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

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Summary

Background and purpose Centrally active antihistamines impair cognitive performance, particularly sensorimotor performance. The present study aimed 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 3-way, double blind, cross-over design. Treatments were single oral doses of 4 mg dexchlorpheniramine, 1 mg lorazepam and placebo. Behavioural effects were assessed measuring reaction times and effects on brain activity were assessed by Event Related Potentials (ERPs).

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 ERPs. Lorazepam slowed reaction times and interacted with perceptual manipulations as shown by effects on reaction times.

Conclusions and implications This study confirms that the histamine system is involved in sensory information processing and shows 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.

Keywords: Sensorimotor Performance; Histamine H_1 Antagonists; Benzodiazepines; Evoked Potentials; Additive Factor Method; Reaction Time; Sedation; Sensory; Motor

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 *et al.*, 1999; Theunissen *et al.*, 2004; Van Ruitenbeek *et al.*, 2008; Verster *et al.*, 2004). However, little is known about the specific effects of H_1 receptor blockade on the cognitive subprocesses involved in performance on 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 one of the contributing factors. Degeneration or dysfunction of histamine neurons has been found in Alzheimer's disease, Parkinson's disease, epilepsy, ADHD and schizophrenia (For review see: Esbenshade *et al.*, 2006; Onodera *et al.*, 1994; Passani *et al.*, 2000; Witkin *et al.*, 2004; Yanai *et al.*, 2007). So, drugs that increase histamine function, such as antagonists or inverse agonist for the H3 receptor, are expected to be valuable new treatments for such disorders.

Better knowledge on 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 psychophysiologoical approach.

The behavioural approach consists 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 (Sanders, 1980; Smulders *et al.*, 1999; Sternberg, 1969). So, if a drug interacts with a task factor which 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 investigated the effects of antihistamines using this framework, but with inconsistent results. According to the investigators results of the first study suggested that antihistamines may compromise perceptual processing (Gaillard and Verduin 1983), whereas results of a subsequent study were taken to indicate that they primarily affect motor processes (Gaillard *et al.* 1988). In the first study, results were not significant, however, 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 remains 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, i.e. using event related potentials (ERP's) 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 (Polich, 2007; Riedel, 2006).

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 reduces the amplitude of the P300 (Beauducel *et al.*, 2006). The latency of this component has been shown to increase after degradation of SQ (McCarthy *et al.*, 1981). In addition, the Lateralized Readiness Potential (LRP) is a response related component. Effects on response preparation, such as increasing response complexity (RC), increases 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 (S-locked P300). Effects on response related processes are identified by an increased interval between the onset of the LRP and response (R-locked LRP).

A consistent finding is that antihistamines delay the P300 latency. For example, studies have found that chlorpheniramine or pheniramine increased the P300 latency during performance on an Odd-Ball task (Loring *et al.*, 1989; Seidl *et al.*, 1997; Simons *et al.*, 1994). 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 sensory stages of information processing (Gaillard *et al.*, 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; Leufkens *et al.*, 2007; Turner *et al.*, 2006). Moreover, effects of benzodiazepines have been found to interact with SQ and motor processes (Pang *et al.*, 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 (Riba *et al.*, 2005; Rockstroh *et al.*, 1991).

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 ERP's, this study assessed the effects of dexchlorpheniramine as a representative centrally active and specific H_1-antagonist on sensory and motor stages of cognitive processing. Dexchlorpheniramnie was expected to negatively affect sensory stages and therefore interact with SQ as measured by prolonged reaction time and S-locked P300 peak latency. In addition, this is the first study to assess the effects on response related processes as measured with the response locked LRP onset latency. This study shows that central H_1 blockade impairs the processing of sensory information.

