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RESEARCH PAPER

Histamine H_1 receptor blockade predominantly impairs sensory processes in human sensorimotor performance

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Background and purpose: Centrally active antihistamines impair cognitive performance, particularly sensorimotor performance. The aim of the present study was to further elucidate the scarcely studied subprocesses involved in sensorimotor performance, which may be affected by H_1 receptor blockade. Better knowledge about the cognitive deficits associated with histamine dysfunction can contribute to better treatment of clinical disorders in which histamine hypofunction may be a contributing factor, such as in schizophrenia.
Experimental approach: Interactions of dexchlorpheniramine with specific task manipulations in a choice reaction time task were studied. Task demands were increased at the level of sensory subprocesses by decreasing stimulus quality, and at the level of motor subprocesses by increasing response complexity. A total of 18 healthy volunteers (9 female) aged between 18 and 45 years participated in a three-way, double-blind, crossover design. Treatments were single oral doses of 4 mg dexchlorpheniramine, 1 mg lorazepam and placebo. Behavioural effects were assessed by measuring reaction times and effects on brain activity by event-related potentials.
Key results: Dexchlorpheniramine significantly slowed reaction times, but did not significantly interact with task manipulations. However, it did significantly interact with stimulus quality, as measured by event-related potentials. Lorazepam slowed reaction times and interacted with perceptual manipulations, as shown by effects on reaction times.
Conclusions and implications: The results confirm that the histamine system is involved in sensory information processing and show that H_1 blockade does not affect motoric information processing. Histamine hypofunction in clinical disorders may cause impaired sensory processing, which may be a drug target.
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Abbreviations: AFM, additive factor method; CRT, choice reaction time; CTT, critical tracking task; ERP, event-related potential; LRP, lateralized readiness potential; MT, motor time; RC, response complexity; R-locked, response-locked; S-locked, stimulus-locked; SQ, stimulus quality

Introduction

Several studies have shown that centrally active histamine H_1 receptor antagonists, frequently used for the treatment of seasonal allergic rhinitis and urticaria, produce sedation and impair cognitive performance, in particular complex sensorimotor performance, such as tracking and car driving (Hindmarch and Shamsi, 1999; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Van Ruitenbeek *et al.*, 2008). However, little is known about the specific effects of H_1 receptor blockade on the cognitive subprocesses involved in performance of such tasks.

Better knowledge about the cognitive deficits associated with reduced histamine activity (e.g. as induced by H_1-antagonists) can ultimately contribute to better diagnosis and treatment of clinical disorders in which histamine dysfunction seems to be one of the contributing factors. Degeneration or dysfunction of histamine neurons has been found in Alzheimer's disease, Parkinson's disease, epilepsy, attention

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deficit hyperactivity disorder and schizophrenia (for review see Onodera *et al.*, 1994; Passani *et al.*, 2000; Witkin and Nelson, 2004; Esbenshade *et al.*, 2006; Yanai and Tashiro, 2007). So, drugs that increase histamine function, such as antagonists or inverse agonist for the H_3 receptor, are expected to be valuable new treatments for such disorders.

Better knowledge of the specific cognitive deficits associated with histamine dysfunction in humans can be derived from studies assessing the behavioural effect of centrally active H_1-antagonists in healthy volunteers. The aim of the present study was to clarify which subprocesses underlying sensorimotor performance are impaired by the representative antihistamine dexchlorpheniramine, which has been shown to affect sensorimotor performance (Van Ruitenbeek *et al.*, 2008). To this end, we adopted a behavioural and a psychophysiological approach.

The behavioural approach consisted of the additive factor method (AFM) (Sternberg, 1969). Within this framework, human information processing between stimulus and response is dissected into a series of discrete stages, which represent distinct elementary cognitive operations, such as perceptual encoding, decision making and response preparation (Bonin-Guillaume *et al.*, 2004). Roughly, these can be regarded as sensory, central and motor stages. Several task factors have been established that influence individual stages. For example, by decreasing stimulus quality (SQ), the perceptual process of feature extraction can be slowed, resulting in a longer reaction time. Identifying the specific processing stages that are affected by drugs can be done using the AFM. The basic logic is that if two factors interact, they affect at least one common stage (Sternberg, 1969; Sanders, 1980; Smulders *et al.*, 1999). So, if a drug interacts with a task factor that affects a specific stage, it is concluded that the drug affects at least that particular stage (e.g. Frowein, 1981; Frowein *et al.*, 1981). Only two studies have investigated the effects of antihistamines using this framework, but with inconsistent results. According to the investigators, results of the first study suggest that antihistamines may compromise perceptual processing (Gaillard and Verduin, 1983), whereas the results of a subsequent study were taken to indicate that they primarily affect motor processes (Gaillard *et al.*, 1988). In the first study, however, results were not significant, probably due to a small sample size and low dose of the drug. In the second study, the antihistamine was found to interact with SQ in a reaction time task, but also to impair tracking performance. As the latter study did not include manipulations of task demands affecting motor processing, it was unclear whether the antihistamine had generally sedating or specific effects on sensorimotor processing.

The second approach to identify the locus of effects of a drug is a psychophysiological approach, that is, using event-related potentials (ERPs) as markers to detect changes in specific stages of information processing. The latencies to the peak of the potentials are typically regarded as the time at which subprocesses occur after stimulus presentation. The P300 component is a central component and is thought to be associated with evaluation of a stimulus just before a decision takes place (Riedel *et al.*, 2006; Polich, 2007). The amplitude of the P300 is thought to reflect the resources available for stimulus processing. For example, increased task demands to which attention is directed reduce the amplitude of the P300 (Beauducel *et al.*, 2006). The latency of this component has been shown to increase after degradation of SQ (McCarthy and Donchin, 1981). In addition, the lateralized readiness potential (LRP) is a response-related component. Effects on response preparation, such as increasing response complexity (RC), increase the interval between the LRP onset and the response. The locus of the drug effect can thus be determined using the P300 and LRP. Effects on stimulus-related processes are identified by an increased interval between the stimulus and P300 [stimulus-locked (S-locked) P300]. Effects on response-related processes are identified by an increased interval between the onset of the LRP and response [response-locked (R-locked) LRP].

