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ORIGINAL INVESTIGATION

An extract of *Salvia* (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers

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Abstract
Rationale Species of *Salvia* (sage) have a long-standing reputation in European medical herbalism, including for memory enhancement. In recent controlled trials, administration of sage extracts with established cholinergic properties improved cognitive function in young adults.
Objectives This randomised, placebo-controlled, double-blind, balanced, five-period crossover study investigated the acute effects on cognitive performance of a standardised extract of *Salvia officinalis* in older adults.
Materials and methods Twenty volunteers (>65 years of age, mean=72.95) received four active doses of extract (167, 333, 666 and 1332 mg) and a placebo with a 7-day wash-out period between visits. Assessment involved completion of the Cognitive Drug Research computerised assessment battery. On study days, treatments were administered immediately following a baseline assessment with further assessment at 1, 2.5, 4 and 6 h post treatment.
Results Compared with the placebo condition (which exhibited the characteristic performance decline over the day), the 333-mg dose was associated with significant enhancement of secondary memory performance at all testing times. The same measure benefited to a lesser extent from other doses. There also were significant improvements to accuracy of attention following the 333-mg dose. In vitro analysis confirmed cholinesterase inhibiting properties for the extract.
Conclusions The overall pattern of results is consistent with a dose-related benefit to processes involved in efficient stimulus processing and/or memory consolidation rather than retrieval or working memory efficiency. These findings extend those of the memory-enhancing effects of *Salvia* extracts in younger populations and warrant further investigation in larger series, in other populations and with different dosing regimes.

Keywords *Salvia* · Sage · Memory · Cognition · Cognitive decline · Acetylcholine · Cholinesterase · Attention · Age-related memory decline · Alzheimer's disease

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Introduction

Amongst medicinal plants, species of *Salvia* (sage) have a long-standing reputation as cognition enhancing agents (Kennedy and Scholey 2005; Imanshahidi and Hosseinzadeh 2006; Perry et al. 1999). The *Salvia* genus contains some 900 species of which three, *Salvia officinalis*, *S. lavandulaefolia* and *S. miltiorrhiza* are particularly notable

for their reputed beneficial effects on behavioural function, including treatment for depression, memory disorders and age-related memory decline (Howes et al. 2003; Perry et al. 2000a, b, 2002).

Systematic and mechanistic studies into the effects of *Salvia* extracts have revealed multiple activities potentially relevant to brain function, aging and the preventative and symptomatic treatment of mild cognitive impairment and even Alzheimer's disease. These include pro-cholinergic (including cholinesterase inhibition), anti-inflammatory, antioxidant and oestrogenic properties (Imanshahidi and Hosseinzadeh 2006; Kennedy and Scholey 2005; Kennedy et al. 2005; Bartram 1998; Mantle et al. 2000; Tildesley et al. 2003, 2005). Of these, positive cholinergic modulation may be particularly important in light of the degeneration of basal forebrain cholinergic pathways associated with aging, mild cognitive impairment and dementia (e.g. Herholz et al. 2005; Muir 1997). Several *Salvia* species are capable of in vitro inhibition of both butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE; Perry et al. 1996, 2000a, 2001; Savelev et al. 2003, 2004; Tildesley et al. 2003, 2005). Similar effects are also observed in vivo, at least for AChE, suggesting that relevant components of *Salvia* can cross the blood–brain barrier and increase cholinergic transmission via cholinesterase inhibition (Perry et al. 2002).

Several significant effects have been found in previous controlled trials into the acute effects of *Salvia* on behavioural function in healthy young adult humans. These include dose-dependent anxiolytic-like mood effects, coupled with improved attentional function, following administration of a dried leaf preparation of *S. officinalis* with both anti-AChE and anti-BuChE properties (Kennedy et al. 2005). Tildesley et al. (2005) reported positive effects on three mood dimensions of 'alertness', 'contentedness' and 'calmness' following administration of a standardised essential oil of *S. lavandulaefolia* (Spanish sage). The extract used had AChE inhibiting properties and, in two experiments using similar methodology to the present study, significantly improved memory in a dose-dependent manner (Tildesley et al. 2003, 2005). Specifically, following oral administration of *Salvia*, both immediate and delayed verbal memory were significantly improved for up to 4 h (Tildesley et al. 2003, 2005). Similar dose-selective memory enhancement was observed in a second study where significantly improved accuracy of memory was observed for a 25-μL dose 1 h following treatment, with enhanced speed of retrieval 4 and 6 h post dose for a 50 μL treatment (Tildesley et al. 2005).

Given the above factors, it is pertinent to examine the extent to which positive cognitive effects previously found in healthy young cohorts may also be detected in healthy older individuals using the methodology employed in a series of previous studies (e.g. Kennedy et al. 2001a, b, 2002a, b, 2003; Tildesley et al. 2003, 2005). Here we report the first randomised, placebo-controlled, double-blind, balanced crossover study investigating the acute effects on cognition of a standardised extract of sage in cognitively intact older people. A secondary aim was to establish whether the specific extract used had anti-cholinesterase properties.

Materials and methods

Participants

Twenty volunteers (nine female) aged 65–90 years (mean= 72.9) were recruited for the trial which was approved by the Northumbria University Psychology Division Ethics Committee and the Local Regional Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki. Participants signed their informed consent and completed a medical health questionnaire. All were Caucasian non-smokers and in good health. Exclusion criteria included any history of epilepsy, anxiety, depression or psychiatric disorders, allergies to drugs, cardiovascular disease, kidney disease, liver disease and/or gastrointestinal diseases, or concurrent medically prescribed or over-the-counter medications.

Participants were asked to refrain from caffeine products on testing days and alcohol from at least 12 h prior to baseline assessments on study days.

Cognitive measures

Cognitive performance was evaluated using the Cognitive Drug Research computerised assessment battery, which includes tasks assessing secondary and working memory and aspects of attention. The battery has established validity and sensitivity having been validated in numerous clinical trials including those involving anti-dementia drugs (McKeith et al. 2000). The battery is also sensitive to the acute effects of nutritional interventions (Scholey and Kennedy 2004) and herbal extracts (Kennedy et al. 2001a, b, 2002a, b, 2003) including sage (Tildesley et al. 2003, 2005).

