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Review

Cognitive domains affected by histamine H_1-antagonism in humans: A literature review

P. Van Ruitenbeek, A. Vermeeren, W.J. Riedel*

Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands, P.O. Box 616, 6200 MD Maastricht, The Netherlands

ARTICLE INFO

Article history:
Accepted 24 April 2010
Available online 8 June 2010

Keywords:
Histamine
H_1-antagonist
Human cognition

ABSTRACT

The neurotransmitter histamine has been suggested to be involved in cognitive functioning. Generally, studies in animals have shown a decrease in performance after decreasing histamine neurotransmission and improved performance after increasing histamine neurotransmission. It is unclear, however, what role histamine plays in cognition in humans. Up until now, most data are derived from studies and reviews that aimed to assess the sedative potential of H_1-antagonists and not the effects on cognition in particular. The objective of this paper is specifically to review which cognitive domains are affected by H_1-antagonists. Taken together, 90 experimental studies on the performance effects of sedative H_1-antagonists published between 1973 and 2009 were reviewed. Results showed that psychomotor skills and attention are most frequently impaired and memory the least. Tasks assessing memory that were affected usually required rapid responses. It was concluded that both the complexity of the task as well as the demand for information processing speed determines the sensitivity to the effects of central H_1-antagonism. The importance of the sensitive cognitive domains to histaminergic dysfunction, as well as the relation between histamine related decrease in arousal and task performance deserve further research.

Contents

* *Corresponding author*. Fax: +31 43 3884560.
E-mail address: p.vanruitenbeek@maastrichtuniversity.nl (P. Van Ruitenbeek).
URL: http://www.maastrichtuniversity.nl/web/Faculteiten/FPN.htm (P. Van Ruitenbeek).

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doi:10.1016/j.brainresrev.2010.04.008

1. Introduction

Thirty-five years ago Schwartz (Schwartz, 1975, 1977; Schwartz et al., 1980) suggested that histamine is a neurotransmitter in the mammalian central nervous system and that it plays a role in arousal. The histaminergic cells in the tuberomammillary nucleus project to most areas of the brain where activation of postsynaptic H_1 and H_2 receptors leads to excitatory transmission or increased neuronal firing (Haas et al., 2008). Histaminergic transmission is terminated primarily by enzymatic breakdown and inhibition of synthesis and release via activation of presynaptic H_3 autoreceptors (Arrang et al., 1983). At present the role of histamine in sleep/wake regulation is well established (Monti, 1993; Saper et al., 2005). Next to its role in arousal, the widespread presence of histaminergic projections and receptors suggest a role in various central nervous system functions, including cognitive performance.

Animal studies support an important role for histamine in cognitive functioning. A recent review of these studies (Alvarez, 2009) shows that reductions in histaminergic activity, due to lesions of the tuberomammillary nucleus or administration of H_1- and/or H_2-antagonists, affect performance on tasks of learning and memory. Even more interesting are findings that newly developed H_3-receptor antagonists, that increase histamine neurotransmission, can improve cognitive performance on many tasks, especially learning and memory in impaired animals (e.g. Bernaerts et al., 2004; Komater et al., 2005; Medhurst et al., 2007; Orsetti et al., 2001; for review see: Esbenshade et al., 2006; Witkin and Nelson, 2004). Such drugs may therefore have potential as new treatments for cognitive deficits in humans.

Relatively little is known, however, about the specific role of histamine in human cognition, as compared to other monoamine neurotransmitters. In spite of the large number of studies that have been conducted assessing the effects of antihistamines or H_1-antagonists on human performance, few attempts have been made to determine the cognitive domains most vulnerable to histaminergic dysfunction. Most studies focussed on the differences between antihistamines with respect to their potential to penetrate the blood–brain barrier and produce sedative effects (for reviews see: McDonald et al., 2008; O'Hanlon and Ramaekers, 1995; Shamsi and Hindmarch, 2000; Theunissen et al., 2009).

The aim of the present paper, therefore, is to review the effects of H_1-antagonists on cognitive performance in healthy volunteers to determine which cognitive domains are specifically vulnerable to histaminergic hypofunction. The relative sensitivity of different domains of cognitive functioning (e.g. perceptual processing, motor responses, memory and attention) to the effects H_1-antgonism may help to elucidate the role of histamine in human cognition. It can be hypothesized that cognitive functions in which histamine plays an important role are more sensitive to effects of H_1-antagonists than functions that are less dependent on histaminergic activity.

In order to review the literature, databases were searched for experimental studies reporting effects of H_1-antagonists on tests assessing performance in cognitive domains such as attention, psychomotor skills, speed of discrete responding, memory, perception, sensory visual functions, and driving. Specific antihistamines to be included in the search were identified from previous reviews comparing their potential to penetrate the blood–brain barrier and produce sedation (for reviews see: Hindmarch and Shamsi, 1999; McDonald et al., 2008; O'Hanlon and Ramaekers, 1995; Shamsi and Hindmarch, 2000; Theunissen et al., 2009). Experimental studies reporting no significant effects of an H_1-antagonist or verum on subjective feelings of sedation or performance were excluded, as sensitivity of the procedures used was not demonstrated.

2. Results

The literature search resulted in 132 potentially useful papers. From these, articles were selected according to the criteria described in the Experimental procedures section, which resulted in 90 papers published from 1973 until December 2009. The papers described the effects of 24 different H_1-antagonists in different dosages (Table 1). A total of 668 assessments have been included from these studies, of which 496 were assessments of cognitive performance and 172 assessments of subjective or objective sleepiness. Of the 496 cognitive performance assessments reported, 242 indicated impairment according to a liberal significance criterion of $p<0.05$ (LC) and 69 according a more strict criterion of $p<0.01$ (SC). The number of assessments differed substantially between cognitive domains, ranging from 5 assessments in the domain of visual sensory function to 128 assessments in the attentional domain. Significant effects according to $p<0.05$ are therefore reported as percentage of the total number of assessments per domain. The percentage of impairment according to the strict criterion (SC, $p<0.01$) will be indicated between brackets.

The drug most studied is diphenhydramine in oral doses ranging between 25 mg and 100 mg. The effects of the 50 mg dose have been assessed using tests in nearly all cognitive domains discussed in the present paper. Therefore, in addition to the impairment ratio of all drugs studied within a domain, the effects of diphenhydramine will be used as the prototypical drug to determine which domains are sensitive to its impairing effects.

Table 1 – Treatments and dose and their respective abbreviations.

Treatment	Dose	Abbreviation
Azatadine	4 mg, 8 mg	AZ4, AZ8
Brompheniramine	4 mg, 10 mg, 12 mg	B4, B10, B12
	12 mg extended release	B12er
Carbinoxamine	12 mg	CA12
Chlorpheniramine	4 mg, 10 mg	C4, C10
	12 mg extended release	C12er
Cetirizine	5 mg, 10 mg, 15 mg, 20 mg	CE5, CE10, CE15, CE20
Clemastine	1 mg, 2 mg	CL1, CL2
Cinnerazine	15 mg, 30 mg, 45 mg	
Cyclizine	25 mg, 50 mg, 100 mg	CY25, CY50, CY100
Dexchlorpheniramine	2 mg, 4 mg	DC2, DC4
	1 mg (i.v.), 2 mg (i.v.)	DC1iv, DC2iv
	6 mg extended release	DC6er
Dimethindene	5 mg	DI5
Dimenhydrinate	50 mg	DIM50
Diphenhydramine	25 mg, 50 mg, 75 mg, 100 mg	DH25, DH50, DH75, DH100
	1 mg/kg, 50 mg (i.v.)	DH1 mg/kg, DH50iv
Fexofenadine	60 mg	FEX60
Hydroxyzine	20 mg, 25 mg, 30 mg, 50 mg	H20, H25, H30, H50
Ketotifen	1 mg, 2 mg	K1, K2
Loratidine	10 mg	LO10
Mequitazine	5 mg, 10 mg	MQ5, MQ10
Mizolastine	5 mg, 15 mg, 20 mg, 40 mg, 45 mg	MZ5, MZ15, MZ20, MZ40, MZ45
Olopatadine	5 mg, 10 mg	OL5, OL10
Promethazine	10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 50 mg	P10, P12.5, P20, P25, P30, P50
Rupatidine	20 mg, 40 mg, 80 mg	RU20, RU40, RU80
Temelastine	100 mg	TEM100
Terfenadine	60 mg	TER60
Triprolidine	2.5 mg, 5 mg, 7.5 mg, 10 mg	T2.5, T5, T7.5, T10
	10 mg extended release	T10er

Treatment names are listed in the left column, the dose used in the centre column and the respective abbreviation in the right column. The abbreviations are used throughout the tables.

