550.026	221.567
Divided Attention Response Time Deficit[2]						
Baseline	43	41.000	140.582	42	82.786	154.637
Interim (4 weeks)	41	44.659	137.976	39	44.231	111.542
Endpoint (12 weeks)	40	101.625	196.371	38	57.526	132.567
SERIAL SUBTRACTION TASK **Serial 3 Subtraction, Number of Correct Responses**						
Baseline	43	39.837	15.816	42	39.381	13.949
Interim (4 weeks)	41	39.439	17.762	41	41.585	13.733
Endpoint (12 weeks)	40	40.175	14.672	38	44.026	12.536
Serial 7 Subtraction, Number of Correct Responses						
Baseline	43	27.581	12.743	42	27.738	12.688
Interim (4 weeks)	41	28.000	13.524	41	28.610	11.526
Endpoint (12 weeks)	40	27.850	13.235	38	32.947	11.905

ARROW FLANKERS TASK

Overall Accuracy

Baseline	43	95.659	7.031	42	96.567	4.638
Interim (4 weeks)	41	97.358	4.039	41	97.216	3.889
Endpoint (12 weeks)	40	97.625	3.239	38	96.009	6.261

Congruent Flankers Condition Accuracy

Baseline	43	98.061	2.813	42	97.420	4.483
Interim (4 weeks)	41	97.967	3.929	41	97.967	3.780
Endpoint (12 weeks)	40	97.846	3.299	38	98.318	3.265

Incongruent Flankers Condition Accuracy

Baseline	43	97.802	3.005	41	97.222	4.521
Interim (4 weeks)	41	97.221	5.625	41	97.425	4.230
Endpoint (12 weeks)	40	97.083	5.832	38	96.125	7.765

Neutral Flankers Condition Accuracy

Baseline	41	98.103	3.133	42	98.214	4.107
Interim (4 weeks)	41	97.899	4.015	41	97.696	4.344
Endpoint (12 weeks)	40	98.263	3.062	37	97.597	4.950

No-Go Flankers Condition Accuracy

Baseline	41	92.480	9.092	42	90.874	8.192
Interim (4 weeks)	41	94.309	9.938	41	92.887	8.653
Endpoint (12 weeks)	40	96.668	6.201	37	93.470	6.253

Accuracy During Congruent vs Neutral Conditions (Faciliatory Effect)[3]

Baseline	41	0.000	2.635	42	-0.794	2.899
Interim (4 weeks)	41	0.068	3.010	41	0.271	2.835
Endpoint (12 weeks)	40	-0.417	3.302	37	0.675	4.213

Accuracy During Incongruent vs Neutral Conditions (Interference Effect)[4]

Baseline	41	-0.204	2.873	41	-0.948	3.547
Interim (4 weeks)	41	-0.678	4.016	41	-0.271	2.548
Endpoint (12 weeks)	40	-1.181	6.029	37	-1.577	5.302

Overall Response Time of Correct Responses

Baseline	43	594.233	62.865	42	595.833	64.905
Interim (4 weeks)	41	596.951	73.289	41	588.390	63.457
Endpoint (12 weeks)	40	595.450	71.745	38	588.184	59.200

	N	Mean	SD	N	Mean	SD
Correct Response Time During Congruent Condition						
Baseline	43	577.814	57.814	42	582.905	65.292
Interim (4 weeks)	41	582.463	70.483	41	574.390	58.579
Endpoint (12 weeks)	40	577.900	71.310	38	573.395	58.983
Correct Response Time During Incongruent Condition						
Baseline	43	618.186	70.968	42	616.524	68.163
Interim (4 weeks)	41	614.902	74.301	41	607.976	67.364
Endpoint (12 weeks)	40	620.675	76.732	38	608.895	63.980
Correct Response Time During Neutral Condition						
Baseline	41	582.390	63.828	42	588.786	66.729
Interim (4 weeks)	41	593.561	79.450	41	582.902	68.403
Endpoint (12 weeks)	40	588.550	72.482	37	582.108	61.168
Correct Response Time During Congruent vs Neutral Conditions (Faciliatory Effect)[5]						
Baseline	41	-6.878	21.742	42	-5.881	23.175
Interim (4 weeks)	41	-11.098	25.314	41	-8.512	24.764
Endpoint (12 weeks)	40	-10.650	22.258	37	-9.459	20.382
Correct Response Time During Incongruent vs Neutral Conditions (Interference Effect)[6]						
Baseline	41	29.805	29.748	42	27.738	28.084
Interim (4 weeks)	41	21.341	23.899	41	25.073	23.756
Endpoint (12 weeks)	40	32.125	27.863	37	25.459	28.758

[1] Calculated as recognition accuracy for divided attention words - recognition accuracy for focused attention words. Negative scores indicate poorer accuracy due to divided attention.

