

E. Wezenberg · R. J. Verkes · B. G. C. Sabbe ·
G. S. F. Ruigt · W. Hulstijn

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

Received: 10 March 2005 / Accepted: 23 May 2005 / Published online: 22 July 2005
© Springer-Verlag 2005

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

E. Wezenberg (✉) · R. J. Verkes
Department of Psychiatry (333),
Radboud University Nijmegen Medical Center,
P.O. 9101, 6500 HB Nijmegen, The Netherlands
e-mail: E.Wezenberg@psy.umcn.nl
Tel.: +31-24-3613601
Fax: +31-24-3540561

B. G. C. Sabbe · W. Hulstijn
Collaborative Antwerp Psychiatric Research Institute (CAPRI),
University of Antwerp,
Universiteitsplein 1,
B-2610 Antwerp (Wilrijk), Belgium

G. S. F. Ruigt
Clinical Pharmacology Department (XW3113), NV Organon,
P.O. 20, 5340 BH Oss, The Netherlands

W. Hulstijn
Nijmegen Institute for Cognition and Information (NICI),
Radboud University Nijmegen,
P.O. 9102, 6500 HC Nijmegen, The Netherlands

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 schizotypal 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 visuo-spatial 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

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

200 Hz and a spatial accuracy of 0.2 mm (de Jong et al. 1996).

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

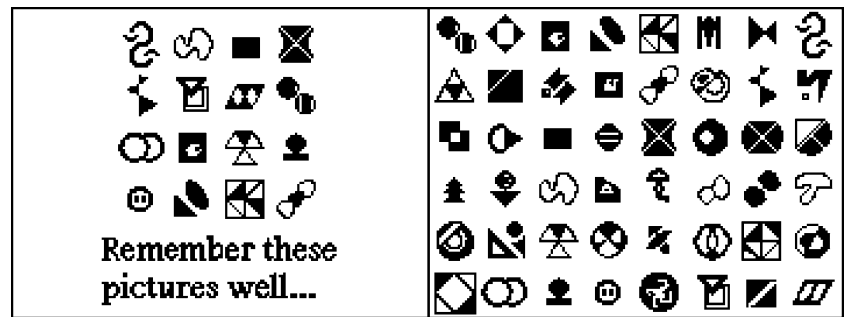
Verbal memory test

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.

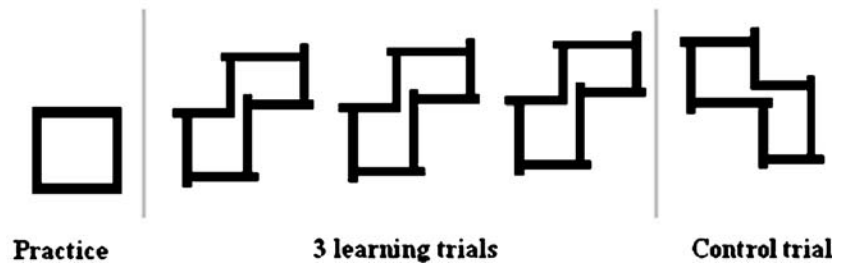
Motor learning tests (with visuospatial component)

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

TRIAL ORDER



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.

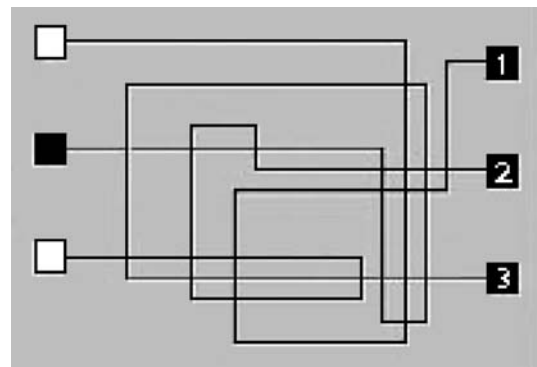


Fig. 3 Example of a simple trial in the tangle test

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	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
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 <i>df</i> (1,15)	Placebo vs rivastigmine <i>df</i> (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.