The selection of computer-controlled tasks from the system was administered with randomly ordered parallel forms of the tests being presented at each testing session. Presentation was via desktop computers with high-resolution VGA colour monitors. 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 for each of the assessment sessions

with each session involving a different, matched stimulus set where appropriate. The equivalence of the parallel forms has been established by ensuring for example that the words in each form are balanced for length, imagery and frequency in the language. Pictures are taken from categories and the pictures in each category have been rated for overall similarity. Furthermore, the order in which any one volunteer receives the various forms is randomised, so that any differences in difficulty which may remain cannot have a systematic influence on the study outcome. Tests were administered in the following order.

Word presentation Fifteen words, matched for frequency and concreteness, were presented in random sequence on the monitor for the participant to remember. Stimulus duration was 1 s, as was the inter-stimulus 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 correct words produced. Errors and intrusions (rare in this population) were subtracted from total words generated, 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 for the participant to remember. Presentation occurred at the rate of 1 every 3 s, with a stimulus duration of 1 s.

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 inter-stimulus 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 towards 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 (percent), reaction time (milliseconds) 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 response button as quickly as possible. There were 50 trials, of which the stimulus word was chosen randomly with equal probability, with a randomly varying inter-stimulus interval between 1 and 3.5 s. Reaction times (millisecond) and accuracy (percent) 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 millisecond, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages which were used to derive a '% greater than chance performance' score (% of original targets + % of novel targets correctly identified − 100), thus chance performance would give a score of zero and correct identification of all original and novel stimuli would give a score of 100.

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, and as quickly as possible. This was repeated two further times with different stimuli and probe digits. Mean reaction times were measured in millisecond, 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 they could remember from the word presentation task. 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 it was recognised as being included in the original list of words by pressing the 'YES' or 'NO' button as appropriate and as quickly as possible. Mean reaction times were measured in millisecond, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages which were used to derive a '% greater than chance performance' score (between zero and 100).

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 millisecond, 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.

Cognitive factors

The individual task outcomes from the battery were collapsed into five cognitive 'factors', as recommended following their derivation by factor analysis (Wesnes et al. 2000) and as utilised previously (e.g. Kennedy et al. 2002; Scholey and Kennedy 2004). The 'secondary memory' factor was 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 (adjusted for errors and intrusions). One hundred percent accuracy across the four tasks would generate a maximum score of 400 on this index. The 'working memory' factor was 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 measure. The 'speed of memory' factor was derived by combining the reaction times of the four computerised memory tasks—numerical working memory, spatial working memory, delayed word recognition, and delayed picture recognition (units are summed milliseconds for the four tasks). The 'accuracy of attention' factor was 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. Finally the 'speed of attention' factor was 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).

Treatments

The active treatment for the study was a standardised ethanolic (70%) extract of dried *S. officinalis* leaf of known and invariant provenance, in an approximate concentration ratio of 7.5:1 leaf/extract. The *S. officinalis* from which the dried ethanolic extract was produced was grown in England, latitude 51°–53° north, longitude 1°–3° west, in soil that was either sand/sandy loam or chalk/chalky loam. The plant material was grown according to defined production protocols and Good Agricultural Practice standards, and was harvested between November and March. The leaf was dried at temperatures less than 60°C by either artificial heating or by the application of dehumidified blown air.

The leaves were first made into a crude extract by immersion of the material in an aqueous solvent (70% ethanol) at room temperature for a sufficient time, typically 48 h for all the soluble phytochemicals to dissolve. The solution was then concentrated using a climbing film evaporator or in a finishing still under a vacuum and dried in either a vacuum oven or by lypophilisation (freeze drying). The resulting compound was milled, using 44 mesh, into a powder resulting in an extract of dried leaf material of *S. officinalis*.

When submitted to analysis by a combination of ^{1}H Nuclear Magnetic Resonance spectroscopy and pattern recognition, the extract could be differentiated from those of a different *Salvia* species, different varieties of *S. officinalis* grown in the same location or elsewhere and the same variety of *S. officinalis* grown under the same conditions at the same geographical locations but harvested outside the defined harvest period therefore allowing standardisation of the extract.

The extract was encapsulated by Essential Nutrition, Brough, East Yorkshire, UK. Each coated tablet contained either 167 or 333 mg of *S. officinalis* extract plus excipients/manufacturing agents (25 mg microcrystalline cellulose BP, 3 mg crospovidone BP, 20 mg sodium starch glycollate BP, 3 mg colloidal anhydrous silica BP, 3 mg magnesium stearate). Placebo pills contained 277 mg of microcrystalline cellulose BP plus manufacturing agents and 60 mg nutritional fibre. Participants received oral doses of four pills, each combination of active and placebo pills corresponding to 0 (placebo), 167, 333, 666 or 1332 mg of the standardised sage extract depending on that day's treatment. Randomisation and dispensing of treatments were undertaken by disinterested third parties who had no other involvement in the study.

Procedure

Participants attended the laboratory on six occasions. The first was a practice day which was identical to subsequent study days with the exception that no treatment was administered. This served to minimise practice effects and to ensure that performance lay within established limits for this age group. Data from the practice day were not analysed further. The order of treatment on the five subsequent study visits followed a balanced treatment order which was ensured by random allocation of each participant

to a Latin square. Each study day comprised five identical testing sessions The first was a pre-dose testing session which established baseline performance for that day, followed immediately by the day's treatment. Assessments began at 1, 2.5, 4 and 6 h following administration of the day's treatment. There was a 7-day wash-out period between visits.

Acetylcholinesterase assay

Acetylcholinesterase inhibition was assayed as described by Perry et al. (1996). One 167 mg sage extract tablet was subjected to agitation in 10 mL 80% ethanol in a sealed glass beaker for 2 h at room temperature. The suspension was then filtered through a type 1 Whatman filter. Filtrates were compared with 80% ethanol alone (as control) for effects on human acetylcholinesterase activity (final assay concentration 0.1 U/mL).

Acetylcholinesterase activity in the presence of the sage extract filtrate was compared to that measured in the presence of 80% ethanol alone. Acetylthiocholine iodide (ATChI), 5:5-dithiobis-2-nitrobenzoic acid (DTNB) and sodium bicarbonate were purchased from Sigma Co., UK. An assessment of human cholinesterase inhibition was carried out on 96-well microtitre plates using the colorimetric method of Ellman et al. (1961) optimised and adapted for a microplate reader. A typical run consisted of 5 μL of human AChE solution, at final assay concentrations of 0.03 U/mL; 200 μL of 0.1 M phosphate buffer pH 8; 5 μL of DTNB at a final concentration of 0.3 mM prepared in 0.1 M phosphate buffer pH 7 with 0.12 M of sodium bicarbonate; and 5 μL of the test solution. The reactants were mixed in a 96-well microtitre plate and the mixture preincubated for 15 min at 30°C. The reaction was initiated by adding 5 μL of ATChI at final concentrations of 1 mM. Samples were assayed in triplicate. To monitor any non-enzymatic hydrolysis in the reaction mixture, two blanks for each run were prepared in triplicate. Change in absorbance at 405 nm was measured on a Titertek Multiscan MCC/340 96-well plate reader for a period of 6 min at 30°C.

