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ORIGINAL INVESTIGATION

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Modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects

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Abstract *Rationale:* The central cholinergic system is implicated in cognitive functioning. The dysfunction of this system is expressed in many diseases like Alzheimer's disease, dementia of Lewy body, Parkinson's disease and vascular dementia. In recent animal studies, it was found that selective cholinergic modulation affects visuospatial processes even more than memory function. *Objective:* In the current study, we tried to replicate those findings. In order to investigate the acute effects of cholinergic drugs on memory and visuospatial functions, a selective anticholinergic drug, biperiden, was compared to a selective acetylcholinesterase-inhibiting drug, rivastigmine, in healthy elderly subjects. *Methods:* A double-blind, placebo-controlled, randomised, cross-over study was performed in 16 healthy, elderly volunteers (eight men, eight women; mean age 66.1, SD 4.46 years). All subjects received biperiden (2 mg), rivastigmine (3 mg) and placebo with an interval of 7 days between them. Testing took place 1 h after drug intake (which was around T_{max} for both drugs). Subjects were presented with tests for episodic memory (wordlist and picture memory), working memory tasks (N-back, symbol recall) and motor learning (maze task, pursuit rotor). Visuospatial abilities were assessed by tests with high visual scanning components (tangled lines and Symbol Digit Substitution Test). *Results:* Episodic memory was impaired by biperiden. Rivastigmine impaired recognition parts of the episodic memory performance. Working memory was non-significantly impaired by biperiden and not affected by rivastigmine. Motor learning as well as visuospatial processes were impaired by biperiden and improved by rivastigmine. *Conclusions:* These results implicate acetylcholine as a modulator not only of memory but also of visuospatial abilities.

Keywords Biperiden · Rivastigmine · Anticholinergic · Acetylcholinesterase inhibitor · Memory · Visuospatial processes · Healthy elderly volunteers

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Introduction

Insight into the major role of the central cholinergic system in memory arose from the finding that cognitive deficits are correlated with extensive cholinergic cell loss in the brain in Alzheimer's disease (AD). Pharmacological studies were able to show impaired cognitive performance after blocking central cholinergic pathways by use of anticholinergic drugs. Subsequent studies showed that this process could be reversed by enhancing cholinergic function with the treatment of cholinesterase inhibitors (ChEis) (Blokland 1995; Everitt and Robbins 1997; Muir 1997). The type of cognitive functions modulated by the acetylcholine (ACh) system varies from learning and memory to visuospatial abilities, attention and other cortical modulation of sensory information by changing the signal-to-noise ratio of neural transmission (Lucas-Meunier et al. 2003). In contrast to animal research, human research mainly focussed on the learning and memory modulating effects of ACh, concentrating on the ACh receptor antagonist, scopolamine and the ChEi physostigmine. Generally, the findings indicate that encoding processes, and not retrieval processes of the declarative memory functions, are

negatively affected by scopolamine (Atri et al. 2004; Mintzer and Griffiths 2003), and that the administration of physostigmine can restore the memory functioning back to normal (Flood and Cherkin 1986; Hammond et al. 1987; Mewaldt and Ghoneim 1979).

In animal studies, more specific methods can be used to disable the cholinergic system. Central nervous system (CNS) cholinergic pathways can be totally destroyed by several excitotoxic lesioning methods (Everitt and Robbins 1997; Muir 1997; Robbins et al. 1997a; Sarter and Bruno 1998a). Many of the early studies using excitotoxic lesions in the nucleus basalis of Meynert in rats showed a broad range of impaired performance on various learning paradigms like the Morris water maze, delayed-non-matching-to-position and passive avoidance tasks (Dunnett et al. 1991; Fibiger 1991; Muir 1997). These early toxins were not solely selective for cholinergic neurons; therefore, it is interesting that most of the more recent studies using new highly selective toxin for ACh neurons, 192 IgG-saporin, could not reproduce the earlier findings (Baxter et al. 1995; Baxter and Gallagher 1996; De Rosa et al. 2001; Gutierrez et al. 1999; Power et al. 2003; Torres et al. 1994; Wenk et al. 1994). This suggests that the selective decrease of cholinergic function might not impair learning and memory performance (Blokland 1995). Recent animal studies have shown that selective decrease of cholinergic function markedly impaired measures of attention and visuospatial performance (like a five-choice serial reaction time task, a continuous performance test of visual attention and an animal version of Posner's orientation task). Due to these findings, the focus of interest in animal research has shifted from learning and memory to attentional and visuospatial functions (Muir 1997; Voytko 1996; Voytko et al. 1994).

Data concerning the effects of ChEis in patients suffering from AD, as well as Lewy body dementia (LBD), Parkinson's disease (PD) and vascular dementia (VaD), show that ACh not only influences memory, but also attention and neuropsychiatric symptoms (Corey-Bloom 2002; Lucas-Meunier et al. 2003; Poirier 2002; Sarter and Bruno 1998b).

On the other hand, as mentioned before, in healthy volunteer studies, relatively little attention has been paid to the effects of cholinergic modulation on other than memory-related cognitive functions, like visuospatial and attentional abilities, and the studies that have used non-selective cholinergic drugs (scopolamine and physostigmine). Nevertheless, these few studies do seem to indicate that visuospatial processes can be impaired by anticholinergic compounds and facilitated by ChEi (Curran et al. 1991; Kopelman and Corn 1988; Meador et al. 1993; Mintzer and Griffiths 2003). In support of this view are the results of two patient studies: one study that looked into the effects of chronic co-administration of rivastigmine in schizophrenia, where it was found that rivastigmine lead to a significant improvement in spatial working memory (Sharma et al. 2004). The other study looked into the effects of physostigmine on cognition in schizotypical personality disorder and found a positive effect also on spatial working memory (Kirrane et al. 2001). The question arises as to whether the same results as in the animals can be reproduced in human healthy volunteers. We hypothesized that selective cholinergic drugs as compared to scopolamine and physostigmine would show little effect on memory performance and more on visuospatial performance.

