ELSEVIER

Physiology & Behavior 83 (2005) 699–709

PHYSIOLOGY & BEHAVIOR

Positive modulation of mood and cognitive performance following administration of acute doses of *Salvia lavandulaefolia* essential oil to healthy young volunteers

N.T.J. Tildesley[a], D.O. Kennedy[a], E.K. Perry[b], C.G. Ballard[c], K.A. Wesnes[a,d], A.B. Scholey[a,*]

[a]*Human Cognitive Neuroscience Unit, Division of Psychology, Northumbria University, Newcastle upon Tyne, NE1 8ST UK*
[b]*Medical Research Council, Newcastle General Hospital, Newcastle upon Tyne, NE4 6BE UK*
[c]*Wolfson Research Centre, Institute for Ageing and Health, Newcastle General Hospital, Newcastle upon Tyne, NE4 6BE UK*
[d]*Cognitive Drug Research Ltd, Goring-on-Thames, RG8 0EN UK*

Received 5 February 2004; received in revised form 9 September 2004; accepted 14 September 2004

Abstract

Members of the Sage family, such as *Salvia officinalis* and *Salvia lavandulaefolia*, have a long history of use as memory-enhancing agents coupled with cholinergic properties that may potentially be relevant to the amelioration of the cognitive deficits associated with Alzheimer's disease. The current study utilised a placebo-controlled, double-blind, balanced, crossover design in order to comprehensively assess any mood and cognition modulation by *S. lavandulaefolia*. Twenty-four participants received single doses of placebo, 25 μl and 50 μl of a standardised essential oil of *S. lavandulaefolia* in an order dictated by a Latin square. Doses were separated by a 7-day washout period. Cognitive performance was assessed prior to the day's treatment and at 1, 2.5, 4 and 6 h thereafter using the Cognitive Drug Research (CDR) computerised test battery. Subjective mood ratings were measured using Bond–Lader visual analogue scales. The primary outcome measures were scores on the five cognitive factors that can be derived by factor analysis of the task outcomes from the CDR battery. The results showed that administration of *S. lavandulaefolia* resulted in a consistent improvement for both the 25- and 50-μl dose on the 'Speed of Memory' factor. There was also an improvement on the 'Secondary Memory' factor for the 25-μl dose. Mood was consistently enhanced, with increases in self-rated 'alertness', 'calmness' and 'contentedness' following the 50-μl dose and elevated 'calmness' following 25 μl. These results represent further evidence that *Salvia* is capable of acute modulation of mood and cognition in healthy young adults. The data also suggest that previous reports of memory enhancement by *Salvia* may be due to more efficient retrieval of target material.

Keywords: Sage; Salvia; Mood; Cognition; Memory; Attention; Cognitive enhancement

1. Introduction

Plants of the *Salvia* genus have a pan-cultural history of usage, with traditional medicinal applications in, among others, ancient Greek, Roman [1], Ayurvedic [2], indigenous American Indian [3] and traditional Chinese medical systems [4,5].

Salvia officinalis was in common usage throughout Europe by medieval times, and features in British herbal apothecaries from the 16th century onwards [6]. Its suggested uses included those as a general treatment to enhance 'head and brain' functioning, improve the memory, quicken the senses and delay age-associated cognitive decline [7]. The many contemporary indications for *S. officinalis* include the alleviation of poor memory, mental confusion, depression, vertigo, as an anti-inflammatory, and use as a treatment for the symptoms of the menopause [8].

The majority of potentially bioactive hydrocarbons in plant essential oils are terpenoids. *Salvia lavandulaefolia*

* Corresponding author. Tel.: +44 191 227 4468; fax: +44 191 2273190.
E-mail address: a.scholey@unn.ac.uk (A.B. Scholey).

0031-9384/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2004.09.010

(Spanish Sage) has a similar composition to *S. officinalis*, with the exception that it lacks a high concentration of the thujone (a terpenoid ketone characterised chemically as bicyclo(3,1,0)hexan-3-one, 4-methyl-1-(1-methylethyl)-(1*S*-(1-,4,5-α)), which is toxic in large doses. It has therefore been suggested that *S. lavandulaefolia* may provide an equally efficacious, but more suitable, treatment [9]. In terms of the whole herb, both sage species contain about 1.0–2.8% volatile oil [10]. It has been suggested that the monoterpenoids (having 10 carbon atoms with at least one double bond) in sage, namely, α-Pinene, β-Pinene, 1,8-Cineole, Thujone, Camphor and Geraniol, contribute to (but may not be completely responsible for) the activity of the whole herb [11].

Both *S. officinalis* and *S. lavandulaefolia* have been reported to have a number of in vitro properties relevant to behaviour. These include dose-dependent inhibition of human brain acetylcholinesterase (AChE). This effect has been observed for the essential oil and alcoholic extracts of both fresh and dried leaves [12]. The effect appears to be due to synergistic interaction between components, as the level of dose-dependent inhibition of erythrocyte AChE by *S. lavandulaefolia* essential oil was not predicted by the effects of single constituents [13]. This in vitro anti-cholinesterase activity of the essential oil of *S. lavandulaefolia* has also been confirmed ex vivo, with the demonstration of an effect similar to physostigmine on the contractile response of the isolated guinea pig ileum [11]. Furthermore, oral administration of *S. lavandulaefolia* to aged rats resulted in in vivo inhibition of AChE in selected brain areas [5]. Inhibition of AChE in the striatum, but not in the hippocampus or cortex, was found following administration of the lowest dose (20 μl). At the higher dose (50 μl), a reduction in AChE activity was found in both the striatum and the hippocampus but again not in the cortex [5].

It has also been reported that the *S. officinalis* leaf had 'appreciable' levels of antioxidant activity, in comparison to recognised herbal antioxidants such as *Ginkgo biloba* and *Panax ginseng* [14]. Antioxidant properties of the essential oil of *S. lavandulaefolia* [11], and a number of single constituents common to both *S. officinalis* and *S. lavandulaefolia* have also been reported [11,15–17]. In vitro research also lends support to the anti-inflammatory and oestrogenic properties that have been historically attributed to *Salvia* species [8], with demonstrations of anti-inflammatory actions by an ethanolic extract of *S. lavandulaefolia* and several of its constituents, and human oestrogen receptor binding activity by the essential oil of *S. lavandulaefolia*, and its monoterpenoid component *geraniol* [11].