Analyses

One-sample *t* tests were conducted comparing the sample's pre-treatment scores on each cognitive factor with the corresponding population means for 65 to 90 year olds (see Wesnes 2003).

Change from baseline scores on study days was computed for each cognitive measure, at each time point and every dose. These data were subjected to a general linear model analysis of variance (ANOVA) with terms fitted to the model for dose (placebo, 167, 333 and 666 and 1332 mg), session (1, 2.5, 4 and 6 h), dose × session and participant. The statistical approach followed that recommended by Keppel (1991). Thus the initial omnibus ANOVA was employed solely to determine the MSError for the appropriate planned comparisons. Keppel recommends reporting of the ANOVA be eschewed in favour of utilising focussed *t* tests, as pre-planned, which incorporate MSError from the ANOVA.

The primary analysis involved planned comparisons of the change-from-baseline factor scores comparing each of the active treatments and placebo at each time point utilising *t* tests calculated with the mean squares for 'dose × time × subjects', obtained from the initial ANOVA as an error term, as recommended by Keppel (1991). To ensure protection from Type I error all these analyses were two-tailed, restricted to planned comparisons and constrained by the number of conditions minus one at each time point.

Results

Pre-treatment cognitive measures

During the initial practice day, all volunteers' scores lay within established limits for cognitively intact individuals in this age range (Wesnes 2003). The high cognitive functioning of the cohort was confirmed by one-sample *t* tests comparing the sample's scores for each factor with those of the normative population data for this age range (Wesnes 2003). The summary data for the cognitive factors are presented in Table 1. With the exception of the working memory factor, the sample's scores were significantly higher than the norms for this age range. This was reflected in the baseline scores on individual tasks—all were significantly higher than the population mean with the exception of simple reaction time and accuracy of choice reaction time, digit vigilance, and both spatial and numeric working memory.

In terms of the magnitude of these significant differences, the secondary memory factor's scores were in the order of one standard deviation (a difference of 51 units compared with a standard deviation for norms of 47). For speed of memory, the difference was 550 units compared with a normative SD of 929. For accuracy of attention, the difference was 1.2 units and the SD for norms is 3.9. For speed of attention, the difference was 78 units compared with a SD for norms of 125.

Treatment effects on cognitive measures

The effects of *Salvia* administration on cognitive outcomes are summarised in Fig. 1 (depicting the cognitive factors) and Table 2 (showing individual task outcomes). For each

Table 1 Baseline cognitive performance of sample compared with normative data for the same age range

Measure	Normative mean, SEM	Sample mean, SEM	*t* (df=19)	*P*
Secondary memory	151.8, 2.49	202.5, 13.322	3.805	0.001
Accuracy of attention	90.51, 0.137	91.75, 0.584	2.121	0.047
Speed of memory	4,256, 48.99	3,704.5, 154.102	3.579	0.002
Speed of attention	1,227, 4.413	1,149, 27.256	2.854	0.01
Working memory	16.31, 1.79	16.98, 2.70	1.137	0.270

For each factor normative means (with SEM) are presented alongside sample means (with SEM). Scores are shown for secondary memory, accuracy of attention, speed of memory, speed of attention and working memory. Probabilities associated with differences from placebo are indicated (see text for details).

measure dose × time, ANOVAs were conducted solely to generate mean square errors for subsequent pre-planned comparisons (see above). However, for completeness, where the initial ANOVA revealed significant main effects or interactions these are included below (non-significant effects are not reported except where statistical trends may inform interpretation).

Secondary memory There was a significant main effect of treatment on performance of the 'secondary memory' factor [$F(4,228)=2.81$, $p=0.031$]. Planned comparisons revealed that, compared with placebo, following administration of 333 mg of *Salvia* performance on the 'secondary memory' factor was significantly improved across all testing sessions (1 h [$t(228)=2.78$, $p=0.0058$], 2.5 h [$t(228)=3.98$, $p=0.00009$], 4 h [$t(228)=3.48$, $p=0.0005$] and 6 h [$t(228)=3.10$, $p=0.002$], see Fig. 1). There was also a significant improvement in performance for the 167-mg dose at the 2.5- and 4-h testing sessions (2.5 h [$t(228)=2.37$, $p=0.018$] and 4 h [$t(228)=2.49$, $p=0.013$]).