A variety of memory and learning tests were selected, with and without visuospatial aspects. In addition, a set of tests with visuospatial elements was selected with and without memory components. The cholinergic drugs, biperiden and rivastigmine, were chosen as study medication. Biperiden is a muscarinic receptor antagonist with much higher affinity for the muscarinic 1 (M1) receptor than scopolamine, which is rather non-selective (Guthrie et al. 2000; Jones and Shannon 2000). M1 selectivity is relevant because the M1 receptors are primarily located in the hippocampus and cerebral cortex. They are associated with cognitive function and cell loss in AD (Bymaster et al. 1993; Everitt and Robbins 1997; Jones and Shannon 2000; Mash et al. 1985).

Theoretically, a selective M1 agonist would have been the preferred choice as comparison drug; however, most drugs that had been taken into clinical trials have now been discontinued due to lack of efficacy, unacceptable side effects and poor plasma pharmacokinetics (Eglen et al. 2001). Therefore, we have chosen for a registered ChEi rivastigmine that has proven to be effective in improving cognition in AD and has an acceptable side effect profile (Birks et al. 2003). In addition, it has a favourable pharmacokinetic profile. As opposed to physostigmine, it is relatively selective for the CNS. It primarily affects the hippocampus and neocortex, the regions most affected by AD (Enz et al. 1993).

Other reasons for choosing these drugs lie in their clinical relevance and in the general lack of knowledge of their cognitive effects. Biperiden is one of the drugs used to alleviate tremors in PD and extrapyramidal symptoms caused by antipsychotic agents (Guthrie et al. 2000). Rivastigmine is used to delay and reverse cognitive aspects of disease progress in AD and LBD (Birks et al. 2003; Wild and Petit 2004). Both scopolamine and physostigmine, the drugs that are commonly used in this field of research, are mainly used for research purposes. Their cognitive effects are well known.

Materials and methods

Subjects

The study was approved by the local Medical Ethics Committee. All subjects gave their informed consent before participating in the study.

To prevent ceiling effects on cognitive measures, this study was performed in healthy elderly volunteers, because it is known that both cholinergic and cognitive functions decline with age and can be improved by ACh inhibitors. Sixteen healthy elderly volunteers completed this study,

eight men and eight women. The mean age was 66.1 years (SD 4.46, range 60–75 years). They were all in good physical and mental health as determined by medical history, medical examination, ECG and laboratory examination. Mini Mental State Examinations scores were normal (mean 28.13, SD 1.73, range 25–30). Fifteen volunteers were right-handed and one was ambidextrous. The education level varied from primary education to academic level (primary, 3; lower, 2; intermediate, 3; higher, 6; academic, 2).

Drug administration

A double-blind, placebo-controlled, randomised, four-way crossover study was performed with placebo, biperiden 2 mg and rivastigmine 3 mg, and Org24448 500 mg as drug conditions.

For biperiden peak, plasma concentrations are reached 1 to 2 h after single dose administration followed by a rapid initial decline of the concentrations to 12% of the peak values after 6 h, and subsequently followed by a slow terminal elimination phase with concentrations close to or below detection limit at 48 h (Hollmann et al. 1987). In steady state, half-life is 26–40 h in elderly subjects. For rivastigmine, the time to reach maximum plasma concentration ranges from 0.8 to 1.2 h. In elderly healthy volunteers, the plasma elimination half-life is 0.9 to 1.3 h. Renal elimination of the drug's metabolites is rapid and essentially complete after 24 h. Inhibition of ChE activity (in CSF) is significant by 1.2 h, reaches a peak by 2.4 h and declines slowly until approximately 8.5 h (Jann et al. 2002). Org 24448 is an Ampakine, which is known to enhance long-term potentiation, a mechanism associated with consolidation in memory (Staubli et al. 1994). For Org24448, the time to reach maximum plasma concentration after oral administration of Org24448 500 mg is 1.2 h. The terminal elimination half-life is approximately 6–8 h. Because Org 24448 is not a cholinergic compound, the results on this drug will be reported elsewhere.

All drugs were administered in single oral doses, with a washout of 1 week. To achieve a balanced administration order, the drugs were randomised using a Latin-square design (repeated four times). Testing took place 1 h after drug intake (which was around T_{max} for all drugs).

Tests, apparatus and procedure

The tests that were used in this study belong to a cognitive and psychomotor test battery (Wezenberg et al. 2004). In this paper, only the results concerning memory and visuospatial performance are reported. The performance on all tests was recorded by means of a digitizing tablet (WACOM UD-1218-RE), a laptop computer, a pressure-sensitive pen (which could also be used as a cursor) and test forms. The *x* and *y* coordinates of the pen tip on and up to 5 mm above the digitizer were sampled with a frequency of 200 Hz and a spatial accuracy of 0.2 mm (de Jong et al. 1996).