Alzheimer's disease is characterized by the presence of amyloid plaques, neurofibrillary tangles and marked cholinergic degeneration. Numerous other disease processes are implicated, including free radical damage, inflammation and compromised oestrogen activity. On the basis of the cholinergic, antioxidant, anti-inflammatory and oestrogenic properties of *S. lavandulaefolia*, and the fact that all but one currently available treatments for AD focus on increasing ACh availability, it has been suggested that *S. lavandulaefolia* may provide a novel treatment for Alzheimer's disease [5,12,18]. A recent parallel-group, placebo-controlled trial reported some protection against declines in cognitive performance in sufferers of mild to moderate Alzheimer's disease during 4 months administration of *S. officinalis* [19]. Such an effect is not surprising given the range of mechanisms potentially relevant to dementia that *Salvia* may target. In particular, the plant's acetylcholinesterase inhibitory properties, with a consequent increase in synaptically available acetylcholine, may serve to ameliorate the cognitive disturbances associated with cholinergic neuron and receptor loss and dysregulation. Additionally, *Salvia* is well tolerated and without the attendant side effects of currently available treatments [5]. Added anti-inflammatory and antioxidant properties may also convey additional benefits, while interaction with oestrogen receptors raises the possibility of further potentially beneficial effects, including increased cerebral blood flow, anti-inflammatory actions and neuroprotective and neurotrophic effects in brain tissue [20].

In our own laboratory, we have undertaken a series of studies into the potential behavioural effects of herbal extracts. As a starting point, we have assessed the acute effects of a number of standardised extracts on mood and cognition in healthy young adults. It is particularly relevant that any such substances should theoretically be capable of modulating cognitive performance in healthy population. That is, where drugs which reverse cognitive impairments have been assessed in healthy cohorts they tend to benefit function, although it is theoretically possible that some treatments may be effective only in impaired populations. A randomised, double-blind, placebo-controlled trial evaluating the effects of a range of doses (25, 50, 100 and 150 μl) of essential oil of *S. lavandulaefolia* in healthy young volunteers showed that administration of only the lowest doses, 25 and 50 μl, significantly improved memory for a word recall task compared with placebo [21].

The current study investigated the dose- and time-dependent acute cognitive and mood effects of ingestion of two single doses (25 and 50 μl, these being the most efficacious in a previous study) of the essential oil of *S. lavandulaefolia* (and a placebo) in healthy young volunteers, using the Cognitive Drug Research (CDR) computerised assessment battery, serial subtraction tasks, and the Bond–Lader mood scales.

2. Materials and methods

2.1. Participants

Sixteen female and eight male undergraduate volunteers (mean age 23.21 years, range 18–37) took part in the study, which was approved by the Joint Ethics Committee of Newcastle and North Tyneside Health Authority. Prior to

participation, each volunteer signed an informed consent form and completed a medical health questionnaire. All participants reported that they were in good health, and were taking no illicit recreational drugs. Additionally, they were free of any 'over-the-counter' or prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Habitual smokers were excluded from the study. All participants abstained from caffeine-containing products throughout each study day, and alcohol for a minimum of 12 h prior to the first testing session of the morning.

2.2. Cognitive measures

The Cognitive Drug Research (CDR) computerised assessment battery has been used in hundreds of European and North American drug trials, and has been shown to be sensitive to acute cognitive improvements [22,23], as well as impairments with a wide variety of substances [24,25].

A tailored version of the CDR battery was used. This has previously been found to be sensitive to modulation of cognitive function as a consequence of acute ingestion of *Melissa officinalis* [26], *Ginkgo biloba* [27,28], and *Panax ginseng* [29,28], and acute and chronic administration of a *Ginkgo biloba/Panax ginseng* combination [28,30–32]. The running order of the tasks is illustrated in Fig. 1. The selection of computer controlled tasks from the system was administered with parallel forms of the tests being presented at each testing session. Presentation was via desktop computers with high-resolution VGA colour monitors, and, with the exception of written word recall tests, all responses were recorded via two-button (YES/NO) response boxes. The entire selection of tasks took approximately 20 min.

Tests were administered in the following order:

Word Presentation: Fifteen words, matched for frequency and concreteness, were presented in sequence on the monitor for the participant to remember. Stimulus duration was 1 s, as was the interstimulus interval.

Immediate Word Recall: The participant was allowed 60 s to write down as many of the words as possible. The task was scored as number of words produced, minus errors and intrusions and the resulting score was converted into a percentage.

Picture Presentation: A series of 20 photographic images of everyday objects and scenes were presented on the monitor at the rate of 1 every 3 s, with a stimulus duration of 1 s, for the participant to remember.

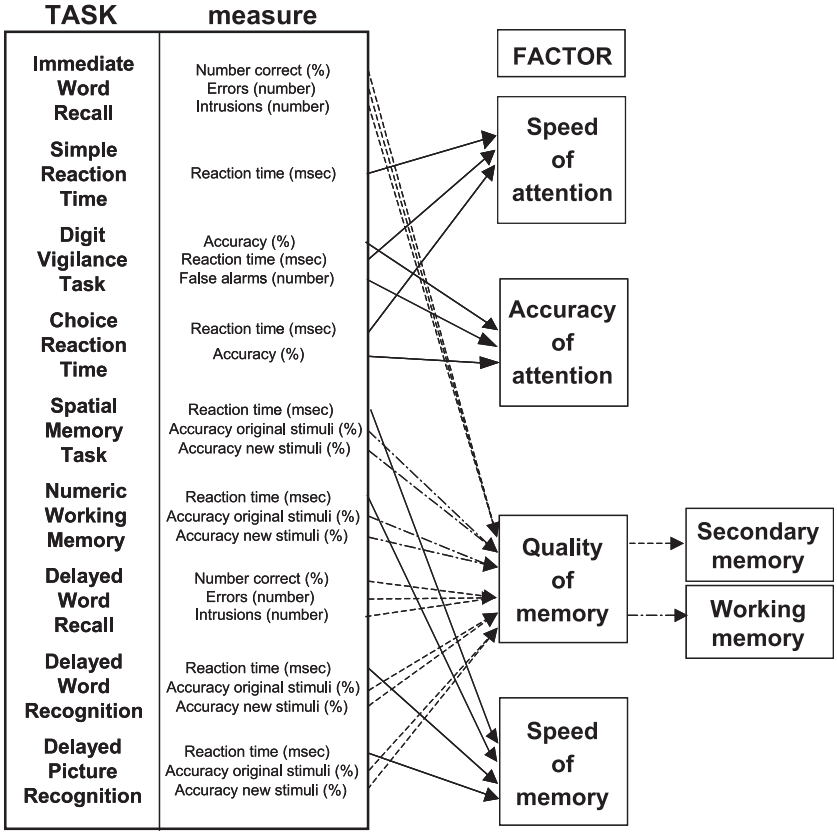

Fig. 1. Schematic representation of the CDR battery showing (from left to right) running order of tasks, individual task outcome measures and the composition of the four factors derived by factor analysis. Arrows indicate that a task outcome measure contributes to the given factor 'Speed of Attention', 'Accuracy of Attention', 'Quality of Memory' or 'Speed of Memory'. Differential dotted lines indicate contribution to both Quality of Memory and to either 'Working Memory' or 'Secondary Memory' (adapted from Kennedy et al. [27,38]).