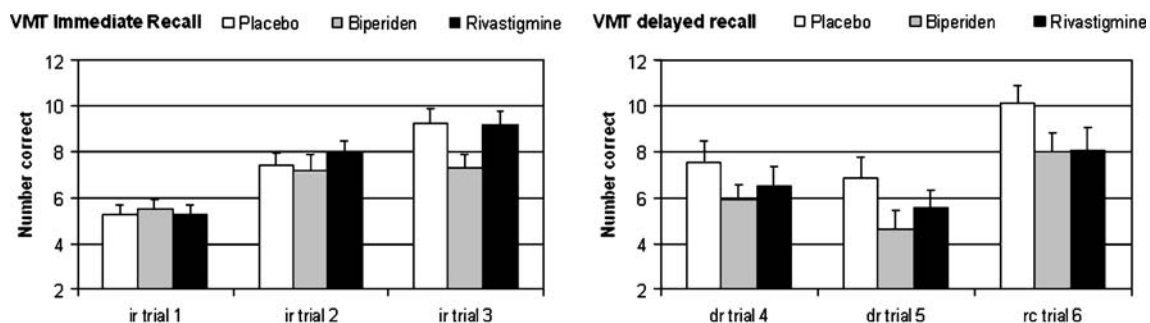


Fig. 4 Results on the Verbal Memory Test (VMT). Immediate recall results are to the left (ir trials 1–3). Delayed recall trials (dr trials 4 and 5) and recognition trial (rc trial 6) are to the right

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.

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) \times 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 \times 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.

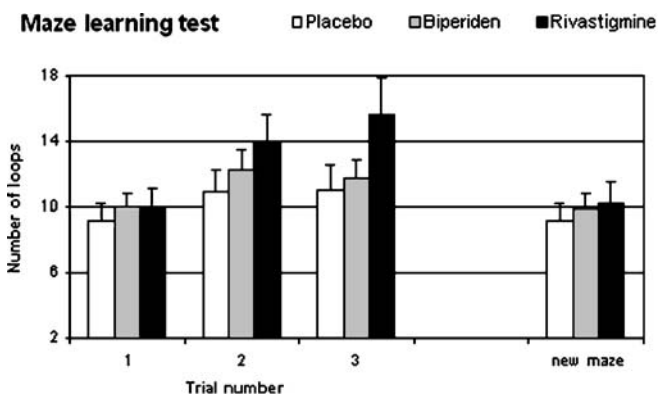


Fig. 5 Results for maze learning test on trials 1–3 and the new maze for placebo, biperiden and rivastigmine

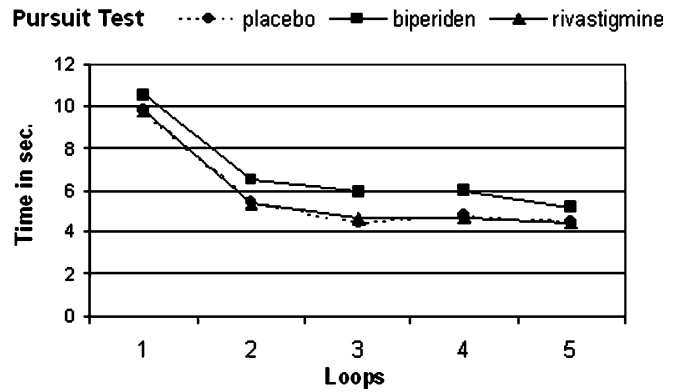


Fig. 6 Results for the Pursuit Test. Time to perform a loop for the first five loops is depicted here

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		
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i>	<i>M</i>	<i>SD</i>	<i>F</i>
SEMPv	<i>T</i> ₀	349	37	353	41		343	37	
	<i>T</i> _{max}	336	29	332	26	1.14	334	35	<1
ERT	<i>T</i> ₀	290	25	288	28		288	32	
	<i>T</i> _{max}	297	44	305	51	1.13	301	50	<1
CRT	<i>T</i> ₀	375	51	370	42		372	47	
	<i>T</i> _{max}	375	53	375	56	<1	374	57	<1
VAS	<i>T</i> ₀	43.75	13.20	47.56	12.56		45.00	12.50	
Alertness (more-less)	<i>T</i> _{max}	47.00	18.96	53.93	8.54	<1	58.56	12.54	1.64
VAS	<i>T</i> ₀	39.81	15.05	39.38	14.24		40.44	13.24	
Calmness (more-less)	<i>T</i> _{max}	41.81	14.96	41.81	14.64	<1	40.19	15.14	<1
VAS	<i>T</i> ₀	38.94	17.56	42.06	11.45		39.19	17.18	
Contentedness (more-less)	<i>T</i> _{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.