Table 1 Order of the tests and the relative time to drug administration at the start of each test

Tests	Relative time after drug intake (min)
VMT, IR trials	60
SDST	67
SDRT 1st	69
VMT, DR 1st	72
Tangle	77
Picture memory	90
Figure Copying Task	95
SDRT 2nd	98
VMT, DR 2nd and RC	102
Maze learning task	122
N-back task	132

Only tests that will be reported in this paper are displayed
VMT Verbal Memory Test, *IR trials* immediate recall trials, *DR 1st* first delayed recall trial, *DR 2nd* second delayed recall trial, *RC* recognition trial, *SDST* Symbol Digit Substitution Test, *SDRT 1st* first recall trial of the SDST

To familiarize the subjects with the tests and procedures, they were invited to the hospital to perform a practice session within 1 week before the actual study days. All tests had five equal versions for four test days and one practice day; test versions were counterbalanced over test days. The order of the tests as well as the relative time to dose at the start of each test is displayed in Table 1.

Episodic memory tests

Verbal memory test

Based on the classical Auditory Verbal Learning Test (Vakil and Blachstein 1993), a variant was made consisting of a list of 18 words. The classic test uses 15 words; however, to prevent ceiling effects, and moreover, to make the test very difficult and to resemble a state of dementia, a longer wordlist was chosen. The list was presented verbally three times, and under normal circumstances, subjects are supposed to remember more words after each trial. Directly after each presentation and after an interval of 5 and 30 min, subjects were asked to recall as many words as they could remember. After the last delayed recall trial, a list of 36 words was presented from which they had to recognize the 18 correct words. The incorrect words were distracters and resembled the correct words in a semantic or phonologic manner. The outcome measures are number of correct scores for the three immediate recall trials, the two delayed recall trials and the delayed recognition trial.

Picture memory

Visual memory or picture memory has been used widely as a measure of immediate and delayed memory for the

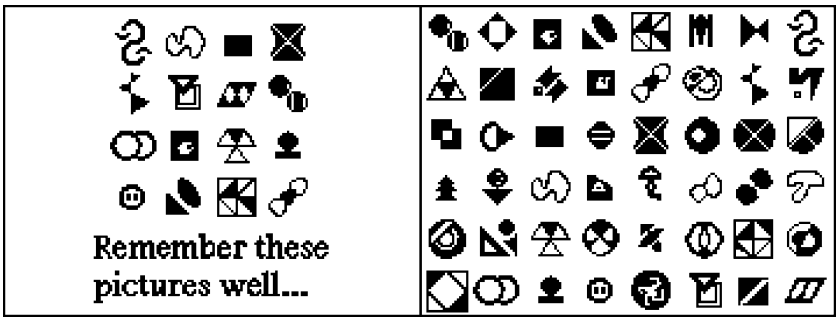

Fig. 1 Example of picture memory test. To the left are the 16 pictures that need to be learned. To the right are where the 16 correct ones need to be recognized

detection of cognitive change in all sorts of conditions. The picture memory task used in this study was modelled after a task used for the detection and localisation of brain damage by Petrides and Milner (1982). That visual memory tests are also sensitive for cholinergic (and other) drug effects has been shown by many studies (Kikuchi et al. 1999; Peretti et al. 1997; Rammsayer et al. 2000; Robbins et al. 1997b).

An example of the test is depicted in Fig. 1. In the first part of this test (the immediate visual recognition part), a matrix of 16 abstract visual designs was presented, which had to be memorized. Thereafter, a matrix of 48 designs was presented, and the 16 original designs had to be identified by pointing them out. The second part of the test started with the presentation of the correctly remembered designs, which were interspersed among other designs (again together 48 designs). Subjects were asked again to learn these designs and to recognize them out of 48 designs, but now, only one at a time. After each choice, the matrix was scrambled, containing the same 48 designs, and the subjects had to point out the next design. This continued until all designs had been recognized or until two mistakes in a row had been made.

This test evaluates visual recognition and self-ordered retrieval, and the outcome measures are number of correct in part 1 and part 2.

Working memory tests

N-back task

For the measurement of working memory, an N-back task was chosen that is widely used for the detection of working memory deficits in schizophrenia (Meyer-Lindenberg et al. 2001; Weinberger et al. 1996). In the present version of this test, subjects were presented with a starting circle and six possible target circles surrounding the starting circle on the computer monitor, which reflects the same positions as on the paper form. In the 1-back condition, subjects had to respond to the stimulus that was presented in the previous trial. In the 2-back condition, subjects had to respond to the stimulus that was presented two trials before. Both conditions had two parts with either 25 correct trials or the number that could be attained in 2-min duration.

The outcome measure is 'movement time to reach target', which is faster when working memory is improved and slower when working memory is impaired. The measure 'distance covered to reach target' was added as a control variable because movement time is dependent of the distance needed to cover. One subject did not perform this test.

Symbol digit recall test

This test comes directly after the Symbol Digit Substitution Test (SDST), which will be discussed in the last paragraph of this section. When subjects were finished with the SDST, they were again presented with the symbols from the SDST, now one at a time, and asked to point out the corresponding numbers.

This test is based on an extended procedure of the SDST by Kaplan et al. (1991) to measure incidental learning. The outcome measures are the number of correctly identified symbols and the response times.

Motor learning tests (with visuospatial component)

Maze learning task

To study the effect of cholinergic modulation on motor learning, we used the maze learning task form developed by van Mier et al. (1993). In several studies (among one PET study), it was shown that this task assesses motor learning without sight (van Mier et al. 1993, 1998) (for an example, see Fig. 2). The maze designs are cutout designs creating a path for the pen to traverse. The maze consists of eight line segments, with a complete path of 24 cm; the width of the paths is 0.5 cm, the depth 0.15 cm. To simplify decision making, the maze consists of straight lines with 90° angles. Only two opposite direction choices can be made at each intersection, one of which comes to a dead end. The length of each dead end path is 0.5 cm. The maze forms a closed loop, meaning start and end points are the same. There are four equal versions and a practice square. Subjects were instructed to close their eyes and find their way in the maze and make as many loops as possible in 2 min. They started with a practice maze for 30 s, then three trials with the maze and afterwards another trial with the rotated maze (subjects were told they had a new maze).

