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Antihistamine Induced Blood Oxygenation Level Dependent Response Changes Related to Visual Processes During Sensori-Motor Performance

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Abstract: The histaminergic involvement in selective processes underlying its role in human sensori-motor performance is largely unknown. Recently, selective effects of central H_1-inverse agonism on sensory visual processes were observed in electrophysiological—but not behavioral data; a discrepancy suggested to result from speeded response-choice related processes. This study attempts to establish the effects on visual processes and identify putative compensatory mechanisms related to increased visual and response-choice task demands by assessing H_1-inverse agonism induced changes in blood oxygenation level dependent (BOLD) response. Twelve participants received oral doses of dexchlorpheniramine 4 mg, lorazepam 1 mg, and placebo in a three-way crossover designed study. Brain activity was assessed for choice reaction time task performance in a 3 T magnetic resonance scanner 2 h after drug administration. Participants responded with their left or right hand and index or middle finger as indicated by the laterality of stimulus presentation and identity of the stimulus, respectively. Stimuli were intact or visually degraded and responses were compatible or incompatible with the laterality of stimulus presentation. Both dexchlorpheniramine and lorazepam affected the BOLD response in the occipital cortex indicating affected visual information processing. Dexchlorpheniramine decreased BOLD response in the dorsal precuneus and left precentral gyrus as part of a motor network, which however might not be interpreted as a compensatory mechanism, but may be the upstream consequence of impaired visual processing. *Hum Brain Mapp 35:3095–3106, 2014.* © **2013 Wiley Periodicals, Inc.**

Key words: histamine; GABA; cognition; functional magnetic resonance imaging; BOLD; sensori motor function

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INTRODUCTION

The neurotransmitter histamine seems involved in cognitive functioning in experimental animals and humans by interacting with the histamine H_1-, H_2-, and H_3-receptors in the central nervous system. In studies using experimental animals, evidence comes from a variety of methods. Studies using H_1-receptor and/or H_2-receptor knock-out mice [e.g. (Dai et al., 2007; Zlomuzica et al., 2009)], experimental reductions in the histamine synthesizing enzyme histidine decarboxylase [e.g. (Dere et al., 2003; Kamei et al., 1993)] and studies using H_3-receptor antagonists [for reviews see: (Esbenshade et al., 2008; Passani et al., 2004; Witkin and Nelson, 2004)] have all shown induced cognitive performance changes. In humans, evidence for the role of histamine in cognition is mainly indicated by the effects of centrally active H_1-receptor antagonists/inverse agonists (i.e., antihistamines), which impair performance in a variety of cognitive domains including simple sensorimotor speed [for review see: (Van Ruitenbeek et al., 2010a)]. These studies include imaging studies to determine the brain areas in which activity is affected by antihistamines [Mochizuki et al., 2002; Okamura et al., 2000], but only few studies have assessed whether histamine plays a role in specific cognitive processes (e.g., processing of visual information), or whether it affects cognitive performance as a modulator of neuronal activity throughout the entire brain [Wada et al., 1991].

Two lines of research suggest a nonselective role for histamine in cognition. First, from a neurobiological point of view, widespread projections to the entire cortex originate from the histamine containing cells primarily located in the tuberomammillary nucleus (TMN) of the hypothalamus [Brown et al., 2001; Haas et al., 2008]. In addition, histamine H_1-receptor inverse agonists cetirizine [Tashiro et al., 2002] and dexchlorpheniramine [Tagawa et al., 2001; Yanai et al., 1992] have shown widespread binding to H_1-receptors in the cingulate-, prefrontal-, orbitofrontal-, temporal-, and occipital cortex, striatum, and thalamus. Second, in a recent review of the effects of H_1-antagonism/inverse agonism on human cognitive performance, the authors observed that across assessments the proportion of detected antihistamine induced impairments increases with task complexity [Van Ruitenbeek et al., 2010a]. Although this supports impairing effects on many cognitive processes, effects on selective processes cannot be excluded.

Indeed, some studies observed selectivity of the effects of H_1-inverse agonists in healthy humans using reaction time measures and electrophysiology and suggested that effects on sensory processes were responsible for observed impairments [Gaillard and Verduin, 1983; Van Ruitenbeek et al., 2009]. However, detection of affected sensory processes seems to depend on the measure used; Van Ruitenbeek et al. [2009] observed a modulation of sensory processes based on event related potentials (ERP), in absence of changes in reaction time. This discrepancy may be explained by assuming information in the brain to be processed according to an information processing model with linear (or cascaded) sequence of information processing stages [Miller et al., 1995; Sanders, 1980]. In such a model, delays in one stage can be compensated for in another stage whereby reaction time—as the end measure of all processes—seems unaffected. In their study, Van Ruitenbeek et al. [2009] observed no effects of the antihistamine drugs on motor related processes and proposed that central response choice processes might be the locus of compensation, but such hypothesis remains to be tested.

Using functional magnetic resonance imaging (fMRI), this study aims to test the two hypotheses that: (a) histamine plays a selective role in sensory cognitive processes and; (b) that H_1-inverse agonism evokes compensatory mechanisms during response choice, as indicated by task related brain activity. Selective dexchlorpheniramine induced effects are defined as effects on sensory processes, but not response choice processes. Task manipulations designed to increase sensory- and response-choice processing demands were applied to determine process specific and region specific drug effects. Based on previous studies, manipulation of stimulus quality (SQ) is expected to affect activity in the primary visual cortex [Bar et al., 2001; Schumacher and D'Esposito, 2002] and stimulus-response incompatibility is expected to increase activation in a response choice network [Dassonville et al., 2001; Matsumoto et al., 2004; Schumacher and D'Esposito, 2002]. If H_1-antagonists/inverse agonists selectively affect sensory processes, then they should augment effects of SQ, but not effects of stimulus response compatibility (SRC) as indicated by activity changes in associated networks. Furthermore, we hypothesize that augmentation of SQ effects is compensated for during response choice. Consequently, such interaction should not be observed in reaction time data, but functional MRI data should show altered activity in brain areas involved in response choice following the presentation of a degraded stimulus and administration of the H_1-inverse agonist.