Acknowledgements Funding was provided by NV Organon. We would like to thank them for their financial and technical support to perform this study.

We would also like to thank Jan Leijtens and Drs. Sevla Cinar for their helpful assistance in data collection and analysis.

This experiment complies with the current laws of the Netherlands.

References

- Ammons RB (1947) Acquisition of motor skill. 2. Rotary pursuit performance with continuous practice before and after a single rest. *J Exp Psychol* 37:393–411
- Atri A, Sherman S, Norman KA, Kirchoff BA, Nicolas MM, Greicius MD, Cramer SC, Breiter HC, Hasselmo ME, Stern CE (2004) Blockade of central cholinergic receptors impairs new learning and increases proactive interference in a word paired-associate memory task. *Behav Neurosci* 118:223–236
- Baxter MG, Gallagher M (1996) Intact spatial learning in both young and aged rats following selective removal of hippocampal cholinergic input. *Behav Neurosci* 110:460–467
- Baxter MG, Bucci DJ, Wiley RG, Gorman LK, Gallagher M (1995) Selective immunotoxic lesions of basal forebrain cholinergic cells—effects on learning and memory in rats. *Behav Neurosci* 109:714–722
- Bentley P, Vuilleumier P, Thiel CM, Driver J, Dolan RJ (2003) Effects of attention and emotion on repetition priming and their modulation by cholinergic enhancement. *J Neurophysiol* 90:1171–1181
- Bentley P, Husain M, Dolan RJ (2004) Effects of cholinergic enhancement on visual stimulation, spatial attention, and spatial working memory. *Neuron* 41:969–982
- Birks J, Grimley Evans J, Iakovidou V, Tsolaki M (2003) Rivastigmine for Alzheimer's disease (Cochrane Review). In: *The Cochrane Library*, Issue 3
- Bittner AC, Carter RC, Krause M, Kennedy RS, Harbeson MM (1983) Performance Evaluation Tests for Environmental Research (Peter)—Moran and computer batteries. *Aviat Space Environ Med* 54:923–928
- Bittner AC, Carter RC, Kennedy RS, Harbeson MM, Krause M (1986) Performance Evaluation Tests for Environmental Research (Peter)—evaluation of 114 measures. *Percept Mot Skills* 63:683–708
- Blokland A (1995) Acetylcholine: a neurotransmitter for learning and memory? *Brain Res Rev* 21:285–300
- Bond A, Lader M (1974) Use of analog scales in rating subjective feelings. *Br J Med Psychol* 47:211–218
- Bouma A, Mulder J, Lindeboom J (1998) *Neuropsychologische diagnostiek, handboek*. Zwets & Zeitlinger, Lisse
- Bridgeman B (2000) Interactions between vision for perception and vision for behavior. In: Rossetti Y, Revonsuo A (eds) *Beyond dissociation: interaction between dissociated implicit and explicit processing*. John Benjamins, Amsterdam, pp 17–40
- Buffett-Jerrott SE, Stewart SH (2002) Cognitive and sedative effects of benzodiazepine use. *Curr Pharm Des* 8:45–58
- Bymaster FP, Heath I, Hendrix JC, Shannon HE (1993) Comparative behavioral and neurochemical activities of cholinergic antagonists in rats. *J Pharmacol Exp Ther* 267:16–24
- Cohen J, Braver TS, Brown JW (2002) Computational perspectives on dopamine function in prefrontal cortex—commentary. *Curr Opin Neurobiol* 12:223–229
- Corey-Bloom J (2002) The ABC of Alzheimer's disease: cognitive changes and their management in Alzheimer's disease and related dementias. *Int Psychogeriatr* 14:51–75
- Curran HV, Schifano F, Lader M (1991) Models of memory dysfunction—a comparison of the effects of scopolamine and lorazepam on memory, psychomotor performance and mood. *Psychopharmacology* 103:83–90
- de Jong WP, Hulstijn W, Jogems-Kosterman BJM, Smits-Engelsman BCM (1996) OASIS software and its application in experimental handwriting research. In: Simmers ML, Leedham CG, Thomassen AJWM (eds) *Handwriting and drawing research: basic and applied issues*. IOS, Amsterdam
- De Rosa E, Hasselmo ME, Baxter MG (2001) Contribution of the cholinergic basal forebrain to proactive interference from stored odor memories during associative learning in rats. *Behav Neurosci* 115:314–327
- Dunnett SB, Everitt BJ, Robbins TW (1991) The basal forebrain cortical cholinergic system—interpreting the functional consequences of excitotoxic lesions. *Trends Neurosci* 14:494–501