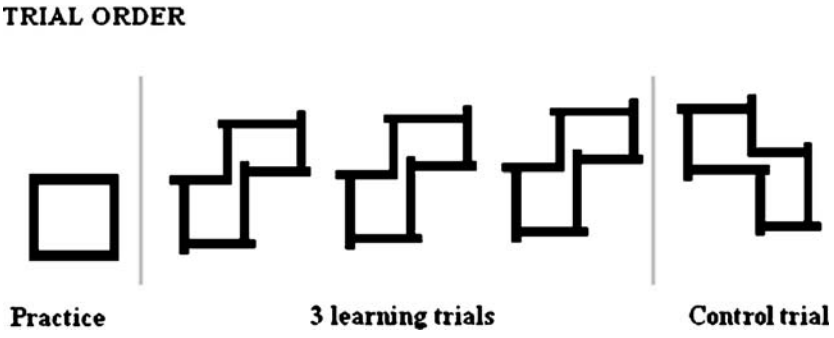

Fig. 2 Example of the maze test

This was done to control for a general increase in motor speed instead of improved motor learning.

The outcome measure is 'number of completed loops' in 2 min.

Pursuit task

To measure implicit procedural learning, a computerized version of the rotor pursuit task was used. This test is based on the classical rotary pursuit task (Ammons 1947; Siegel 1990). It is a continuous motor task. Subjects had to follow the movement of a large target stimulus on the computer screen with a cursor by moving the pen over the XY tablet. The speed of the target gradually increases when the cursor is contained within the target but slows down quite quickly when it is not. The target follows a spatially predictable circular path over the screen. The outcome measures for procedural learning are the 'total number of rotations' and 'time per loop' (i.e. one 360° tracking of the target) for the first five loops.

Visuospatial information processing tests (without learning)

Tangle

The tangle task is a purely visual task requiring high concentration for visually tracking a particular line winding through two to four other lines.

The tangled lines were presented on the screen. The line that had to be visually traced to the end was indicated by a yellow square. On subsequent trials the tangles increased in complexity; they got longer and made more 90° turns. The paper form had a start area and five target areas, numbered 1 to 5, which reflect the maximum target areas on the screen, starting with only three target areas as in the example in Fig. 3.

This test is modelled after the visualisation test from the 'kit for factor referenced cognitive tests' of Ekstrom et al. (1976) and French (1954). It was selected by the US NAVY to study environmental and other time-course effects and has good task stability and reliability (Bittner et al. 1983, 1986). The outcome measure is the number of correct trials in 2 min.

Symbol digit substitution test

This test is a variant of the subtest from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1981). Subjects have to substitute the symbols for digits 1–9 on the basis of a given key. The outcome measure is the total number of digits completed in 90 s.

According to Hege et al. (1997) and Lezak (1995), this task measures many cognitive components like visuospatial scanning, intermediate memory, perceptual motor speed and speed of cognitive processing. Therefore, subsequent analyses were performed to attempt to disentangle these cognitive processes. Based on pen pressure, movement trajectories were defined as either pen-up periods or pen-down periods. This allowed for subsequent analysis of matching times and movement (writing) times in the SDST. For the motor component, the mean writing times were computed. For the more cognitive component, the mean matching times were computed. These analyses have been previously performed by Jogems-Kosterman et al. (2001), Sabbe et al. (1999) and van Hoof et al. (1998).

Control measures: sedation tests and adverse events

Before dose and 60 min after drug administration, subjects performed several tests measuring various aspects of sedation.

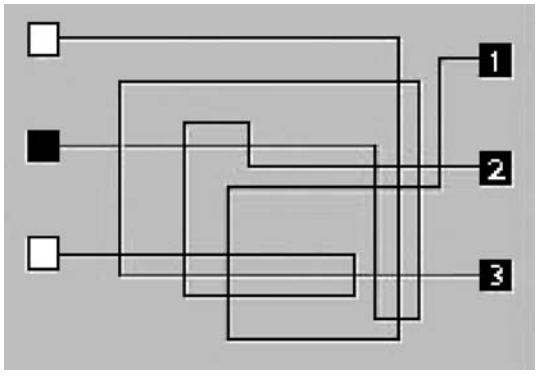

Fig. 3 Example of a simple trial in the tangle test

Neurophysiologic sedation

The measure Saccadic Eye Movements (SEM) was chosen as neurophysiologic measure for sedation. For the saccadic test, subjects were presented with sudden changes of target position at random intervals. The target consists of an array of light emitting diodes on a bar fixed at 50 cm in front of the head support. The size of the steps was fixed at 30° (15 from middle to left–right). The outcome measure is the overall mean peak velocity.

Behavioural sedation

As behavioural measures, Simple (SRT) and Choice Reaction Time Test (CRT) were chosen. In the SRT, a yellow square was presented on the monitor at random intervals (0.5–1.5 s). Subjects were instructed to press the response button on the response module as fast as possible following the detection of the target. There are 20 targets in the trial and the outcome measure is the mean reaction time. In the CRT, the words 'left' and 'right' were presented randomly on the monitor and subjects had to press the corresponding buttons on the response module as fast as possible. There are 20 targets in the trial and the outcome measure is the mean reaction time.