2.1. *Cognition*

Fig. 1 presents an overview of the number of assessments and impaired performance per domain and subcategory. Attention was most frequently assessed (128 times) and was impaired in 47% of the assessments. Psychomotor skills and speed of discrete responding were also frequently assessed (95 and 89 times, respectively) and showed impaired performance in 58% and 54% of the times, respectively. Memory functioning was assessed 85 times, but impaired performance only in 28% of the occasions. This is followed by perception, which was assessed 71 times of which an impairment was found in 48%. Driving performance has been assessed much less frequently (23 times), but appears highly sensitive as impaired performance was found in 78%. Finally, sensory functions have been assessed only 5 times and were affected by antihistamines in 60% of the times.

2.1.1. *Attention*

The effects of the H_1-antagonists on tasks assessing attention have been assessed extensively (i.e. 128 times) and lead to impaired performance on 60 occasions (47%, SC=13%) (Table 2).

Of these measures, divided attention was most frequently impaired (64%, SC=24%). Divided attention was assessed 25 times of which 16 times impaired performance was found. The impairment ratios for selective, spatial, sustained attention and performance on categorization tasks all ranged between 40 and 60%. Within this range selective attention was impaired most frequently i.e. 57% of the times (4/7, SC=0%). Second, spatial attention was found to be impaired in 43% of the times (3/7, SC=14%). However, these functions have only been assessed infrequently. In contrast, tasks assessing sustained attention and categorization tasks (e.g. Digit Symbol Substitution Tasks, Card Sorting Task) were used 30 and 59 times, respectively. Performance on these tasks was impaired in 43% (13/30, SC=3%) and 41% (24/59, SC=15%) of the assessments, respectively, which suggests that sustained attention and performance on categorization tasks are also sensitive to the effects of H_1-antagonism

Similar to the impairment ratios for all drugs, diphenhydramine impaired performance on tasks of divided attention, sustained attention and categorization tasks Diphenhydramine in doses ranging between 25 and 100 mg induced impaired performance in 100% (9/9, SC=22%) of the assessments of divided attention and in 44% (7/16, SC=19%) of the assessments using categorization task. However, sustained attention was assessed less frequently, as performance was impaired 3 times of the 6 assessments (50%). Similarly spatial attention has been assessed only 6 times, but appears also sensitive, as 3 (50%) times performance was impaired. So, similar to the impairment ratio for all drugs, tasks assessing attention functioning appear sensitive to the impairing effects of diphenhydramine.

2.1.2. *Psychomotor skills*

Psychomotor skills (Table 3) are complex functions as a large number of cognitive operations are involved. It may be expected that psychomotor skills are sensitive to drug impairing affects, as performance may deteriorate when any of the process is affected by an H_1-antagonist. Indeed, effects on psychomotor skills were measured on 95 occasions and was impaired in 58% (55/95, SC=19%) of the assessments, which strongly indicated impaired performance.

Eye–hand coordination – typically assessed by tracking tests – was most frequently assessed (73 times) and in 63% of the times H_1-antagonists induced impaired performance (46/73, SC=23%). In contrast, motor speed as assessed by symbol copying and finger tapping tests, involve less cognitive operations and was slowed less frequently i.e. in 33% of the 18 measurements (SC=6%). Postural stability was assessed only 4 times, but impaired performance in 75% of the measurements (SC=0%). However, postural stability does not depend on controlled cognitive operations and may represent impaired vestibular function.

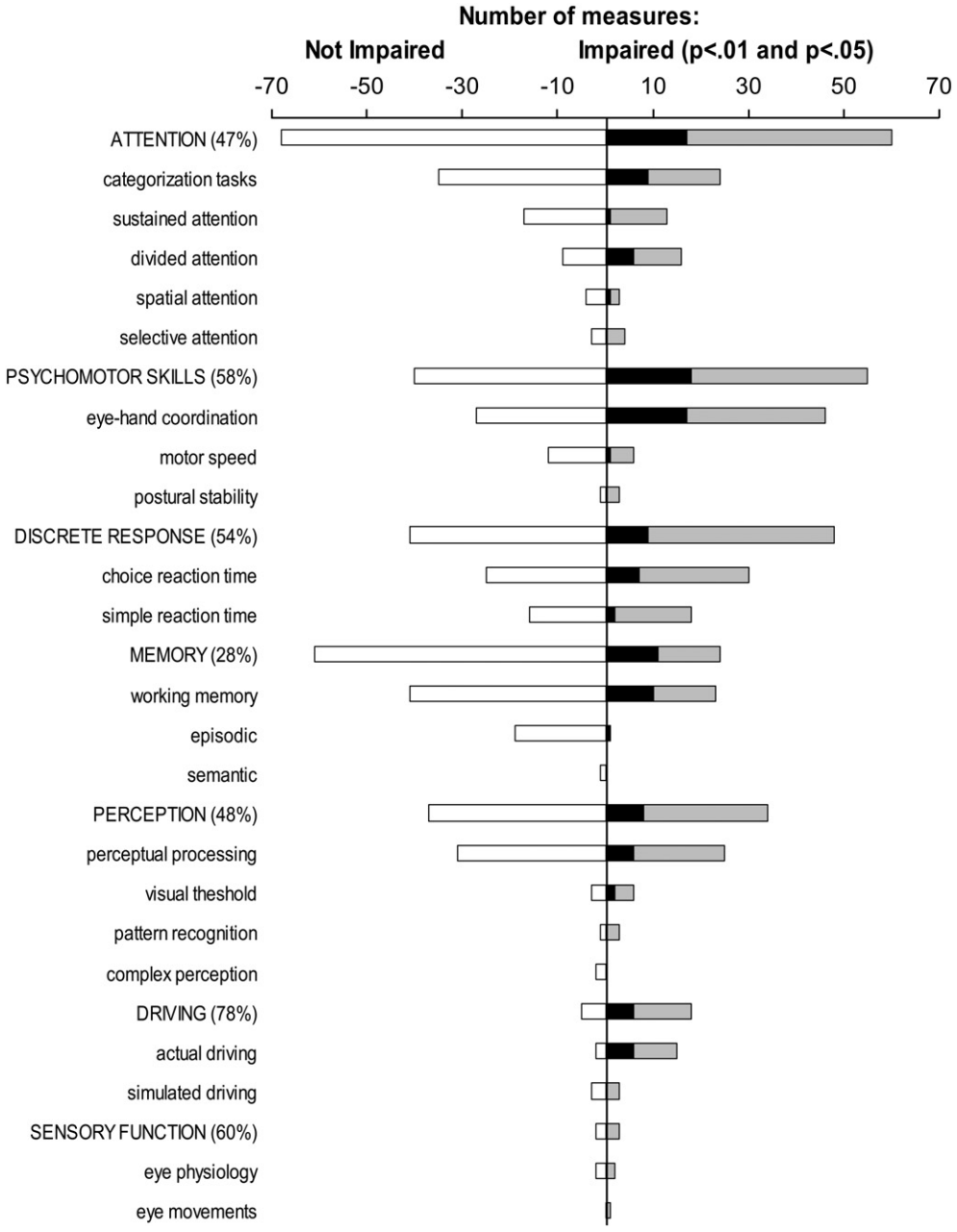

Fig. 1 – The bars on the left indicate the number of assessments that did not show impaired performance on cognitive domains presented on the y-axis. The bars on the right show the number of performance impairments. The black section of the bar indicates an impairment with significance level $p < .01$.

Diphenhydramine impaired performance on eye–hand coordination in 80% of 10 occasions (8/10), postural stability in 67% out of the 3 times (2/3) and motor speed in 20% out of 5 times (1/5), which also suggests that eye–hand coordination is highly sensitive to H_1-antagonism. This sensitivity is supported by the fact that the lower dose of diphenhydramine impaired eye–hand coordination.

The results suggest that H_1-antagonists strongly affect psychomotor skills. The tasks that were used do not discriminate between different cognitive processes underlying performance, however. The affected processes that cause the impairment may be motor related processes as performance on tasks emphasizing these processes is affected. Nevertheless, these are affected to a lesser extent than eye–hand coordination, which suggests that other processes are impaired as well.

2.1.3. *Speed of discrete responding*

Performance on reaction time tasks involves much less complex cognitive operations compared to psychomotor skills. Performance on reaction time tasks (Table 4) depends relatively more on functioning of sensory and motor processes. Slowing of any of those processes, results in a decrease in

Table 2 – Effects of H1-antagonists on attention.