MATERIAL AND METHODS

Participants

Twelve right-handed participants (six female) aged between 18 and 45 years (20.8 ± 0.6 SEM) were recruited by advertisements in local newspapers and public buildings (e.g., University) and were financially compensated for their time. Participants were physically and mentally healthy as determined by a prestudy medical history questionnaire and physical examination by the medical supervisor. Physical examination included vital signs, a 12 lead electrocardiogram, blood chemistry and hematology and urinalysis to check for pregnancy and presence of drugs of abuse (amphetamine, benzodiazepine, cocaine, opiate, cannabis, and methamphetamine). In addition, a MR suitability questionnaire checked for the presence of nonremovable metal

objects and signs of claustrophobia. Exclusion criteria were a history or presence of drug or alcohol abuse, mental or physical disorders including gastrointestinal, hepatic, renal, cardiovascular, or neurological diseases, a body mass index outside the limits of 18 and 30 kg/m^2, blood pressure outside the limits of 100 and 150 Hg systolic and 60 and 90 Hg diastolic, drinking more than 21 standard alcoholic consumptions per week or more than six caffeinated drinks per day and smoking more than five cigarettes per day. Furthermore, volunteers did not report use of any concomitant medication when asked on every treatment day. Females were allowed to take contraceptives, and were excluded if pregnant or in a lactation period.

All participants received written information about all aspects of the study, were given the opportunity to ask questions, and gave written informed consent. The study was approved by the Medical 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 [Seoul, Korea, 2008: (World-Medical-Association 1964, 2008)].

Study Design and Treatment

The study was designed and conducted according to a double blind, placebo controlled, three-way crossover design. Treatments were oral doses of placebo and immediate release formulations of the H_1-inverse agonist dexchlorpheniramine 4 mg and the benzodiazepine lorazepam 1 mg. Dexchlorpheniramine was chosen as tool drug for several reasons: (a) it readily crosses the blood brain barrier with a 2 mg dose binding to over 76% of the H_1 receptors in the brain [Yanai et al., 1995], (b) it has a short T_{max} of 2.8 h [Huang et al., 1982], (c) it has a suitable half life of approximately 28 h [Huang et al., 1982], (d) even though it has some affinity for the M1 receptor, it is reasonably selective for the H_1 receptor compared with other 1st generation antihistamines [Laduron et al., 1982], and (e) has a high binding affinity for the H_1-receptor [Henz, 2001; Laduron et al., 1982]. Lorazepam was used as an active control treatment for its known sedative effect by increasing GABA-ergic activity [Mohler and Okada, 1977; Olkkola and Ahonen, 2008]. Lorazepam has a Tmax of approximately 2 h and a half-life of approximately 12 h [Busto et al., 2000; Greenblatt, 1981; Greenblatt et al., 1976]. Treatment days were separated by at least 4 days to minimize carry-over effects, and treatment order was randomized and counterbalanced across participants.

Experimental Tasks

Subjective alertness

Subjective evaluations of alertness were assessed by using a Dutch version of a series of 16 visual analog scales (100 mm), which provide factor analytically defined summary scores for "alertness," "contentedness," and "calmness" [Bond and Lader, 1974].

Choice reaction time task

Following a previous study [Van Ruitenbeek et al., 2009], a Choice Reaction Time (CRT) task was designed to assess feature extraction and response choice information processing by manipulating SQ and SRC according to a 2 × 2 design. The task consists of repeated presentation of one of two stimuli (pictures of numbers 2 and 5) presented as a dot pattern and surrounded by a rectangular frame of dots. Stimuli are presented for 2,000 ms and time between offset of the stimulus and presentation of the next stimulus is jittered pseudo-randomly between 8,000 and 12,000 ms while the response was recorded. Presentation of stimuli is balanced in frequency of appearance on the left or right side of a fixation cross. Stimulus location—left or right—indicates the hand to respond with. Participants had to press a button as fast as possible with the indicated hand by using their index finger whenever a 2 appeared and using their middle finger whenever a 5 appeared on the screen.

The task consisted of a 28-min event related run of 126 trials, consisting of 14 null events, i.e., a black screen, and 112 event trials consisting of 56 stimulus-response compatible and 56 stimulus-response incompatible trials. Compatible trials were indicated by a "+" fixation sign before stimulus onset, which meant the participant had to respond with the hand on the same side as the presented stimulus. Incompatible trials are indicated by an "×" fixation sign indicating the participant to respond with the hand opposite to the side of the presented stimulus, thereby increasing response choice demands. Feature extraction demands were increased by visually degrading 50% of all stimuli by randomly placing 20 dots from the frame at random positions in the field within the frame on 78 positions not occupied by dots of the digit [Steyvers and Gaillard, 1993].

Reaction time was measured in milliseconds, accuracy in percentage correct, and brain activity using blood oxygenation level dependent (BOLD) MRI.

Procedure

Participants visited the test facility six times; once for a screening visit, two times to practice the task within 2 weeks before the first treatment visits and three times for a treatment visit. Please see Figure 1 for a description of treatment day procedures.