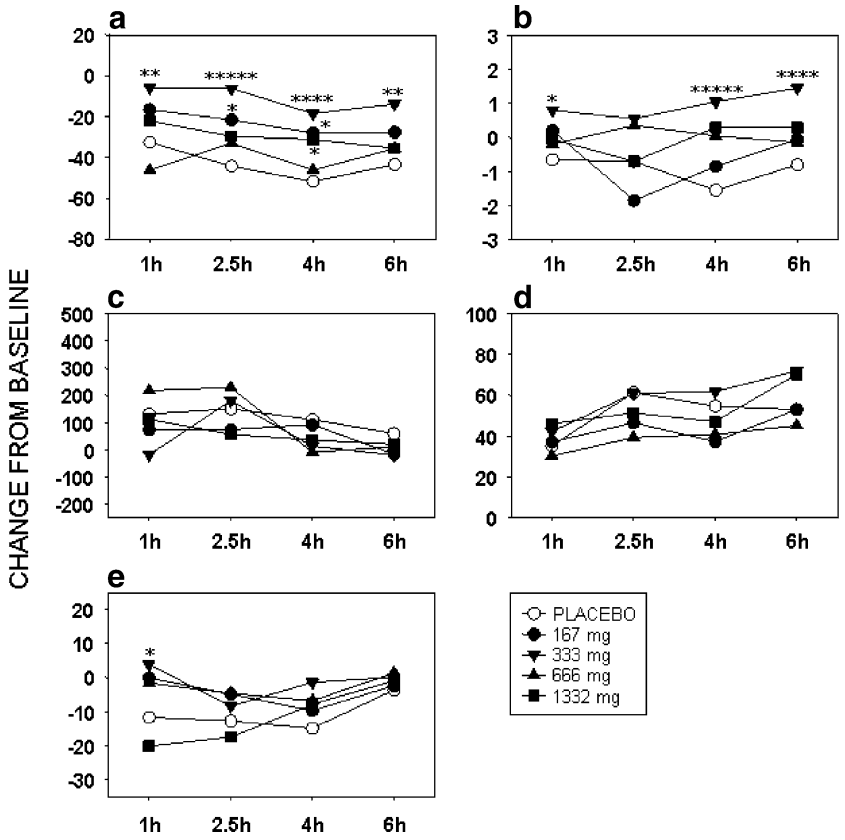

Fig. 1 Effects of a standardised extract of *Salvia officinalis* (167, 333, 666, 1332 mg) and placebo on cognitive factors derived from CDR battery scores. Mean change from baseline scores are shown for **a** secondary memory, **b** accuracy of attention, **c** speed of memory, **d** speed of attention and **e** working memory. *Asterisks* signal significant effects compared with the corresponding placebo score (*$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.001$; *****$p<0.0005$)

Table 2 Effects of *Salvia officinalis* standardised extract on individual task outcome measures from the CDR battery (shown in order of presentation)

Measure		Pre-dose		Post-dose change from baseline score							
		Baseline score		1 h		2.5 h		4 h		6 h	
Immediate word recall (% accuracy)	Placebo	34.50	*2.66*	−3.67	*3.22*	−7.00	*1.93*	−7.67	*2.05*	−4.50	*2.27*
	167 mg	34.33	*2.79*	−4.33	*2.12*	**−2.50**	***2.36***	−7.33	*2.26*	−5.67	*2.07*
	333 mg	30.33	*2.70*	−0.33	*2.72*	**0.67**	***2.45***	**−1.00**	***2.67***	−1.17	*2.72*
	666 mg	34.67	*1.97*	−7.00	*2.24*	−6.17	*1.91*	−7.00	*1.84*	−5.00	*2.55*
	1332 mg	35.33	*2.27*	−6.33	*2.02*	−5.83	*1.96*	−7.00	*1.96*	−8.33	*2.37*
Simple reaction time (ms)	Placebo	273.75	*10.19*	16.75	*7.11*	21.58	*6.55*	20.59	*8.17*	24.35	*7.31*
	167 mg	282.76	*12.00*	*15.14*	*8.80*	9.38	*7.51*	26.27	*11.29*	14.27	*8.98*
	333 mg	275.51	*11.35*	13.15	*6.66*	17.99	*6.05*	18.58	*7.43*	27.74	*6.94*
	666 mg	282.41	*9.71*	13.30	*6.23*	25.33	*6.72*	25.31	*7.59*	28.65	*12.45*
	1332 mg	274.00	*10.53*	27.62	*5.17*	31.91	*6.31*	30.87	*7.68*	30.48	*7.69*
Digit vigilance accuracy (%)	Placebo	97.70	*0.53*	−0.30	*0.55*	−0.30	*0.47*	−0.20	*0.61*	−0.90	*0.70*
	167 mg	97.80	*0.43*	0.50	*0.68*	−1.00	*0.42*	**−1.00**	***0.53***	−0.90	*0.51*
	333 mg	97.80	*0.60*	0.40	*0.64*	**−0.60**	***0.83***	**0.30**	***0.80***	0.90	*0.69*
	666 mg	97.70	*0.57*	−0.30	*0.68*	0.60	*0.54*	**−0.60**	***0.70***	−0.20	*0.68*
	1332 mg	97.20	*0.59*	0.20	*0.56*	−0.20	*0.65*	−0.10	*0.80*	0.90	*0.57*
Digit vigilance reaction time (ms)	Placebo	404.67	*8.70*	9.87	*4.94*	19.96	*6.94*	26.44	*7.77*	18.74	*6.12*
	167 mg	410.32	*11.14*	13.34	*8.00*	19.61	*8.66*	**1.55**	***8.60***	20.66	*9.33*
	333mg	402.35	*10.08*	8.96	*7.94*	21.48	*8.81*	20.36	*6.41*	18.71	*8.07*
	666 mg	413.01	*12.63*	5.51	*6.80*	8.85	*7.81*	**2.61**	***9.22***	6.16	*8.57*
	1332 mg	412.06	*8.75*	5.50	*8.49*	9.32	*7.23*	**6.77**	***6.99***	13.76	*6.09*
Choice reaction time accuracy (%)	Placebo	97.70	*0.53*	−0.30	*0.55*	−0.30	*0.47*	−0.20	*0.61*	−0.90	*0.70*
	167 mg	97.80	*0.43*	0.50	*0.68*	−1.00	*0.42*	−1.00	*0.53*	−0.90	*0.51*
	333 mg	97.80	*0.60*	0.40	*0.64*	−0.60	*0.83*	0.30	*0.80*	**0.90**	***0.69***
	666 mg	97.70	*0.57*	−0.30	*0.68*	0.60	*0.54*	−0.60	*0.70*	−0.20	*0.68*
	1332 mg	97.20	*0.59*	0.20	*0.56*	−0.20	*0.65*	−0.10	*0.80*	**0.90**	***0.57***
Choice reaction time (ms)	Placebo	467.15	*11.03*	8.58	*9.36*	19.80	*10.03*	7.70	*8.44*	9.94	*8.73*
	167 mg	460.22	*11.68*	8.75	*8.43*	17.49	*7.60*	9.55	*5.97*	18.27	*6.98*
	333 mg	452.29	*10.50*	20.16	*6.10*	21.50	*5.77*	**22.85**	***8.05***	**25.35**	***7.30***
	666 mg	469.53	*10.64*	11.48	*7.53*	5.20	*6.77*	12.93	*9.08*	10.39	*9.45*
	1332 mg	465.97	*13.62*	13.02	*7.97*	10.13	*8.19*	9.52	*7.83*	**26.12**	***9.76***
Spatial memory (% >chance)	Placebo	86.63	*4.84*	−8.44	*5.74*	−12.56	*6.53*	−13.44	*9.14*	−6.56	*5.70*
	167 mg	84.81	*4.26*	−2.56	*5.03*	−6.06	*6.90*	−11.81	*9.20*	−4.56	*6.64*
	333 mg	87.25	*4.52*	4.25	*3.32*	−9.44	*6.84*	−0.19	*3.54*	−2.06	*4.68*
	666 mg	92.06	*4.24*	−7.38	*7.18*	−10.63	*6.88*	−9.38	*7.66*	−5.88	*6.53*
	1332 mg	91.06	*4.06*	−20.81	*8.48*	−12.25	*5.05*	−4.19	*2.49*	−3.19	*2.62*
Spatial memory reaction time (ms)	Placebo	872.41	*35.79*	82.87	*48.71*	54.46	*44.42*	50.77	*55.11*	60.14	*46.56*
	167 mg	896.54	*50.04*	11.73	*49.17*	−7.71	*28.66*	39.73	*67.39*	−16.31	*37.93*
	333 mg	865.32	*38.61*	−56.11	*39.99*	80.99	*54.18*	48.23	*47.50*	−10.02	*46.90*
	666 mg	877.67	*46.33*	32.04	*41.29*	170.92	*96.91*	−10.93	*38.09*	4.55	*49.14*
	1332 mg	870.03	*47.39*	23.09	*60.22*	24.39	*47.83*	−13.92	*39.96*	−5.27	*43.17*
Numeric working memory (% >chance)	Placebo	89.89	*3.06*	**−3.22**	***2.43***	−0.22	*2.32*	−1.44	*1.57*	2.89	*1.67*
	167 mg	89.33	*2.79*	2.44	*1.91*	1.11	*2.20*	2.11	*1.67*	2.11	*2.00*
	333 mg	92.11	*2.23*	−0.45	*2.08*	1.00	*2.58*	−1.22	*1.78*	2.22	*2.19*
	666 mg	86.78	*3.15*	**5.78**	***3.23***	**6.00**	***2.87***	2.56	*3.91*	7.22	*2.64*
	1332 mg	92.11	*2.39*	0.67	*0.93*	**−5.22**	***2.02***	−3.67	*2.25*	2.22	*1.84*
Numeric working memory reaction time (ms)	Placebo	792.64	*35.56*	−47.33	*14.79*	1.03	*25.09*	−14.53	*29.76*	−58.15	*19.16*
	167 mg	757.62	*32.92*	−11.44	*11.19*	−1.64	*26.16*	18.25	*26.58*	−21.35	*16.21*
	333 mg	776.56	*39.69*	−36.85	*23.78*	−33.39	*18.56*	−43.17	*15.72*	−56.01	*21.63*
	666 mg	792.10	*32.19*	−21.28	*21.18*	−27.10	*18.43*	−31.15	*22.33*	−36.84	*15.03*
	1332 mg	756.69	*39.93*	−15.46	*21.20*	24.30	*19.80*	−22.53	*22.49*	−28.99	*18.82*
Delayed word recall (% accuracy)	Placebo	27.33	*3.74*	−14.83	*2.99*	−16.33	*2.54*	−15.33	*3.32*	−15.00	*3.62*
	167 mg	22.33	*2.53*	**−9.67**	***2.08***	**−8.83**	***3.24***	−11.67	*2.51*	−11.67	*2.77*
	333 mg	22.33	*2.64*	**−6.00**	***2.84***	**−7.67**	***2.46***	−11.67	*2.79*	−9.17	*2.91*