[2] Calculated as response time for focused attention words - response time for divided attention words. Positive scores indicate slower response due to divided attention.

[3] Calculated as accuracy during congruent trials - accuracy during neutral trials. Positive scores indicate better accuracy in the presence of congruent flankers.

[4] Calculated as accuracy during incongruent trials - accuracy during neutral trials. Negative scores indicate poorer accuracy in the presence of incongruent flankers.

[5] Calculated as correct response time during congruent trials - correct response time during neutral trials. Negative scores indicate faster responses in the presence of congruent flankers.

[6] Calculated as correct response time during incongruent trials - correct response time during neutral trials. Positive scores indicate slower responses in the presence of incongruent flankers.

Table S5. NASA Task Load Index – Subjective Appraisal of Cognitive Battery

		Placebo			Curcumin		Placebo	
	n	Mean	sd		n	Mean	Mean	sd
Mental Demand								
Baseline	43	68.093	17.490	41	72.244		2.400	15.368
Interim (4 weeks)	41	70.171	15.043	40	72.425		1.803	11.406
Endpoint (12 weeks)	40	68.525	15.828	38	68.316		2.519	15.530
Temporal Demand								
Baseline	43	59.000	16.248	42	55.667		2.613	16.937
Interim (4 weeks)	41	57.439	18.231	41	56.293		3.189	20.422
Endpoint (12 weeks)	40	56.850	20.322	38	55.026		3.157	19.460
Physical Demand								
Baseline	43	28.000	18.431	42	26.095		2.824	18.301
Interim (4 weeks)	41	28.390	23.484	41	29.683		3.262	20.887
Endpoint (12 weeks)	40	28.000	21.775	38	27.842		3.145	19.384
Own Performance								
Baseline	43	44.698	23.403	42	43.262		3.158	20.463
Interim (4 weeks)	41	44.317	22.366	41	36.049		2.844	18.210
Endpoint (12 weeks)	40	44.475	21.770	38	36.526		3.010	18.557
Effort								
Baseline	43	67.628	14.844	42	69.381		2.563	16.613
Interim (4 weeks)	41	70.171	12.667	41	66.439		2.637	16.882
Endpoint (12 weeks)	39	66.513	16.065	38	64.342		2.782	17.152
Frustration								
Baseline	43	44.488	23.719	42	42.143		3.455	22.394
Interim (4 weeks)	41	52.293	23.579	41	42.805		3.586	22.964
Endpoint (12 weeks)	40	44.825	23.132	38	37.474		3.616	22.291