Simple Reaction Time: The participant was instructed to press the 'YES' response button as quickly as possible every time the word 'YES' was presented on the monitor. Fifty stimuli were presented with an interstimulus interval that varied randomly between 1 and 3.5 s. Reaction times were recorded in milliseconds.

Digit Vigilance Task: A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits were presented in the centre of the screen at the rate of 80 per minute and the participant was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit. The task lasted 1 min and there were 15 stimulus–target matches. Task measures were accuracy (%), reaction time (ms) and number of false alarms.

Choice Reaction Time: Either the word 'NO' or the word 'YES' was presented on the monitor and the participant was required to press the corresponding button as quickly as possible. There were 50 trials, of which the stimulus word was chosen randomly with equal probability, with a randomly varying interstimulus interval of between 1 and 3.5 s. Reaction times (ms) and accuracy (%) were recorded.

Spatial Working Memory: A pictorial representation of a house was presented on the screen with four of its nine windows lit. The participant was instructed to memorise the position of the illuminated windows. In 36 subsequent presentations of the house, one of the windows was illuminated and the participant decided whether or not this matched one of the lighted windows in the original presentation. The participant made their response by pressing the 'YES' or 'NO' response button as quickly as possible. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli was recorded as percentages which were used to derive a '% greater than chance performance' score.

Numeric Working Memory: Five digits were presented sequentially for the participant to hold in memory. This was followed by a series of 30 probe digits for each of which the participant decided whether or not it had been in the original series and pressed the 'YES' or 'NO' response button as appropriate as quickly as possible. This was repeated two further times with different stimuli and probe digits. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli was recorded as percentages which were used to derive a '% greater than chance performance' score.

Delayed Word Recall: The participant was again given 60 s to write down as many of the words as possible. The task was scored as number correct, errors and intrusions and the resulting score was converted into a percentage.

Delayed Word Recognition: The original words plus 15 distractor words were presented one at a time in a randomised order. For each word the participant indicated whether or not he recognised it as being included in the original list of words by pressing the 'YES' or 'NO' button as appropriately and as quickly as possible. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli was recorded as percentages which were used to derive a '% greater than chance performance' score.

Delayed Picture Recognition: The original pictures plus 20 distractor pictures were presented one at a time in a randomised order. For each picture, participants indicated whether or not it was recognised as being from the original series by pressing the 'YES' or 'NO' button as appropriate and as quickly as possible. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli was recorded as percentages which were used to derive a '% greater than chance performance' score.

2.3. Primary cognitive outcome measures

The above measures were collapsed into the five outcome factors derived from the battery by factor analysis, and the global 'Quality of Memory' measure (see Wesnes et al. [32] for details), as previously utilised by Kennedy et al. [26–30], and Wesnes et al. [31,32]. The contribution of each individual task outcome to the outcome factors is represented in Fig. 1.

2.4. Memory

'*Quality of Memory*' *measure:* derived by combining the 'Secondary Memory' and 'Working Memory' factor scores (see below).

'*Secondary Memory*' *factor:* derived by combining the percentage accuracy scores (adjusted for proportions of novel and original stimuli where appropriate) from all of the secondary memory tests—word recognition, picture recognition, immediate word recall and delayed word recall (with adjustments to the total % correct for errors and intrusions on the latter two tasks). One hundred percent accuracy across the four tasks would generate a maximum score of 400 on this index.

'*Working Memory*' *factor:* derived by combining the percentage accuracy scores from the two working memory tests—spatial working memory and numeric working memory. One hundred percent accuracy across the two tasks would generate a maximum score of 200 on this index.

'*Speed of Memory*' *factor:* derived by combining the reaction times of the four computerised memory tasks—numeric working memory, spatial memory, delayed word recognition and delayed picture recognition (units are summed milliseconds for the four tasks).

2.5. Attention

'*Speed of Attention*' *factor:* derived by combining the reaction times of the three attentional tasks—simple reaction

time, choice reaction time and digit vigilance (units are summed milliseconds for the three tasks).

'*Accuracy of Attention*' *factor:* derived by calculating the combined percentage accuracy across the choice reaction time and digit vigilance tasks with adjustment for false alarms from the latter test. One hundred percent accuracy across the two tasks would generate a maximum score of 100.

2.6. Subjective mood measure

2.6.1. Bond–Lader visual analogue scales

The 16 visual analogue scales of Bond–Lader [33] were combined as recommended by the authors to form three mood factors: 'alert', 'calm' and 'content'.

2.7. Serial subtraction tasks

2.7.1. Serial Sevens

A modified computerised version of the Serial Sevens test was utilised. The original verbal Serial Sevens test [34] has appeared in a number of forms, including as part of the Mini-Mental State Examination [35]. It has been used to assess cognitive impairment during hypoglycaemia [36,37], and has also been used to investigate the relationship between increased blood glucose levels and cognitive performance [38–40].

In the current study, computerised versions of serial subtractions were implemented (see Ref. [39] for details), here using tests of 2 min duration. For the Serial Sevens task, a standard instruction screen informed the participant to count backwards in sevens from the given number, as quickly and accurately as possible, using the numeric keypad to enter each response. Participants were also instructed verbally that if they were to make a mistake they should carry on subtracting from the new incorrect number. A random starting number between 800 and 999 was presented on the computer screen, which was cleared by the entry of the first response. Each three-digit response was entered via the numeric keypad with each digit being represented on screen by an asterisk. Pressing the enter key signalled the end of each response and cleared the three asterisks from the screen. The task was scored for the total number of subtraction and number of errors. In the case of incorrect responses, subsequent responses were scored as positive if they were correct in relation to the new number.

The Serial Threes task was identical to the Serial Sevens, except that it involved serial subtraction of threes.

2.8. Treatments

Depending on the condition to which the participant was allocated on that particular day, the combination of two identical capsules corresponded to a dose of either 0 (a sunflower oil placebo), 25 μl, or 50 μl of *S. lavandulaefolia* essential oil (Baldwins, London, UK) in sunflower oil. Capsules were dispensed in the laboratory for oral administration following the baseline assessment.

2.9. Procedure

Each participant was required to attend a total of four study days that were conducted 7 days apart, to ensure a sufficient washout between conditions. Testing took place in a suite of laboratories with participants visually isolated from each other.

On arrival at their first session on the first day, participants were randomly allocated to a treatment regime using a Latin square design which counterbalanced the order of treatments across the three active days of the study.

The first day was identical to the following three, except that no treatment (active or placebo) was offered to allow familiarisation with the test battery and procedure. Data from the five sessions of this practice day were not included in any analysis.

Each study day comprised five identical testing sessions. The first was a pre-dose testing session which established baseline performance for that day, and was immediately followed by the day's treatment on visits 2 to 4. Further testing sessions began at 1, 2.5, 4 and 6 h following consumption of the day's treatment.