- Eglen RM, Choppin A, Watson N (2001) Therapeutic, opportunities from muscarinic receptor research. *Trends Pharmacol Sci* 22:409–414
- Ekstrom RB, French JW, Harmon H, Dermen D (1976) Manual for the kit of factor referenced cognitive tests. Educational Testing Service, Princeton, NY
- Enz A, Amstutz R, Boddeke H, Gmelin G, Malanowski J (1993) Brain selective inhibition of acetylcholinesterase—a novel approach to therapy for Alzheimer's disease. *Prog Brain Res* 98:431–438
- Everitt BJ, Robbins TW (1997) Central cholinergic systems and cognition. *Annu Rev Psychol* 48:649–684
- Fibiger HC (1991) Cholinergic mechanisms in learning, memory and dementia—a review of recent-evidence. *Trends Neurosci* 14:220–223
- Flood JF, Cherkin A (1986) Scopolamine effects on memory retention in mice—a model of dementia. *Behav Neural Biol* 45:169–184
- French JW (1954) Manual for kit of selected tests for reference aptitude and achievement factors. Educational Testing Service, Princeton, NY
- Gold PE (2003) Acetylcholine modulation of neural systems involved in learning and memory. *Neurobiol Learn Mem* 80:194–210
- Guthrie SK, Manzey L, Scott D, Giordani B, Tandon R (2000) Comparison of central and peripheral pharmacologic effects of biperiden and trihexyphenidyl in human volunteers. *J Clin Psychopharmacol* 20:77–83
- Gutierrez H, Gutierrez R, Silva-Gandarias R, Estrada J, Miranda MI, Bermudez-Rattoni F (1999) Differential effects of 192IgG-saporin and NMDA-induced lesions into the basal forebrain on cholinergic activity and taste aversion memory formation. *Brain Res* 834:136–141
- Hammond EJ, Meador KJ, Aungdin R, Wilder BJ (1987) Cholinergic modulation of human P3 event-related potentials. *Neurology* 37:346–350
- Hege SG, Ellinwood EH Jr, Wilson WH, Helligers CA, Graham SM (1997) Psychomotor effects of the anxiolytic abecarnil: a comparison with lorazepam. *Psychopharmacology (Berl)* 131:101–107
- Hollmann M, Muller-Peltzer H, Greger G, Brode E, Perucca E, Grimaldi R (1987) Pharmacokinetic-dynamic study on different oral biperiden formulations in volunteers. *Pharmacopsychiatry* 20:72–77
- Jann MW, Shirley KL, Small GW (2002) Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. *Clin Pharmacokinet* 41:719–739
- Jogems-Kosterman BJM, Zitman FG, van Hoof JJM, Hulstijn W (2001) Psychomotor slowing and planning deficits in schizophrenia. *Schizophr Res* 48:317–333
- Jones CK, Shannon HE (2000) Muscarinic cholinergic modulation of prepulse inhibition of the acoustic startle reflex. *J Pharmacol Exp Ther* 294:1017–1023
- Kaplan E, Fein D, Morris R, Delis D (1991) Wais-R as a neuropsychological instrument. The Psychological Corporation, San Antonio, TX
- Kikuchi M, Wada Y, Nanbu Y, Nakajima A, Tachibana H, Takeda T, Hashimoto T (1999) EEG changes following scopolamine administration in healthy subjects—quantitative analysis during rest and photic stimulation. *Neuropsychobiology* 39:219–226
- Kirrane RM, Mitropoulou V, Nunn M, Silverman J, Siever LJ (2001) Physostigmine and cognition in schizotypal personality disorder. *Schizophr Res* 48:1–5
- Knoblich G, Kircher TJJ (2004) Deceiving oneself about being in control: conscious detection of changes in visuomotor coupling. *J Exp Psychol Hum Percept Perform* 30:657–666
- Kopelman MD, Corn TH (1988) Cholinergic blockade as a model for cholinergic depletion—a comparison of the memory deficits with those of Alzheimer-type dementia and the alcoholic Korsakoff syndrome. *Brain* 111:1079–1110
- Lezak MD (1995) *Neuropsychological assessment*, 3rd edn. Oxford University Press, New York
- Lucas-Meunier E, Fossier P, Baux G, Amar M (2003) Cholinergic modulation of the cortical neuronal network. *Pflugers Arch* 446:17–29