Table S6. Physiological measures

			Placebo			Curcumin	
		n	Mean	sd	n	Mean	sd
Renal and Liver Function							
Sodium (mmol/L)	Baseline	43	141.860	2.178	42	141.381	1.987
	Endpoint (12 weeks)	39	141.436	1.759	37	141.514	1.909
Potassium (mmol/L)	Baseline	43	4.530	0.290	42	4.483	0.348
	Endpoint (12 weeks)	39	4.415	0.300	37	4.478	0.350
Chloride (mmol/L)	Baseline	43	106.279	1.919	42	106.000	1.767
	Endpoint (12 weeks)	39	105.923	1.612	37	106.081	1.963
Bicarbonate (mmol/L)	Baseline	43	30.721	1.968	42	30.524	2.144
	Endpoint (12 weeks)	39	30.231	2.311	37	30.189	1.956
Urea (mmol/L)	Baseline	43	6.247	2.020	42	5.867	1.656
	Endpoint (12 weeks)	39	5.882	1.459	37	5.757	1.272
Creatinine (µmol/L)	Baseline	43	79.256	13.206	42	77.524	16.959
	Endpoint (12 weeks)	39	78.308	11.855	37	80.730	15.064
UricAcid (mmol/L)	Baseline	43	0.339	0.087	42	0.321	0.104
	Endpoint (12 weeks)	39	0.334	0.089	37	0.321	0.095
Calcium (mmol/L)	Baseline	43	2.352	0.076	42	2.309	0.094
	Endpoint (12 weeks)	39	2.327	0.067	37	2.331	0.088
djusted Calcium (mmol/L)	Baseline	43	2.375	0.078	42	2.335	0.092
	Endpoint (12 weeks)	39	2.348	0.055	37	2.348	0.083
Phosphate (mmol/L)	Baseline	43	1.092	0.156	42	1.128	0.126
	Endpoint (12 weeks)	39	1.122	0.151	37	1.139	0.154
T.Protein (g/L)	Baseline	43	69.163	3.970	42	69.119	4.702
	Endpoint (12 weeks)	39	68.436	3.662	37	68.568	4.381
Albumin (g/L)	Baseline	43	38.605	1.978	42	38.429	2.154
	Endpoint (12 weeks)	39	38.846	1.981	37	39.108	1.792
ALP (U/L)	Baseline	43	72.186	16.796	42	70.119	18.075
	Endpoint (12 weeks)	39	70.590	16.671	37	65.108	16.017
Bilirubin (µmol/L)	Baseline	43	10.907	3.822	42	12.429	5.438
	Endpoint (12 weeks)	39	10.769	3.383	37	12.405	5.241
GGT (U/L)	Baseline	41	23.268	15.022	42	21.476	10.703
	Endpoint (12 weeks)	37	23.892	16.571	37	19.973	12.036
AST (U/L)	Baseline	43	20.977	5.054	42	20.929	3.023
	Endpoint (12 weeks)	38	20.921	4.327	36	21.917	4.519
ALT (U/L)	Baseline	41	20.220	7.904	42	18.071	6.256
	Endpoint (12 weeks)	37	20.568	8.792	36	20.278	8.879
Glucose (mmol/L)	Baseline	42	5.507	0.778	42	5.400	0.868
	Endpoint (12 weeks)	39	5.490	1.249	37	5.584	1.156
Lipids							
Triglycerides (mmol/L)	Baseline	42	1.257	0.612	42	1.157	0.629
	Endpoint (12 weeks)	38	1.216	0.687	37	1.170	0.620
Total_Chol (mmol/L)	Baseline	43	5.216	1.064	42	5.095	1.297
	Endpoint (12 weeks)	39	5.226	0.959	37	5.038	1.207
HDL_Chol (mmol/L)	Baseline	43	1.584	0.428	42	1.731	0.578
	Endpoint (12 weeks)	38	1.605	0.400	37	1.657	0.540

LDL_Chol (mmol/L)	Baseline	43	3.070	0.939	42	2.879	0.926
	Endpoint (12 weeks)	38	3.050	0.879	37	2.884	0.870
NonHDL_Chol (mmol/L)	Baseline	43	3.656	0.926	42	3.383	1.008
	Endpoint (12 weeks)	38	3.632	0.872	37	3.405	1.019
LDLHDL_Ratio	Baseline	43	2.084	0.678	41	1.766	0.592
	Endpoint (12 weeks)	38	2.037	0.692	36	1.844	0.627
CholHDL_Ratio	Baseline	43	3.477	0.783	41	3.085	0.763
	Endpoint (12 weeks)	38	3.434	0.796	36	3.186	0.817
Inflammation							
hsCRP (mg/L)	Baseline	42	2.126	2.774	37	2.573	3.331
	Endpoint (12 weeks)	39	2.438	3.634	35	2.014	2.586
ESR (mm/h)	Baseline	43	7.814	5.779	42	8.405	7.487
	Endpoint (12 weeks)	39	7.462	5.190	37	7.324	7.196
IL6 (pg/ml)	Baseline	43	1.765	0.710	40	1.696	0.565
	Endpoint (12 weeks)	39	1.806	0.760	36	1.602	0.484
IL1B (pg/ml)	Baseline	43	0.560	0.251	40	0.533	0.234
	Endpoint (12 weeks)	39	0.536	0.228	35	0.516	0.190
TNFa (pg/ml)	Baseline	43	1.615	0.396	41	1.600	0.464
	Endpoint (12 weeks)	39	1.513	0.240	37	1.525	0.296
Oxidative Stress							
8OHdG(ng/mL)	Baseline	43	5.181	1.533	41	4.923	1.641
	Endpoint (12 weeks)	39	5.022	1.251	37	4.891	1.337
teinCarbonyls (nmol/mg)	Baseline	43	4.769	1.614	41	5.180	1.788
	Endpoint (12 weeks)	39	4.675	1.537	36	5.165	1.725
Neuronal Function							
BDNF (pg/ml)	Baseline	43	24275.174	7721.800	41	23587.705	6435.074
	Endpoint (12 weeks)	39	23846.659	5250.689	36	22789.782	5630.611
AB40 (pg/ml)	Baseline	43	180.652	85.298	38	156.301	48.586
	Endpoint (12 weeks)	39	177.109	69.749	33	161.655	47.180
AB42 (pg/ml)	Baseline	13	90.295	44.638	11	166.106	157.325
	Endpoint (12 weeks)	12	86.528	31.517	10	171.518	139.650