Each testing session comprised completion of the Bond–Lader visual analogue scales, the CDR test battery and finally the Serial Threes and Serial Sevens computerised subtraction tasks.

2.10. Statistics

Scores from individual measures were combined to form the 'Quality of Memory' measure, and the five cognitive factor scores. These, the individual task outcome measures, Serial Threes and Serial Sevens scores, and the three mood outcomes derived from the Bond–Lader visual analogue scales, were analysed as 'change from baseline' using the Minitab statistical package. The initial analysis was made using repeated-measures analyses of variance. Following the recommendations of Kepple [41], the omnibus F test was eschewed in favour of planned comparisons which were made between the placebo and each of the two active treatment conditions (25 μl salvia and 50 μl of salvia) at each time point. Pre-planned comparisons were made using utilising t tests with the mean squares for 'Dose×Time×Subjects' as an error term [41]. To ensure the overall protection level all testing was two-tailed, comparisons were strictly planned prior to the study, were restricted to the number of conditions minus one at each time-point, and only probabilities associated with these pre-planned comparisons were calculated.

3. Results

A preliminary report including word recall scores only from this study has been published elsewhere [42].

3.1. Baseline scores

Prior to analysis of change from baseline data, mean pre-dose raw baseline scores for all three conditions (placebo, 25 μl, and 50 μl) for each of the primary outcome measures ('Quality of Memory', the five cognitive factors, mood scale scores and serial subtraction scores) were subjected to a one-way repeated-measures analysis of variance. There was a single significant difference in baseline performance [$F(2,46)=3.5$, $p=0.039$], with post hoc comparisons (Dunnett's) revealing that following the 50-μl dose, participants scored fewer errors ($p<0.05$) on the Serial Threes task than while in the placebo condition.

3.2. Cognitive factor outcome measures

Mean raw and change from baseline cognitive factor outcome measure scores for each condition across each session are displayed in Fig. 2.

3.2.1. Quality of Memory measure

Planned comparisons revealed a significant improvement in the accuracy of memory task performance, in comparison to placebo, for the 25-μl dose of sage at 1 h post-dose [$t(138)=2.85$, $p=0.005$]. There was also a trend towards improved performance for the same dose at 4 h post-dose [$t(171)=1.71$, $p=0.09$].

3.2.2. Secondary Memory factor

The 25-μl dose of sage was associated with a significant improvement on the 'Secondary Memory' factor at 1 h post-dose [$t(138)=2.66$, $p=0.009$]. There was also a strong

Measure		Pre-dose Baseline score	Post-dose change from baseline score: 1 hour	2.5 hours	4 hours	6 hours
Quality of Memory (% X 6)	placebo	402.10 9.55	-51.16 11.12	-45.88 6.81	-58.87 12.20	-49.65 10.92
	25 μl	391.44 12.10	-16.68 10.82	-47.52 9.31	-38.18 12.61	-59.03 12.75
	50 μl	392.90 10.68	-34.98 11.12	-41.61 10.32	-51.84 13.14	-43.82 11.79
Secondary Memory (% X 4)	placebo	221.25 10.13	-41.67 10.10	-39.43 6.80	-46.44 12.22	-33.04 7.80
	25 μl	209.03 11.71	-14.03 10.07	-34.88 9.08	-26.11 10.14	-41.60 9.52
	50 μl	211.74 10.28	-25.83 10.47	-33.82 9.68	-33.68 10.26	-31.88 9.96
Working Memory (% X 2)	placebo	180.85 2.68	-9.50 3.61	-6.46 2.44	-12.43 2.84	-16.61 5.25
	25 μl	182.41 2.46	-2.66 3.12	-12.65 4.87	-12.07 4.54	-17.43 6.58
	50 μl	181.17 2.33	-9.15 3.14	-7.79 4.15	-18.16 6.45	-11.94 5.70
Speed of Memory (summed msecs)	placebo	2450.2 69.14	-77.84 34.09	47.15 51.38	50.40 67.73	-18.59 64.29
	25 μl	2493.1 87.58	2.77 30.98	-72.70 49.16	-44.38 45.62	-97.02 51.71
	50 μl	2575.2 90.14	-40.98 30.76	-27.71 69.06	-106.1 60.26	-138.7 81.83
Quality of Attention (%)	placebo	90.67 0.52	-0.83 0.76	-2.04 0.67	-1.87 0.96	-1.25 0.75
	25 μl	90.79 0.51	-1.21 0.74	-2.13 0.79	-1.29 0.89	-0.92 0.73
	50 μl	90.87 0.62	-0.63 0.70	-1.38 0.55	-2.04 0.90	-2.29 1.26
Speed of Attention (summed msecs)	placebo	1054.8 24.13	15.55 12.96	31.08 14.55	57.44 21.01	33.66 14.34
	25 μl	1059.7 26.54	-0.16 12.96	29.47 22.97	21.24 16.01	17.10 14.43
	50 μl	1088.3 48.14	-3.40 13.68	3.17 42.70	31.48 27.53	-3.77 40.67

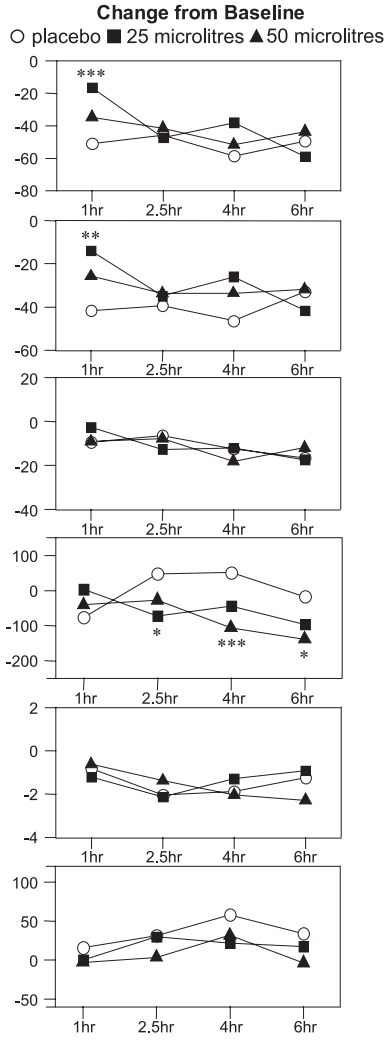

Fig. 2. Effects of *S. lavandulaefolia* essential oil (25 and 50 μl) and placebo on cognitive measures: 'Quality of Memory', 'Secondary Memory', 'Working Memory', 'Speed of Memory', 'Speed of Attention', and 'Accuracy of Attention'. The table presents means (with standard errors in italics) of baseline scores and change from baseline scores for each dose of *Salvia*. Graphs represent the change from baseline scores for the relevant outcome measure (*$p=0.05$, **$p=0.01$, ***$p=0.005$ compared to the corresponding placebo score). Units are as per the table.

trend towards improved performance for the same dose at 4 h post-dose [$t(138)=1.96$, $p=0.052$]. Reference to the single tasks which contribute to this factor (see Fig. 1) suggests that 50 μl evinced a greater improvement than placebo on the immediate word recall task at 1 h [$t(138)=2.24$, $p=0.026$] and 4 h [$t(138)=2$, $p=0.047$]. There was a strong trend towards improvement for the 25-μl dose at 1 h post-dose [$t(138)=1.96$, $p=0.052$]. Word recognition task performance was also improved for both doses at the 4-h testing session [25 μl: $t(138)=2.26$, $p=0.025$; 50 μl: $t(138)=2.05$, $p=0.04$], while picture recognition task performance was improved at 1 and 2.5 h for the 25-μl dose [$t(138)=2.79$, $p=0.006$ and $t(138)=2.3$, $p=0.022$, respectively].