A consistent finding is that antihistamines delay the P300 latency. For example, studies have found that chlorpheniramine and pheniramine increased the P300 latency during performance on an Odd-Ball task (Loring and Meador, 1989; Simons *et al.*, 1994; Seidl *et al.*, 1997). A delay in the duration of any process occurring before the P300 leads to a delay of the P300 peak amplitude. Therefore, these findings are in line with studies in which SQ was manipulated and suggest that H_1-blockade affects the sensory stages of information processing (Gaillard and Verduin, 1983; Gaillard *et al.*, 1988). However, the effects of antihistamines on motor processes and associated ERP components are largely unknown.

To demonstrate sensitivity of the tasks and procedures we included the benzodiazepine lorazepam (1 mg) as an active control drug. Similar to H_1-antagonsists, benzodiazepines induce sedation and impair sensorimotor performance (Bond *et al.*, 1983; Curran, 2000; Turner *et al.*, 2006; Leufkens *et al.*, 2007). Moreover, effects of benzodiazepines have been found to interact with SQ and motor processes (Pang and Fowler, 1994). In addition, they are known to affect latency and amplitude of several ERP components (Curran *et al.*, 1998; Riba *et al.*, 2005) including P300 (Pompeia *et al.*, 2003) and motor-related evoked potentials (Rockstroh *et al.*, 1991; Riba *et al.*, 2005).

To summarize, the specificity of antihistamine-induced psychomotor impairment is unknown and such knowledge may aid the search for treatments for disorders in which specific processes are affected. Using Sternberg's AFM and measuring ERPs, in this study we assessed the effects of dexchlorpheniramine, a representative centrally active and specific H_1-antagonist, on sensory and motor stages of cognitive processing. Dexchlorpheniramine was expected to affect sensory stages negatively and therefore interact with SQ, as measured by prolonged reaction time and S-locked P300 peak latency. This is the first time effects on response-related processes have been assessed by measuring the R-locked LRP onset latency. The results show that central H_1 blockade impairs the processing of sensory information.

Methods

Subjects

Eighteen healthy right-handed subjects (nine female) between 18 and 45 years (mean $\pm$ SD: 24.2 $\pm$ 7.3 years) were recruited by means of advertisements in local newspapers and

were paid for their participation. Subject's health was screened using a medical history questionnaire and a physical examination, including a 12-lead electrocardiogram, blood chemistry and haematology, and urinary tests for pregnancy and drug abuse (amphetamine, benzodiazepine, cocaine, opiates, cannabis and metamphetamine). Exclusion criteria were a significant history or presence of any mental or physical disorder; gastrointestinal, hepatic, renal, cardiovascular or neurological. Also, drug abuse, a body mass index outside the limits of 18 and 28 $kg \cdot m^{-2}$, blood pressure outside the limits of 100 and 150 mm Hg systolic and 60 and 90 mm Hg diastolic and drinking more than 20 standard alcoholic consumptions per week or five beverages containing caffeine per day were regarded as exclusion criteria. For women, pregnancy and lactation were also regarded as exclusion criteria. No drugs or medication, except oral contraceptives, aspirin and acetaminophen, were allowed to be taken from a week before the first test day until the end of the study. Smoking and the use of caffeine were prohibited on test days and the use of alcohol from 24 h before and during each test day. Subjects were allowed to have breakfast at home before 7 h 30 min so that drug intake 3 h later would be on a nearly empty stomach.

All subjects received written information about the study procedures and signed an informed consent form prior to enrolment. The study was approved by the ethics committee of Maastricht University and University Hospital Maastricht and carried out in accordance with the World Medical Association Declaration of Helsinki and its amendments (Edinburgh, 2000).

Study design and treatments

The study was conducted according to a double-blind, placebo-controlled, three-way crossover design. Treatments were single oral doses of dexchlorpheniramine 4 mg and lorazepam 1 mg (all immediate release formulations) and placebo and were spaced apart by a washout period of at least 4 days. Within the choice reaction time (CRT) task, SQ and RC were varied and consisted of two levels each. The order of treatment and sequence of task conditions were counterbalanced between subjects.

Procedure

Subjects were individually trained to perform all tasks in two practice sessions within 2 weeks prior to their first treatment day. On treatment days subjects arrived at the university at 9 h 00 min. Between 9 h 00 min and 9 h 30 min, the inclusion and exclusion criteria were checked. At 10 h 00 min subjects performed a short version of each task to remind them of the procedures. At 10 h 30 min the study medication was ingested. The test battery consisted of the CRT task, critical tracking task (CTT) and subjective drowsiness, and these were performed between 12 h 00 min and 13 h 00 min. A previous study (Van Ruitenbeek *et al*., 2008) has shown that the peak impairment of dexchlorpheniramine is around 1.5 h post treatment.

Behavioural assessments

CRT task The CRT used in this study was based on that used by Smulders *et al*. (1995). The speed of the information processing of the sensory and motor stages was assessed by manipulating the quality of the visual stimuli and complexity of the responses respectively. Smulders *et al*. (1995) found additive effects of SQ and RC on reaction time. In addition, they found selective effects of SQ on the interval between the stimulus and P300 peak latency and selective effects of RC on the interval between the LRP onset and the response.