- Mash DC, Flynn DD, Potter LT (1985) Loss of M2 muscarinic receptors in the cerebral-cortex in Alzheimer's disease and experimental cholinergic denervation. *Science* 228:1115–1117
- Meador KJ, Moore EE, Nichols ME, Abney OL, Taylor HS, Zamrini EY, Loring DW (1993) The role of cholinergic systems in visuospatial processing and memory. *J Clin Exp Neuropsychol* 15:832–842
- Mewaldt SP, Ghoneim MM (1979) Effects and interactions of scopolamine, physostigmine and methamphetamine on human memory. *Pharmacol Biochem Behav* 10:205–210
- Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, Berman KF (2001) Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry* 158:1809–1817
- Mintzer MZ, Griffiths RR (2003) Lorazepam and scopolamine: a single-dose comparison of effects on human memory and attentional processes. *Exp Clin Psychopharmacol* 11:56–72
- Muir JL (1997) Acetylcholine, aging, and Alzheimer's disease. *Pharmacol Biochem Behav* 56:687–696
- Nordberg A, Nilsson-Hakansson L, Adem A, Lai Z, Winblad B (1989) Multiple actions of THA on cholinergic neurotransmission in Alzheimer brains. *Prog Clin Biol Res* 317:1169–1178
- Peretti CS, Danion JM, Kauffmannmuller F, Grange D, Patat A, Rosenzweig P (1997) Effects of haloperidol and amisulpride on motor and cognitive skill learning in healthy volunteers. *Psychopharmacology* 131:329–338
- Petrides M, Milner B (1982) Deficits on subject-ordered tasks after frontal-lobe and temporal-lobe lesions in man. *Neuropsychologia* 20:249–262
- Poirier J (2002) Evidence that the clinical effects of cholinesterase inhibitors are related to potency and targeting of action. *Int J Clin Pract* 127:6–19
- Power AE, Vazdarjanova A, McGaugh JL (2003) Muscarinic cholinergic influences in memory consolidation. *Neurobiol Learn Mem* 80:178–193
- Rammesayer TH, Rodewald S, Groh D (2000) Dopamine-antagonistic, anticholinergic, and GABAergic effects on declarative and procedural memory functions. *Brain Res Cogn Brain Res* 9:61–71
- Robbins TW, McAlonan G, Muir JL, Everitt BJ (1997a) Cognitive enhancers in theory and practice: studies of the cholinergic hypothesis of cognitive deficits in Alzheimer's disease. *Behav Brain Res* 83:15–23
- Robbins TW, Semple J, Kumar R, Truman MI, Shorter J, Ferraro A, Fox B, McKay G, Matthews K (1997b) Effects of scopolamine on delayed-matching-to-sample and paired associates tests of visual memory and learning in human subjects: comparison with diazepam and implications for dementia. *Psychopharmacology* 134:95–106
- Sabbe B, Hulstijn W, van Hoof J, Tuynman-Qua HG, Zitman F (1999) Retardation in depression: assessment by means of simple motor tasks. *J Affect Disord* 55:39–44
- Sarter M, Bruno JP (1998a) Age-related changes in rodent cortical acetylcholine and cognition: main effects of age versus age as an intervening variable. *Brain Res Rev* 27:143–156
- Sarter M, Bruno JP (1998b) Cortical acetylcholine, reality distortion, schizophrenia, and Lewy body dementia: too much or too little cortical acetylcholine? *Brain Cogn* 38:297–316
- Sharma T, Hughes C, Aasen I, Kumari V (2004) A placebo-controlled double-blind investigation of cognitive effects of rivastigmine in schizophrenia. *Biol Psychiatry* 55:275
- Siegel D (1990) A multivariate study of pursuit rotor skill development. *Res Q Exerc Sport* 61:201–205
- Staubli U, Rogers G, Lynch G (1994) Facilitation of glutamate receptors enhances memory. *Proc Natl Acad Sci U S A* 91:777–781
- Thiel CM, Bentley P, Dolan RJ (2002) Effects of cholinergic enhancement on conditioning-related responses in human auditory cortex. *Eur J Neurosci* 16:2199–2206