Table S7. Medians and interquartile ranges

	Placebo			Curcumin		
	Median	25th	75th	Median	25th	75th
STAI-T	29	24	34	27	22	31.25
BDI	3	1	5	2	0	6

	Placebo			Curcumin		
	Median	25th	75th	Median	25th	75th
CHG_ANXIOUS_V1	5	-2	19	4	-2.5	18
CHG_ANXIOUS_V2	4	-2.5	9.5	1	-3	11.5
CHG_ANXIOUS_V3	4	-3	12	2	-3	13.25
CHG_CONCENTRATION_V1	-40	-59	-7	-48.5	-69	-31
CHG_CONCENTRATION_V2	-29	-61	-0.5	-41	-65.5	-14
CHG_CONCENTRATION_V3	-47	-63.5	-11.75	-45.5	-57.5	-17.5
CHG_FATIGUE_V1	9	0	22	14	2	29.5
CHG_FATIGUE_V2	2	-4	21.5	2	-5.5	11.5
CHG_FATIGUE_V3	5	-5.5	14	3	-5	13.25

	Placebo			Curcumin		
	Median	25th	75th	Median	25th	75th
GHQ_SomaticSymptoms_V1	3	2	7	3	2	7
GHQ_SomaticSymptoms_V2	3	2	6.5	4	2	5.5
GHQ_SomaticSymptoms_V3	4	2	7	3	2	7
GHQ_AnxietyInsomnia_V1	4	2	6	4	2	7
GHQ_AnxietyInsomnia_V2	4	3	7	3	1	5
GHQ_AnxietyInsomnia_V3	3	2	5	3	1	6
GHQ_SocialDysfunction_V1	7	6	8	7	6	7
GHQ_SocialDysfunction_V2	7	6	7	7	6	7
GHQ_SocialDysfunction_V3	7	6	7	7	6	7
GHQ_Depression_V1	0	0	1	0	0	1
GHQ_Depression_V2	0	0	0	0	0	0
GHQ_Depression_V3	0	0	0	0	0	0
GHQ_Total_V1	14	11	19	14.5	10	20.25
GHQ_Total_V2	13	11	19	14	9.5	18.5
GHQ_Total_V3	14	12	18	12	10	19
CFS14_Total_V1	14	13	15	14	14	16
CFS14_Total_V2	14	13	16	14	13	14.5
CFS14_Total_V3	14	14	18	14	14	15
CFS14_PhysicalFatigue_V1	8	7	8.25	8	8	9.25
CFS14_PhysicalFatigue_V2	8	7.5	9	8	8	8
CFS14_PhysicalFatigue_V3	8	8	10	8	8	8
CFS14_MentalFatigue_V1	6	5.75	6	6	6	6
CFS14_MentalFatigue_V2	6	6	6.5	6	5.5	6
CFS14_MentalFatigue_V3	6	6	7	6	6	6
POMS_TMD_V1	2	-11	17	3	-11.5	10.5
POMS_TMD_V2	3.5	-6.75	20.75	-1	-16.5	10.5