Subjective sedation

As a measure for subjective sedation, a Visual Analogue Scale (VAS) was added (Bond and Lader 1974). The VAS is a questionnaire of 16 visual analogue scales from which three factors are derived that assesses subjective in subjective alertness, calmness and contentment. Another subjective control measure was the reported adverse events (AEs). Whenever subjects reported an AE, this was recorded by MedDRA (6.1) coding.

Statistical analyses

Statistical evaluation (using SPSS 11 for Windows) was performed with GLM repeated measures analysis of variance (ANOVA) with 'drugs' as within-subject factor for all tests. For the Verbal Memory Test (VMT) and Symbol Digit Recall Test (SDRT), also the results for the within-subject factor 'trial' and the interaction between 'trial' and 'drugs' were analyzed. Only the results of the planned contrasts, placebo vs biperiden and placebo vs rivastigmine, will be reported in the results section.

Results

The descriptive statistics of the tests are presented in Table 2, and the results of the analysis are presented in Table 3.

Episodic memory

Verbal memory test

As can be seen in Fig. 4, test scores gradually increased from trial 1 to 3 (trial 1 to 3, $F(2,14)=55.47$, $p<.001$);

Table 2 Means and standard deviations per task and drug condition

	Placebo		Biperiden		Rivastigmine	
	M	SD	*M*	SD	*M*	SD
Picture memory task						
Part 1	6.75	2.24	6.31	2.47	5.75	2.65
Part 2	5.25	1.53	4.63	1.41	4.25	1.69
Pursuit						
No. of rotations	10.56	2.94	9.60	3.70	11.45	3.65
N-back						
1-back TDM	0.70	0.13	0.77	0.14	0.70	0.14
1-back TCM	3.68	0.55	4.26	0.85	3.65	0.54
2-back TDM	0.74	0.23	0.79	0.16	0.72	0.17
2-back TCM	4.69	2.19	4.63	2.00	4.21	1.14
SDRT						
STM (correct)	1.94	1.65	2.69	1.54	3.25	1.69
STM (RT)	3.54	0.72	4.08	1.16	3.49	0.70
LTM (correct)	2.19	1.56	1.75	1.57	2.06	1.29
LTM (RT)	3.16	0.67	3.71	1.04	3.23	1.03
Tangle						
No. correct	12.56	1.32	12.50	1.46	13.13	1.15
SDST						
No. correct	40.69	9.54	36.50	9.45	43.06	10.09
Matching time	1.72	0.51	2.02	0.57	1.62	0.57
Writing time	0.63	0.17	0.61	0.12	0.61	0.20

M Mean, *SD* standard deviations. N-back: *'TDM'* movement time to reach target, *'TCM'* distance covered to reach target. SDRT: *STM* Short Term Memory trial, *LTM* Long Term Memory trial, *RT* response time

Table 3 *F* and *p* values per task and drug condition

	Placebo vs biperiden *df*(1,15)	Placebo vs rivastigmine *df*(1,15)
Verbal memory test		
IR (trial 1 vs 3×drugs)	12.16**	<1
DR (trial 4 vs 5×drugs)	18.52***	3.45#
RC trial 6	5.12*	5.77*
Picture memory task		
Part 1	<1	4.80*
Part 2	2.250	7.06*
N-back		
1-back TDM	2.28	<1
1-back TCM	6.37*	<1
2-back TDM	4.32#	<1
2-back TCM	<1	<1
SDRT		
STM (no. correct)	3.29#	9.10**
STM (response time)	7.05*	<1
LTM (no. correct)	<1	<1
LTM (response time)	5.72*	<1
Maze learning		
Trial (1–3)×drugs	<1	4.93*
Trial (3–4)×drugs	1.15	5.21*
Pursuit		
No. of rotations	2.88	3.49#
Time per loop	6.15*	<1
Tangle		
No. correct	<1	4.23#
SDST		
No. correct	3.52#	5.34*
Matching time	6.96*	2.53
Writing time	<1	<1

Verbal Memory Test: *IR* immediate recall, *DR* delayed recall, *RC* recognition. N-back: *TDM* movement time to reach target, *TCM* distance covered to reach target. SDRT: *STM* Short Term Memory trial, *LTM* Long Term Memory trial
#$p<.10$, *$p<.05$, **$p<.01$, ***$p<.001$

however, from trial 1 to 3, this increase was significantly lower for biperiden compared to placebo. Rivastigmine scores did not improve learning compared to placebo scores on trials 1, 2 or 3.

In the delayed recall trials, test scores declined from trial 4 to trial 5 [$F(1,15)=23.13$, $p<.001$]. In both trials, the biperiden performance was lower compared to placebo. Again rivastigmine did not improve recall; rather, the reverse was marginally significant.

In the delayed recognition trial (trial 6), the test scores approximately returned to the level of trial 3. Biperiden scores and also rivastigmine scores were significantly decreased compared to placebo.

Picture memory

The visual recognition of pictures was not significantly decreased by biperiden in part 1 (simple visual memory) or in part 2 (self-ordered retrieval).

As in the verbal memory test, rivastigmine did not improve but rather impaired performance in both recognition measures.

Working memory

N-back task

Working memory as assessed by the N-back task showed significant larger movements by biperiden in the simple condition, but not in the more difficult condition. Furthermore, a trend of impaired performance was found on the movement times in the more difficult, but not the simple, condition. Rivastigmine had no effect on either measure.

Symbol digit recall test

The measure ‘number correct’ showed a trend of improvement for biperiden. For rivastigmine, also a small but significant improvement was found compared to placebo.

The measure ‘response time’ was impaired by biperiden, whereas rivastigmine did not show any effect.