3.2.3. Working Memory factor

There were no significant differences on the 'Working Memory' factor. There was, however, a single significant improvement on the numeric working memory task at 1 h post-dose for 25 μl of sage oil [$t(138)=2.2$, $p=0.029$]. Given the nature of the statistical analysis, it seems unwise to overinterpret such single significant comparisons.

3.2.4. Speed of Memory factor

Performance on the 'Speed of Memory' factor was improved for both doses of essential oil, with participants performing faster, relative to placebo, in the 25-μl condition at 2.5 h [$t(138)=2.34$, $p=0.021$] with a trend towards the same at 4 h post-dose [$t(138)=1.85$, $p=0.066$], and following 50 μl at 4 [$t(138)=3.05$, $p=0.003$] and 6 h post-dose [$t(138)=2.35$, $p=0.02$].

Reference to the individual tasks which contribute to this factor (see Fig. 1) suggests that both doses of essential oil were associated with a greater increase in speed than placebo on the picture recognition task, with improvements associated with 25 μl at 2.5 h [$t(138)=2.08$, $p=0.039$], and with both 25 and 50 μl at 4 h [$t(138)=2.61$, $p=0.01$ and $t(138)=2.88$, $p=0.005$, respectively], and 6 h post-dose [$t(138)=2.05$, $p=0.042$ and $t(138)=1.99$, $p=0.048$, respectively]. Similarly, while the 50-μl dose was associated with increased speed on the spatial memory task at 2.5 h [$t(138)=3.5$, $p=0.0006$] and 4 h [$t(138)=2.03$, $p=0.044$], both doses evinced faster performance at 6 h post-dose [$t(138)=2.17$, $p=0.03$ and $t(138)=3.7$, $p=0.0003$, respectively]. There was also a single increase in speed associated with the 25-μl dose on the numeric working memory task at 2.5 h post-dose [$t(138)=2.09$, $p=0.039$].

3.2.5. Quality of Attention factor

There were no significant differences on the 'Quality of Attention' factor, or the measures that load onto it.

Measure		Pre-dose Baseline score	Post-dose change from baseline score: 1 hour	2.5 hours	4 hours	6 hours
Serial 3s Responses	placebo	59.46 *3.95*	4.33 *1.76*	5.54 *2.56*	5.38 *2.06*	1.71 *2.64*
	25 μl	60.92 *2.98*	1.83 *1.68*	6.00 *2.35*	4.54 *2.95*	5.63 *2.89*
	50 μl	57.58 *4.38*	7.04 *1.66*	6.33 *1.94*	5.92 *1.63*	8.67 *1.96*
Serial 3s Errors	placebo	4.83 *1.05*	-0.04 *0.90*	-0.83 *0.87*	-2.33 *2.07*	-0.79 *0.83*
	25 μl	4.42 *0.88*	0.88 *0.90*	0.38 *0.56*	1.00 *1.20*	0.50 *0.59*
	50 μl	2.58 *0.86*	0.96 *0.90*	2.08 *1.08*	2.58 *0.86*	1.17 *0.91*
Serial 7s Responses	placebo	35.79 *2.31*	1.50 *1.04*	1.63 *1.23*	0.21 *1.18*	-2.75 *1.31*
	25 μl	33.33 *2.09*	1.67 *1.05*	2.38 *1.43*	3.08 *1.29*	2.38 *1.34*
	50 μl	34.71 *2.61*	3.33 *0.94*	1.42 *1.53*	2.63 *1.04*	3.00 *1.51*
Serial 7s Errors	placebo	3.63 *0.74*	0.38 *0.78*	0.75 *0.70*	-0.38 *0.86*	0.08 *0.80*
	25 μl	3.92 *0.49*	-0.17 *0.78*	-0.63 *0.55*	-0.13 *0.49*	0.04 *0.61*
	50 μl	3.54 *0.41*	0.42 *0.78*	0.58 *0.52*	0.33 *0.66*	1.08 *1.22*

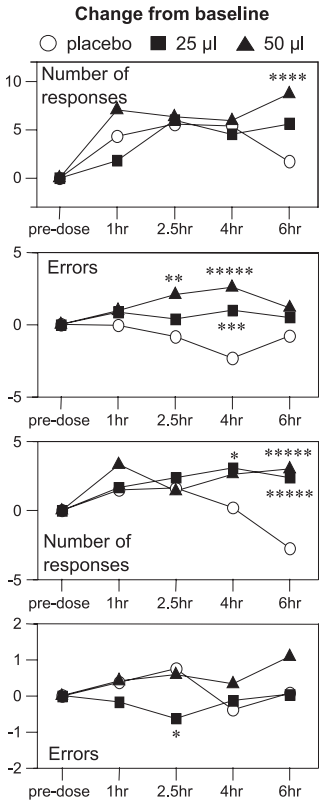

Fig. 3. Effects of *S. lavandulaefolia* essential oil (25 and 50 μl) and placebo on serial subtraction performance. The table presents means (with standard errors in italics) of baseline and change from baseline scores for each treatment in terms of both total responses and errors on both the Serial Threes and Serial Sevens tasks. Graphs represent the change from baseline scores for the relevant outcome measure (*$p=0.05$, **$p=0.01$, ***$p=0.005$, ****$p=0.001$, *****$p=0.0005$ compared to the corresponding placebo score).

3.2.6. Speed of Attention factor

There were no significant differences on this factor. There was one single significant improvement in speed on the choice reaction time task (which contributes to this factor) for the 25-μl dose of sage at 4 h post-dose [$t(138)=3.29$, $p=0.001$]. It seems likely that this represents a chance fluctuation in performance.

3.3. Serial subtractions

Mean raw and change from baseline serial subtraction scores for each condition across each session are displayed in Fig. 3.