Cognitive domain/task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Attention ($n=128$)		**47% (60/128)**	**13% (17/128)**	
Spatial attention ($n=7$)	CE10[4]	**43% (3/7)**	**14% (1/7)**	[4](Gupta et al., 2004); [9](Curran et al., 1998); [41](Oken et al., 1995); [47](Grunberger et al., 1988); [73](Moskowitz and Burns, 1988)
	DH50[9,47] DH1 mg/kg[41]	DH25[4], DH50[73], DH1 mg/kg[41]	DH1 mg/kg[41]	
Sustained attention ($n=30$)		**43% (13/30)**	**3% (1/30)**	[1](Turner et al., 2006); [5](Nicholson et al., 2003; [7]2000, [8]2002); [26](Clubley et al., 1979); [28](Roth et al., 1987); [39](Cohen et al., 1985); [43](Biehl, 1979); [63](Vuurman et al., 1994); [72](Kay et al., 1997); [73](Moskowitz and Burns, 1988); [74](Nicholson and Turner, 1998); [79](Seidel et al., 1990, [80]1987); [88](Parrott and Wesnes, 1987); [105](Fine et al., 1994)
	AZ4[43]	AZ8[43]		
	CE5[74], CE10[74], CE15[74]			
	CI15[8], CI30[88], CI45[8]			
	CL2[63]			
	CY25[26], CY100[26]			
		DC4[43]		
	DH50[1,28], DH75[1] DH100[1]	DH25[105], DH50[72,73] H25[79,80]	DH50[72]	
	MZ20[63], MZ40[63]			
	P12.5[88]	P10[7,74], P25[5,88] T2.5[39], T5[39]		
Selective attention ($n=7$)		**57% (4/7)** FEX360[49]	**0% (0/7)**	[2](Acons et al., 2006); [49](Theunissen et al., 2006a); [61](Kerr et al., 1994)
	MZ15[61] P30[2] T10[61]	MZ5[61], MZ45[61]		
		TER60[61]		
Divided attention ($n=25$)		**64% (16/25)**	**24% (6/25)**	[11](Theunissen et al., 2006b); [13](Witek et al., 1992); [14](Witek et al., 1995); [21](Mattila et al., 1986); [23](Roehrs et al., 1993); [45](van Ruitenbeek et al., 2008); [55](Hindmarch and Shamsi, 2001); [63](Vuurman et al., 1994); [65](Gaillard et al., 1988); [71](Seppala et al., 1981); [72](Kay et al., 1997); [73](Moskowitz and Burns, 1988); [75](Theunissen et al., 2006c); [76](Theunissen et al., 2004); [77](Verster et al., 2003a,b); [85](Ramaekers et al., 1992); [104](Richardson et al., 2002)
	B12[71] C4[14]			
		CE10[85]		
	CL1[65,71]	CL2[63]		
	DC2[45], DC6er[75,76]	DC4[45], DC6er[11] DH25[14]	DC4[45], CL2[63]	
		DH50[13,14,21,23,72,73,77,104]	DH50[21,72]	
	MQ10[11]			
		MZ20[63], MZ40[63]	MZ20[63], MZ40[63]	
		T10[55]		
	TEM100[21]			
Categorization tasks ($n=59$)		**41% (24/59)**	**15% (9/59)**	[1](Turner et al., 2006); [2](Acons et al., 2006); [3](Vuurman et al., 2004); [4](Gupta et al., 2004); [5](Nicholson et al., 2003, [7]2000, [8]2000); [13](Witek et al., 1992, [14]1995); [15](Gengo et al., 1990); [16](Swire et al., 1989); [17](Gengo et al., 1989); [18](Lee et al., 1988); [19](Bradley and Nicholson, 1987); [21](Mattila et al., 1986); [24](Nicholson and Stone, 1983); [25](Hamilton et al., 1982); [26](Clubley et al., 1979); [27](Baugh and Calvert, 1977); [28](Roth et al., 1987); [29](Nicholson and Stone, 1986); [38](Barbanoj et al., 2004); [44](Carruthers et al., 1978); [49](Theunissen et al., 2006b); [57](Bradley and Nicholson, 1986); [75](Nicholson et al., 1991); [88](Parrott and Wesnes, 1987); [99](De Brabander and Deberdt, 1990)
	C4[14], C10[75], C12er[18] CE5[15], CE10[4,15]			
	CE20[15]	CE20[15]		
	CI15[8], CI30[88], CI45[8]	CI30[88]		
	CY25[26], CY50[25], CY100[25,26]			
	DH25[14]	DH25[4]		
	DH50[3,13,14,15,28,99]	DH50[1,15,17,21,28], DH100[1]	DH50[17,44], DH50iv[44]	
	DH75[1,27]			
	DIM5[75]			
		FEX360[49]		
	H50[27,99]	H25[38] LO40[19]		
	MQ5[24]	MQ10[24]		
	P12.5[88], P30[2]	P10[7], P12.5[88], P25[5,88]	P12.5[88], P25[5,88]	
	RU10[38], RU20[38], RU40[38]	RU80[38]		
	T5[75]	T7.5[16], T10[24,19,29,57]	T7.5[16], T10[24,29]	

Effects of first generation H_1-antagonists on measures of attention. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

Table 3 – Effects of H_1-antagonists on psychomotor skills.

Cognitive domain/task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Psychomotor skills ($n=95$)		**58% (55/95)**	**19% (18/95)**	
Eye–hand coordination ($n=73$)		**63% (46/73)**	**23% (17/73)**	[2](Acons et al., 2006); [3](Vuurman et al., 2004); [5](Nicholson et al., 2003); [7](Nicholson et al., 2000); [11](Theunissen et al., 2006); [13](Witek et al., 1992, [14]1995); [19](Bradley and Nicholson, 1987); [21](Mattila et al., 1986); [24](Nicholson and Stone, 1983); [27](Baugh and Calvert, 1977); [29](Nicholson and Stone, 1986); [33](Kamei et al., 2003); [40](Levander et al., 1991); [43](Biehl, 1979); [45](van Ruitenbeek et al., 2008); [50](Cohen et al., 1987); [52](Franks et al., 1978); [53](Kulshrestha et al., 1978); [56](Hindmarch et al., 2002); [57](Bradley and Nicholson, 1986); [60](Shamsi et al., 2001); [61](Kerr et al., 1994); [63](Vuurman et al., 1994); [65](Gaillard et al., 1988); [69](Linnoila, 1973); [71](Seppala et al., 1981); [72](Kay et al., 1997); [73](Moskowitz and Burns, 1988); [74](Nicholson and Turner, 1998); [75](Theunissen et al., 2006c, [76]2004); [77](Verster et al., 2003a,b); [78](Schroeder et al., 1985); [82](Clarke and Nicholson, 1978); [83](Nicholson, 1979); [84](Nicholson and Stone, 1982); [85](Ramaekers et al., 1992); [88](Parrott and Wesnes, 1987);
	AZ4[43]	AZ8[43]		
	B12[71]	B4[83], B12er[83]		
	C4[14,53]	C4[82,83]	C4[82]	
	CE10[74,85]	CE5[74], CE15[74] CI30[88]	CE5[74], CE15[74]	
	CL1[71]	CL1[65,82], CL2[63]	CL2[63]	
	DC4[52], DC6er[11,75,76]	DC2[45], DC4[33,43,45]	DC2[45], DC4[45]	
	DH25[69]	DH25[14]		
	DH50[69]	DH50[3,13,14,21,50,72,73,77], DH75[27] DIM50[78], DIM100[78]	DH50[3]	
	LO40[19]			
	MQ10[11]	MQ5[24], MQ10[24]		
	MZ5[61], MZ15[61], MZ20[63]	MZ40[63], MZ45[61]	MZ40[63]	
	H20[40]			
	OL10[33]			
	P2.5[88], P25[60,88], P30[2]	P10[7,74,82], P25[5,78], P30[56], P50[78] T2.5[83], T10[19,24,29,57,61,84], T10er[83]	P10[8], P10[82], P25[5,78] T10[19,24,29,83,84]	
	TEM100[21] TER60[61]			
Postural stability ($n=4$)		**75% (3/4)**	**0% (0/4)**	[3](Vuurman et al., 2004); [50](Cohen et al., 1987); [52](Franks et al., 1978); [100](Gandon and Allain, 2002)
		DC4[52]		
	DH50[3]	DH50[50,100]		
Motor speed ($n=18$)		**33% (6/18)**	**6% (1/18)**	[9](Curran et al., 1998); [18](Lee et al., 1988); [25](Hamilton et al., 1982); [26](Clubley et al., 1979); [29](Nicholson and Stone, 1986); [39](Cohen et al., 1985); [40](Levander et al., 1991); [41](Oken et al., 1995); [43](Biehl, 1979); [44](Carruthers et al., 1978)
	AZ4[43]	AZ8[43] C12er[18]		
	CY25[26], CY50[25], CY100[25,26]			
		DC4[43]		
	DH50[9,44], DH1 mg/kg[41], DH50iv[44]	DH50[9]		
	H20[40]			
	T2.5[39], T5[39]	T10[29]	T10[29]	

Effects of first generation H_1-antagonists on measures of psychomotor skills. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

performance on reaction time tasks and may partially account for the decrement in psychomotor skills.