MATERIALS AND METHODS

Subjects

Eighteen healthy right handed subjects (nine female) between 18 and 45 years (mean ± SD: 24.2 ± 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 m^{-2}, blood pressure outside the limits of 100 and 150 Hg systolic and 60 and 90 Hg diastolic and drinking more than 20 standard alcoholic consumptions per week or 5 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 hours before and during each test-day. Subjects were allowed to have breakfast at home before 7:30am so that drug intake 3 hours 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, 3-way crossover design. Treatments were single oral doses of dexchlorpheniramine 4 mg (Schering-Plough BV, Utrecht, The Netherlands) and lorazepam 1 mg (Hexal BV, Hillegom, The Netherlands) (all immediate release formulations) and placebo and were spaced apart by a washout period of at least 4 days. Within the choice reaction time 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 two weeks prior to their first treatment day. On treatment days subjects arrived at the University at 9:00am. Between 9:00am and 9:30am the inclusion and exclusion criteria were checked. At 10:00am subjects performed a short version of each task to remind them of the procedures. At 10:30am the study medication was ingested. The test-battery consisted of the Choice Reaction Time Task, Critical Tracking Task and Subjective Drowsiness and were performed between 12:00am and 1:00pm. A previous study (Van Ruitenbeek *et al.*, 2008) has shown that the peak impairment of dexchlorpheniramine is around 1.5 hours post treatment.

Behavioural assessments

Choice reaction time task

The choice reaction time task (CRT) used in this study was based on Smulders *et al.*, (1995). The speed of information processing of the sensory and motor stages were 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 which each lasted approximately 4 minutes and in which 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 7 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, i.e. 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 *et al.*, 1988).

Critical tracking task.

The Critical Tracking Task (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 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 critical tracking task is sensitive to the effects of H_1-blockade between 1.5 and 2.5 hours 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 *et al.*, 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

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. Offline they were referenced to both left and right mastoids. The FPz electrode was used as ground electrode. Horizontal 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 a 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 length 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.

LRP's 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 criterium (Miller *et al.*, 1998; Ulrich *et al.*, 2001).

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 ERP's after placebo treatment were analyzed using repeated measures analysis of variance of a 2x2 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 measures and ERP's in the CRT were analysed in a 3x2x2 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 *et al.*, 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.

[Insert table 1 about here]

<u>Choice reaction time task – task manipulations</u>

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

Choice reaction time task – Treatment effects

Reaction time, accuracy and motor time

Treatment had a significant main effect on overall reaction time ($F(2,16) = 15.5$, p = 0.001). Drug-placebo contrasts showed that both dexchlorpheniramine and lorazepam prolonged reaction time ($F(1,17) = 12.0$, p = 0.003; $F(1,17) = 29.8$, 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 significant main effect on the S-locked P300 latencies ($F(2,16) = 2.7$, $p = 0.099$). However, Treatment did interact with SQ ($F(2,16) = 5.4$, $p = 0.016$). Dexchlorpeniramine increased the effect of SQ on this interval nearly significant ($F(1,17) = 4.4$, $p = 0.052$), while 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 ($F(1,17) = 8.2$, $p = 0.011$), while dexchlorpheniramine did not ($F(1,17) < 1$). Treatment did not interact with RC or SQ ($Fs(2,16) < 1$) (figure 2).

[Insert figures 1 and 2 about here]

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 ($F(2,16) < 1$) and 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).

[Insert figures 3 and 4 about here]

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, Treatment did interact with RC ($F(2,16) = 4.8$, $p = 0.023$). Lorazepam prevented a decrease of the amplitude of the P300 in the complex response condition compared with placebo ($F(1,17) = 10.2$, $p = 0.005$).

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 significantly affected MT ($F(2,16) = 3.6$, $p = 0.052$). Lorazepam significantly increased MT with 31.6 ms on average ($F(1,17) = 7.2$, $p = 0.016$), while dexchlorpheniramine had no significant effect ($F(1,17) < 1$). SQ had no significant effect on MT ($F(1,17) < 1$) and did not interact with 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 was 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 near significantly 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 (±SE) lambda of 4.16 (±0.14) after placebo administration to an average (±SE) 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 not significantly ($F(1,17) = 2.4$, $p = 0.141$).