Table 2 (continued)

Measure		Pre-dose		Post-dose change from baseline score							
		Baseline score		1 h		2.5 h		4 h		6 h	
	666 mg	23.00	*2.71*	**−7.67**	***2.0***	**−7.17**	***2.88***	−11.33	*2.32*	−11.33	*2.78*
	1332 mg	22.83	*2.48*	**−9.83**	***1.96***	**−10.67**	***2.47***	**−10.00**	*2.95*	−11.00	*2.51*
Word recognition	Placebo	55.67	*4.39*	−10.67	*4.55*	−9.67	*3.91*	−18.34	*4.71*	−14.00	*4.43*
(% >chance)	167 mg	47.00	*4.34*	−2.00	*5.03*	−8.00	*4.09*	**−8.33**	***3.83***	−12.00	*4.04*
	333 mg	43.67	*4.34*	**5.33**	***4.03***	**3.33**	***4.20***	**0.33**	***3.82***	**−0.67**	***4.04***
	666 mg	51.00	*4.08*	−18.67	*4.48*	−6.62	*5.42*	**−7.31**	***3.90***	−11.00	*4.94*
	1332 mg	48.00	*4.32*	**0.00**	***4.30***	−2.67	*5.73*	−10.00	*4.80*	−11.00	*4.65*
Word recognition	Placebo	909.77	*47.14*	37.95	*23.42*	59.32	*26.86*	23.63	*28.67*	17.88	*30.63*
reaction time (ms)	167 mg	941.27	*61.67*	20.84	*37.76*	10.04	*32.56*	−13.21	*23.23*	−17.61	*34.93*
	333 mg	869.54	*47.04*	56.12	*20.60*	68.93	*38.12*	6.06	*19.07*	41.72	*28.20*
	666 mg	890.30	*39.64*	129.25	*70.99*	63.97	*22.92*	16.23	*27.27*	49.19	*29.71*
	1332 mg	878.55	*52.77*	68.09	*23.49*	16.80	*16.88*	25.48	*29.12*	32.59	*32.19*
Picture recognition	Placebo	68.00	*4.64*	−1.75	*4.62*	−5.75	*3.76*	−7.25	*3.85*	−5.75	*3.23*
(% >chance)	167 mg	63.25	*4.52*	−2.00	*4.89*	−2.75	*4.42*	1.25	*3.30*	1.25	*3.73*
	333 mg	71.75	*4.55*	−7.00	*3.79*	−5.00	*3.30*	−6.25	*2.94*	−8.25	*3.06*
	666 mg	73.00	*4.14*	−8.75	3.05	−9.50	4.97	−14.75	*3.58*	−5.75	3.65
	1332 mg	65.75	*5.40*	−1.75	4.88	−5.50	5.21	−2.00	*4.37*	−3.00	4.17
Picture recognition	Placebo	985.92	*33.57*	57.52	*25.67*	35.55	*19.88*	50.75	*31.65*	39.34	*22.70*
reaction time (ms)	167 mg	971.20	*39.49*	52.40	*23.22*	72.86	*23.51*	47.07	*23.19*	39.45	*26.10*
	333 mg	994.36	*46.99*	18.36	*24.66*	63.48	*26.49*	2.78	*23.31*	4.66	*28.59*
	666 mg	1009.80	*51.14*	77.90	*21.63*	21.23	*23.05*	16.91	22.24	−5.57	22.59
	1332 mg	986.97	*44.66*	36.11	*23.76*	−9.24	*28.24*	47.55	32.60	21.97	38.41

Mean baseline and change from baseline scores are presented, with standard errors in italics.
Significant differences from placebo are shown in bold font (see text for details).