Of the 89 measurements assessing speed of discrete responding 54% (48/89, SC=10%) indicated slowed performance. Simple reaction time was slowed on 53% of the 34 measurements (18/34, SC=6%). Impairment ratio on the choice reaction time task was nearly the same, i.e. 55% of the 55 assessments (30/55, SC=13%). Assuming pure insertion of processes, the choice reaction time task includes the additional process of 'response choice' as compared to the simple reaction time task. As impairment ratios do not increase for the choice reaction time task, it may be suggested that antihistamines only have a small or no effect on the central process of response choice in addition to slowed sensory and/or motor processes.

A similar pattern was seen after diphenhydramine administration. The difference between the impairment ratio on the simple and choice reaction time tasks was small. Simple reaction time speed was slowed on 57% of the occasions (4/7) and choice reaction time was slowed 50% of the times (6/12). Performance after administration of lowest dose of diphenhydramine (25 mg) was impaired on both tasks, indicating that both measures are sensitive to the impairing effects of diphenhydramine.

Table 4 – Effects of H_1-antagonists on speed of discrete responding.

Cognitive domain/ task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Speed of discrete responding ($n=89$)		**54% (48/89)**	**10% (9/89)**	
Simple reaction time ($n=34$)		**53% (18/34)**	**6% (2/34)**	[3](Vuurman et al., 2004); [4](Gupta et al., 2004); [18](Lee et al., 1988); [25](Hamilton et al., 1982); [26](Clubley et al., 1979); [28](Roth et al., 1987); [35](Tagawa et al., 2002); [36](Tashiro et al., 2002); [37](Tashiro et al., 2004); [38](Barbanoj et al., 2004); [39](Cohen et al., 1985); [40](Levander et al., 1991); [43](Biehl, 1979); [44](Carruthers et al., 1978); [45](van Ruitenbeek et al., 2008); [47](Grunberger et al., 1988); [48](Adamus et al., 1987); [50](Cohen et al., 1987); [52](Franks et al., 1978); [53](Kulshrestha et al., 1978); [57](Bradley and Nicholson, 1986)
	AZ4[43]	AZ8[43]		
	C4[53]	C12er[18]		
	CE10[4]			
	CY25[26], CY50[25]			
	CY100[26]	CY100[25]		
	DC2[35], DC4[52], DC6er[35]	DC2[45], DC4[43,45]	DC4[45]	
	DH50[3,28,50]	DH25[4], DH50[44,47], DH50iv[44]	DH50[47]	
	H20[40]	H25[38], H30[36,37]		
	K2[48]			
		RU10[38], RU20[38], RU40[38], RU80[38]		
	T2.5[39], T10[57]	T5[39]		
Choice reaction time ($n=55$)		**55% (30/55)**	**13% (7/55)**	[1](Turner et al., 2006); [2](Acons et al., 2006); [4](Gupta et al., 2004); [5](Nicholson et al., 2003); [6](van Ruitenbeek et al., 2009); [12](Hindmarch et al., 1999); [14](Witek et al., 1995); [21](Mattila et al., 1986); [31](Volkerts et al., 1992); [32](Mochizuki et al., 2002); [33](Kamei et al., 2003); [35](Tagawa et al., 2002); [36](Tashiro et al., 2002, [37]2004); [38](Barbanoj et al., 2004); [43](Biehl, 1979); [45](van Ruitenbeek et al., 2008); [47](Grunberger et al., 1988); [52](Franks et al., 1978); [55](Hindmarch and Shamsi, 2001); [56](Hindmarch et al., 2002); [59](Ridout et al., 2003); [60](Shamsi et al., 2001); [61](Kerr et al., 1994); [65](Gaillard et al., 1988); [68](Levin et al., 1984); [69](Linnoila, 1973); [70](Millar and Standen, 1982); [71](Seppala et al., 1981); [88](Parrott and Wesnes, 1987)
	AZ4[43], AZ8[43]			
	B12[71]	B10[70]	B10[70]	
		C4[14]		
	CL1[71]	CL1[65]		
	CE10[4]			
		CI30[88]		
	DC4[6,33,43,52]	DC2[35,45], DC4[32,45], DC6er[35]	DC6er[35]	
	DH25[38,69], DH50[1,21,47,69]	DH25[4,14], DH50[13,14], DH75[1]		
		DH100[1]	DH100[1]	
	H25[38]	H30[36,37], H50[59]	H50[59]	
	MZ5[61], MZ15[61], MZ45[61]			
	OL10[33]	P12.5[88], P25[5,60,68,88], P30[2,12,56]	P25[5], P30[2,56]	
	RU10[38], RU20[38]	RU40[38], RU80[38]		
	T10[55]	T5[31], T10[61]		
	TEM100[21]			
	TER60[61]			

Effects of first generation H_1-antagonists on measures of speed of discrete responding. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

2.1.4. *Memory*

The effects of H_1 blockade on memory performance (Table 5) have been assessed 85 times, most frequently using tests of working memory (64/85) and episodic memory (20/85).

A total of 24 assessments (28%, SC=13%) showed impaired performance, nearly all (23/24) in tests of working memory. Of the 64 assessments of working memory 36% (SC=16%) indicated impaired performance. In contrast, episodic memory performance was impaired only once in 20 assessments (5%, SC=5%). Semantic memory was measured only once and was not impaired.

In correspondence with the overall findings, significant memory impairment by diphenhydramine was only found in tests of working memory (26%; 5/19), and not in tests of episodic (0/9) or semantic memory (0/1). There were no clear dose effects, as the highest dose (100 mg) failed to induce impaired performance while the lowest dose (25%) did.

2.1.5. *Perception*

Tasks in which the emphasis is on perceptual functions (visual and temporal) were assessed 71 times and performance was impaired in 48% (34/71, SC=11%) of the occasions (Table 6).

Perceptual processing speed (Critical Flicker/Fusion Frequency) has been assessed most frequently (i.e. 56 times). These measurements indicated slowed perceptual speed in 45% of the times (25/56, SC=11%).

In contrast, other measures of visual functions have been assessed less frequently. Visual threshold was measured only 9 times and was impaired in 67% of the occasions (6/9, SC=22%). Despite the small number of assessments the impairment induced by the relatively low dose of 2 mg dexchlorpheniramine may indicate that the visual threshold is sensitive to histaminergic manipulations. Pattern recognition was assessed in only 3 studies. Nevertheless, the results

Table 5 – Effects of H_1-antagonists on memory.

Cognitive domain/task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Memory ($n=85$)		**28% (24/85)**	**13% (11/85)**	
Working memory ($n=64$)	AZ4[43], AZ8[43]	**36% (23/64)**	**16% (10/64)**	[1](Turner et al., 2006); [3](Vuurman et al., 2004); [4](Gupta et al., 2004); [5](Nicholson et al., 2003); [13](Witek et al., 1992); [16](Swire et al., 1989); [19](Bradley and Nicholson, 1987); [21](Mattila et al., 1986); [26](Clubley et al., 1979); [27](Baugh and Calvert, 1977); [30](Gevins et al., 2002); [31](Volkerts et al., 1992); [38](Barbanoj et al., 2004); [41](Oken et al., 1995); [43](Biehl, 1979); [45](van Ruitenbeek et al., 2008); [47](Grunberger et al., 1988); [52](Franks et al., 1978); [55](Hindmarch and Shamsi, 2001); [61](Kerr et al., 1994); [63](Vuurman et al., 1994); [68](Levin et al., 1984); [72](Kay et al., 1997); [76](Theunissen et al., 2004); [77](Verster et al., 2003a,b); [85](Ramaekers et al., 1992); [88](Parrott and Wesnes, 1987); [103](Tsujii et al., 2007)
	CE10[4]	CE10[85] CL2[63]		
	CY25[26], CY50[26], CY100[26]	CY100[26]		
	DC6er[76]	DC2[45], DC4[52]	DC2[45], DC4[52]	
	DH50[1,3,13,21,47,77]	DH25[4], DH50[30,72]	DH50[72]	
	DH75[1], DH100[1], DH1 mg/kg[41]	DH75[27]		
	MZ5[61], MZ45[61]	MZ15[61], MZ20[63], MZ40[63] H25[38]	MZ20[63], MZ40[63]	
	LO10[19]			
		K1[103]	K1[103]	
	P12.5[88], P25[68,88], P30[2]	P25[5]		
	RU10[38], RU20[38], RU40[38], RU80[38]	RU80[38]	P25[5]	
	T7.5[16], T10[61] TEM100[21] TER60[61]	T5[31], T10[19,55]		
Semantic memory ($n=1$)	DH50[3]	**0.0% (0/1)**	**0.0% (0/1)**	[3](Vuurman et al., 2004)
Episodic memory ($n=20$)		**5% (1/20)**	**5% (1/20)**	[1](Turner et al., 2006); [2](Acons et al., 2006); [3](Vuurman et al., 2004); [5](Nicholson et al., 2003); [9](Curran et al., 1998); [18](Lee et al., 1988); [45](van Ruitenbeek et al., 2008); [47](Grunberger et al., 1988); [76](Theunissen et al., 2004); [77](Verster et al., 2003a,b); [88](Parrott and Wesnes, 1987); [98](Carter and Cassaday, 1998); [99](De Brabander and Deberdt, 1990); [100](Gandon and Allain, 2002)
	C4[98,98,98], C12er[18] CI30[88] DC4[45],DC6er[76] DH25[9], DH50[1,3,9,77,100], DH75[1], DH100[1] H50[99]			
	P12.5[88], P25[88], P30[2]	P25[5]	P25[5]	