The task consisted of a repeated presentation of the numbers 2 and 5 on a computer screen for 200 ms. The stimuli consisted of small squares surrounded by a frame of squares. The squares consisted of grids of 6 by 6 pixels. The time between offset of a stimulus and the presentation of the next stimulus was varied between 1500 and 2200 ms. Subjects had to respond as fast as possible by pressing a left or right hand button with their left or right index finger when a 2 or a 5 appeared respectively. The task consisted of four blocks of 112 trials; each lasted approximately 4 min, and half of the stimuli were visually degraded and half of the stimuli were intact. Degradation was achieved by placing 20 squares (42%) from the frame at random positions in the field within the frame not occupied by the 26 squares of the digit. There were seven degraded versions of each digit of comparable difficulty to prevent subjects from responding to learned features of the stimulus instead of recognizing the digit.

In two blocks (complex blocks; C) RC was increased by asking the subjects to press three buttons instead of one (simple blocks; S) in the following sequence: index, ring and middle finger. The pressing of the first button indicated the reaction time. The time (ms) between the first button press and the third was also recorded as 'motor time' (MT). The blocks were presented in the order SCCS to one half of the subjects and CSSC to the other half.

The primary performance variable in this task is the average reaction time of the correct responses for the four different task conditions, that is, intact-simple, degraded-simple, intact-complex and degraded-complex and accuracy scores, which were logarithmically transformed due to the non-linear nature of a decrease in accuracy (Dickman and Meyer, 1988).

Critical tracking task The CTT measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex *et al*., 1966). Error is displayed as a horizontal deviation of a yellow triangle from the midpoint on a horizontal scale. Compensatory movements null the error by returning the triangle to the centre. The frequency of the error gradually increases until the subject loses control. The frequency at which control is lost is the critical frequency or lambda-c ($rad \cdot s^{-1}$). The CTT includes five trials of which the highest and lowest scores are removed. The average of the three remaining scores is the final score. A previous study has shown that the CTT is sensitive to the effects of H_1-blockade between 1.5 and 2.5 h after treatment (Van Ruitenbeek *et al*., 2008).

Visual analogue scales Subjective drowsiness is assessed using a series of 16 analogue scales of 100 mm. These provide three factor analytically defined summary scores for 'drowsiness', 'contentedness' and 'calmness' (Bond and Lader, 1974), of which drowsiness was of main interest. Visual analogue scales have been shown to be sensitive to the sedative effects of antihistamines (Van Ruitenbeek *et al*., 2008).

Event-related potentials
During performance on the CRT subjects' EEG activity was recorded to measure the P300, LRP and P150 associated with correct responses. Dependent variables were duration of the interval (ms) between stimulus and P300 peak amplitude (S-locked P300) and between the response and the P300 peak amplitude (R-locked P300), and the interval between the stimulus onset and LRP onset (S-locked LRP) and between the response and LRP onset (R-locked LRP). In addition, the amplitude of the S-locked and R-locked P300 was determined as a measure of resource availability for stimulus processing.

Recordings and signal analysis electroencephalography (EEG) activity was recorded from an array of 32 electrodes from the standard 10–20 system using an electrocap (Jasper, 1957). All electrodes were filled with electrode-gel and were line-referenced to the right mastoid electrode. Off-line they were referenced to both left and right mastoids. The FPz electrode was used as ground electrode. Horizontal electrooculogram (EOG) was recorded using electrodes attached to the outer canthi of the eyes and vertical EOG was recorded from electrodes attached above and below the left or right eye and in line with the pupil.

All electrode impedances were kept below 5 kΩ. Signals were amplified using Neuroscan Synamps amplifiers and collected using Neuroscan software. All signals were sampled at a 1000 Hz and filtered online using a 100 Hz low-pass filter and a 0.1 Hz high-pass filter.

Continuous signals obtained during the performance on the CRT were filtered off-line using a 1 Hz high-pass filter after which EEG was corrected for vertical and horizontal eye movements according to a procedure by Semlitsch *et al*. (1986). The S-locked sweeps were obtained by epoching from 100 ms before until 1000 ms after stimulus presentation and the interval between sweep onset and stimulus served as baseline. The R-locked sweeps were obtained by epoching from 475 ms before to 625 ms after the response. For the analysis of the P300 all sampled EEG and EOG epochs were low pass-filtered using a 3.6 Hz low-pass filter and for the LRP the data were filtered using an 11.1 Hz low-pass filter. Sweeps containing artefacts exceeding ±75 μV on the FZ, CZ, PZ, OZ, C3 or C4 electrodes were rejected. This resulted in an average acceptance of 92% of the epochs.

The lengths of the S-locked and R-locked intervals of the P300 were determined at the Cz electrode site. The S-locked P300 signals were determined as the time between onset of the stimulus and the latency of the largest maximum in a window between 333 and 463 ms as determined by the latency of the P300 of the grand average. The R-locked P300 intervals were determined as the time between the largest maximum of the P300 component and the given response in a window between 132 ms before and 68 ms after the response as determined by the latency of the grand average at the same site.

The LRPs were computed by subtracting C4 from C3, point by point, for right- and left-hand trials and subtracting left-hand from right-hand trials. The onset latencies of the S-locked and R-locked LRP waveforms were determined using the jackknife scoring method with a fixed 1 μV criterion (Miller *et al*., 1998; Ulrich and Miller, 2001).

Materials
Dexchlorpheniramine was obtained from Schering-Plough BV (Utrecht, the Netherlands) and lorazepam from Hexal BV (Hillegom, the Netherlands).