The same dose also was associated with a trend towards improvement performance at both the 1- and 6-h testing sessions (1 h [$t(228)=1.66$, $p=0.09$] and 6 h [$t(228)=1.65$, $p=0.09$]). An improvement in performance was also found for the highest dose (1332 mg) of *Salvia* at the 4-h testing session only [$t(228)=2.15$, $p=0.03$] (see Fig 1a).

With reference to the single task outcomes contributing to the 'secondary memory' factor, the initial ANOVA revealed a significant main effect of treatment on the delayed word recognition task [$F(4,228)=2.78$, $p=0.033$]. Planned comparisons showed that improvement in delayed word recognition was consistent across all testing sessions for the 333-mg dose (1 h [$t(228)=3.54$, $p=0.0004$], 2.5 h [$t(228)=2.87$, $p=0.0043$], 4 h [$t(228)=4.13$, $p=0.00005$] and 6 h [$t(228)=2.95$, $p=0.0035$]. The 167-mg dose evinced a significant improvement at the 4-h session [$t(228)=2.21$, $p=0.027$] and a trend towards improvement at the 1-h session [$t(228)=1.91$, $p=0.056$]. For the 666-mg dose, improvements were evident at 4 h post dose [$t(228)=2.44$, $p=0.015$] with a trend at 1 h [$t(228)=1.77$, $p=0.07$]. There were also significant improvements on the word recognition task at 1 h post dose for the 1332-mg dose [$t(228)=2.36$, $p=0.019$] with a trend at 4 h [$t(228)=1.84$, $p=0.066$].

Additionally there was a trend towards a main effect of treatment for immediate word recall [$F(4,228)=2.31$, $p=0.066$]. On this measure, there was a significant improvement for the 167-mg dose at 2.5 h post dose [$t(228)=1.97$, $p=0.049$], and at the 2.5- and 4-h sessions following 333 mg of *Salvia* (2.5 h [$t(228)=3.36$, $p=0.0009$] and 4 h [$t(228)=2.92$, $p=0.0038$]).

Following administration of the lowest dose (167 mg), significant improvements were found for the delayed word recall task at 1 and 2.5 h post dose (1 h [$t(228)=2.09$, $p=0.036$] and 2.5 h [$t(228)=3.04$, $p=0.002$]) with trends for at the 4- and 6-h sessions (4 h [$t(228)=1.48$, $p=0.13$] and 6 h [$t(228)=1.35$, $p=0.17$], see Table 2). Significant improvements in delayed word recall were also evident for the 333-mg dose of *Salvia* at 1 h [$t(228)=3.59$, $p=0.0004$], 2.5 h [$t(228)=3.52$, $p=0.0005$] and 6 h post dose [$t(228)=2.37$, $p=0.019$]. Administration of the 666-mg dose evinced improvements at 1 h [$t(228)=2.91$, $p=0.004$] and 2.5 h [$t(228)=3.72$, $p=0.0002$] whilst the highest dose (1332 mg) revealed improvements at 1, 2.5 and 4 h post dose (1 h [$t(228)=2.03$, $p=0.043$], 2.5 h [$t(228)=2.30$, $p=0.022$], 4 h [$t(228)=2.17$, $p=0.031$]).

Accuracy of attention Compared with placebo there was a significant improvement for 'accuracy of attention' follow-

ing administration of 333 mg of *Salvia* (1 h [$t(228)=2.15$, $p=0.031$], 4 h [$t(228)=3.87$, $p=0.0001$] >and 6 h [$t(228)=3.35$, $p=0.0009$]) and a trend for the 2.5-h session [$t(228)=1.86$, $p=0.06$]. There was also a significant improvement following the two highest doses at the 4-h testing session (666 mg [$t(228)=2.38$, $p=0.017$] and 1332 mg [$t(228)=2.75$, $p=0.006$] see Fig. 1b).

There were significant effects associated with individual tasks contributing to the 'accuracy of attention' factor. Digit vigilance accuracy was improved following the 333-mg dose at 2.5 and 4 h [[$t(228)=3.07$, $p=0.002$ and $t(228)=3.69$, $p=0.002$, respectively] with trends towards improvements at 1 h [$t(228)=1.84$, $p=0.066$] and 6 h [$t(228)=1.84$, $p=0.066$]. Improvements were also evident at the 4-h testing session for the 167-mg dose [$t(228)=2.76$, $p=0.006$] and 666 mg [$t(228)=3.38$, $p=0.0008$]. There were also improvement in choice reaction time accuracy for the 333- and 1332-mg doses at 6 h [$t(228)=2.77$, $p=0.006$ in both cases].

Speed of memory There were no significant effects for any dose on the 'speed of memory' factor (Fig. 1c), nor on any task contributing to the factor (Table 2).

Speed of attention There were no significant effects on the 'speed of attention' factor (Fig. 1d). However, examining the individual tasks which load on these factors revealed that the 333-mg dose produced slower responses in the choice reaction task at 4 and 6 h [$t(228)=2.02$, $p=0.044$] and [$t(228)=2.06$, $p=0.041$], respectively and a further decline in performance for the 1332-mg dose of *Salvia* at 6 h [$t(228)=2.16$, $p=0.032$]. No adverse events were reported at any dose.

Working memory There was a significant improvement in performance on the 'working memory' factor, compared with placebo, following administration of the 333-mg dose of *Salvia* at the 1-h testing session [$t(228)=2.10$, $p=0.036$]. There was also a trend towards improved performance for the same dose at the 4-h session [$t(228)=1.82$, $p=0.068$]. Regarding individual tasks contributing to this factor, there was a trend towards a main effect of treatment for numeric working memory [$F(4,228)=2.19$, $p=0.078$].

Cholinesterase inhibition

The results of the cholinesterase assay are presented in Fig. 2. The mean activity in presence of ONP22 was 0.0077153 compared with a mean activity for ethanol alone of 0.016599. This translates to a mean percent inhibition of the extract equivalent to 53.52%.