Effects of first generation H_1-antagonists on measures of memory. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

(3/4; 75%, SC=0%) suggest that perceptual processes may be sensitive to the effects of antihistamines. Finally, complex perceptual functions (time and speed perception) were assessed twice and were not impaired. Processing of the complex patterns, time and speed, appear to be less affected by the H_1-antagonists as compared with processing of simple visual information as assessed with critical flicker/fusion tasks. However, further studies need to be conducted to establish this difference in effects as only one study assessed the effects on temporal perception.

Within this domain of perception the effects of diphenhydramine were assessed on perceptual processing speed and impaired performance on 4 out of 7 assessments (57%). The high impairment ratio is in accordance with the ratio of all treatments. In contrast, the effects of diphenhydramine on visual threshold, pattern recognition and complex perceptual functions were not studied. Therefore, the pattern of results obtained by studying the effects of all treatments could not be confirmed by the effects of diphenhydramine.

2.1.6. *Driving*

Effects on driving performance (Table 7) have been assessed much less frequently i.e. 23 times. As car driving is a highly complex task involving many cognitive functions it is expected that performance is sensitive to the sedative effects of H_1-antagonists. Indeed, performance was impaired in 78% (18/23, SC=26%) of the occasions, which was largely due to actual driving performance (15/17; 88%, SC=35%). On 6 occasions a simulator was used and 17 times actual driving performance was assessed in an 'on the road driving test'. Of the 6 assessments using a simulated driving test 3 indicated impaired performance after the administration of the H_1-antagonist (50%, SC=0%).

Diphenhydramine 50 mg was studied 4 times and consistently impaired performance on all occasions (100%, SC=20%). The effects of 25 mg have not been studied using tests of actual driving, so based on the ability of 25 mg to impair performance, the sensitivity cannot be compared to other tasks. However, considering the high impairment ratios of

Table 6 – Effects of H_1-antagonists on perception.

Cognitive domain/ task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Perception ($n=71$)		**48% (34/71)**	**11% (8/71)**	
Pattern recognition ($n=4$)	LO40[19]	**75% (3/4)** T5[31], T10[19,57]	**0% (0/4)**	[19](Bradley and Nicholson, 1987); [31](Volkerts et al., 1992); [57](Bradley and Nicholson, 1986)
Visual threshold ($n=9$)	DC1iv[34]	**67% (6/9)** DC2[35], DC6er[35], DC2iv[34] H30[36,37]	**22% (2/9)** DC2[35], DC6er[35]	[24](Nicholson and Stone, 1983); [34](Okamura et al., 2000); [35](Tagawa et al., 2002); [36](Tashiro et al., 2002, [37]2004)
	MQ5[24], MQ10[24]	T10[24]		
Complex perceptual functions ($n=2$)	B12[71] CL1[71]	**0% (0/2)**	**0% (0/2)**	[71](Seppala et al., 1981)
Perceptual processing speed ($n=56$)	AZ4[43], AZ8[43] B12[71] C4[53], C12er[18] CE10[4]	**45% (25/56)** CI30[88]	**11% (6/56)**	[3](Vuurman et al., 2004); [4](Gupta et al., 2004); [9](Curran et al., 1998); [12](Hindmarch et al., 1999); [16](Swire et al., 1989); [18](Lee et al., 1988); [21](Mattila et al., 1986); [24](Nicholson and Stone, 1983, [29]1986); [30](Gevins et al., 2002); [33](Kamei et al., 2003); [38](Barbanoj et al., 2004); [43](Biehl, 1979); [47](Grunberger et al., 1988); [48](Adamus et al., 1987); [53](Kulshrestha et al., 1978); [55](Hindmarch and Shamsi, 2001); [56](Hindmarch et al., 2002); [57](Bradley and Nicholson, 1986); [59](Ridout et al., 2003); [60](Shamsi et al., 2001); [61](Kerr et al., 1994); [63](Vuurman et al., 1994); [68](Levin et al., 1984); [71](Seppala et al., 1981); [76](Theunissen et al., 2004); [88](Parrott and Wesnes, 1987); [100](Gandon and Allain, 2002); [103](Tsujii et al., 2007); [110](Hou et al., 2007)
	CL1[30,71] DC4[33,43], DC6er[76] DH50[3,9,47]	CL2[30,63] DH25[4], DH50[21,100], DH75[110]		
	H25[38] K2[48] MQ5[24], MQ10[24]	H25[38], H50[59] K1[103]	K1[103]	
	MZ5[61], MZ15[61]	MZ20[63], MZ40[63], MZ45[61]	MZ20[63], MZ40[63]	
	OL10[33] P12.5[88]	P25[60,68,88], P30[12,56]	P25[88]	
	RU10[38], RU20[38], RU40[38], RU80[38] T10[55] TEM100[21]	RU80[38] T7.5[16], T10[24,29,57,61] TER60[61]	T7.5[16], T10[29]	

Effects of first generation H_1-antagonists on measures of perception. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

both the liberal and strict significance criterion, it may be stated that actual driving is a highly sensitive task.

2.1.7. *Sensory visual function*

More sensory functions have been assessed the least, i.e. 5 times and only in the visual domain of which 60% (SC=0%) indicated an impairment (Table 8). Physiology of the eye (i.e. pupillary functions) were impaired in 50% of the assessments (2/4, SC=0%), due to effects of diphenhydramine. The 75 mg dose more clearly induced an impairment (Hou et al., 2007), while the 50 mg dose only induced an impairment on static pupil diameter measures and not on dynamic functions (Grunberger et al., 1988). As the 50 mg dose may not be a sufficient dose to induce consistent effects, static pupil diameter could be less sensitive. Taken together, these five assessments indicate that sensory visual functions can be affected by H_1-antagonists. However, data are limited as few studies have been conducted.

2.2. *Sedation*

Histamine has been known to be involved in sleep–wake regulation (Saper et al., 2001; Saper et al., 2005). During sleep histaminergic activity is decreased while in a waking state histaminergic neurons in the tuberomammillary nucleus are

Table 7 – Effects of H_1-antagonists on driving performance.

Cognitive domain/task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Driving ($n=23$)		**78% (18/23)**	**26% (6/23)**	
Simulated driving ($n=6$)		**50% (3/6)**	**0% (0/6)**	[15](Gengo et al., 1990); [17](Gengo et al., 1989); [20](Tashiro et al., 2008)
	CE5[15], CE10[15], CE20[15]			
		DC6er[20]		
		DH50[15,17]		
Actual driving ($n=17$)		**88% (15/17)**	**35% (6/17)**	[3](Vuurman et al., 2004); [11](Theunissen et al., 2006d); [31](Volkerts et al., 1992); [59](Ridout et al., 2003); [63](Vuurman et al., 1994); [75](Theunissen et al., 2006c); [76](Theunissen et al., 2004); [85](Ramaekers et al., 1992); [89](Tashiro et al., 2005); [90](Verster et al., 2003a,b); [91](Vuurman et al., 2007); [106](Vermeeren et al., 2002)
		CE10[85,106]		
		CL2[63]	DC6er[11]	
		DC6er[11,75,76]		
		DH50[3,90]	DH50[3]	
		EM2[106], EM4[106]		
	H30[89], H50[59]	H50[91]	H50[91]	
		MQ10[11]	MQ10[11]	
		MZ20[63], MZ40[63]	MZ20[63], MZ40[63]	
		T5[31]		

Effects of first generation H_1-antagonists on measures of driving. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

most active. Therefore, blockade of the excitatory H_1-receptor leads to decreased wakefulness (Table 9).