3.3.1. Serial Threes

There were significant differences on both the number of responses and the number of errors on the Serial Threes task. Following 50 μl of sage, participants' speed of performance improved significantly at the 6-h testing session, in comparison to a decline for placebo [$t(138)=3.44$, $p=0.0008$]. There was also a strong trend in the same direction for the 25-μl condition [$t(138)=1.93$, $p=0.055$]. In contrast to this, the 50-μl condition evinced more errors at 2.5 h post-dose [$t(138)=2.68$, $p=0.008$], and both doses were associated with more errors at 4 h post-dose [25 μl: $t(138)=3.07$, $p=0.003$, and 50 μl: $t(138)=4.52$, $p=0.00001$]. While the increase in errors following the 50-μl dose has to be viewed with caution in light of the significant reduction in errors at baseline for this condition (see above under 'baseline scores'), and the possibility that the increase in errors therefore represents a regression to the mean, it is interesting to note that pre-dose scores for 25 μl were largely indistinguishable from placebo.

3.3.2. Serial Sevens

Performance was improved following both doses of sage on the Serial Sevens task. In comparison to placebo, participants generated more subtractions above baseline performance at 4 h post-dose following 25 μl [$t(138)=2.02$, $p=0.045$], and at 6 h post-dose following both doses of sage [25 μl: $t(138)=3.6$, $p=0.0004$, and 50 μl: $t(138)=4.05$, $p=0.00009$]. There was also a single significant reduction in errors following 25 μl at 2.5 h post-dose [$t(138)=2.21$, $p=0.029$].

3.4. Bond–Lader mood scales

Mean raw and change from baseline scores on the 'alert', 'content' and 'calm' factors derived from the Bond–Lader visual analogue scales for each condition across each session are displayed in Fig. 4.

3.4.1. 'Alert' factor

Participants' subjective ratings showed that, in comparison to baseline ratings, they rated themselves as more alert than placebo following ingestion of 50 μl of sage at all testing sessions, with this reaching significance at 2.5 h [$t(138)=2.34$, $p=0.02$], and 4 h [$t(138)=2.58$, $p=0.01$] testing sessions.

3.4.2. 'Calm' factor

Participants also scored higher on the 'calm' factor than at the baseline testing session, in comparison to placebo,

Measure		Pre-dose Baseline score	Post-dose change from baseline score: 1 hour	2.5 hours	4 hours	6 hours
'Alert'	placebo	58.18 3.76	4.38 2.64	2.91 2.59	1.05 3.33	5.02 3.01
	25 μl	56.44 4.46	6.11 2.85	5.27 3.50	-0.26 3.74	1.89 4.98
	50 μl	58.23 3.89	8.38 2.98	9.44 2.67	8.25 3.02	8.79 4.48
'Calm'	placebo	68.77 2.64	-6.00 3.12	-15.44 6.96	-9.88 3.80	-13.69 4.04
	25 μl	63.33 3.60	-4.33 3.26	-2.19 4.00	-4.44 5.17	-1.65 4.49
	50 μl	61.92 4.38	3.77 3.25	-0.23 3.71	1.60 5.91	1.77 4.47
'Content'	placebo	70.51 3.18	-0.61 2.18	0.58 1.65	-2.98 2.15	-2.38 2.60
	25 μl	73.66 2.73	1.50 2.19	-2.17 3.19	-6.31 3.08	-1.59 1.87
	50 μl	69.46 3.37	1.75 2.17	4.32 3.36	5.40 3.25	4.12 4.77

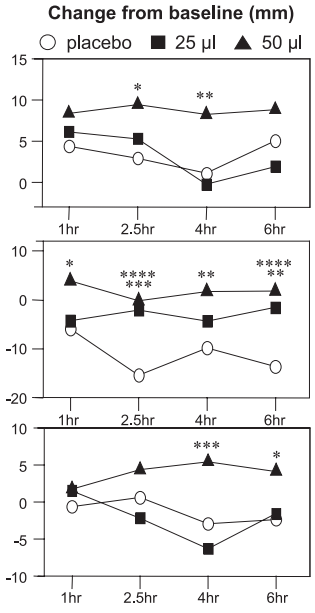

Fig. 4. Effects of *S. lavandulaefolia* essential oil (25 and 50 μl) and placebo on Bond–Lader mood scale factor scores: 'Alert', 'Content' and 'Calm'. The table presents means (with standard errors in italics) of baseline scores and change from baseline scores for each treatment. Graphs represent the change from baseline scores for the relevant outcome measure (*$p=0.05$, **$p=0.01$, ***$p=0.005$, ****$p=0.001$ compared to the corresponding placebo).

following 50 μl of sage at all testing sessions [1 h: $t(138)=2.22$, $p=0.028$; 2.5 h: $t(138)=3.46$, $p=0.0007$; 4 h: $t(138)=2.6$, $p=0.01$; 6 h post-dose: $t(138)=3.52$, $p=0.0006$]. Similarly, having ingested 25 μl of sage oil, participants rated themselves as having become more 'calm' than after taking the placebo at all time points, with this reaching significance at 2.5 h [$t(138)=3.01$, $p=0.003$] and 6 h post-dose [$t(138)=2.74$, $p=0.007$].

3.4.3. 'Content' factor

Participants also rated themselves as having become significantly more content, in comparison to placebo, in the 50-μl condition at the 4 h [$t(138)=2.96$, $p=0.0036$], and 6 h [$t(138)=2.3$, $p=0.023$] testing sessions.

4. Discussion

Compared with placebo, both doses of *S. lavandulaefolia* oil resulted in improved performance on all three elements of the testing battery employed in the current study (the CDR system, Serial Subtractions and the Bond–Lader mood scales).

Improved performance on the primary cognitive measures derived from the CDR battery was restricted to memory performance, with specific improvements for the lowest dose (25 μl) on the 'Secondary Memory' factor at the 1-h post-dose testing session, and on the 'Speed of Memory' factor at the 2.5-h testing session. The 50-μl dose was associated with improved 'Speed of Memory' at both the 4- and 6-h testing sessions. Reference to the single task outcomes showed that the sage oil conditions were associated with improved performance on a number of tasks. Unsurprisingly, these were almost exclusively restricted to enhancement for both doses on the component tasks making up the 'Secondary Memory' and 'Speed of Memory' factors. It is notable that all of the significant changes on the tasks from the CDR battery reflected an improvement in performance. 'Secondary memory' incorporates elements of learning, consolidation and retrieval of episodic information, while 'Speed of Memory' specifically reflects retrieval efficiency. It therefore seems likely that the previously reported improvements in word memory [21] may be due to improved retrieval processes.