Image Acquisition

MRI data were acquired using a 3 T Siemens Magnetom Allegra Head Scanner with a single channel quadrature transceiver head coil. All participants completed three experimental sessions, in which T1-weighted volumes and

T2*-weighted BOLD contrast volumes were obtained. Functional images (24 slices, 963 volumes) were recorded with interleaved transaxial slices aligned approximately with the anterior–posterior commissure line using a gradient echo planar imaging acquisition sequence (TR = 1,500 ms, TE = 30 ms). A whole brain scan was obtained using 3.5 mm^3 voxels in 64 × 64 matrix and a field of view (FOV) of 224 mm^2, with a 0.5 mm gap between the slices. Structural imaging data were collected using a high resolution T1-weighted MP-RAGE sequence, including 192 slices and 1 mm^3 voxels. Participants were bedded in foam cushions minimizing head movement. Earplugs were used to diminish noise-distraction and a headphone and microphone ensured the communication between participant and experimenter. Participants could alarm the experimenter by using a squeeze ball at any time during measurement. The computer-task was back-projected on a screen at the back side of the scanner and a mirror attached to the head coil allowed the participant to comfortably see the screen.

Image Preprocessing

Using BrainVoyager QX 2.2 software [Brain-Innovation, Maastricht, The Netherlands; Goebel et al., 2006], all acquired functional data were corrected for motion in a three-dimensional (3D) space and low frequency temporal drifts were removed using a temporal high-pass filter in two cycles per time course. The first two volumes were discarded because of T1 saturation effects. To control for movement artifacts, volumes containing translational movement of more than 0.5 mm or rotational movement of more than 0.5 mm on the edge of the brain between two consecutive volumes were identified and modeled as event of a separate factor; "movement error" [Power et al., 2012]. The functional data from the second and third treatment sessions were aligned to the anatomical data from the first session: first, the individual functional data were co-registered with anatomical data from the same session. Second, anatomical and functional data from the first treatment session were normalized to standard 3D Talairach space [Talairach and Tournoux, 1988]. Third, anatomical data from every second and third session were transformed to match the normalized anatomical data from the first session. Finally, the resulting translational parameters were used to align (normalize) the functional data to the normalized first session anatomical data. Functional time series were spatially smoothed using a Gaussian filter (8 mm FWHM) and linked to individual files containing onset and duration of the task events. Events were defined as the time between the onset of stimulus presentation and the correct response. The BOLD response was modeled using a two-gamma Hemodynamic Response Function to account for the hemodynamic delay used by default in BrainVoyager QX [Goebel et al., 2006].

Statistical Analysis

Visual analog scales data were separately analyzed for the three factors (Alertness, Contentedness, and Calmness) using analyses of variances (ANOVA) for repeated measures with Treatment (three levels: placebo, dexchlorpheniramine, and lorazepam) as within subjects factor.

For CRT behavioral data, effects of Treatment (three levels: placebo, dexchlorpheniramine, and lorazepam), SQ (two levels: intact and degraded) and SRC (two levels: compatible and incompatible) on reaction time (ms) and accuracy (percentage of correct responses) were analyzed in a 3 × 2 × 2 model using ANOVA for repeated measures in SPSS 18.0 software package. Only reaction times for correct responses were analyzed.

For the imaging data, a priori regions of interest (ROIs) were defined separately for SQ and SRC based on previous studies. For SQ, the ROIs consisted of the primary visual cortex (VC: BA17 and BA18). For SRC, the ROIs consisted of the superior parietal cortex (SPC: BA5 and BA7), motor cortex (MC: BA6), anterior cingulate cortex (ACC: BA24, BA32, and BA33), and dorsolateral prefrontal cortex (DLPFC: BA9 and BA46). Beta weights were calculated using a Random Effects General Linear Model analysis (RFX GLM: Multi Study/Multi Participant) with Treatment, SQ, SRC, six individual movement parameters (three translational and three rotational) and movement error as independent variables and the BOLD-response as dependent variable for SQ and SRC ROIs separately. As a second level analysis, main effects of the SQ and SRC were determined for both sets of ROIs separately in PLC using a 2 × 2 RFX ANCOVA with SQ and SRC as independent variables and a cluster forming

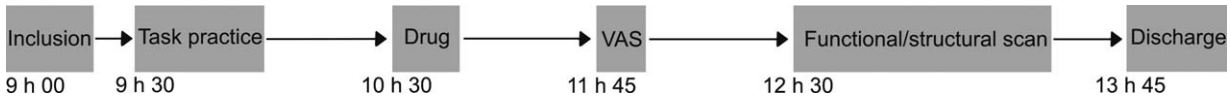

Figure 1.

On treatment visits, participants arrived at the research facility at 9 h whereupon inclusion and exclusion criteria were checked. At 9 h 30 min, participants performed the task once on a desktop personal computer to remind them of the task procedures. Participants received the treatments at 10 h 30 min. At 11 h 45 min, before participants entered the scanner subjective alertness was evaluated using visual analog scales. Participants entered the scanner at 12 h, the anatomical scan started around 12 h 30 min, the functional scan during which the participant performed a CRT task started around 13 h. After the scanning session, participants received a light lunch and were escorted to their home.

voxelwise $P < 0.05$, which was used only to ensure that task manipulations were effective. Further for each a priori ROI, main effects of Treatment and Treatment by SQ/SRC interactions were determined in a $2 \times 2 \times 3$ RFX ANCOVA with SQ, SRC and Treatment as independent variables using $P < 0.05$ per voxel as cluster forming threshold. To correct for multiple comparisons: (1) minimal sizes of clusters of significant voxels (CS) were defined for each comparison, keeping the overall false detection rate of significant clusters below 5%. This method is based on Forman et al. [1995] and suggested by Goebel et al. [2006]. (2) Clusters of activity showing main effects of Treatment or Treatment by SQ/SRC interaction were only accepted as significant if $P < 0.001$ on a cluster level. Areas of activity showing main effects and interactions were further specified by extracting beta values and analyzing drug-placebo contrasts using SPSS 18 using $\alpha = 0.05$ for the average beta per cluster.