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

This study aimed to determine the locus of effects of H_1-blockade on sensorimotor processing in humans using the additive factor method and ERP's. 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 drowsiness following dexchlorpheniramine administration was comparable to that 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 (Ramaekers *et al.*, 1994; Robbe, 1990; Vermeeren *et al.*, 2002; Vuurman *et al.*, 1994) whereas the present study used subjects of both sexes. Post-hoc analysis of Treatment effects 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, while the performance of men did. The interaction between Treatment and Gender was not significant, however. In contrast, lorazepam caused a marked decrease in performance in both sexes. Since lorazepam also increased MT in the CRT, the effects may partially be due to muscle relaxation (Olkkola *et al.*, 2008).

Both treatments slowed reaction times in the CRT. The effect of dexchlorpheniramine on the stimulus-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 other studies in which antihistamines caused the P300 latencies to increase (Loring *et al.*, 1989; Meador *et al.*, 1989; Seidl *et al.*, 1997). It needs some consideration that slowing of information processing may be related to impaired attention induced by antihistamines which has frequently been found (e.g. Bower *et al.*, 2003; Fine *et al.*, 1994). 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 current 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 the 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 would affect 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 what stage this would be. 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 a process before response programming (e.g. response choice) so that the effect of SQ was not increased by dexchlorpheniramine as measured with reaction time.

The Treatment by RC interaction as measured with the S-locked LRP is, however, problematic for the assumption of strictly serially ordered and discrete processing stages. Although not supported by some (De Jong *et al.*, 1988), it has been suggested that information processing is not entirely serial and discrete (Miller *et al.*, 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 than 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 *et al.*, 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. In that case, however, lorazepam is 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, other studies found increased P300 latencies after the administration of lorazepam (Curran *et al.*, 1998; Pooviboonsuk, 1996). However, they all administered 2 mg orally which is twice the dose that was administered in this study. It is possible that only high dosages 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) did not find triazolam to increase the effect of SQ on the S-locked P300 peak latency, while 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) did not observe effects of 1 mg lorazepam on the R-locked LRP-onset latencies. Therefore, it seems unlikely that response related processes within the central nervous system were affected.

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, 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, i.e. in the interval between P300 and response onset.

In conclusion, this paper shows that both drugs affect at least 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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Statement of conflict of interest

The study was paid by, carried out at, and only reported within Maastricht University. AV has received grants from GlaxoSmithKline. At times during the study, WJR has been 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

REFERENCES

Beauducel, A, Brocke, B, Leue, A (2006) Energetical bases of extraversion: effort, arousal, EEG, and performance. *Int J Psychophysiol* 62(2): 212-223.

Bond, A, Lader, M (1974) The use of analogue scales in rating subjective feelings. *Britisch Journal of Medical Psychology* 47: 211-218.

Bond, A, Lader, M, Shrotriya, R (1983) Comparative effects of a repeated dose regime of diazepam and buspirone on subjective ratings, psychological tests and the EEG. *Eur J Clin Pharmacol* 24(4): 463-467.

Bonin-Guillaume, S, Blin, O, Hasbroucq, T (2004) An additive factor analysis of the effect of depression on the reaction time of old patients. *Acta Psychol (Amst)* 117(1): 1-11.

Bower, EA, Moore, JL, Moss, M, Selby, KA, Austin, M, Meeves, S (2003) The effects of single-dose fexofenadine, diphenhydramine, and placebo on cognitive performance in flight personnel. *Aviat Space Environ Med* 74(2): 145-152.

Chauncey, K, Grainger, J, Holcomb, PJ (2008) Code-switching effects in bilingual word recognition: a masked priming study with event-related potentials. *Brain Lang* 105(3): 161-174.

Curran, HV (2000) Psychopharmacological approaches to human memory. In: *Cognitive neuroscience*, Gazzaniga (ed), pp 797-804.