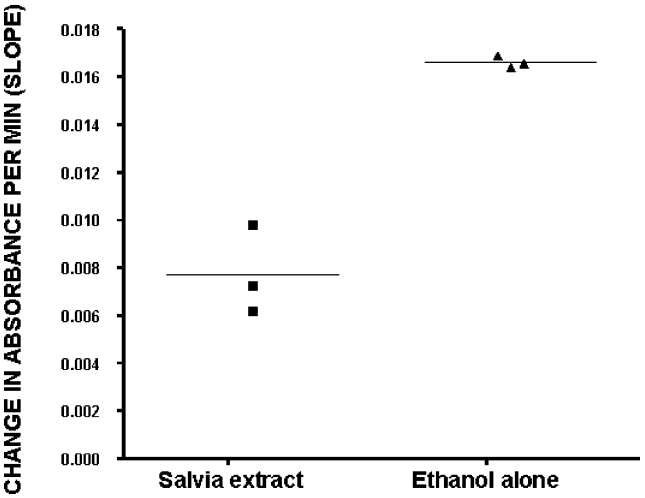

Fig. 2 Inhibition of human cholinesterase by extract of *Salvia officinalis* (*squares*) compared with an ethanol control (*triangles*). Values reflect rate of hydrolysis of acetylthiocholine by human acetylcholinesterase (see text). Three samples each are shown for the active treatment and control with the mean values depicted by *horizontal lines*

Discussion

This study has shown for the first time that administration of a standardised *Salvia* extract can improve cognitive function in healthy older individuals (Fig. 1 and Table 2). Additionally the extract showed considerable anti-cholinesterase inhibition, approximately halving the breakdown of substrate by human cholinesterase (Fig. 2).

The most striking behavioural effect was a dose-specific improvement in secondary memory performance, with significant enhancement compared with placebo at all time points for the 333-mg dose. Reference to Fig. 1 shows that whilst in the placebo condition memory performance showed a characteristic decline over the day (e.g. Kennedy et al. 2001a, b, 2002a, b, 2003; Tildesley et al. 2003, 2005), this decline was not evident in the 333-mg condition where performance was consistently significantly higher than placebo. There was a similar, though more modest, improvement compared with placebo in the 167-mg condition. This finding is consistent with reports of benefits to memory following administration of the essential oil of a related *Salvia* species, *S. lavandulaefolia*, in healthy young adults: Tildesley et al. (2003, 2005) found similar, albeit less striking, dose-dependent memory improvements in healthy adults using the same methodology as the present study, suggesting that the extracts may share common behavioural properties which may be related to components contained therein. Like these previous studies, an interesting dose-dependent pattern of enhancement was observed here. In the current study, there was some enhancement of memory (at 2.5 and 4 h only) associated with the 167-mg

dose, clear and sustained memory improvement for the 333-mg dose at all time points, but little or no effects at the 666- and 1332-mg doses, respectively (see Fig. 1a). This 'inverted U' dose–response pattern may reflect the action of a single active component. However, it seems more likely, given the variety of known bioactivities of sage species (Imanshahidi and Hosseinzadeh 2006; Kennedy and Scholey 2005), that these effects are due to the action of multiple components interacting in complex and possibly synergistic ways (see Scholey et al. 2005 for an overview of these issues). Thus enhancing memory effects predominate for the 333-mg dose but are expressed to a lesser extent at other doses, with no mnemonic effects at the highest dose.

Examining the individual tasks which load onto the factor reveals the tasks which contribute most to secondary memory effects. There were significant benefits to word recognition across all time points following the 333-mg dose. This was coupled with significant enhancement of immediate word recall at 2.5 and 4 h, and of delayed word recall at all but the 4-h session for the same dose. Examination of the effects of other doses on word recall reveals that immediate word recall was improved at 2.5 h only for the 167-mg dose, whereas delayed word recall was improved by all doses at 1 and 2.5 h (although these effects were closest to placebo scores for the 167-, 666- and 1332-mg doses). Only the highest dose improved delayed word recall at 4 h. The general pattern of greater effects for delayed than immediate word recall may simply reflect the fact that more cognitive resources are necessary during delayed word recall and more effortful processes may be more amenable to enhancement. On the other hand, recognition processes are usually considered to be less effortful than recall, and word recognition was enhanced at all time points by the 333-mg dose. It is also worth noting that the effects on word recall were a true reflection of memory accuracy rather than an effect of more errors and/or intrusions in the placebo group. Examination of the data showed that only five subjects exhibited one or two errors and only three had one or two intrusions.

This enhancement of both verbal recall and recognition suggests that the treatment may be acting on hippocampal structures underpinning secondary memory processing. This supposition could be tested empirically by examining the effects of *S. officinalis* on the 'remember/know' paradigm (for a review see Gardiner and Richardson-Klavehn 2000). It is argued that recognition memory can be differentiated into 'familiarity' responses mediated by extra-hippocampal areas including the perirhinal cortex in the temporal lobes, whilst more conscious 'remember' responses depend more upon the hippocampi (Aggleton and Brown 1999). Furthermore, the left and right hippocampi may be differentially involved in verbal and pictorial material, respectively—since there were no effects on picture memory we can tentatively speculate that these effects may involve the left hippocampus. Clearly this matter could be addressed with more certainty using functional imaging technology, our groups are actively pursuing this area.

Although we do not wish to over-interpret the present data by attempting to translate them into clinically meaningful effects, it is worth noting that the overall superiority for secondary memory of the most effective (333 mg) dose to placebo was approximately 30 units (see Fig. 1a). This comfortably exceeds that seen previously for a ginkgo–ginseng combination in healthy middle-aged volunteers (Wesnes et al. 2000). Comparing a normal population of the age-range in the present study to that in healthy 18 to 25 year olds shows a decline in the secondary memory factor of 43.2 units (95% confidence intervals 36.4 to 50.2). The benefits seen in the present study thus reflect a substantial reversal of the deterioration which typically occurs over approximately five decades of normal ageing. Furthermore, it is worth emphasising that this was a high-functioning sample. Although no formal IQ measure was taken, the group's performance exceeded the norms for this age (Table 1). Thus it seems that the effects of this extract are unlike those of the 'wakefulness promoting' modafinil where, at least in young volunteers, cognition-enhancing effects (improved vigilance and speed of processing) appear to differentially affect those with lower IQ (Randall et al. 2005). Examining the magnitude of the baseline characteristics, we see that the differences in the secondary memory factor's scores were in the order of one standard deviation, equating to a large effect size. For the other factors, the effects sizes were in the medium to small range. Since baseline functioning on the secondary memory factor is relatively better than on the other factors, and memory appeared to be the most improved by the extract, we might tentatively suggest that the sage extract is doing more than simply 'normalising' lower than average performance, and clearly the findings from these and other agents need to be replicated in various age groups and populations.