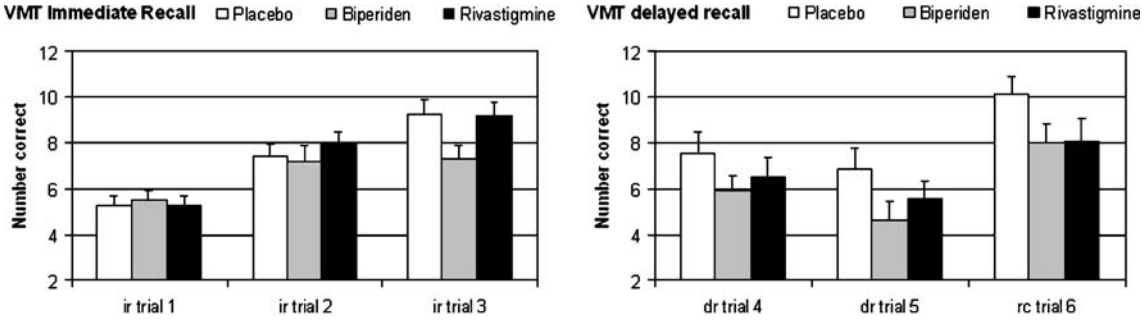

Fig. 4 Results on the Verbal Memory Test (VMT). Immediate recall results are to the left (ir trials 1–3). Delayed recall trials (dr trials 4 and 5) and recognition trial (rc trial 6) are to the right

Motor learning

Maze learning task

As can be seen in Fig. 5, the number of completed loops gradually increased from trial 1 to 3 (trial 1 to 3, $F(1,15)=11.01$, $p=.006$). The improvement in performance over trials was markedly stronger for rivastigmine than for placebo. No effects were found for biperiden.

To test whether the results of rivastigmine reflect improved motor speed instead of improved learning, the results of the new maze were compared to the trials of the old maze. If only motor speed was improved by rivastigmine, these performances should also have been improved. However, there was no interaction between trial (new vs old) × drug [$F(3,10)<1$], which indicates that it appears justified to conclude that rivastigmine improved motor learning in this task.

Pursuit test

The measure 'total number of rotations' appeared to show deterioration in performance for biperiden; however, this effect did not reach significance. There was a trend of improvement in performance for rivastigmine.

The results of the procedural learning measure 'time per loop' can be seen in Fig. 6. The time per loop was increased for biperiden compared to placebo; no effects were found for rivastigmine. There was no interaction between drug × loop (1–5), indicating that the difference between biperiden and placebo was constant over loops.

Visuospatial processes

Tangle

Visuospatial processes, as measured by the number of correctly solved tangles, were not affected by biperiden and tended to be improved after rivastigmine intake.

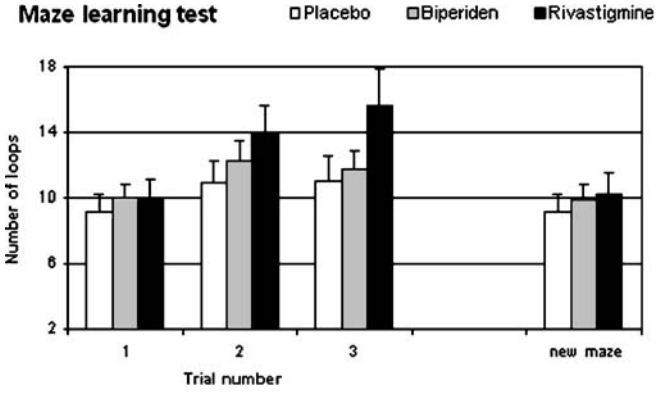

Fig. 5 Results for maze learning test on trials 1–3 and the new maze for placebo, biperiden and rivastigmine

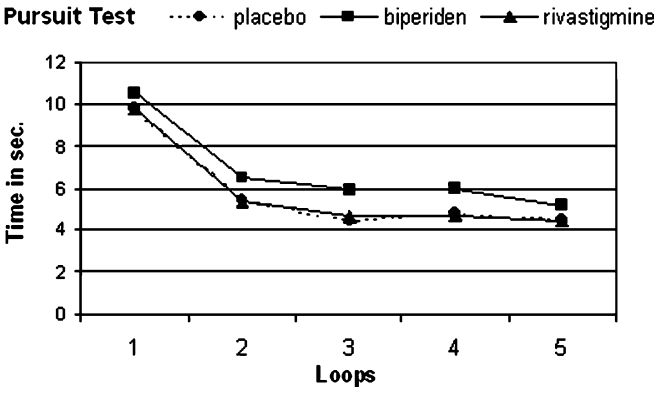

Fig. 6 Results for the Pursuit Test. Time to perform a loop for the first five loops is depicted here

Symbol digit substitution test

The outcome measure 'number correct' showed a trend of impaired performance for biperiden and a significant improved performance for rivastigmine. Subsequent analyses showed a significant increase in matching time for biperiden and no effects in writing time. Rivastigmine showed a non-significant improvement in both matching and writing time.

Control measures: sedation tests, AEs and sources of individual variation

As can be seen in Table 4, sedation, as assessed by the peak velocity of the SEM and the ERT and CRT tests, did not differ between drug conditions, neither did the subjective feelings as measured by the VAS.

The AEs are displayed in Table 5. To assess the impact of the reported AEs in the drug conditions, all analyses were repeated with AE (yes or no) as a between-subject factor. This was repeated for only the nausea complaints on rivastigmine performance. No significant negative effects were found for either measurement.

To control for the effect of sources of individual variation, additional analysis were performed with age and MMSE scores as covariates. The effects of age and MMSE scores were very limited and could not explain the current group findings for both drugs.