RESULTS

Behavioral Data

Subjective alertness

Treatment showed a main effect on alertness ($F_{2,10} = 4.4$, $P < 0.042$). Drug-placebo contrasts showed that lorazepam significantly decreased subjective alertness as compared to placebo ($F_{1,11} = 5.2$, $P < 0.044$), while dexchlorpheniramine did not. There were no significant treatment effects on contentedness or calmness (Table I).

CRT task

As expected, degraded stimuli prolonged reaction time ($F_{1,11} = 30.0$, $P < 0.001$) and decreased accuracy ($F_{1,11} = 12.2$, $P < 0.005$). Stimulus-response incompatibility prolonged reaction time ($F_{1,11} = 8.9$, $P < 0.012$), but did not significantly decrease accuracy. Task manipulations did not interact as measured by both reaction time and accuracy, indicating independence of manipulated processes (Table I).

Overall, reaction times differed significantly between treatments across all task conditions ($F_{2,10} = 10.9$, $P < 0.003$). Both dexchlorpheniramine and lorazepam significantly prolonged reaction time ($F_{1,11} = 13.6$, $P < 0.004$ and $F_{1,11} = 22.8$, $P < 0.001$, respectively). Treatment effects did not interact with SQ or with SRC. Accuracy also differed between treatments ($F_{2,10} = 7.1$, $P < 0.012$). Compared with placebo, lorazepam significantly decreased accuracy ($F_{1,11} = 13.8$, $P < 0.003$), but dexchlorpheniramine effects failed to reach significance ($F_{1,11} = 4.0$, $P < 0.072$). Treatment effects did not interact with either SQ or SRC (Table I).

fMRI Data

Task manipulations

RFX repeated measures ANCOVA identified two areas in the primary visual cortex in which BOLD response

TABLE I. Drug effects on subjective alertness and choice reaction time performance

Task		Mean ± SEM						Main effects Treatment			Interactions Treatment × SQ			Treatment × SRC		
Measure		PLC		DEX 4		LOR 1		F	df	P	*F*	df	P	*F*	df	*P*
VAS																
Alertness (mm)		64.0 ± 7.5		64.7 ± 5.6		48.0 ± 6.0*		**4.4**	**2.10**	**0.042**						
Contentedness (mm)		78.7 ± 3.7		75.5 ± 4.5		74.2 ± 3.8		1.1	2.10	0.369						
Calmness (mm)		82.8 ± 3.5		73.4 ± 6.0		77.4 ± 3.1		2.6	2.10	0.119						
CRT		Intact	Degraded	Intact	Degraded	Intact	Degraded									
Reaction time (ms)	Compatible	897 ± 53	1,090 ± 63	995 ± 64	1,155 ± 65	1,157 ± 92	1,391 ± 99	**10.9**	**2.10**	**0.003**	1.2	2.10	0.329	<1	2.10	0.868
	Incompatible	951 ± 52	1,093 ± 68	1,017 ± 50	1,185 ± 75	1,208 ± 127	1,446 ± 91									
Accuracy (%)	Compatible	97 ± 2	88 ± 4	94 ± 1	85 ± 3	87 ± 3	78 ± 4	**7.1**	**2.10**	**0.012**	<1	2.10	0.977	1.9	2.10	0.204
	Incompatible	96 ± 1	88 ± 3	93 ± 2	85 ± 2	83 ± 5	74 ± 5									

Mean (±SEM) values for behavioral measures after the treatment with placebo (PLC), dexchlorpheniramine 4 mg (DEX4) or lorazepam 1 mg. (LOR1). *F*-values, degrees of freedom, and *P*-values are given for the main effect of Treatment and the interactions between Treatment and Stimulus Quality (SQ) and between Treatment and Stimulus Response Compatibility (SRC). Significant effects are indicated in bold font and an asterisk indicates significant Drug-placebo contrasts for VAS scores. Drug-placebo contrasts for the CRT are described in CRT task section of the text.

TABLE II. Effect of task manipulations on BOLD response

Brain area	Brodmann area	BOLD after increased task demands	Cluster size (mm^3)	Talairach coordinates		
				X	*Y*	*Z*
Stimulus quality (CS > 39, $F_{1,11} > 4.84$, $P < 0.05$)						
Right posterior occipital cortex	18	↑	3,065	26	−88	−5
Left posterior occipital cortex	18	↑	3,578	−21	−88	−10
Stimulus response compatibility (CS > 33, $F_{1,11} > 4.84$, $P < 0.05$)						
—						

Effects of Stimulus Quality and Stimulus Response Compatibility on the BOLD response during placebo. Active areas are given in average Talairach coordinates, Brodmann area numbers and cluster size in mm^3. Minimal Cluster Size (CS in number of 3 × 3 × 3 mm^3 voxels), *F*-value threshold and *P*-value threshold are given for each effect and the direction of change after increased task demands are indicated by the arrows.

change after presentation of visually degraded stimuli exceeded statistical threshold during placebo, as identified by a main effect of SQ ($F_{1,11} > 4.84$; $P < 0.05$). Presentation of degraded stimuli led to a significant increase in BOLD response in the left and right posterior occipital cortex.

SRC did not significantly change activity in brain areas, therefore, effects of the treatments and treatment by SRC interactions in these ROIs were not further analyzed. Please consult Table II for details.

Treatments

Within the SQ ROI, Treatment showed a main effect in the right posterior inferior occipital cortex (BA17) ($F_{2,10} = 13.5$, $P < 0.001$). Both dexchlorpheniramine and lorazepam decreased brain activity across task conditions ($P < 0.036$ and $P < 0.001$, respectively). A main effect of Treatment was also observed in the left posterior superior occipital cortex (BA17) ($F_{2,10} = 10.7$, $P < 0.001$). Lorazepam significantly decreased brain activity ($P < 0.001$), but the decreasing effect of dexchlorpheniramine failed to reach significance ($P < 0.068$). Please consult Table III for further details and Figure 2 for a graphical representation.