This is reflected in the measures of daytime sleepiness, which were assessed 23 times by the multiple sleep onset latency test (MSLT; Carskadon and Dement 1987). In 91% (21/23, SC=35%) sleep onset latency was shortened by the H_1-antagonist as compared to placebo. In addition, two studies using wrist actigraphy to assess daytime activity showed a significant reduction in daytime behavioural activity following the use of a sedative antihistamine (Hindmarch et al., 1999; Kamei et al., 2003). Effects of diphenhydramine on multiple sleep onset latency were assessed 6 times after doses between 50 and 100 mg. All doses had significant effects (100%, SC=67%). These results show that diphenhydramine is capable of inducing clear sedation and sleepiness in doses of 50 mg and higher.

Subjective sedation was assessed 147 times and in 75% H_1-antagonists induced subjectively rated sedation (110/147, SC=18%). Diphenhydramine 25 mg was used 5 times and induced subjective sedation on all occasions. These results indicate that if an antihistamine induces performance impairment, it is also likely to induce sedation. However, the fact that some studies did not show any effect on subjective sedation, but impaired performance on other measures, indicates that people taking antihistamines may not always be able to judge the level of impairment by judging the level of sedation.

3. Discussion

The aim of this review was to determine which cognitive domains are most sensitive to H_1-antagonism. Taken together, if the LC is applied, driving is impaired most frequently (78%) by centrally active H_1-antagonists, followed by sensory visual functions (60%), psychomotor skills (58%, in particular eye–hand coordination), speed of discrete responding (54%, in particular choice reaction time), perception (48%, in particular visual threshold and pattern recognition), and attention (47%, in particular divided attention). Finally, memory performance was impaired in 28% of the assessments (in particular working memory). When applying the SC, driving was impaired in

Table 8 – Effects of H_1-antagonsists on sensory visual functions.

Cognitive domain/task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Sensory visual function ($n=5$)		**60% (3/5)**	**0% (0/5)**	
Physiology of the eye ($n=4$)		**50% (2/4)**	**0% (0/4)**	[47](Grunberger et al., 1988); [76](Theunissen et al., 2004); [110](Hou et al., 2007)
	DC6er[76]			
	DH50[47]	DH50[47], DH75[110]		
Eye movements ($n=1$)		**100% (1/1)**	**0% (0/1)**	[50](Cohen et al., 1987)
		DH50[50]		

Effects of first generation H_1-antagonists on measures of sensory visual function. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

Table 9 – Effects of H_1-antagonists on measures of sedation.

Cognitive domain/task	No impairment	Impairment		References
		$p<0.05$	$p<0.01$	
Sedation ($n=172$)		**77% (133/172)**	**20% (35/172)**	
Multiple sleep onset latency ($n=23$)		**91% (21/23)**	**35% (8/23)**	[1](Turner et al., 2006); [5](Nicholson et al., 2003, [7]2000, [8]2002); [23](Roehrs et al., 1993);
		C10[75]		
	CE5[74], CE15[74]	CE10[74]	CE10[74]	[27](Baugh and Calvert, 1977);
		CI15[8], C45[8]		[28](Roth et al., 1987); [29](Nicholson and Stone, 1986);
		DH50[1,23,28,104], DH75[1], DH100[1]	DH50[27,104]	[31](Volkerts et al., 1992); [74](Nicholson and Turner, 1998); [75](Nicholson et al., 1991); [80](Seidel et al., 1987, [79]1990);
			DH75[1], DH100[1]	[104](Richardson et al., 2002)
		DIM5[75]		
		H25[79,80],		
		P10[7,8,74], P25[5]	P25[5]	
		T2.5[29], T5[29,31,75]	T5[29,75]	
Daytime activity ($n=2$)		**100% (2/2)**	**0% (0/0)**	[12](Hindmarch et al., 1999); [33](Kamei et al., 2003)
		DC4[33]		
		P30[12]		
Subjective sedation ($n=147$)		**75% (110/147)**	**18% (27/147)**	[1](Turner et al., 2006); [2](Acons et al., 2006); [3](Vuurman et al., 2004); [4](Gupta et al., 2004); [5](Nicholson et al., 2003); [6](van Ruitenbeek et al., 2009); [7](Nicholson et al., 2000, [8]2002); [9](Curran et al., 1998); [30](Ridout & Hindmarch, 2003); [12](Hindmarch et al., 1999); [13](Witek et al., 1992; [14]1995); [15](Gengo et al., 1990); [16](Swire et al., 1989); [17](Gengo et al., 1989); [18](Lee et al., 1988); [19](Bradley and Nicholson, 1987); [20](Tashiro et al., 2008); [21](Mattila et al., 1986); [22](Seidel et al., 1987); [24](Nicholson and Stone, 1983); [25](Hamilton et al., 1982); [26](Clubley et al., 1979); [29](Nicholson and Stone, 1986); [30](Gevins et al., 2002); [32](Mochizuki et al., 2002); [33](Kamei et al., 2003); [34](Okamura et al., 2000) [35](Tagawa et al., 2002); [36](Tashiro et al., 2002); [37](Tashiro et al., 2004); [38](Barbanoj et al., 2004); [39](Cohen et al., 1985); [40](Levander et al., 1991); [41](Oken et al., 1995); [44](Carruthers et al., 1978); [45](van Ruitenbeek et al., 2008); [46](Goetz et al., 1991); [47](Grunberger et al., 1988); [48](Adamus et al., 1987); [50](Cohen et al., 1987); [52](Franks et al., 1978); [53](Kulshrestha et al., 1978); [55](Hindmarch and Shamsi, 2001); [56](Hindmarch et al., 2002); [57](Bradley and Nicholson, 1986); [59](Ridout et al., 2003); [60](Shamsi et al., 2001); [61](Kerr et al., 1994); [63](Vuurman et al., 1994); [65](Gaillard et al., 1988); [66](Gaillard and Verduin, 1983); [68](Levin et al., 1984); [69](Linnoila, 1973); [70](Millar and Standen, 1982); [71](Seppala et al., 1981); [72](Kay et al., 1997); [74](Nicholson and Turner, 1998); [74](Nicholson and Turner, 1998); [75](Nicholson et al., 1991); [76](Theunissen et al., 2004); [77](Verster et al., 2003b); [78](Schroeder et al., 1985); [79](Seidel et al., 1990); [81](Simons et al., 1996); [82](Clarke and Nicholson, 1978); [83](Nicholson, 1979); [84](Nicholson and Stone, 1982); [85](Ramaekers et al., 1992); [88](Parrott and Wesnes, 1987); [89](Tashiro et al., 2005); [90](Verster et al., 2003a) [91](Vuurman et al., 2007); [98](Carter and Cassaday, 1998) [99](De Brabander and Deberdt, 1990); [100](Gandon and Allain, 2002); [103](Tsujii et al., 2007); [104](Richardson et al., 2002); [105](Fine et al., 1994); [106](Vermeeren et al., 2002); [108](Moser et al., 1978); [110](Hou et al., 2007)
	B4[83], B12er[83]	B10[70], B12[71]		
	C4[83]	C4[14,53,82,98], C10[75], C12er (increase)[18]		
	CE5[15], CE10[15,106], CE20[15]	CE5[74], CE10[4,24,74,85], CE15[74]	CE10[74], CE15[74]	
	CL1[65,82]	CL1[71], CL2[63]		
		CI15[8], CI30[88], CI45[8]		
		CY25 (increase)[26], CY100[25,26]	DC4[45]	
	DC4[33], DC6er[20]	DC2[35,45], DC4[6,32,45,52]		
	DC1iv[34], DC2iv[34]	DC6er[35,76]		
	DI5[75]			
	DIM50[78]	DIM100[78]	DH50[1,21,47,72,104]	
		DH25[4,14,69,105]		
		DH50[1,3,9,13,14,15,17,21,30,44,47], DH50[50,69,72,77,81,90,100,104], DH75[1,110], DH100[1,108], DH1 mg/kg[41], DH50iv[44]	DH75[1], DH100[1,108]	
	EM2[106]	EM4[106]		
		FEX60[10]		
	H25[22]	H20[40], H25[38,79], H30[36,37,89], H50[59,91,99]	H30[89], H50[59,91,99]	
		K1[103], K2[48]	K1[103]	
	LO10[19]			
	MQ5[24], MQ10[24]			
	MZ5[61], MZ15[61], MZ45[61]	MZ20[63], MZ40[63]		
	OL10[33]	OL5[10]		
	P10[82], P30[12]	P10[7,74], P12.5[88], P25[5,5,60,68,78,88], P30[2,56] P50[78]	P12.5[88], P25[5,5,68,88]	
		RU20[38], RU40[38], RU80[38]		
		TEM100[21]		
	TER60[61]			
	T2.5[83]	T2.5[39], T5[39], T7.5[16], T10[19,24,29,55,57,61,84]		
	T5[75,75], T10[er83]			

Effects of first generation H_1-antagonists on measures of sleepiness. Drugs and doses (see Table 2 for abbreviations) were classified as causing no significant impairment, or significant impairment at a $p<0.05$ and $p<0.01$ level. The likelihood of impairment found for separate dependent measures in this cognitive domain is indicated in bold. It was calculated as the percentage of significant impairments found within the total number of assessments. The ratio is indicated between brackets.