Discussion

To our knowledge, this is the first study to show that rivastigmine improves visuospatial processes, besides some aspects memory in healthy elderly subjects.

The present study found that the M1 antagonist biperiden caused clear-cut negative effects on measures of episodic memory and working memory, whereas the negative effects on visuospatial measures were less strong and less clear. For rivastigmine, marked positive effects were found on motor learning and visuospatial processes, and no

Table 4 Overview of results of control measures

		Placebo		Biperiden			Rivastigmine		
		M	SD	*M*	SD	*F*	M	SD	*F*
SEMpv	T_0	349	37	353	41		343	37	
	T_{max}	336	29	332	26	1.14	334	35	<1
ERT	T_0	290	25	288	28		288	32	
	T_{max}	297	44	305	51	1.13	301	50	<1
CRT	T_0	375	51	370	42		372	47	
	T_{max}	375	53	375	56	<1	374	57	<1
VAS	T_0	43.75	13.20	47.56	12.56		45.00	12.50	
Alertness (more–less)	T_{max}	47.00	18.96	53.93	8.54	<1	58.56	12.54	1.64
VAS	T_0	39.81	15.05	39.38	14.24		40.44	13.24	
Calmness (more–less)	T_{max}	41.81	14.96	41.81	14.64	<1	40.19	15.14	<1
VAS	T_0	38.94	17.56	42.06	11.45		39.19	17.18	
Contentedness (more–less)	T_{max}	38.44	16.66	41.88	14.57	<1	49.13	6.09	4.10[#]

The reported *F* values are drug×time interactions. T_0 is the baseline measurement. T_{max} is the measurement of the drug effects at the time of maximum efficacy. SEMpv, peak velocity in degrees per second. ERT and CRT, time in milliseconds. VAS, in centimetres, 'more–less' indicate the scaling of the VAS items. 0 indicates more alertness and 100 indicate less alertness
M Mean, *SD* standard deviations
[#]$p<.10$

Table 5 Overview of adverse events (AE)

	Total no. of subjects with AE's	No. of AEs		
		Somnolence	Dizziness	Nausea (vomiting)
Placebo	5	5	0	0
Biperiden	7	4	3	0
Rivastigmine	9	4	1	4 (3)

positive and even negative effects on measures of episodic memory.

Modulation of cognitive processes: memory

First we summarize the results concerning the effects of the drugs on memory: For biperiden, clear negative effects were found on the measures for episodic memory in immediate recall, delayed recall and recognition of verbal material. Visual recognition performance was unaffected. For rivastigmine, no positive effects were found in measures of episodic memory, and surprisingly, a negative effect was found in the recognition of both verbal and visual material. Working memory, measured by the N-back task, showed moderate negative effects on accuracy and response speed for biperiden, whereas rivastigmine did not affect performance. In short-term memory (SDRT), biperiden showed again negative effects, as it did on other memory tasks, it prolonged response times, and in this test, rivastigmine showed improved accuracy on the same measure. However, this effect is very small, and in contrast to the other memory tasks, therefore, it is not unlikely to be an accidental finding. In motor learning, biperiden impaired movement time over all trials in the pursuit task; however, as this was equal over all loops, it is more likely that attentional impairments caused this decrement than impaired learning processes. For rivastigmine, interestingly, positive effects were found that actually did affect motor learning. In the maze task, a relative increase in number of loops was found over consecutive trials, whereas performance dropped to baseline when a new maze was offered.

Overall biperiden showed results that are in agreement with the literature on other anticholinergic drugs in humans as it impaired episodic memory performance (Mintzer and Griffiths 2003). These findings have relevance for clinical practice because this drug is commonly prescribed to alleviate extrapyramidal side effects caused by antipsychotic medication; we therefore suggest to use caution in choosing the dose as it clearly impairs cognitive functioning.

Our results of a negative impact of rivastigmine on episodic memory, on the other hand, are in sharp contrast to most of the literature on the effects of the same or other ChEi in the AD populations and healthy volunteers, where generally, positive results have been found (Bentley et al. 2003; Birks et al. 2003). In AD patients, this positive effect is mostly measured by a change in ADAS-cog score. The ADAS-cog is a test battery used to measure changes in the core features of the cognitive impairments in AD, and has a memory, praxis and language domain.

There are a few other studies that failed to find positive effects of ACh inhibitors, but they were performed in other populations than AD patients. One of those studies found that in patients with schizotypic personality disorder, administration of physostigmine did not improve performance in a verbal learning test, but only improved performance in a spatial performance test (Kirrane et al. 2001). Another study that could not find positive effects used a tone-shock conditioning reinforcement paradigm with physostigmine. The author suggested that an overactive cholinergic system leads to increased processing of be-

haviourally irrelevant stimuli and thereby did not improve conditioning (Thiel et al. 2002).

What also should be taken into consideration when trying to find an explanation for differential results between the effects of ACh in AD patients vs our healthy volunteers is that the CNS cholinergic pathways work differently in both groups. Evidence was found in a study by Nordberg et al. (1989) that tacrine (an early ChEi) enhanced ACh release in AD brain tissue, whereas it decreased ACh release in normal control tissue in post-mortem brains. These results were attributed to the normal working of negative feedback mechanisms (mediated via presynaptic muscarinic autoreceptors) that is defective in AD brains. It could be that this mechanism is responsible for the neutral and negative effects that were found in the current study, although it does not explain the positive effects found on visuospatial performance.