Interactions of treatment by task manipulation

Treatment by SQ interactions in SQ related ROIs did not survive multicomparisons correction. To test the second hypothesis; in ROIs for SRC, treatment significantly modulated the effect of SQ in the dorsal precuneus ($F_{2,10} = 10.2$, $P < 0.001$) and in the left precentral gyrus ($F_{2,10} = 6.7$, $P < 0.001$). During placebo, the BOLD response increased after the presentation of a degraded stimulus, while presenting a degraded stimulus after dexchlorpheniramine significantly decreased the BOLD response in the dorsal precunceus ($F_{1,11} = 19.5$, $P < 0.001$). The effect of SQ was not significantly different for lorazepam and placebo. In the left precentral gyrus, BOLD was increased after presentation of a degraded stimulus during placebo, while a degraded stimulus caused a decrease in BOLD during lorazepam ($F_{1,11} = 18.7$, $P < 0.001$) and dexchlorpheniramine ($F_{1,11} = 20.5$, $P < 0.001$). Please see Table IV for details and Figure 3 for a visual representation of the results.

DISCUSSION

This study aimed to determine if histamine plays a role in selective cognitive processes associated with visual SQ. Impaired performance after intake of an H_1-inverse agonist and task manipulations provided tools to study the selectivity of the performance impairment, where altered brain activity and an interaction between the treatment and task manipulation as measured with reaction times indicate an effect of the treatment on a particular cognitive process [Sanders, 1980; Sternberg, 1969; Van Ruitenbeek et al., 2009]. Following a previous study [Van Ruitenbeek et al., 2009] and assuming a linear stage model of

TABLE III. Drug effects on BOLD response in a priori ROIs

Brain area	Brodmann area	Main effect treatment		Drug-placebo contrasts		Talairach coordinates		
		$F_{2,10}$=	*P* <	*P* <		*X*	*Y*	*Z*
Stimulus quality ROI (CS > 40, $F_{2,10} > 4.84$, $P < 0.05$)				Dex4	Lor1			
R. posterior inferior occipital cortex	17	13.5	0.001	0.036	0.001	11	−98	6
L. posterior superior occipital cortex	17	10.7	0.001	0.068	0.001	−19	−92	18

Main effects of drug treatment and drug-placebo contrasts on BOLD response in regions of interest (ROIs) expected to show effects of SQ. Active areas with a minimal cluster size of 40 functional voxels for SQ and are indicated by name, Brodmann area number and Talairach coordinates. Significance of main effects is indicated by *F*- and *P*-values and drug-placebo contrasts by their *P*-values.

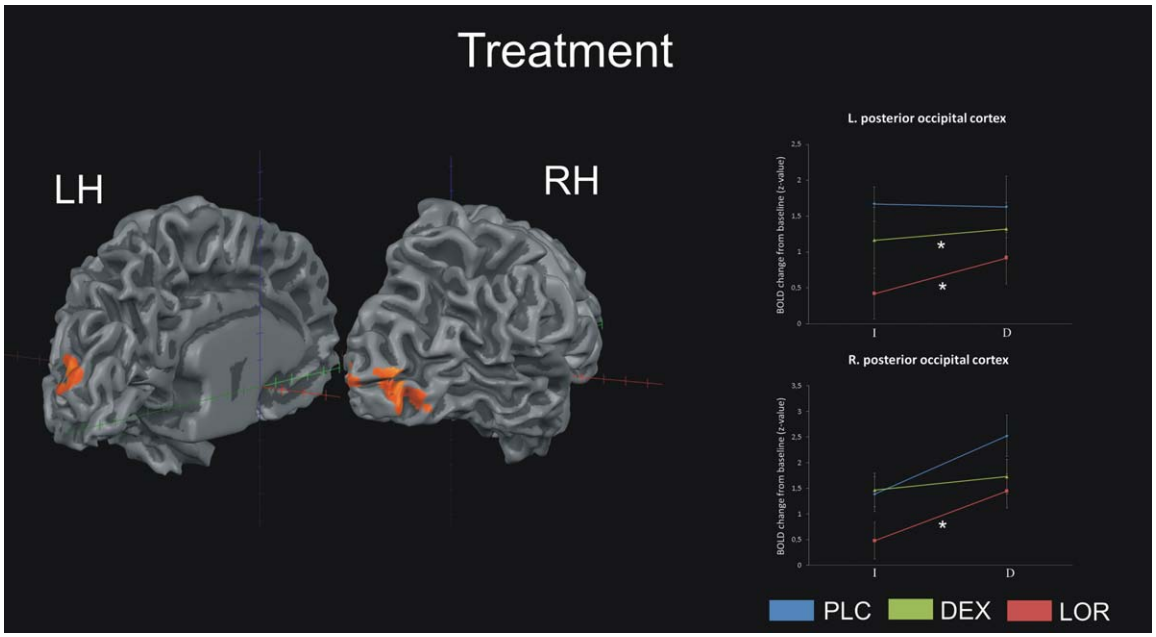

Figure 2.
Colored patches represent main effects of treatment on the BOLD response in Brodmann areas 17 and 18 ($F_{2,10} > 4.84$; $P < 0.05$) with a minimal cluster size of 40 functional voxels. Graphs represent BOLD response data for the three treatment conditions and for intact (I) and degraded (D) stimulus presentations. Significant drug-placebo contrasts are indicated by "*".