In addition to the improvements to memory, there were some improvements in attentional performance, again predominantly for the 333-mg dose, at all but the 2.5-h time point (Fig. 1b). The 'accuracy of attention' measure is derived from performance on tasks where the subject is required to categorise present/absent stimuli, or to ignore irrelevant in favour of relevant stimuli. As such it is a measure of selective attention. Significant changes to performance of the digit vigilance task are largely responsible for this effect (Table 2). The fact that there were fewer effects on simple and choice reaction time suggests that positive effects of the extract may become apparent at higher levels of cognitive load. We have seen this effects before following administration of another herbal com-

pound to young adults (Scholey and Kennedy 2002) and have argued that it may be due to a combination of neurochemical and metabolic processes (Scholey et al. 2001, 2002). Such effects were not observed in two previous studies into the effects of *S. Lavandulaefolia* in younger samples (Tildesley et al. 2003, 2005). The attentional data are largely consistent with a recent study using a cholinesterase-inhibiting dried leaf of *S. officinalis* preparation. Although the studies had different aims, outcomes and populations, Kennedy et al. (2005) found a dose-dependent improvement in selective attention performance as assessed by performance on a variant of the Stroop task. In that study, the effects were evident at both 1 and 4 h post dosing. No secondary memory measure was used in the Kennedy et al. (2005) study so we cannot make any comparison with the most striking findings here.

Differences in patterns of behavioural effects presumably reflect differences in active components between species, and fractions isolated from the same species. We have observed similar effects for another member of the Labiatae family, *Melissa officinalis* (lemon balm), where different patterns of behavioural effects were observed for a concentrated extract compared with a dried leaf preparation (Kennedy et al. 2002, 2003). The former extract had negligible cholinergic activity whilst the latter preparation exhibited marked nicotinic and muscarinic receptor binding. They also raise the intriguing possibility that the level of refinement of herbal extracts may in some cases actually reduce their psychopharmacological activity, a notion which is very different to the mono-pharmacological philosophy of much allopathic medicine. As well as emphasising the need for adequate standardisation techniques in this field, such findings caution against over-generalisation of the results of studies such as these. They also underline the need for a comprehensive programme of research into the behavioural effects of different plant extracts.

The pattern of results is particularly interesting since the primary effect is on memory rather than attention. The 'secondary memory' factor comprises score from tasks specifically assessing declarative memory. This is important in relation to potential neurochemical substrates of the effects of *Salvia*. Although the cholinergic system is a candidate target for the extract, and we found anti-cholinesterase inhibition for the extract (Fig. 2), increased cholinergic activity might be expected to predominantly affect attentional measures with a secondary and less pronounced effect on memory (Scholey 2002). Other potential neurotransmitter targets include noradrenaline, serotonin, dopamine and the glutamate NMDA receptor (e.g. Scholey 2002; Seamans and Yang 2004). Whilst it is tempting to speculate on the mechanisms underlying these effects, they are likely to stem from multiple influences on the physiological substrates of behaviour. Thus although the modulation of cholinergic transmission, verified in vitro, may play a role in both attentional and mnemonic effects, these other systems are likely involved. The interaction of *S. officinalis* with these has not been characterised but the possibility of additive or synergistic effects cannot be ruled out.

Further research is needed to establish which chemical constituents in the *Salvia* extract are relevant to memory enhancement. The major monoterpenoid constituents of *S. lavandulaefolia* essential oil inhibit erythrocyte AChE with varying degrees of potency (Miyazawa et al. 1997). With IC50s ranging between 0.4 and 0.7 mM, 1,8-cineole (15–30% of essential oil) and α-pinene (4–7%) show the most cholinesterase inhibition. These figures are reasonably consistent with the level of inhibition found for the present extract. Extrapolating from the level of inhibition (Fig. 2) and dilution factors, we can estimate that the IC50 for the current extract is approximately 0.4 mg/mL. This is less active by two orders of magnitude than the mainstream anticholinesterases physostigmine, rivastigmine and donepezil (with IC50s in the nanomolar range, Ogura et al. 2000), again suggesting that non-cholinergic mechanisms are involved in the current extracts cognition-enhancing properties. Additionally the constituents contained within *Salvia* may combine non-linearly to produce cholinesterase inhibition. A combination of the major monoterpenoid constituents (camphor, 1,8-cineole, borneol, α-pinene and β-pinene) reconstituted in a naturally occurring ratio was significantly less potent than that of the whole oil (Perry et al. 2003; Savelev et al. 2003, 2004). The monoterpenoids may therefore act synergistically to inhibit AChE. This idea is supported by a study of the anticholinesterase constituents of *S. lavandulaefolia* essential oil where it was concluded that inhibitory activity results from complex synergistic and antagonistic interactions between constituent terpenoids (Savelev et al. 2003). For example, minor synergy was found between 1,8-cineole and α-pinene, 1,8-cineole and caryophyllene epoxide, and antagonism was found to occur between 1,8-cineole and camphor. The extent to which these and other individual components contribute to the cholinesterase inhibition from the present extract merits further investigation.

The effects described in this paper have obvious implications for the treatment of age-related memory problems and even possibly Alzheimer's disease. Indeed significant improvement in cognition (assessed using the ADAS-Cog) has been reported in a sample with mild/moderate Alzheimer's disease in a 4-month, placebo-controlled trial of a *Salvia* extract (Akhondzadeh et al. 2003). However the harvesting and extraction of *Salvia* was not highly controlled, nor was the extract used well characterised. Thus whilst such results are extremely

encouraging, it is important to replicate them using better characterised extracts. The use of standardised growing procedures, coupled with detailed extraction information (as here) may go some way to addressing such issues.

The results of the current study demonstrate a significant acute improvement of cognition following the administration of sage, with particular benefits for secondary memory. This is a very favourable response profile as memory impairments are the core deficits of mild cognitive impairment and early Alzheimer's disease. In contrast, existing anti-dementia treatments have a primary effect on attention and only a secondary benefit on memory. Sage therefore has potential as an agent not only for general enhancement of cognition in older people, here using a well-controlled trial and extract with established cholinesterase inhibition, but also in Alzheimer's disease either alone or as an adjunct to more conventional therapies. Further work is needed to assess the effects of both acute and chronic administration of *Salvia* extracts in such populations.

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