POMS_TMD_V3	6	-12	15	-2	-10	6
POMS_AngerHostility_V1	3	0	6	2	1	5
POMS_AngerHostility_V2	3	1	6.5	2	0	4
POMS_AngerHostility_V3	2	0	4	1	0	4
POMS_ConfusionBewilderment_V1	4	2	8	4	3	6
POMS_ConfusionBewilderment_V2	5	2	7	3	2	5
POMS_ConfusionBewilderment_V3	5	2	7	3	2	6
POMS_DepressionDejection_V1	1	0	5	2	0	3.5
POMS_DepressionDejection_V2	3	1	6.75	2	0	5
POMS_DepressionDejection_V3	2	0	3	2	0	3
POMS_FatigueInertia_V1	5	2	6	5.5	2	8
POMS_FatigueInertia_V2	5	3	10.5	4	0.5	7
POMS_FatigueInertia_V3	6	4	11	5	2	7
POMS_TensionAnxiety_V1	5	3	8	5	2	7
POMS_TensionAnxiety_V2	5	3	8	3	1.5	6
POMS_TensionAnxiety_V3	4	3	7	4	1	6
PSS_V1	10.5	8	14.25	11	8	15
PSS_V2	11	6.5	15	11	7.5	15
PSS_V3	10	7	14	11	8	14
PSQI_C1_Subjective_Quality_V1	1	1	1	1	0	1
PSQI_C1_Subjective_Quality_V2	1	0.25	1	1	0	1
PSQI_C1_Subjective_Quality_V3	1	0	1	1	1	1
PSQI_C2_SleepLatency_V1	1	0	1	1	0	1
PSQI_C2_SleepLatency_V2	1	0	1	0	0	1
PSQI_C2_SleepLatency_V3	1	0	1	1	0	1
PSQI_C3_Sleep_Duration_V1	0	0	1	0	0	0.5
PSQI_C3_Sleep_Duration_V2	0	0	1	0	0	0.5
PSQI_C3_Sleep_Duration_V3	0	0	1	0	0	1
PSQI_C4_Sleep_Efficacy_V1	1	0	3	0	0	2
PSQI_C4_Sleep_Efficacy_V2	1	0	3	1	0	1
PSQI_C4_Sleep_Efficacy_V3	1	0	2	1	0	2
PSQI_C5_Sleep_disturbances_V1	1	1	2	1	1	2
PSQI_C5_Sleep_disturbances_V2	1	1	2	1	1	2
PSQI_C5_Sleep_disturbances_V3	1	1	2	1	1	2
PSQI_C6_Use_of_Medication_V1	0	0	0	0	0	0
PSQI_C6_Use_of_Medication_V2	0	0	0	0	0	0
PSQI_C6_Use_of_Medication_V3	0	0	0	0	0	0
PSQI_C7_Day_Dysfunction_V1	1	1	1	1	1	1
PSQI_C7_Day_Dysfunction_V2	1	1	1	1	1	1
PSQI_C7_Day_Dysfunction_V3	1	1	2	1	1	1
PSQI_Global_Score_V1	5	3	7.5	5	3	7
PSQI_Global_Score_V2	5.5	4	7	4	3	7.5
PSQI_Global_Score_V3	5	4	7	6	3	7

	Placebo			Curcumin		
	Median	25th	75th	Median	25th	75th
DATT_TotalRT_V1	1529	1385	1671	1476.5	1395	1667.75
DATT_TotalRT_V2	1536	1371.5	1695.5	1453	1381.5	1615.5

	Median	25th	75th	Median	25th	75th
DATT_TotalRT_V3	1525.5	1375	1675.25	1507	1375.5	1601.25
DATT_FocusedRT_V1	1486	1309	1635	1491	1367.75	1598.75
DATT_FocusedRT_V2	1504	1331	1652.5	1424	1345.5	1553.5
DATT_FocusedRT_V3	1472.5	1359.5	1588	1495.5	1380.25	1613.25
DATT_DividedRT_V1	1514	1390	1688	1521	1375.75	1766.25
DATT_DividedRT_V2	1544	1375.5	1678	1457.5	1386	1638.75
DATT_DividedRT_V3	1548.5	1410.25	1718.5	1536.5	1396.75	1643.25
DATT DivRT-FocRT V1	26	-47	98	53	5.75	156.5
DATT DivRT-FocRT V2	54	-58	160.5	42	-47	127
DATT DivRT-FocRT V3	70.5	-11.5	168.75	50	-27.25	128.25

	Placebo			Curcumin		
	Median	25th	75th	Median	25th	75th
AF_ACC_Con_vs_Neu_V1	0	0	0	0	-2.78	0
AF_ACC_Con_vs_Neu_V2	0	0	0	0	-2.78	2.78
AF_ACC_Con_vs_Neu_V3	0	-2.09	0	0	0	2.78
AF_Con_RT_V1	587	533	625	574.5	546.5	618.5
AF_Con_RT_V2	571	534.5	641	575	535	618.5
AF_Con_RT_V3	567	524	642	555.5	539.5	601.75
NASA_PhysicalDemand_V1	25	12	39	22.5	12	39.25
NASA_PhysicalDemand_V2	21	9.5	52.5	22	14	45
NASA_PhysicalDemand_V3	22	10.25	40.5	23.5	13.5	36.25