Another possible explanation might be that acetylcholinesterase inhibitors have an inverted U-shape function on cognitive performance as dopaminergic compounds (Cohen et al. 2002). In that case, subjects would only respond in a positive manner if they would receive the right dose of rivastigmine. Subjects might have had the optimum dose at the beginning and end of the test battery as the positive results at those times indicated. However, the dose might have been too high between 90 and 110 min after drug administration, when the tests were performed where negative results were found. An 'overdose' could then have caused the impairments in the two episodic memory tests. Unfortunately, we have no serum concentrations to control for individual differences in absorption or metabolism, which might substantiate this explanation.

Modulation of cognitive processes: visuospatial abilities

Improved visuospatial performance was found for rivastigmine, as it tended to increase the number of correct scores in the tangles task. No impairment was found for biperiden on this measure. The SDST measures 'number correct' and 'matching time' have, next to intermediate memory aspects, a strong visuospatial scanning component. Results on these measures showed impaired performance for biperiden and improved performance for rivastigmine. The results of the other tests with (visuo-) spatial components, like the tangle, pursuit and the maze learning task, all showed at least a tendency of improved performance after rivastigmine. This suggests that the results on the SDST were more likely to be caused by the modulation of visuospatial processes than by changes in memory processes. This idea is supported by the findings that the direction of effects in the visual memory tests (both drugs either impair or have no effect) is different from the direction of effects on the SDST (biperiden impairs performance and rivastigmine enhances it). Following this interpretation, the negative effects of biperiden and the positive trends and effects of rivastigmine can be attributed to changes in visuospatial scanning performance.

In general, the data regarding the cholinergic modulation of the visuospatial performance are in line with the results of the few other human studies that looked into the effects of other cholinergic drugs on similar processes. In one study, scopolamine impaired performance on visuospatial tasks, although mixed effects were found on measures of visuospatial memory (Meador et al. 1993). Other studies showed that physostigmine generally increased reaction times and accuracy performance in spatial attention tasks (Bentley et al. 2003, 2004; Witte et al. 1997). The positive results on motor learning and visuospatial performance are also in line with the results of animal experiments (for reviews, see Gold 2003 and Power et al. 2003).

Are the effects of rivastigmine dependent on type of neural pathway?

Overall, there seems to be a division in type of tests where rivastigmine showed positive results vs negative results on cognitive performance. The tests showing positive effect all hold a visuospatial component, whereas the tests that showed a negative impact all hold a recognition memory component. This might have a relation to the 'two-systems theory of visual perception', which is an adaptation from the theory about 'what and where pathways' in the brain. The original theory was postulated by Ungerleider and Mishkin (1982) and started with the finding that the outputs from the primary visual cortex follow two general pathways. The first projects to the inferior temporal cortex are a region associated with object recognition (the ventral pathway). The other projects to the posterior parietal cortex are a region associated with spatial perception (the dorsal pathway). The authors proposed that these paths process fundamentally different types of information. The ventral path is associated with object perception and recognition. The dorsal path is implicated in identifying the location of an object. The more recent version of the 'two-systems theory of visual perception' also makes a division, now between a 'what path' and a 'how path' in information processing. The what path processes information that is needed to consciously identify objects (e.g. form, color), whereas the how path processes information that is needed for online movement control (e.g. location in space) and is assumed not to be consciously accessible (Bridgeman 2000; Knoblich and Kircher 2004). It appears that the negative results on recognition of words and pictures fit in the what path processing and the positive results on motor-learning and visuospatial performance in the how path processing. This would imply that how path processing would be more sensitive to increased levels of ACh than the what path processing. The question remains whether this theory offers an explanation for ACh modulation in total or of specifically the effects of ACh increase in visual information processing because it cannot explain the findings of biperiden or the results found for non-visual (in this case, verbal) material.

Limitations

It should be noted that the present study has some limitations. It might be argued that the memory tests were too difficult for this age group. Usually, wordlists of ten items are used in neuropsychological research in elderly subjects (Bouma et al. 1998; Lezak 1995). We used 18-item wordlists and a set of 16 pictures. This was done on the one hand to make learning more difficult, as it is in dementia, and on the other hand to prevent possible ceiling effects.

Furthermore, there were no specific attentional tests in the test battery, so we could not control for specific changes in attention. From other studies using drugs with well-known effects on attention next to memory, we know that impaired attention shows up on tests of sedation (see the review of Buffett-Jerrott and Stewart 2002 on benzodiazepines). We tried to control this by looking at several sedation measures, and because these did not show any effects of cholinergic modulation, we thought it is safe to conclude that no big attentional effects were present in our study.

Another issue is that in this study, only one dose of each drug was used. A multiple-dose study would give more insight, as the chosen doses may have been too low or too high to find the effects on the tests used in this study. It should be noted, however, that we did choose dosages that are known to have a clinical relevant effect.

Conclusion

In summary, the results of the present study demonstrated that a single dose of 2 mg of biperiden showed clear negative effects on both episodic and working memory, and that a single dose of 3 mg of rivastigmine showed both positive and negative effects on memory measures and only positive effects on visuospatial performance in healthy elderly volunteers.

The conclusion that can be drawn from these findings is that the modulation of visuospatial processes in humans does not totally resemble the animal findings, which might result from the many differences between rat and human neurophysiology. It did point us in the direction of a new topic in ACh research: the modulation of visuospatial processes. We therefore advise further research into this specific cognitive domain with ACh inhibitors in AD patients, as it may be expected to find the most positive effects in that domain.

To finish, we would like to repeat our concern about the use of biperiden to alleviate extra pyramidal side effects in clinical practice; due to its impairing cognitive effects, we suggest to be careful in choosing the dose.

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This experiment complies with the current laws of the Netherlands.

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