Curran, HV, Pooviboonsuk, P, Dalton, JA, Lader, MH (1998) Differentiating the effects of centrally acting drugs on arousal and memory: an event-related potential study of scopolamine, lorazepam and diphenhydramine. *Psychopharmacology (Berl)* 135(1): 27-36.

de Jong, R, Wierda, M, Mulder, G, Mulder, LJ (1988) Use of partial stimulus information in response processing. *J Exp Psychol Hum Percept Perform* 14(4): 682-692.

Dickman, SJ, Meyer, DE (1988) Impulsivity and speed-accuracy tradeoffs in information processing. *J Pers Soc Psychol* 54(2): 274-290.

Esbenshade, TA, Fox, GB, Cowart, MD (2006) Histamine H3 receptor antagonists: preclinical promise for treating obesity and cognitive disorders. *Mol Interv* 6(2): 77-88, 59.

Fine, BJ, Kobrick, JL, Lieberman, HR, Marlowe, B, Riley, RH, Tharion, WJ (1994) Effects of caffeine or diphenhydramine on visual vigilance. *Psychopharmacology (Berl)* 114(2): 233-238.

Frowein, HW (1981) Selective effects of barbiturate and amphetamine on information processing and response execution. *Acta Psychol (Amst)* 47(2): 105-115.

Frowein, HW, Gaillard, AW, Varey, CA (1981) EP components, visual processing stages, and the effect of a barbiturate. *Biol Psychol* 13: 239-249.

Gaillard, AWK, Gruisen, A, De Jong, R (1988) The influence of antihistamines on human performance. *European Journal of Clinical Pharmacology* 35: 249-253.

Gaillard, AWK, Verduin, CJ (1983) The combined effects of an antihistamine and pseudoephidrine on human performance. *Journal of drug research* 8(7): 1929-1936.

Geyer, MA, Krebs-Thomson, K, Braff, DL, Swerdlow, NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology (Berl)* 156(2-3): 117-154.

Hindmarch, I, Shamsi, Z (1999) Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy* 29 Suppl 3: 133-142.

Jasper, HH (1957) The ten-twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology* 10: 371-375.

Jex, HR, McDonnell, JD, Phatak, AV (1966) A "critical" tracking task for man-machine research related to the operator's effective delay time. I. Theory and experiments with a first-order divergent controlled element. NASA CR-616. *NASA Contract Rep NASA CR*: 1-105.

Leufkens, TR, Vermeeren, A, Smink, BE, van Ruitenbeek, P, Ramaekers, JG (2007) Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. *Psychopharmacology (Berl)* 191(4): 951-959.

Loring, DW, Meador, KJ (1989) Central nervous system effects of antihistamines on evoked potentials. *Ann Allergy* 63(6 Pt 2): 604-608.

McCarthy, G, Donchin, E (1981) A metric for thought: a comparison of P300 latency and reaction time. *Science* 211(4477): 77-80.

Meador, KJ, Loring, DW, Thompson, EE, Thompson, WO (1989) Differential cognitive effects of terfenadine and chlorpheniramine. *J Allergy Clin Immunol* 84(3): 322-325.

Miller, J, Hackley, SA (1992) Electrophysiological evidence for temporal overlap among contingent mental processes. *J Exp Psychol Gen* 121(2): 195-209.

Miller, J, Patterson, T, Ulrich, R (1998) Jackknife-based method for measuring LRP onset latency differences. *Psychophysiology* 35(1): 99-115.

Miller, J, van der Ham, F, Sanders, AF (1995) Overlapping stage models and reaction time additivity: effects of the activation equation. *Acta Psychol (Amst)* 90(1-3): 11-28.

Northoff, G, Pfennig, A, Krug, M, Danos, P, Leschinger, A, Schwarz, A, Bogerts, B (2000) Delayed onset of late movement-related cortical potentials and abnormal response to lorazepam in catatonia. *Schizophr Res* 44(3): 193-211.

Olkkola, KT, Ahonen, J (2008) Midazolam and other benzodiazepines. *Handb Exp Pharmacol*(182): 335-360.