On the serial subtraction tasks, both doses of sage resulted in sustained improvement in the speed of performance, with the 50-μl dose resulting in more subtractions than placebo at the final (6 h) testing session on both Serial Threes and Serial Sevens. Similarly, the 25-μl dose resulted in more Serial Sevens responses at both 4 and 6 h. While Serial Sevens accuracy gradually improved for the placebo condition over the course of the first four testing sessions, the opposite was true for both treatment conditions, with significantly more errors at 2.5 h for 50 μl, and at 4 h for both doses. This last finding has to be viewed in the context of significantly reduced errors for 50 μl at the pre-dose baseline testing session (suggesting regression to the mean rather then a positive pharmacological effect for this dose), and improved accuracy of performance for the lower dose at 2.5 h on the Serial Threes task (suggesting a shift in speed/accuracy tradeoff at this time point). It also remains a possibility that speeded performance, coupled with reduced accuracy on this task, represents a consequence of aspects of a more positive mood, in particular, in terms of increased 'calmness' for both doses and increased 'contentedness' for the higher dose. On the other hand, the effects on memory are not wholly consistent with such an interpretation and it may be that mood and cognitive effects are dissociated and underpinned by different neural mechanisms.

The improvements in mood seen for both doses of sage are possibly the most striking findings of the current study. This was most pronounced for the 50-μl treatment where positive effects were evident on all three mood factors of the Bond–Lader scales. These improvements were significantly higher than placebo at 2.5 and 4 h post-treatment on the 'alert' factor, at all time points on the 'calm' factor, and during the later two testing sessions for the 'content' factor. While ratings for the 25-μl dose were largely indistinguishable from placebo on the 'alert' and 'content' factors, this dose too was associated with sustained improvements in ratings on the 'calm' factor which reached significance at both 2.5 h and 6 h post-dose.

This overall profile of results accords well with the properties traditionally attributed to *Salvia* species. Examples of references to the effects of the herb from 16th and 17th century pharmacopoeias include those by Gerard, in 1597, who suggests that "It is singularly good for the head and brain and quickeneth the nerves and memory." Similarly, Culpepper, writing in 1652 in his authoritative 'Complete Herbal', notes that "It also heals the memory, warming and quickening the senses" [7].

To a great extent, the pattern of cognitive modulation also agrees with recent identification of the in vitro cholinergic properties of sage, including cholinesterase inhibition by the *S. lavandulaefolia* preparation used in the current study [42]. The demonstration of specific cholinergic properties for the essential oil can certainly accommodate the improvements seen for both doses of sage on the 'Secondary Memory' and 'Speed of Memory' factors, and their component single task outcomes. Similarly, increased speed on the serial subtraction tasks can be viewed within the context of cholinergic modulation of central executive resources [43].

On the other hand, one might also expect modulation of attentional processes if cholinergic systems were the primary target of the active principles within this preparation. It seems more probable that the cognitive benefits of this preparation stem from an interaction of many processes each of which alone may exert subtle positive or negative effects. Such processes may include hormonal systems, in particular, there have recently been reports of oestrogenic properties for *S. lavandulaefolia* essential oil [11], raising the possibility of wide ranging CNS effects leading to

positive effects on mood and cognition (see Sheperd [20] for a comprehensive review). Additionally, given such properties, one might expect differential gender-specific treatment effects. The gender composition of the cohort tested here (16 females and 8 males) does not lend itself to making such a comparison. However, future studies might usefully be directed at this issue, including examination of the effects of *Salvia* in populations such as post-menopausal women.

In light of the complex composition of the essential oil, it is unlikely, however, that any effects are attributable to one mechanism in isolation, and are more likely to reflect the additive or synergistic effects of a number of different components and/or mechanisms. Particularly pertinent to this point is the striking pattern of mood elevation, with the higher dose of sage resulting in increased ratings of alertness, calmness and contentedness. When both the cognitive and mood effects of the herb are considered, it becomes increasingly unlikely that they are as a result of a single mechanism.

The initial driving force behind the investigation of the cognitive effects of *Salvia* species was the possibility that they may constitute a natural, effective and safe treatment for the 'cholinergic' cognitive decrements associated with Alzheimer's disease [5,12]. Specifically, treatments that inhibit acetylcholinesterase, retarding the catabolism of acetylcholine, and therefore resulting in increased synaptic availability of the neurotransmitter, have been shown to improve memory function in young and aged healthy human cohorts, and are currently the only widely used treatment for Alzheimer's disease [44]. Similarly, treatments with agonistic properties at muscarinic and/or nicotinic receptors may also prove effective in Alzheimer's disease, although no such treatment is currently available for prescription [44]. Interestingly, Galantamine, a plant-derived AChE inhibitor that has recently joined the small rank (including Tacrine, Donepezil and Rivastigamine) of approved treatments for Alzheimer's disease, may also have nicotinic receptor binding properties, possibly leading to up-regulation of acetylcholine release [45]. The essential oil utilised in the current study was shown to have both AChE inhibitory and cholinergic receptor binding properties. Furthermore, there are no reports of negative side effects associated with *S. lavandulaefolia* (or *S. officinalis*) despite usage spanning hundreds, if not thousands, of years. Certainly, the results reported here again demonstrate that this plant may well have cognition-enhancing properties. It is also worth noting that this beneficial modulation of cognitive performance followed single doses of *S. lavandulaefolia*, and was evinced in a cohort of healthy young participants who presumably have no cholinergic deficits.

While amelioration of cognitive decline would undoubtedly be of benefit to sufferers from dementia, the antioxidant and anti-inflammatory properties of the plant [11] may potentially confer long-term protection in the pathogenesis of the disease [46]. Similarly, the mood-enhancing properties of the herb may themselves have applications in the treatment of advanced dementia, in which disturbed mood and agitation feature as a major problem.

The possibility that the positive behavioural effects demonstrated in the current study could also be applied to those suffering from age- or disease-related declines in functioning deserves serious investigation.