- Torres EM, Perry TA, Blokland A, Wilkinson LS, Wiley RG, Lappi DA, Dunnett SB (1994) Behavioral, histochemical and biochemical consequences of selective immunolesions in discrete regions of the basal forebrain cholinergic system. *Neuroscience* 63:95–122
- Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: Engle DJ, Goodale MA, Mansfield RJ (eds) *Analysis of visual behavior*. MIT Press, Cambridge, pp 549–586
- Vakil E, Blachstein H (1993) Rey Auditory–Verbal Learning Test—structure-analysis. *J Clin Psychol* 49:883–890
- van Hoof JJM, Jogems-Kosterman BJM, Sabbe BGC, Zitman FG, Hulstijn W (1998) Differentiation of cognitive and motor slowing in the Digit Symbol Test (DST): differences between depression and schizophrenia. *J Psychiatr Res* 32:99–103
- van Mier H, Hulstijn W, Petersen SE (1993) Changes in motor planning during the acquisition of movement patterns in a continuous task. *Acta Psychologica* 82:291–312
- van Mier H, Tempel LW, Perlmutter JS, Raichle ME, Petersen SE (1998) Changes in brain activity during motor learning measured with PET: effects of hand of performance and practice. *J Neurophysiol* 80:2177–2199
- Voytko ML (1996) Cognitive functions of the basal forebrain cholinergic system in monkeys: memory or attention? *Behav Brain Res* 75:13–25
- Voytko ML, Olton DS, Richardson RT, Gorman LK, Tobin JR, Price DL (1994) Basal forebrain lesions in monkeys disrupt attention but not learning and memory. *J Neurosci* 14:167–186
- Wechsler D (1981) *The psychometric tradition—developing the Wechsler Adult Intelligence Scale*. *Contemp Educ Psychol* 6:82–85
- Weinberger DR, Mattay V, Callicott J, Kotrla K, Santha A, van Gelderen P, Duyn J, Moonen C, Frank J (1996) fMRI applications in schizophrenia research. *Neuroimage* 4:S118–S126
- Wenk GL, Stoehr JD, Quintana G, Mobley S, Wiley RG (1994) Behavioral, biochemical, histological, and electrophysiological effects of 192-IgG-saporin injections into the basal forebrain of rats. *J Neurosci* 14:5986–5995
- Wezenberg E, Hulstijn W, Sabbe B, Ruijt GSF, Verkes RJ (2004) Psychomotor and cognitive effects of lorazepam and D-amphetamine in healthy subjects. Development of sensitive screening tests of psychomotor- and cognitive functions. *Eur Neuropsychopharmacol* 14:S362
- Wild R, Petit T (2004) Cholinesterase inhibitors for dementia with Lewy bodies (Cochrane Review). In: *The Cochrane Library*
- Witte EA, Davidson MC, Marrocco RT (1997) Effects of altering brain cholinergic activity on covert orienting of attention: comparison of monkey and human performance. *Psychopharmacology* 132:324–334