Statistical analysis
All dependent variables were screened for normality of their distributions and no non-normalities were detected. To determine whether task manipulations in the CRT were successful, performance scores and ERPs after placebo treatment were analysed using repeated measures analysis of variance of a 2 × 2 factorial model. Within-subject variables were SQ (intact, degraded) and RC (simple, complex).

Effects of treatment (dexchlorpheniramine, lorazepam, placebo) and interactions with SQ and RC on performance variables and ERPs in the CRT were analysed in a 3 × 2 × 2 factorial model. *F*-values for differences in S-locked and R-locked LRP onset latencies were divided by $(n-1)^2$ to correct for the reduction of variance induced by the jackknife method (Ulrich and Miller, 2001). If overall multivariate *F*-tests indicated a significant difference ($P < 0.05$), data were further analysed using two univariate drug–placebo contrasts.

Performance on the CTT and subjective drowsiness scores were analysed for treatment effects using repeated measures univariate analysis of variance. All data were analysed using SPSS for Windows (version 12.0.1).

Results

Results of task manipulations and treatments on performance and ERPs are presented in Table 1.

CRT task – task manipulations
Degraded stimuli prolonged reaction time (SQ, $F(1,17) = 153.7$, $P = 0.001$), S-locked P300 latency ($F(1,17) = 6.2$, $P = 0.023$) and the S-locked LRP onset latency ($F(1,17) = 23.4$, $P = 0.001$). Stimulus degradation did not increase the interval between the R-locked P300 and the response and the R-locked LRP onset and the response (SQ, $Fs(1,17) < 1$). Degraded stimuli also decreased the accuracy of the response ($F(1,17) = 20.9$, $P = 0.001$), decreased the amplitude of the S-locked P300 ($F(1,17) = 5.1$, $P = 0.038$) and the R-locked P300 amplitude ($F(1,17) = 5.0$, $P = 0.039$).

Increased RC prolonged reaction time (RC, $F(1,17) = 15.5$, $P = 0.001$), the interval between the R-locked P300 and the response ($F(1,17) = 17.4$, $P = 0.001$) and the interval between R-locked LRP onset and the response ($F(1,17) = 8.5$, $P = 0.010$). Contrary to expectations, increased RC led to a decrease in S-locked P300 latency ($F(1,17) = 7.7$, $P = 0.013$) and tended to increase the S-locked LRP onset latency ($F(1,17) = 3.1$, $P = 0.097$). Also, increased RC decreased the S-locked and R-locked P300 amplitude ($F(1,17) = 12.0$ $P = 0.003$ and $F(1,17) = 13.6$, $P = 0.002$ respectively).

There were no significant interactions between SQ and RC (RT: $F(1,17) < 1$, S-locked P300: $F(1,17) < 1$, R-locked P300:

Table 1 Effects of treatments and task manipulations on reaction time and event-related potentials

Choice reaction time task	*Main effect treatment*	*Treatment*SQ*	*Treatment*RC*	*Placebo*		*D4*		*L1*	
	P	*P*	*P*	*Intact*	*Degraded*	*Intact*	*Degraded*	*Intact*	*Degraded*
Reaction time (ms)	<0.01	<0.07	n.s.						**
Simple response				389 (10.6)	422 (12.5)	415 (11.6)	446 (16.8)	428 (11.8)	475 (15.0)
Complex response				420 (11.0)	454 (11.7)	435 (13.5)	475 (17.2)	464 (14.3)	508 (17.3)
S-locked P300 latency (ms)	n.s.	<0.02	n.s.				*		
Simple response				380 (5.2)	392 (8.3)	380 (7.1)	404 (7.7)	378 (8.7)	385 (9.7)
Complex response				370 (7.2)	384 (7.9)	375 (6.9)	395 (7.3)	373 (8.1)	381 (9.4)
R-locked P300 latency (ms)	<0.02	n.s.	n.s.						
Simple response				–14 (12.6)	–22 (10.8)	–20 (9.5)	–18 (8.6)	–35 (10.8)	–37 (10.7)
Complex response				–57 (10.3)	–55 (10.7)	–57 (12.2)	–55 (10.8)	–68 (8.2)	–80 (10.6)
S-locked LRP onset latency (ms)	<0.01	n.s.	0.08				†		
Simple response				237 (0.7)	267 (0.7)	248 (0.7)	300 (0.7)	278 (1.6)	334 (1.6)
Complex response				239 (0.5)	285 (0.8)	239 (0.5)	280 (0.7)	305 (1.1)	368 (2.8)
R-locked LRP onset latency (ms)	n.s.	n.s.	n.s.						
Simple response				–137 (0.6)	–131 (0.4)	–144 (0.7)	–149 (0.7)	–130 (0.5)	–133 (0.6)
Complex response				–169 (0.7)	–166 (1.0)	–183 (1.1)	–202 (1.0)	–176 (1.2)	–162 (2.5)

Lorazepam (L1) increased the effect of stimulus degradation on reaction time and dexchlorpheniramine (D4) increased the effect of stimulus degradation on P300 peak latency. $^{**}P < 0.05$ and $^{*}P < 0.10$, significant or near significant, respectively, differences in effects of stimulus quality (SQ) after treatment when compared with placebo. $^{\dagger}P < 0.10$, near significant difference in effects of RC after treatment when compared with placebo. The results are presented as means with SEMs in parentheses. SEM for LRP onsets presented are uncorrected for utilizing jackknife method.

$F(1,17) = 1.5$, $P = 0.225$, S-locked LRP: $F(1,17) < 1$, R-locked LRP: $F(1,17) < 1$). Together these data indicate successful task manipulations.