References

[1] Ryman D. Aromatherapy. London: Judy Piakus Publishers; 1991. p. 190–4.
[2] MacKintyre A. The complete floral healer. London: Gaia Books; 1996.
[3] Moreau JP, Eck CR, McCabe J, Skinner S. Absorption, distribution and elimination of a labelled extract of Ginkgo biloba leaves in the rat. Presse Medicale 1986;25;15(31):1458–61.
[4] Hsu HY, Chen YP. Oriental Materia Medica: a concise guide. Long Beach (CA): Oriental Healing Arts Institute; 1986.
[5] Perry NSL, Houghton PJ, Jenner P, Keith A, Perry EK. *Salvia lavandulaefolia* essential oil inhibits cholinesterase in vivo. Phytomedicine 2002;9:48–51.
[6] Crellin JK, Philpott J. Herbal medicine: past and present, vol. II. London: Duke Univ. Press; 1990.
[7] Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NSL. Medicinal plants and Alzheimer's disease: from ethnobotany to phytotherapy. J Pharm Pharmacol 1999;51:527–34.
[8] Bartram T. Bartram's encyclopedia of herbal medicine. London: Robinson; 1998.
[9] Mantle D, Pickering AT, Perry EK. Medicinal plant extracts for the treatment of dementia: a review of their pharmacology, efficacy and tolerability. CNS Drugs 2000;13(3):201–13.
[10] Leung AY, Foster S. Encyclopedia of common natural ingredients. Chichester: John Wiley; 1996.
[11] Perry NSL, Houghton PJ, Sampson J, Theobald AE, Hart S, Lis-Balchin M, et al. In-vitro activities of *S. lavandulaefolia* (Spanish Sage) relevant to treatment of Alzheimer's disease. J Pharm Pharmacol 2001;53:1347–56.
[12] Perry N, Court G, Bidet N, Court J, Perry E. European herbs with cholinergic activities: potential in dementia therapy. Int J Geriatr Psychiatry 1996;11:1063–9.
[13] Perry NSL, Houghton P, Theobald A, Jenner P, Perry EK. In-vitro inhibition of human erythrocyte acetylcholinesterase by *Salvia lavandulaefolia* essential oil and constituent terpenes. J Pharm Pharmacol 2000;52:895–902.
[14] Mantle D, Eddeb F, Pickering A. Comparison of relative antioxidant activities of British medicinal plant species in vitro. J Ethnopharmacol 2000;72:47–51.
[15] Djarmati Z, Jankov RM, Djordjevic A, Ribar B, Lazar D, Engel P. Carnosic acid 12-methyl ether-α-lactone, a Ferruginol type diterpene from *Salvia officinalis*. Phytochemistry 1992;31(4):1307–9.
[16] Dorman HPJ, Deans SG, Noble RC. Evaluation in vitro of plant essential oils as natural antioxidants. J Essent Oil Res 1995;7(6): 645–51.
[17] Lamaison JL, Petitjean-Freytet C, Carnat A. Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid. Pharm Acta Helv 1991;66(7):185–8.
[18] Mantle D, Pickering AT, Perry EK. Medicinal plant extracts for the treatment of dementia. A review of their pharmacology, efficacy and tolerability. CNS Drugs 2000b;13(3):201–13.
[19] Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised and placebo-controlled trial. J Clin Pharm Ther 2003;28:53–9.

[20] Shepherd JE. Effects of estrogen on cognition mood, and degenerative brain diseases. J Am Pharm Assoc 2001;41(2):221–8.
[21] Tildesley NTJ, Kennedy DO, Perry KK, Ballard CG, Savelev S, Wesnes KA, et al. *Salvia landulaefolia* (Spanish Sage) enhances memory in healthy young volunteers. Pharmacol Biochem Behav 2003;75:669–74.
[22] Moss MC, Scholey AB, Wesnes KA. Oxygen administration selectively enhances cognitive performance in healthy young adults: a placebo-controlled double-blind crossover study. Psychopharmacology 1998;138:27–33.
[23] Scholey AB, Moss MC, Neave N, Wesnes KA. Cognitive performance, hyperoxia and heart rate following oxygen administration in healthy young adults. Physiol Behav 1999;67:783–9.
[24] Ebert U, Siepmann M, Oertel R, Wesnes K, Kirch W. Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. J Clin Pharmacol 1998;38:720–6.
[25] O'Neill WM, Hanks GW, White L, Simpson P, Wesnes K. The cognitive and psychomotor effects of opioid analgesics: I. A randomised controlled trial of single doses of dextropropoxyphrene, lorazepam and placebo in healthy subjects. Eur J Clin Pharmacol 1995;48:447–53.
[26] Kennedy DO, Scholey AB, Tildesley NTJ, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (Lemon Balm). Pharmacol Biochem Behav 2002b;72:953–64.
[27] Kennedy DO, Scholey AB, Wesnes KA. The dose dependent cognitive effects of acute administration of *Ginkgo biloba* to healthy young volunteers. Psychopharmacology 2000;151:416–23.
[28] Kennedy DO, Scholey AB, Wesnes KA. Modulation of cognition and mood following administration of single doses of *Ginkgo biloba*, *Ginseng* and a *Ginkgo/Ginseng* combination to healthy young adults. Physiol Behav 2002a;75:1–13.
[29] Kennedy DO, Scholey AB, Wesnes KA. Differential, dose-dependent changes in cognitive performance and mood following acute administration of *Ginseng* to healthy young volunteers. Nutr Neurosci 2001a;4(4):295–310.
[30] Kennedy DO, Scholey AB, Wesnes KA. Differential, dose dependent changes in cognitive performance following acute administration of a *Ginkgo biloba/Panax ginseng* combination to healthy young volunteers. Nutr Neurosci 2001b;4(5):399–412.
[31] Wesnes KA, Faleni RA, Hefting NR, Hoogsteen G, Houben JJG, Jenkins E, et al. The cognitive, subjective, and physical effects of a *Ginkgo biloba/Panax ginseng* combination in healthy volunteers with neurasthenic complaints. Psychopharmacol Bull 1997;33:677–83.
[32] Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a Ginkgo-biloba/Panax ginseng combination in healthy middle aged volunteers. Psychopharmacology 2000;152:353–61.
[33] Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Psychol 1974;47:211–8.
[34] Hayman M. Two minute clinical test for measurement of intellectual impairment in psychiatric disorders. Arch Neurol Psychiatr 1942;47:454–64.
[35] Folstein M, Folstein SE, McHugh PR. 'Mini Mental State': a practical method of grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189.
[36] Hale F, Margen S, Rabak D. Postprandial hypoglycaemia and psychological symptoms. Biol Psychiatry 1982;17:125–30.
[37] Taylor LA, Rachman SJ. The effects of blood sugar levels changes on cognitive function, affective state and somatic symptoms. J Behav Med 1987;20:544–9.
[38] Kennedy DO, Scholey AB. Glucose administration, heart rate and cognitive performance: effects of increasing mental effort. Psychopharmacology 2000;149:63–71.
[39] Scholey AB, Harper S, Kennedy DO. Cognitive demand and blood glucose. Physiol Behav 2001;73:585–92.
[40] Scholey AB. Fuel for thought. Psychologist 2001;14(4):196–201.
[41] Keppel G. Design and analysis. New Jersey: Prentice Hall; 1991.
[42] Tildesley NTJ, Kennedy DO, Perry EK, Ballard C, Savelev S, Wesnes KA, et al. *Salvia lavandulaefolia* (Spanish Sage) enhances memory in healthy young volunteers. Pharmacol Biochem Behav 2003;75:669–74.
[43] Rusted JM, Warburton DM. Cognitive models and cholinergic drugs. Neuropsychobiology 1989;21:31–6.
[44] Amenta F, Parnetti L, Gallai V, Wallin A. Treatment of cognitive dysfunction associated with Alzheimer's disease with cholinergic precursors. Ineffective treatments or inappropriate approaches. Mech Ageing Dev 2001;122:2025–40.
[45] Parys W. Development of Reminyl (Galantamine) a novel acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. Alzheimer's Rep 1998;S19-20.
[46] Perry NSL, Bollen C, Perry EK, Ballard C. *Salvia* for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacol Biochem Behav 2003;75:651–9.