Onodera, K, Yamatodani, A, Watanabe, T, Wada, H (1994) Neuropharmacology of the histaminergic neuron system in the brain and its relationship with behavioral disorders. *Prog Neurobiol* 42(6): 685-702.

Osman, A, Bashore, TR, Coles, MG, Donchin, E, Meyer, DE (1992) On the transmission of partial information: inferences from movement-related brain potentials. *J Exp Psychol Hum Percept Perform* 18(1): 217-232.

Pang, E, Fowler, B (1994) Discriminating the effects of triazolam on stimulus and response processing by means of reaction time and P300 latency. *Psychopharmacology (Berl)* 115(4): 509-515.

Passani, MB, Bacciottini, L, Mannaioni, PF, Blandina, P (2000) Central histaminergic system and cognition. *Neurosci Biobehav Rev* 24(1): 107-113.

Polich, J (2007) Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol* 118(10): 2128-2148.

Pompeia, S, Manzano, GM, Galduroz, JC, Tufik, S, Bueno, OF (2003) Lorazepam induces an atypical dissociation of visual and auditory event-related potentials. *J Psychopharmacol* 17(1): 31-40.

Pooviboonsuk, P, Dalton, J. A., Curran, H. V., Lader, M. H. (1996) The effects of single doses of lorazepam on event related potentials and cognitive function. *human psychopharmacology* 11: 241-252.

Ramaekers, JG, O'Hanlon, JF (1994) Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing. *Eur J Clin Pharmacol* 47(3): 261-266.

Riba, J, Rodriguez-Fornells, A, Munte, TF, Barbanoj, MJ (2005) A neurophysiological study of the detrimental effects of alprazolam on human action monitoring. *Brain Res Cogn Brain Res* 25(2): 554-565.

Riedel, WJ, Mehta, M., Unema, P. (2006) Human cognition assessment in drug research. *Current Pharmaceutical Design* 12: 1-15.

Robbe, HWJ, O'Hanlon, J. F. (1990) Effects of acrivastine, acrivastine plus pseudoephidrine and triprolidine on highway driving. *Maastricht, Institute for Drugs Safety and Behavior*: 1-44.

Rockstroh, B, Elbert, T, Lutzenberger, W, Altenmuller, E (1991) Effects of the anticonvulsant benzodiazepine clonazepam on event-related brain potentials in humans. *Electroencephalogr Clin Neurophysiol* 78(2): 142-149.

Sanders, AF (1980) Stage analysis of reaction processes. In: *Tutorials in motor behavior*, Stelmach, GE, Requin, J. (ed). Amsterdam: North-Holland.

Seidl, R, Hauser, E, Bernert, G, Marx, M, Freilinger, M, Lubec, G (1997) Auditory evoked potentials in young patients with Down syndrome. Event-related potentials (P3) and histaminergic system. *Brain Res Cogn Brain Res* 5(4): 301-309.

Semlitsch, HV, Anderer, P, Schuster, P, Presslich, O (1986) A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology* 23(6): 695-703.

Simons, FE, Reggin, JD, Roberts, JR, Simons, KJ (1994) Benefit/risk ratio of the antihistamines (H_1-receptor antagonists) terfenadine and chlorpheniramine in children. *J Pediatr* 124(6): 979-983.

Smulders, FT, Kenemans, JL, Schmidt, WF, Kok, A (1999) Effects of task complexity in young and old adults: reaction time and P300 latency are not always dissociated. *Psychophysiology* 36(1): 118-125.

Smulders, FT, Kok, A, Kenemans, JL, Bashore, TR (1995) The temporal selectivity of additive factor effects on the reaction process revealed in ERP component latencies. *Acta Psychol (Amst)* 90(1-3): 97-109.

Sternberg, S (1969) The discovery of processing stages: extensions of donders' method. *Acta Psychologica* 30: 276-315.