CRT task – treatment effects

Reaction time, accuracy and MT Treatment had a significant main effect on overall reaction time ($F(2,16) = 15.5$, $P = 0.001$). Drug–placebo differences showed that both dexchlorpheniramine and lorazepam prolonged reaction time ($F(1,17) = 12.0$, $P = 0.003$ and $F(1,17) = 29.8$, $P < 0.001$ respectively).

Treatment tended to interact non-significantly with SQ ($F(2,16) = 3.2$, $P < 0.069$), but not with RC ($F(2,16) < 1$). Lorazepam increased the effect of SQ as compared with placebo ($F(1,17) = 6.4$, $P = 0.022$), but dexchlorpheniramine did not ($F(1,17) < 1$).

S-locked and R-locked P300 latencies Treatment did not have a main significant effect on the S-locked P300 latencies ($F(2,16) = 2.7$, $P = 0.099$). However, it did interact with SQ ($F(2,16) = 5.4$, $P = 0.016$). Dexchlorpeniramine increased the effect of SQ on this interval and this reached near significance ($F(1,17) = 4.4$, $P = 0.052$), whereas lorazepam clearly did not ($F(1,17) = 1.4$, $P = 0.246$) (Figure 1).

Mean duration of the interval between the R-locked P300 and the response differed significantly between treatments ($F(2,16) = 5.5$, $P = 0.015$). Lorazepam increased the interval ($F(1,17) = 8.2$, $P = 0.011$), whereas dexchlorpheniramine did not ($F(1,17) < 1$). The treatment did not interact with RC or SQ (*Fs*$(2,16) < 1$) (Figure 2).

R-locked and S-locked LRP Treatment had no main effect on the onset of the R-locked LRP ($F(2,16) = 1.4$, $P = 0.283$) and did not interact with RC ($F(2,16) < 1$) or with SQ ($F(2,16) = 1.04$, $P = 0.376$) (Figure 3).

Treatment did affect S-locked LRP onset latency significantly ($F(2,16) = 6.2$, $P = 0.010$). Lorazepam increased the latency ($F(1,17) = 12.7$, $P = 0.002$), but overall dexchlorpheniramine did not ($F(1,17) = 1.5$, $P = 0.239$). However, RC tended to interact with Treatment ($F(2,16) = 2.9$, $P = 0.080$) and dexchlorpheniramine tended to decrease the S-locked LRP onset latency ($F(1,17) = 3.7$, $P = 0.070$) (Figure 4).

S-locked and R-locked P300 amplitude Treatment did not affect the S-locked P300 amplitude and did not interact with SQ (*Fs*$(2,16) < 1$). However, the treatment did interact with RC ($F(2,16) = 4.8$, $P = 0.023$). Lorazepam prevented the decrease of the amplitude of the P300 in the complex response condition compared with placebo ($F(1,17) = 10.2$, $P = 0.005$).

The treatment also did not have a main effect on the R-locked P300 amplitude ($F(2,16) = 1.3$, $P = 0.298$). In contrast to the results above, Treatment did not interact with RC ($F(2,16) = 1.3$, $P = 0.296$).

Motor time Treatment marginally but significantly affected MT ($F(2,16) = 3.6$, $P = 0.052$). Lorazepam significantly increased MT by, on average, 31.6 ms ($F(1,17) = 7.2$, $P = 0.016$), whereas dexchlorpheniramine had no significant

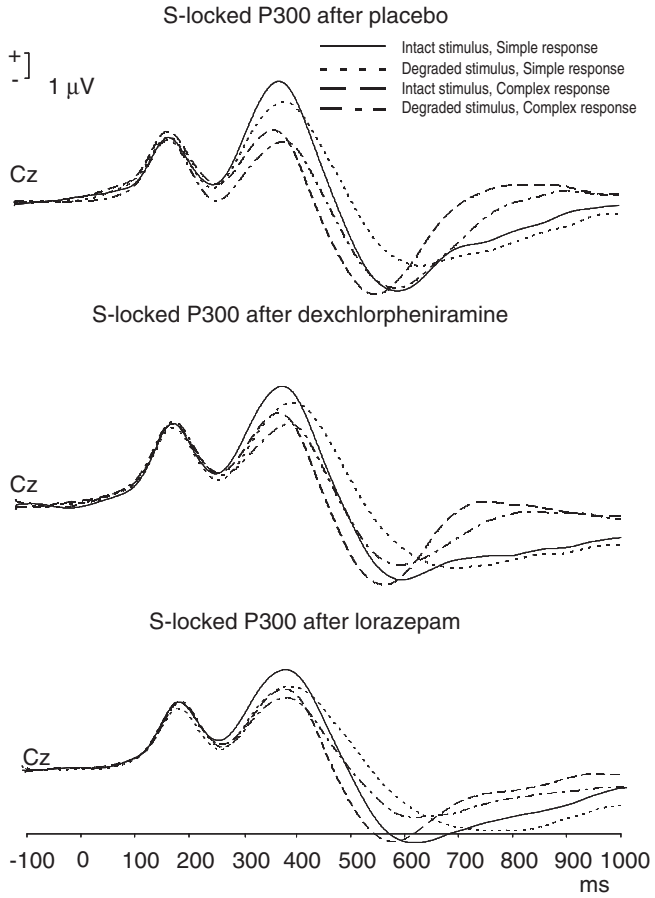

Figure 1 Effects of the treatments and manipulations of stimulus quality and response complexity on the stimulus-locked P300. Stimulus quality increased the peak latency ($P < 0.01$) and interacted with the treatments ($P < 0.02$); this was caused by an increased effect of the degraded stimulus by dexchlorpheniramine ($P < 0.10$).