Table 10 – Effects of diphenhydramine.

Cognitive domain	Diphenhydramine dose			
	100 mg	75 mg	50 mg	25 mg
Driving	n.a.	n.a.	100%	n.a.
Psychomotor skills	n.a.	100%	82%	50%
Sensory visual function	n.a.	100	67%	n.a.
Attention	50%	0%	64%	80%
Perception	n.a.	100%	40%	100%
Speed of discrete responding	100%	100%	36%	60%
Memory	0%	25%	17%	50%

The typical H_1-antagonist diphenhydramine used to indicate cognitive domains sensitive to H_1-antagonism. Percentages indicate the proportion of the treatments that impaired performance on tasks assessing a certain cognitive domain.

26% of the assessments and psychomotor skills, attention and memory were impaired in 19%, 13%, 13%, respectively, by H_1-antagonism. Perception (11%) and speed of discrete responding (10%) were affected less frequently.

To achieve the aim of this review, diphenhydramine has been regarded as a prototypical antihistamine, because it has been used most frequently in a variety of tasks. Effects of diphenhydramine show a similar pattern of results compared with the impairment ratio of all drugs (Table 10). The 50 mg dose has been used most frequently and the effects of this dose on nearly all domains have been assessed. Driving performance (100%), psychomotor skills (82%), sensory visual function (67%) (i.e. eye movements and physiology of the eye), attention (64%), perception (40%) and speed of discrete responding (36%) were frequently impaired by diphenhydramine. Finally, memory was affected least frequently (17%), especially when considering episodic memory.

In general, a pattern emerges in which performance is most frequently impaired in tasks involving the most cognitive operations. Most cognitive domains may be considered to be a Matryoshka doll in which every domain is incorporated in the next. Perception (showing 48% impairment) is incorporated in speed of discrete responding (54% impairment), which is part of psychomotor skills (58% impairment), which is part of car driving (78% impairment). The impairment ratio for sensory visual functions (60%) does not fit this pattern, as it would be expected that the smallest doll is affected the least frequently. However, it must be kept in mind that this domain was only assessed 5 times. Therefore, the ratio is highly sensitive to fluctuations.

Within the domain of attention the most frequently measured and affected function is divided attention (64%). Divided attention tasks often include multiple tasks. Frequently a peripheral search task is combined with an eye–hand coordination task. Measures of divided attention may be found sensitive due to the impaired eye–hand coordination. This notion is supported by the fact that psychomotor skills were impaired in 58% of the occasions. A second reason for the sensitivity of the divided attention tasks is that they are often designed to maximize workload and minimize spare capacity. Therefore, any impairment induced by a treatment is likely to result in measurable performance impairment.

For similar reasons psychomotor skills may be frequently impaired. For example, eye–hand coordination (e.g. compensatory tracking) contains many cognitive operations, like visual information processing, inhibitory control of movement, anticipation and motor control and also has a high workload. Therefore, any induced impairment is likely to be reflected in the overt behaviour. However, it is unclear which of these many processes is/are mainly affected. Studies assessing subprocesses of the cognitive domains should be conducted in order to uncover the underlying impairments.

The number of cognitive operations is much smaller for discrete responding and may, therefore, be one of the smaller Matryoshka dolls. Nevertheless, some authors have assessed even smaller dolls, i.e. specific processes involved in performance on the choice reaction time task. In two studies by (Gaillard and Verduin, 1983; Gaillard et al., 1988) and one by Van Ruitenbeek et al. (2009) the interaction between the effect of an antihistamine and the presentation of visually degraded stimuli was studied. Two of these studies found that the antihistamine interacted or tended to interact with the task manipulation i.e. stimulus degradation (Gaillard and Verduin, 1983; Van Ruitenbeek et al., 2009). Stimulus degradation is known to affect the processing of sensory information. The interaction indicates the effect of antihistamines on at least that same process (Sanders, 1980; Sternberg, 1969). In contrast, in their second study Gaillard et al. (1988) concluded that the antihistamine mainly affected motor related processes. Next to these three studies there are no studies examining the specificity of the effects of antihistamines. Therefore, more studies should be conducted that examine the specificity of the effects of H_1-antagonists.

Memory was affected much less frequent (28%). The lack of effects on episodic memory is in striking difference with the effects of H_1-blockade found in animals (e.g. Alvarez and Ruarte, 2004; Yanai et al., 2008). A possible explanation of this discrepancy is that effects seen in animals may not be directly translatable to man. For example, memory performance in rats is highly dependent on spatial factors and the hippocampus. In contrast, humans are able to use more strategies, mostly verbal ones, even if the stimulus material is spatial in nature and, therefore, more and different brain structures or circuits – mainly cortical – can assumed to be involved. Seemingly similar tasks in rodents and humans such as route finding may be remembered using different cues. While rodents are assumed to rely for memory on spatial cues, humans in a similar paradigm will use verbal cues even if they are deliberately not presented by the experimental paradigm. Hence a seemingly similar task may rely on different neural substrates. This casts doubt on the translatability of animal models to test drug effects on memory or other cognitive functions.

Furthermore, in many cases the task assessing memory functions in animals involves an active element to perform well, like an active avoidance task (e.g. Kamei et al., 1990; Kamei and Tasaka, 1991; Kamei et al., 1993; Prast et al., 1996). An increase in response time may indicate sedation next to impaired memory. This is supported by Molinengo et al. (1999) who showed that diphenhydramine was not able to impair

performance on a passive avoidance task, in which less moving by the animal determines improved performance.

A bulk of evidence that histamine plays a role in memory functioning is derived from studies in which H_3-antagonists improve memory performance in animals. However, the effects may be mediated by other transmitter systems. The H_3-receptor also functions as a heteroreceptor, where it regulates the release of neurotransmitters like acetylcholine, dopamine, serotonin and norepinephrine (Blandina et al., 2004). It has been shown that H_3-receptor activation depresses synaptic activity in the dentate gyrus and hippocampus, which are well known to be involved in memory (Arrang et al., 1985; Brown and Reymann, 1996). Blockade of the H_3-receptor may lead to improved memory performance not directly involving the H_1-receptor.

This review showed that in contrast to episodic memory, working memory was clearly more frequently impaired. Performance on tasks assessing working memory frequently relies on response speed. For example, overall response speed is often the dependent outcome measure of the Sternberg's memory scanning task and, therefore, resembles a choice reaction time task. In such cases antihistamines impair performance in 50% (LC) of the assessments, which approaches the 55% (LC) impairment on the choice reaction time task. In contrast to the working memory tasks, explicit and semantic memory is frequently measured using word learning tasks or recall of information, which is largely irrespective of speed. It may be that information processing speed is affected, but not the functional integrity of memory functions e.g. correct recalling of words.

It should be taken into account that only three studies were conducted that aimed to determine if memory is affected by H_1-antagonism (Curran et al., 1998; Turner et al., 2006; Van Ruitenbeek et al., 2008). Therefore, more such studies should be conducted to support the findings from the present review that episodic memory is not likely to be affected by H_1-antagonism.

There are some limitations to the numbers in the present review that need some consideration. First generation H_1-antagonists have been used as active control treatments for their sedative effects (Curran et al., 1998). Activity of the histaminergic cells in the tuberomammillary nucleus is associated with wakefulness and a decrease in activity of these cells is associated with a decrease in arousal (Saper et al., 2005). A decrease in arousal may cause a non specific decrement in performance. Such a notion is supported by the observation that more complex tasks, involving more processes, are more sensitive to detrimental effects. In addition, effects of lowered arousal may explain the observed performance decrease on tasks associated with speeded response, as lower levels of arousal prolong reaction time. Conversely, task performance that does not rely on speed of responding (e.g. word learning) is affected less frequently. This supports the hypothesis that arousal levels mediate antihistamine-induced performance impairment.

Another possible limitation concerns the fact that some tasks may have been used to evaluate the effects of relatively less sedating antihistamines. This would lead to less significant effects and therefore, an underestimation of the sensitivity of the domain or task. For example, out of the 6 assessments of simulated driving 3 involved the evaluation of the effects of cetirizine, which is less sedative compared to many other antihistamines. All three assessments did not show effects of cetirizine. The sensitivity of simulated driving to the effects of antihistamines may be comparable to actual driving, but was underestimated due to the lack of effects of cetirizine.