Theunissen, EL, Vermeeren, A, van Oers, AC, van Maris, I, Ramaekers, JG (2004) A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor

performance as compared to dexchlorpheniramine, cetirizine and placebo. *Clin Exp Allergy* 34(2): 250-258.

Turner, C, Handford, AD, Nicholson, AN (2006) Sedation and memory: studies with a histamine H-1 receptor antagonist. *J Psychopharmacol* 20(4): 506-517.

Ulrich, R, Miller, J (2001) Using the jackknife-based scoring method for measuring LRP onset effects in factorial designs. *Psychophysiology* 38(5): 816-827.

Van Ruitenbeek, P, Vermeeren, A, Riedel, W (2008) Histamine H_1-receptor blockade in humans affects psychomotor performance but not memory. *J Psychopharmacol* 22(6): 663-672.

Vermeeren, A, Ramaekers, JG, O'Hanlon, JF (2002) Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females. *J Psychopharmacol* 16(1): 57-64.

Verster, JC, Volkerts, ER (2004) Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol* 92(3): 294-303; quiz 303-295, 355.

Vuurman, EF, Uiterwijk, MM, Rosenzweig, P, O'Hanlon, JF (1994) Effects of mizolastine and clemastine on actual driving and psychomotor performance in healthy volunteers. *Eur J Clin Pharmacol* 47(3): 253-259.

Witkin, JM, Nelson, DL (2004) Selective histamine H3 receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous system. *Pharmacol Ther* 103(1): 1-20.

Yanai, K, Tashiro, M (2007) The physiological and pathophysiological roles of neuronal histamine: an insight from human positron emission tomography studies. *Pharmacol Ther* 113(1): 1-15.

List of abbreviations

Additive Factor Method (AFM)

Choice Reaction Time (CRT)

Critical Tracking Task (CTT)

Event Related Potential (ERP)

Lateralized Readiness Potential (LRP)

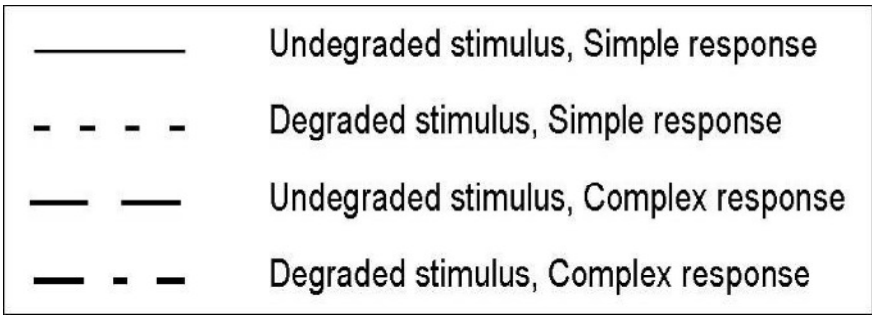
Motor Time (MT)

Response Complexity (RC)

Response Locked (R-locked)

Stimulus Locked (S-locked)

Stimulus Quality (SQ)



Legend for the figures 1 to 4.

Figure 1: Effects of treatment 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 treatment ($p<0.02$) which was caused by an increased effect of the degraded stimulus by dexchlorpheniramine ($p<0.10$).

Figure 2: Effects of treatment and manipulations of stimulus quality and response complexity on the interval between the R-locked P300 and the response. Response complexity and lorazepam increased the interval duration ($p < 0.05$), but did not interact.

Figure 3: Effects of treatment and manipulations of stimulus quality and response complexity on the interval between the R-locked LRP and the response. Both treatments did not prolong the interval. Response complexity did increase the interval ($p<0.01$), but did not interact with treatment.

Figure 4: Effects of treatment and manipulations of stimulus quality and response complexity on the stimulus locked LRP onset latency. Lorazepam and degraded stimuli increased the onset latency (p's < 0.01). Response complexity tended to interact with Treatment ($p < 0.10$) and dexchlorpheniramine tended to decrease the S-locked LRP onset when a complex response has to be given ($p < 0.10$).