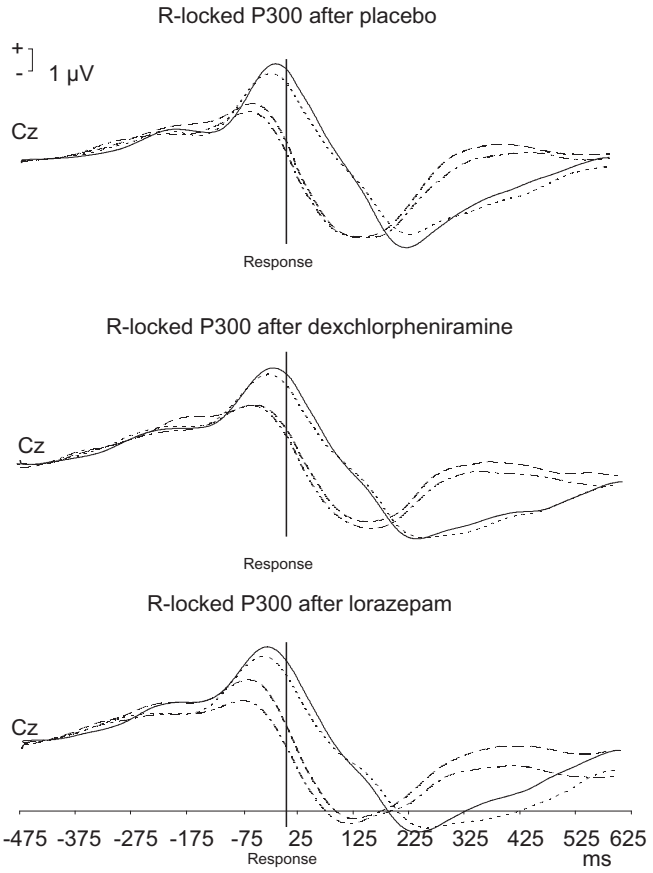

Figure 2 Effects of the treatments and manipulations of stimulus quality and response complexity on the interval between the response-locked (R-locked) P300 and the response. Response complexity and lorazepam increased the interval duration ($P < 0.05$), but the effects of these variables did not interact. For key to lines used see Figure 1.

effect ($F(1,17) < 1$). SQ had no significant effect on MT ($F(1,17) < 1$) and did not interact with the treatment ($F(2,16) = 1.3$, $P = 0.296$).

Accuracy Statistical tests on the log transformed accuracy data revealed a similar pattern of effects as those shown by the reaction time data. Treatment had a main effect ($F(2,16) = 5.9$, $P = 0.012$); lorazepam tended to reduce the accuracy ($F(1,17) = 3.2$, $P = 0.093$). Treatment significantly interacted with SQ ($F(2,16) = 4.8$, $P = 0.023$), but not with RC ($F(2,16) < 1$). The accuracy reducing effect of degraded SQ ($F(1,17) = 45.0$, $P < 0.001$) was enlarged by lorazepam ($F(1,17) = 10.2$, $P = 0.005$) and to a small but not significant extent by dexchlorpheniramine ($F(1,17) = 3.3$, $P = 0.085$).

Critical tracking task
Treatment significantly impaired tracking performance ($F(2,16) = 11.6$, $P = 0.001$); lorazepam decreased the critical frequency from an average (±SEM) lambda of 4.16 (±0.14) after placebo administration to an average lambda of 3.56 (±0.17) ($F(1,17) = 24.4$, $P = 0.001$). Dexchlorpheniramine also decreased the critical frequency to an average lambda of 3.99 (±0.12), but this effect was not significant ($F(1,17) = 2.4$, $P = 0.141$).

Visual analogue scale
Treatment significantly affected subjective drowsiness ($F(2,16) = 7.8$, $P < 0.004$); lorazepam and dexchlorpheniramine increased drowsiness scores from 34.5 (±5.0) to 51.7 (±4.3) ($F(1,17) = 16.6$, $P = 0.001$) and 59.4 (±4.5) ($F(1,17) = 7.9$, $P = 0.012$) respectively.

Discussion and conclusions

The aim of this study was to determine the locus of effects of H_1-blockade on sensorimotor processing in humans using the AFM and ERPs. Effects of the task manipulations in the placebo condition showed an additive pattern of effects of SQ and RC, confirming that the manipulations affected separate stages of information processing. Both treatments had significant sedative effects and impaired sensorimotor performance as measured by the CTT and CRT. The level of subjective