Finally, the fact that most first generation antihistamines have affinity for multiple receptor types from multiple transmitter systems (e.g. cholinergic, noradrenergic) may make interpretation of these results difficult. However, as they all have a high affinity for the H_1-receptor in common, the functions that are sensitive to H_1-antagonism should be affected most frequently. Therefore, as long as a large variety of H_1-antagonists are used and the affinity for other receptors than the H_1-receptor is randomly distributed, the interpretation that some cognitive domains are sensitive to their effects is valid.

In conclusion, this review suggests that H_1-antagonism primarily impairs speed of cognitive information processing, which renders performance on tasks that rely on speed (e.g. discrete responding, eye–hand coordination, divided attention, driving) highly sensitive to H_1-blockade and tasks that rely

Table 11 – Papers excluded from the review.

Exclusion reason	Number of papers	References
No observed sedation	13	(Brookhuis et al., 1993; Dhorranintra et al., 1986; Gordon et al., 2001; Hedges et al., 1971; Higgins et al., 1979; Philipova et al., 2004; Popov et al., 2006; Roberts, 1971; Schilling et al., 1990; Seppala and Savolainen, 1982; Serra-Grabulosa et al., 2001; Telekes et al., 1987; Tharion et al., 1994; Theunissen et al., 2006d)
No acute effects	8	(Betts et al., 1984; Hindmarch, 1976; Hindmarch and Parrott, 1978; Millet et al., 1982; Nicholson et al., 1985; Patat et al., 1995a,b; Starbuck et al., 2000)
Only measured interactions	6	(Barbanoj et al., 2006; Buckey et al., 2004; Hindmarch and Bhatti, 1987; Hyman et al., 1988; Takahashi et al., 2004; Valk and Simons, 2009)
No behaviourally measured cognition	6	(Alford et al., 1992; Roehrs et al., 1984; Sannita et al., 1996; Simons et al., 1995; Simons, 2002; Tashiro et al., 2009)
No verum used	3	(Bhatti and Hindmarch, 1989; Kanamaru et al., 2008; Vincent et al., 1988)
No healthy young volunteers	4	(Gengo et al., 1987; Magerl et al., 2009; Patat et al., 1994; Sato et al., 2007)
Too few subjects	2	(Molson et al., 1966; Pishkin et al., 1983)

Several papers were identified as potentially useful, which were, nevertheless excluded for the reasons mentioned in the first column.

Table 12 – Tasks assessing functions within cognitive domains

Cognitive domain	Task
Attention	
Spatial attention	Covert attention, D2 cancellation, alphabetical cross-out, visual search
Sustained attention	Sustained attention, vigilance, rapid visual information processing
Selective attention	Auditory selective attention, focussed attention, Stroop
Divided attention	Divided attention
Categorization tasks	Trial making, digit symbol substitution, card sorting, rule finding
Psychomotor skills	
Eye–hand coordination	Pursuit rotor, spiral maze, visuomotor coordination, fine motoric test, word typing, compensatory tracking, critical tracking
Postural stability	Body sway
Motor speed	Symbol copying, finger tapping
Speed of discrete responding	
Simple reaction time	Simple reaction time
Choice reaction time	Choice reaction time
Memory	
Working memory	ANAM running memory, digit memory recall/digit span, N-back, Sternberg's memory scanning, logical reasoning, syntactic reasoning, arithmetic
Semantic memory	Semantic verification
Episodic memory	Word association, spatial paired associates learning, word learning, pattern recognition, information recall, source memory
Perception	
Pattern recognition	Letter matching
Visual threshold	Visual discrimination
Complex perceptual functions	Speed anticipation, temporal estimation
Perceptual processing speed	Critical flicker–fusion
Driving	
Simulated driving	Driving simulator tests
Actual driving	Weaving, speed consistency
Sensory visual function	
Physiology of the eye	Pupillary functions
Eye movements	Eye saccades
Sedation	
Multiple sleep onset latency	Multiple sleep latency onset
Daytime activity	Wrist actigraphy
Subjective sedation	Subjective ratings

Cognitive domains are indicated in italics in the left column. These domains are divided into specific areas. Tasks measuring subjects' performance are listed in the right column.

little on speed like episodic memory less sensitive. Second, it appears that a task is more sensitive when more cognitive operations are involved in task performance. As discussed above, driving, divided attention and complex psychomotor functions include multiple cognitive processes related to stimulus perception, decision making, response anticipation and preparation and response execution. In accordance, these domains and tasks have shown to be frequently affected by H_1-antagonism. However, so far, only a few studies have assessed effects of H_1-antagonists on separate underlying processes and came to contradictory conclusions. The specificity of the effects of centrally active H_1-antagonists therefore deserves further studying. Similarly, attention functioning appears sensitive to the effects of H_1-antagonists, but should be investigated as little focus has been directed to the sub-functions of attention.

4. Experimental procedures

4.1. *Literature search*

A computer assisted literature search was conducted in the PsycInfo, Medline, PubMed and EMbase databases to identify placebo and verum controlled experimental studies, which reported the acute effects of orally administered H_1-antagonists on cognitive performance in healthy young (between 18 and 45 years of age) human volunteers. Studies were included if one of the treatments was an H_1-antagonist that (a) produced significant subjective or objective sedation, or (b) that produced significant performance impairment (being the present selection based on previous published reviews), or (c) that is known to occupy more than 50% of H_1 receptors in the central nervous system (Yanai and Tashiro, 2007). In addition studies had to measure the acute effects of an antihistamine using at least one objective measure of cognitive performance. Finally, papers should be published in peer reviewed journals between 1973 and December 2009.

In total 42 studies were excluded from the collection of articles used in the present review. Thirteen studies did not show any sedative effects of the antihistamines and were therefore excluded. Six studies were excluded because they did not measure effects of antihistamines alone, but only in combination with other factors like alcohol or stimulant drugs. Six more studies were excluded because they did not include an objective measure of cognitive functioning. Another three were excluded, because no verum was used as active control treatment or showed no effects. Four studies were excluded for not using healthy young volunteers. Eight papers were excluded because effects were not measured after an acute dose. Finally, two studies were excluded due to probable lack of power, i.e. no significant effects were found in a sample of 4 subjects (Molson et al., 1966; Pishkin et al., 1983) as several studies (Alford et al., 1992; Bradley and Nicholson, 1987; Carruthers et al., 1978; Clarke and Nicholson, 1978; Levin et al., 1984; Nicholson, 1979; Nicholson and Stone, 1982, 1983, 1986; Nicholson et al., 2000, 2002) did show central antihistamine effects using 6 subjects. (For details see Table 11.)

4.2. *Data collection*

The tests used to evaluate antihistamine-induced impairment were categorized by measurement of the following major cognitive domains (Table 12): memory, attention, perception, sensory visual function, speed of discrete responding, psychomotor skills, driving and sedation as an indicator of overall central nervous system functioning.

Memory tests found in the papers included in the review could be clustered as measuring working memory functions, episodic memory or semantic memory. Attention tests found could be clustered into tests measuring spatial aspects of attention (spatial attention), time aspects of attention (sustained attention), resistance to distraction (selective attention), dividing attention over multiple sources (divided attention), and focusing of attention (categorization tasks). Effects of antihistamines on sensory performance have only been measured for the visual modality (eye physiology and eye movements). Effects on perceptual functions have been assessed using tests determining perceptual thresholds in the visual domain, visual pattern recognition, estimations of time and speed (complex perceptual functions), and perceptual processing speed. Tests of speed of responding to discrete stimuli could be clustered into simple and choice reaction time tests, and tests of psychomotor skills could be clustered into tests of motor speed, more eye–hand coordination tests, and postural stability. On-the-road driving tests and driving simulator scenarios were considered a separate category (Driving) as performance in these tests usually requires integration of multiple cognitive functions over a longer period of time. Finally, the sedative effects were evaluated using the objective Multiple Sleep Onset Latency test and day time activity and subjective sedation by subjective ratings.

Existing classifications of psychological tests were used to determine the cognitive domain measured by each test (Hindmarch, 1980; Lezak et al., 2004). Tasks not included in these classifications were categorized according to the authors' description of the test in the original paper.

Next, the effects on performance and sedation of all doses of antihistamines included in a study were recorded. Treatments and doses found are listed in Table 1 with their abbreviations.

When a drug effect was significantly different from placebo at any point in time after the administration of the antihistamine, the effect was listed as 'impairment' in a certain cognitive domain. This was done once using $p<0.05$ as a liberal criterion (LC), and once using $p<0.01$ as a strict criterion (SC) to better control for type 1 errors. In 13 papers this distinction could not be made, however, because only 95% confidence intervals were reported. These studies were included in the calculation of the impairment ratio according to the LC only. Finally, numbers and percentages of impairment were calculated using the number of impairing effects compared to the total number of assessments for each major cognitive domain and the functions within a domain (Tables 2–9).

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