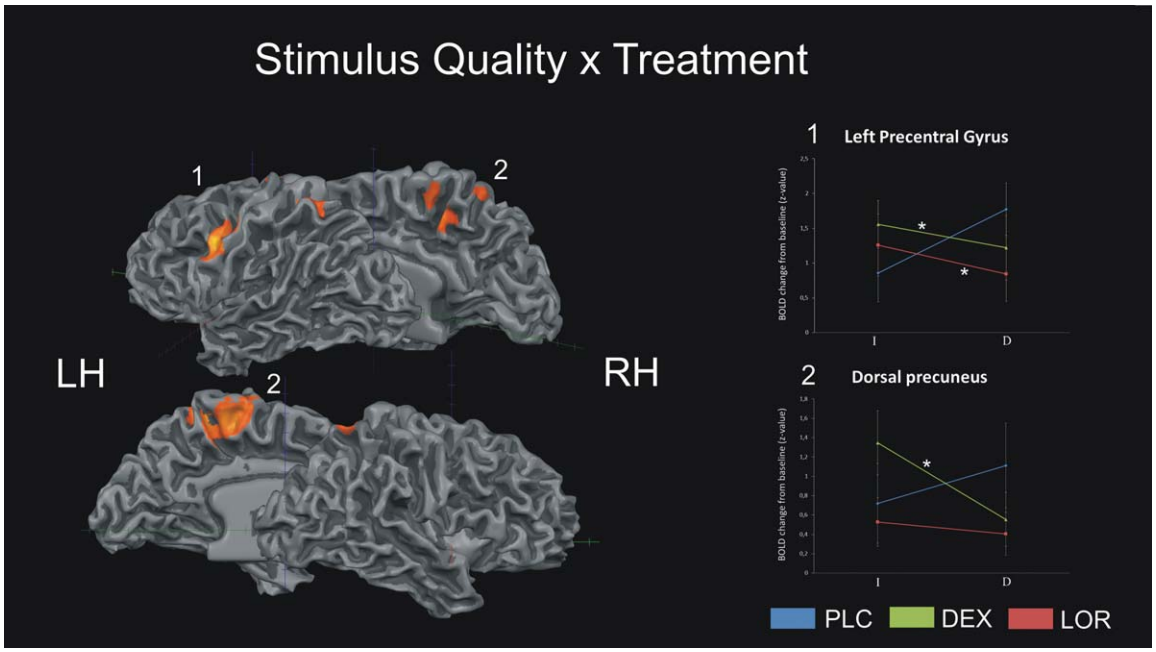

Figure 3.
Colored patches represent treatment by SQ interactions on the BOLD response in SRC related areas ($F_{2,10} > 3.44$; $P < 0.05$) with a minimal cluster size of 39 functional voxels. Graphs represent BOLD response data for the three treatment conditions and for intact (I) and degraded (D) stimulus presentations. Significant drug-placebo interaction contrasts are indicated by "*".

TABLE IV. Drug by Stimulus Quality interaction effects on BOLD response in ROIs

Brain area	Brodmann area	Treatment × SQ interaction		SQ-effect drug-PLC contrasts		Talairach coordinates		
		$F_{2,10}$	$P <$	$P <$		X	Y	Z
SQ ROIs (CS > 40, $F_{2,10} > 3.44$, $P < 0.05$)				Dex4	Lor1			
—	—	—	—	—	—	—	—	—
SRC ROIs (CS > 39, $F_{2,10} > 3.44$, $P < 0.05$)								
Dorsal precuneus	5	10.2	0.001	0.001	n.s.	−8	−37	54
L. precentral gyrus	6	6.7	0.001	0.001	0.001	−47	0	42

A priori ROIs known to be affected by SQ and SRC are indicated by name, Brodmann area, and Talairach coordinates. Significance of interaction effects are indicated by *F*- and *P*-values and drug-placebo interaction contrasts by their *P*-values.

information processing [Smulders et al., 1995], it was hypothesized that the H_1-inverse agonist dexchlorpheniramine would increase the effect of visual stimulus degradation on information processing. In accordance, dexchlorpheniramine affected brain activity associated with visual processes. Second, it was hypothesized that putative increase in processing speed of response choice related processes may compensate for the impairment and thereby attenuate the ability to detect this effect using reaction time, but which should be reflected in altered activity of response choice related brain areas. Indeed dexchlorpheniramine did not interact with visual stimulus degradation as measured with reaction time, but did interact with SQ in brain areas involved in motor response related information processing. However, dexchlorpheniramine decreased the BOLD response during increased visual demands as opposed to the expected increase in BOLD response, which does not support the compensatory hypothesis.

Task Manipulation Effects in Predefined ROIs

ROIs were based on previously published experiments and were used to ensure effective task manipulations. Visually degraded stimuli increased activity in area V2 of the primary visual cortex, which plays a role in low level feature extraction [Grill-Spector and Malach, 2004] and possibly in contour detection in particular [Peterhans and von der Heydt, 1991]. As complexity of visual stimuli increases, processing demands for contour detection also increase, which is reflected by increased activity establishing successful visual manipulations [Malach et al., 1995]. The phenomenon of increased activity with increased demands can be explained by an accumulation model, which states that the peak of the BOLD response occurs when sufficient information is available for information processing to continue [James and Gauthier, 2006]. The model predicts that visual stimuli more difficult to identify require longer processing time, resulting in a larger BOLD response and possibly increased reaction time. The prediction is in accordance with these results and with those from Bar et al. [2001] who found that masked stimuli evoked greater activity in primary visual area V1 as compared with unmasked stimuli.