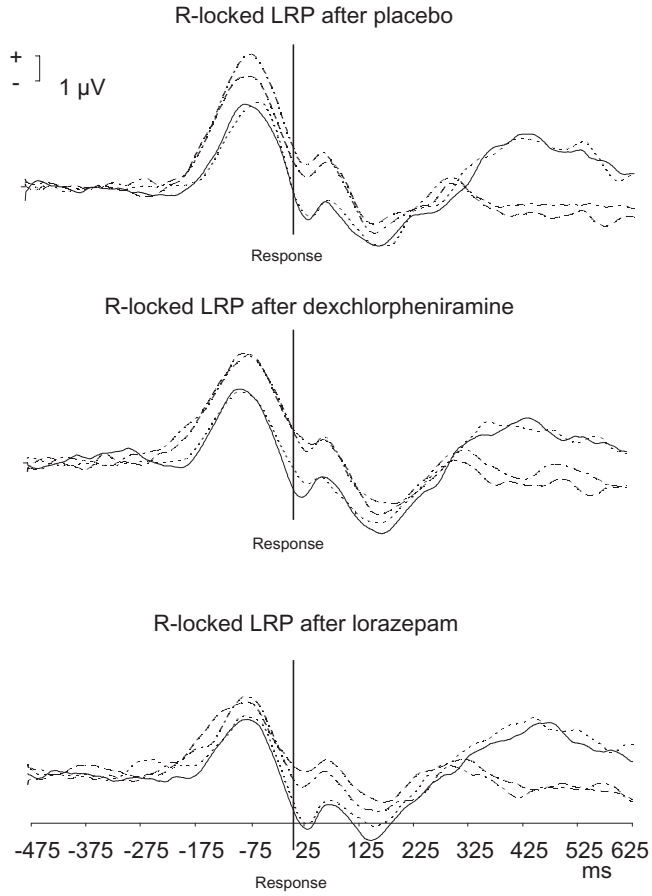

Figure 3 Effects of the treatments and manipulations of stimulus quality and response complexity on the interval between the response-locked (R-locked) lateralized readiness potential (LRP) and the response. Neither treatment prolonged the interval. Response complexity did increase the interval ($P < 0.01$), but did not interact with either treatment. For key to lines used see Figure 1.

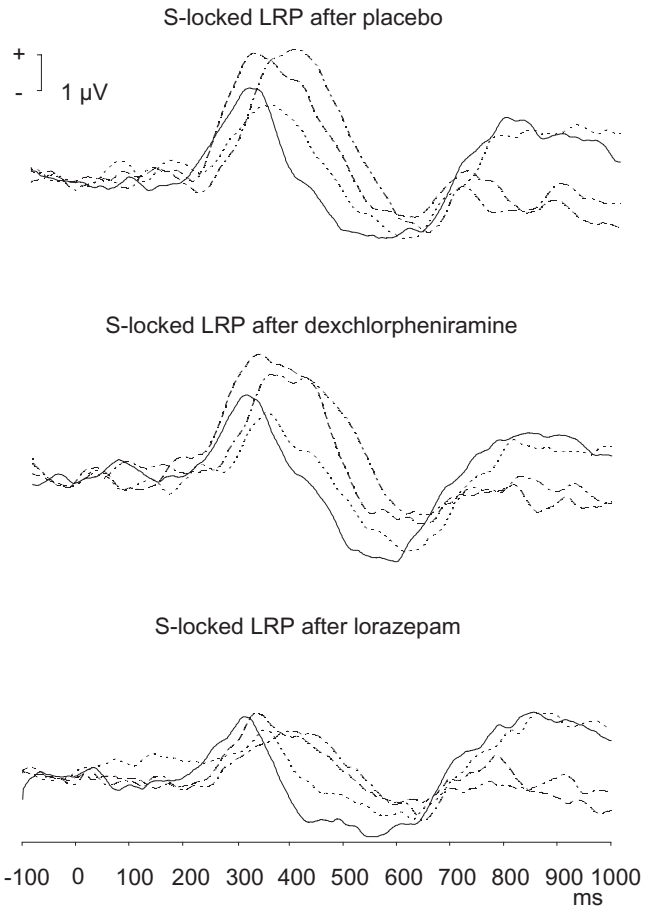

Figure 4 Effects of the treatments and manipulations of stimulus quality and response complexity on the stimulus-locked (S-locked) lateralized readiness potential (LRP) onset latency. Lorazepam and degraded stimuli increased the onset latency (both $P < 0.01$). Response complexity tended to interact with the treatment ($P < 0.10$) and dexchlorpheniramine tended to decrease the S-locked LRP onset when a complex response has to be given ($P < 0.10$). For key to lines used see Figure 1.

drowsiness following dexchlorpheniramine administration was comparable to that obtained in a former study (Van Ruitenbeek *et al.*, 2008).

Dexchlorpheniramine

In contrast to earlier studies, performance on the CTT was not significantly impaired by dexchlorpheniramine. A previous study by our group (Van Ruitenbeek *et al.*, 2008) used only female subjects, because they have been found to be more sensitive to the effects of antihistamines (Robbe, 1990; Ramaekers and O'Hanlon, 1994; Vuurman *et al.*, 1994; Vermeeren *et al.*, 2002), whereas the present study used subjects of either sex. *Post hoc* analysis of the effects of the treatment in men and women in the present study revealed that in contrast to our expectations, the performance of women who received dexchlorpheniramine did not decrease, whereas the performance of men did. However, the interaction between treatment and gender was not significant. In contrast, lorazepam caused a marked decrease in performance in both sexes. As lorazepam also increased MT in the CRT, the effects may partially be due to muscle relaxation (Olkkola and Ahonen, 2008).

Both treatments slowed reaction times in the CRT. The effect of dexchlorpheniramine on the S-locked P300 latency was enlarged if stimuli were degraded, which indicates that the location of the effect was before the P300 peak latency. The effects on processes occurring before 300 ms after stimulus presentation is supported by results from other studies in which antihistamines caused the P300 latencies to increase (Loring and Meador, 1989; Meador *et al.*, 1989; Seidl *et al.*, 1997). The fact that slowing of information processing may be related to impaired attention induced by antihistamines needs to be taken into consideration as this has frequently been found to occur (Fine *et al.*, 1994; Bower *et al.*, 2003). Impaired attention processes are reflected by a decreased P300 amplitude (Polich, 2007). However, we did not observe an effect of dexchlorpheniramine on the P300 amplitude. Therefore, an attention deficit does not explain the effects of dexchlorpheniramine in this study.

To the best of our knowledge, there is no information on effects of antihistamines on response-related processes. In the presents study, dexchlorpheniramine did not have a main

effect on the duration of the interval between the R-locked LRP onset and the response, nor did it interact with RC, as measured by the duration of the interval. Taken together, these results suggest that the effects of dexchlorpheniramine are located before the P300 peak amplitude and that it does not affect response-related processes.