	Placebo			Curcumin		
	Median	25th	75th	Median	25th	75th
Urea_V1	5.80	5.00	6.80	5.60	4.58	6.93
Urea_V3	5.90	4.70	6.70	5.90	5.10	6.80
UricAcid_V1	0.34	0.28	0.37	0.31	0.24	0.37
UricAcid_V3	0.33	0.27	0.39	0.32	0.23	0.38
Calcium_V1	2.33	2.31	2.38	2.31	2.25	2.35
Calcium_V3	2.31	2.28	2.38	2.32	2.27	2.39
Adj._Ca._V1	2.35	2.33	2.41	2.33	2.28	2.40
Adj._Ca._V3	2.34	2.31	2.38	2.34	2.29	2.38
Albumin_V1	38.00	37.00	40.00	38.00	37.00	40.00
Albumin_V3	39.00	37.00	41.00	39.00	38.00	40.00
ALP_V1	70.00	61.00	82.00	66.00	56.75	83.00
ALP_V3	70.00	59.00	77.00	65.00	54.50	75.50
Bilirubin_V1	11.00	8.00	12.00	10.50	8.00	16.25
Bilirubin_V3	10.00	8.00	12.00	11.00	8.00	15.00
GGT_V1	19.00	14.00	27.50	20.00	13.00	27.75
GGT_V3	18.00	14.00	30.00	18.00	11.00	24.00
AST_V1	20.00	18.00	23.00	20.50	19.00	23.00
AST_V3	20.00	17.75	23.00	23.00	19.00	24.75
ALT_V1	17.00	14.00	24.50	16.00	14.00	20.50
ALT_V3	18.00	14.00	26.00	18.00	14.25	24.00
Glucose_V1	5.30	5.10	5.73	5.20	4.90	5.70
Glucose_V3	5.10	4.80	5.60	5.30	4.90	5.85

Triglyceride_V1	1.10	0.80	1.63	0.90	0.70	1.50
Triglyceride_V3	1.05	0.70	1.63	1.00	0.70	1.45
Total_Chol_V1	4.90	4.40	6.10	5.25	4.13	6.10
Total_Chol_V3	5.10	4.50	5.80	5.30	4.15	6.05
NonHDL_Chol_V1	3.60	3.00	4.40	3.30	2.58	4.10
NonHDL_Chol_V3	3.50	3.10	3.95	3.20	2.60	4.25
LDLHDL_Ratio_V1	2.00	1.60	2.70	1.70	1.30	2.00
LDLHDL_Ratio_V3	2.00	1.48	2.43	1.80	1.30	2.18
CholHDL_Ratio_V1	3.50	2.90	4.00	3.00	2.50	3.40
CholHDL_Ratio_V3	3.40	2.80	4.00	3.05	2.43	3.68
hsCRP_V1	0.75	0.38	2.98	0.70	0.30	3.50
hsCRP_V3	0.80	0.30	2.30	0.70	0.30	3.20
ESR_V1	7.00	5.00	11.00	5.00	5.00	9.75
ESR_V3	5.00	5.00	12.00	5.00	2.00	8.00
IL6_V1	1.58	1.22	2.22	1.53	1.34	1.90
IL6_V3	1.56	1.31	2.22	1.45	1.25	1.82
IL1B_V1	0.46	0.41	0.70	0.49	0.36	0.61
IL1B_V3	0.46	0.42	0.61	0.49	0.38	0.61
TNFa_V1	1.57	1.36	1.73	1.51	1.37	1.69
TNFa_V3	1.48	1.38	1.56	1.48	1.30	1.61
8OHdG_V1	5.06	3.85	6.21	4.52	3.77	5.86
8OHdG_V3	4.80	4.04	5.84	4.45	3.90	5.81
BDNF_V1	23792.90	19040.91	28389.71	21520.88	18912.77	28580.81
BDNF_V3	22506.03	20368.97	27036.68	21745.27	18642.58	27349.64
AB40_V1	155.18	128.63	191.39	145.77	119.15	177.66
AB40_V3	153.03	141.68	198.84	157.61	128.46	185.14
AB42 V1	79.08	62.40	93.46	87.47	76.28	267.84
AB42 V3	75.58	61.74	108.05	91.59	78.72	266.54