In contrast to the SQ effects, incompatible responses did not significantly change brain activity compared with activity evoked by compatible responses, while such an effect was present in RT measures. The absence of effects on brain activity suggested unsuccessful manipulations and prevented further identification of treatments augmenting effects of SRC and therefore the selectivity of the drug effects. The lack of SRC effects are in contrast with findings from other authors applying similar, but not identical, manipulations. Changes in motor processes related networks involving superior parietal lobule, prefrontal cortex, dorsal premotor area, and presupplementary motor area have been observed by others [Casey et al., 2002; Cavanna and Trimble, 2006; Dassonville et al., 2001; Iacoboni et al., 1996; Matsumoto et al., 2004; Schumacher and D'Esposito, 2002]. One explanation for the absence of activated areas is that the participants in our study completed two extensive training sessions before the treatment visits, resulting in a lack of increased activity for incompatible responses [Kubler et al., 2006] due to "repetition suppression" effects [Henson and Rugg, 2003], which holds that activity decreases with repeated processing. In addition, the fixation cue occurred before stimulus presentation—on both compatible and incompatible trials—making a preparation of responses possible to some extent. The preparation may have decreased the processing demands of response selection in the premotor cortex on stimulus presentation [Rushworth et al., 2003]. However, Schumacher and D'Esposito [2002] used a similar procedure with highly trained participants and fixation symbols indicating trial type and observed increased activity with incompatible stimulus-response relations in the dorsal prefrontal-, superior parietal-, and anterior cingulate cortex, leaving the question why such effects where not observed in this study open ended.

Treatment Effects

Both dexchlorpheniramine and lorazepam prolonged reaction time, but only lorazepam significantly decreased accuracy. In addition, both treatments significantly decreased the BOLD response only in the left posterior

occipital cortex irrespective of visual task condition. Such a pattern of activity change was also observed in the right occipital cortex, but failed to reach significance for dexchlorpheniramine. On theoretical basis, it was expected that an enlargement of the effect of stimulus degradation by a drug, and not a main effect of a drug, would indicate an effect of that drug on low level stimulus processing [Sternberg, 1969]. Although this may be true for reaction time data, this may not hold for the BOLD response. Impaired performance induced by increased task difficulty and drug administration are both associated with increased reaction time. Therefore, if a drug enhances an impairing effect of SQ, this should result in a disproportional increase in processing time and potentially reaction time. In contrast, neuronal activity as measured by the BOLD response may react differently to increased task demands and drugs, while both result in impaired performance. Increased task demand may result in increased brain activity representing increased effort of a particular brain area, while a drug may decrease neuronal activity also resulting in impaired performance. In our case, degrading the visual stimulus resulted in increased activity in the primary visual cortex, while both drug treatments caused a decrease in activity. As discussed earlier, the posterior occipital cortex is involved in low level visual processing of stimulus properties [Bar et al., 2001; Kleinschmidt et al., 2002]. It may be concluded that both treatments affected visual information processing represented by decreased activity in the primary visual cortex.

The presently supported hypothesis that histamine plays a role in visual information processing is also supported by anatomical data and recently published functional data. Anatomically, the presence of histamine has been observed in the retina, optic nerve, and choroid [Nowak, 1985], in addition to axonal projections from the TMN to the optic chiasm and retina [Gastinger et al., 1999]. Functionally, histamine has recently been shown to be involved in the maturation of the optic chiasm and visual cortex in rats [Bessinis et al., 2012]. Using a spatial memory task performed by healthy humans in a MRI scanner after intake of the combined H_1 agonist/H_3 antagonist betahistine, we observed a decrease in lateral geniculate nucleus activity [Van Ruitenbeek and Mehta, 2013], which plays a well-known role in the visual system. This study extends this knowledge by showing the involvement of histamine in visual information processing in the cortex.

Other studies have also assessed the effects of dexchlorpheniramine on cognitive performance and the associated brain activity changes using positron emission tomography. Both Mochizuki et al. [2002] and Okamura et al. [2000] used a CRT task also loading heavily on visual information processes. They showed activity changes in parietal—and posterior cingulate cortex [Mochizuki et al., 2002] and prefrontal-, anterior cingulate-, and temporal cortex [Okamura et al., 2000] after dexchlorpheniramine administration. In this study, these brain areas were not included as a priori defined ROIs, as the study was conducted to determine the effects of dexchlorpheniramine on selective cognitive processes, i.e., feature extraction and stimulus response choice, by using task manipulations in an event related fMRI design. Nevertheless, results from their studies complement our results by showing that dexchlopheniramine affects activity in additional brain areas related to cognitive functions including attention and spatial cognition [Mochizuki et al., 2002; Okamura et al., 2000].

Lorazepam was used as an active control drug and did establish partial sensitivity of the methods. Most importantly, lorazepam showed central activity in left and right posterior occipital cortex, left precentral gyrus, and posterior precuneus, which was mostly shared with the effects of dexchlorpheniramine, establishing the sensitivity of the measures. In accordance, lorazepam has been known to cause a widespread reduction in brain activity in a large number of areas [Arce et al., 2006; Northoff et al., 2002; Paulus et al., 2005; Schunck et al., 2010; Sperling et al., 2002; Thiel et al., 2002] and induce sedation, which is supported by the present effect on subjective alertness.

Treatment by Task Manipulation Interactions

The impairing effects of treatments on reaction time were not dependent on the visual task manipulations, but were dependent on task manipulation when measured with BOLD response in predefined ROIs related to SRC. These results were predicted and in line with our previous study [Van Ruitenbeek et al., 2009], in which dexchlorpheniramine also did not enhance the reaction time slowing effect of SQ, but did as measured with the latency of P300 ERP. The discrepancy between reaction time and electrophysiological data observed in that particular study led to the hypothesis that compensation for the processing delay might take place in response choice related processes. In this study, the hypothesis was tested by assessing if activity in areas known to be involved in SRC changed following combined dexchlorpheniramime administration and degraded stimulus presentation.