However, in terms of reaction time data an interaction with SQ was not found, but was expected if dexchlorpheniramine affects the feature extraction stage. To explain this, the subjects may have compensated for the effects on feature extraction by decreasing the duration of a different stage following the P300. The question is at what stage does this occur? The increase in reaction time with regard to complex responses tended to be less after the administration of dexchlorpheniramine as compared with placebo. In addition, the interval between the stimulus and the onset of the LRP decreased when subjects were required to give a complex response after administration of dexchlorpheniramine, which suggests that subjects began with their response sooner. Therefore, an increased P300 peak latency might have been compensated for by speeding up of a process before the response programming (e.g. response choice), so that the effect of SQ was not increased by dexchlorpheniramine, as measured with reaction time.

The interaction between Treatment and RC interaction as measured with the S-locked LRP is, however, problematic as this assumes that the processing stages are strictly serially ordered and discrete. Although not supported by some (de Jong *et al.*, 1988), it has been suggested that information processing is not entirely serial and discrete (Miller and Hackley, 1992; Osman *et al.*, 1992). Non-serial stages do not, however, invalidate the assumption of additivity (Miller *et al.*, 1995) and partial information of the stimulus is sufficient to start the programming of the response. It is therefore possible that subjects started response programming before the stimulus had been identified.

The effects on sensory processing are supported by the *post hoc* analysis of the P150 peak amplitude, which was increased after dexchlorpheniramine intake (drug–placebo contrast: $F(1,17) = 5.8$, $P = 0.028$). An increase in amplitude has been interpreted as increased mapping of visual features on higher order representations (Chauncey *et al.*, 2008). It is suggested that visual information processing is impaired and that the increased P150 amplitude possibly reflects a compensatory mechanism.

This study has shown that histamine hypofunction impairs sensory information processing. This may be of relevance for the treatment of schizophrenic patients. Schizophrenia is characterized by changes in sensory processing and it has been found that the histamine system in these patients is affected (Onodera *et al.*, 1994; Witkin and Nelson, 2004). Our findings suggest that the affected histamine system may be involved in the sensory deficits in schizophrenia. Histamine-based drugs may, therefore, be useful as a treatment in this disorder (Geyer *et al.*, 2001).

Lorazepam

Lorazepam increased the effect of SQ on reaction time and accuracy, which suggests that lorazepam affects the stage of feature extraction. If this is the case, lorazepam would be expected to have a main effect on the S-locked P300 peak latency and interact with SQ. We did not observe these temporal effects. In contrast to our results, those from other studies have shown increased P300 latencies after the administration of lorazepam (Pooviboonsuk *et al.*, 1996; Curran *et al.*, 1998). However, in those studies 2 mg lorazepam was administered orally, which is twice the dose that was administered in this study. It is possible that only high doses of this drug are able to increase the S-locked P300 latency and that a dose of 1 mg only has subtle effects on stimulus-driven stages of information processing.

Similar to our results, Pang and Fowler (1994) found that triazolam did not increase the effect of SQ on the S-locked P300 peak latency, although it did increase the effect of SQ on reaction time. Pang and Fowler (1994) argue that this dissociation between effects on the two measures may be due to the slowing of response-related processes. This hypothesis is supported by the finding that lorazepam increased the interval between the R-locked P300 and the response. However, lorazepam did not affect the interval between R-locked LRP onset and the response, which should be observed when response-related processes are affected. Similarly, Riba *et al.* (2005) observed that 1 mg lorazepam did not affect the R-locked LRP onset latencies. Therefore, it seems unlikely that response-related processes within the central nervous system are affected by this drug.

If the effect of lorazepam is neither located before the P300 peak latency nor after the start of response programming, it may be located in the transition between feature extraction and response programming. In support of this hypothesis, lorazepam did increase the S-locked LRP onset latency, indicating a later onset of the response programming. Riba *et al.* (2005) also found increased S-locked LRP onset latencies after the administration of 1 mg alprazolam, and Northoff *et al.* (2000) found that 1 mg lorazepam increased the latencies of late readiness potentials. Our results also show that lorazepam increased the interval between the R-locked P300 and response. These results suggest that the temporal locus of the effect is before the response programming and after identification of the stimulus.

To explain the difference between the temporal (ERP latency) and functional (functional stage) loci of effects, subjects may have shifted the speed–accuracy trade-off in favour of speed, such that subjects tended to guess the identity of the stimulus. If so, the effect on feature extraction is shifted such that subsequent stages of information processing (e.g. response choice) receive poor-quality information on which the decision to respond left or right has to be based. Following such reasoning, the lorazepam-induced delay in feature extraction may be located in central stages, that is, in the interval between P300 and response onset.

In conclusion, our results show that both drugs affect at least the sensory stages of information processing. However, the effects of the treatments differ qualitatively, as shown by the ERPs. Therefore, caution needs to be taken when interpreting the data. The effects of lorazepam on feature extraction resulted in a delayed onset of response programming and increased reaction times. Nevertheless, lorazepam can be used as an active control in studies investigating effects of drugs on

sensory stages. Central H_1-blockade leads to impaired sensory processing, but also to compensating response programming. Sensory disturbances in patients suffering from, for example, schizophrenia, may be related to histamine dysfunction. Therefore, new histamine-based drugs may be useful in treating sensory disturbances in such pathologies.

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Conflict of interest

The study was paid by, carried out at and only reported within Maastricht University. A.V. received grants from GlaxoSmith-Kline. At times during the study, W.J.R. was employed by GlaxoSmithKline R&D, Cambridge, UK and is now employed by Hoffman-LaRoche R&D, Basel, Switzerland while remaining affiliated to Maastricht University. In the authors' opinion, this causes no conflict of interest.

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