ROIs were derived from previous studies that have shown increased BOLD responses with incompatible stimulus-response relations [Dassonville et al., 2001; Matsumoto et al., 2004]. Moreover, Schumacher and D'Esposito [2002] found increased activity in the dorsal prefrontal-, superior parietal-, anterior cingulate-, and lateral premotor cortex in a study using a spatial SRC task comparable with the one used in this study. Despite that, we failed to establish SRC effects in these areas, previous experiments can be taken as indications for areas involved in SRC, allowing the testing of the second hypothesis regarding the compensatory mechanism during response choice.

The combination of degraded stimulus presentation and dexchlorpheniramine administration did change activity in the dorsal precuneus and left precentral gyrus, corresponding to the superior parietal cortex and lateral premotor cortex observed by Schumacher and D'Esposito [2002]. However, a compensatory mechanism is expected to show

an increase in activity, representing increased effort, and not a clear decrease as observed. In fact, in this data, there seems to be no brain area displaying this pattern of activity and which could therefore function as a potential compensatory mechanism preventing an enlarged effect of SQ by dexchlorpheniramine to be observed in the behavioral data. Alternative to the hypothesis that compensation might take place during one particular process, Okamura et al. [2000] observed increased activity in the prefrontal cortex and anterior cingulate and argue that increased effort as a compensatory mechanism may account for this observation. As an alternative explanation to processes where compensation is suggested to take place in a linear stage model, the stages in the model may instead be cascaded [Miller et al., 1995]. In such a model, the onset of subsequent processing stages may start before full completion of a previous stage and thereby compensating for the delay, which may explain the discrepancy between BOLD and behavioral data.

The observed decrease in BOLD response after dexchlorpheniramine (and lorazepam) after degraded stimulus presentation in dorsal precuneus and left precentral gyrus may be explained as treatment effects on visual information processing, which in turn affects motor related processes upstream. If dexchlorpheniramine would affect activity in SRC related brain areas directly, drug induced significant changes in BOLD response after intact stimuli are also expected, but were not observed. Instead, the cumulative effects of these two manipulations on visual information processing in the primary visual cortex may have caused a large (additive) delay in response related activity. It may be speculated that as we used reaction time as end point of the epochs in which the BOLD response was to be captured, the delay in information processing may have caused the associated BOLD response not to be fully captured in stimulus degraded conditions, while information processing continued in the cascaded model resulting in a response. In support, a similar interaction was observed in our previous study [Van Ruitenbeek et al., 2009], which was measured over the Cz electrode located at the top of the scalp near the central sulcus, where such an interaction is also observed in this study. In these two respective studies, dexchlorpheniramine did not significantly change BOLD response and P300 ERP peak latency after the presentation of an intact stimulus, but BOLD decreased and ERP peak latency increased after a degraded stimulus. These findings suggest that the measured BOLD response and ERP peak reflect effects on the same processes. As the temporal resolution of ERP data is much higher than that of fMRI data, we may have captured all activity in the ERP data, but not the BOLD response as the hemodynamic response lags behind and explains the decrease in BOLD observed. ERP measurements, possibly in combination with fMRI, are therefore suggested to study effects of drugs treatments in a cascaded model of information processing. It is predicted that onsets of components indicating onsets of processes that occur just after the manipulated process are not delayed, but have a delayed peak latency.

Limitations

A potential confound of observed changes in BOLD response is that antihistamines may affect the BOLD response through effects on the vasculature. Histamine is known to function as vasodilator by interacting with the H_1-receptor and disrupting the H_1-receptor's activity may therefore be expected to cause relative vasoconstriction [e.g., (Glick et al., 1968; Mills et al., 2007)] and modulate the BOLD response differently in different task conditions throughout the cortex. However, we only observed a main effect of dexchlorpheniramine in the left posterior occipital cortex and task condition dependent decreases in dorsal precuneus and left precentral gyrus. Taken together, this argues strongly against an overall decrease in BOLD response induced by dexchlorpheniramine's effects on vasculature. Nevertheless, future studies should include additional measures of regional cerebral blood flow to address this issue directly [Iannetti and Wise, 2007].

One further potential limitation of this study is that data from three participants showed many signs of sudden (volume to volume) movements. All data were corrected for such movement by defining the activity during the corresponding volume as an event of no interest, which allowed us to still include the data not affected by movement in the analyses. In a repeated measures design, rigorous criteria should be used to exclude excessive movement, as this is known to reduce the reliability of individual subject data [Caceres et al., 2009]. In case of these three participants, the number of "movement errors" (i.e., volume to volume movement > 0.5 mm) ranged from 2 up to as many as 95 per run. Close inspection of the runs after excluding the volumes during which participants have moved showed no signs of any activity pattern being an outlier. As a control measure, BOLD response after left and right handed responses, and stimuli presented in the left and right visual field were contrasted and the expected activity in motor- and visual areas in right and left hemisphere was observed. This activity pattern indicated that the data were not largely confounded by movement artifacts.

CONCLUSIONS

In this study, we have shown that dexchlorpheniramine and lorazepam both modulated visual information processing in the primary visual cortex, supporting the hypothesis that histamine is involved in visual information processing, which is gaining increased support in the literature [Van Ruitenbeek and Mehta, 2013; Van Ruitenbeek et al., 2009, 2010b]. However, specificity of the H_1-inverse agonist effects could not be established, still leaving open the possibility that histamine is involved in multiple cognitive processes. We observed a SQ modulating effect on response related processes that, however, did not reflect the hypothesized

compensatory mechanism. The cascaded model of information processing is now put forward as a mechanism for compensation and the currently observed effect is hypothesized to be the downstream consequence of drug induced effects on at least primary visual information processing.

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