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Antihistamines considerably modulate the cognitive and psychomotor performance of human volunteers

Rawshon Zannat1, Mir Muhammad Nasir Uddin2, Md. Atiar Rahman1*, Jannatul Aklima3 and Md. Mamun Al Amin4

Abstract: This research investigated the modulating effects of antihistamines—Loratadine, Fexofenadine, Meclizine, and Chlorpheniramine on cognitive (executive function, memory, attention, emotion regulation), mood, psychomotor performance, and sedation in healthy human volunteers. Twenty healthy volunteers received Loratadine 10-mg, Fexofenadine 120-mg, Meclizine 50-mg, Chlorpheniramine Maleate 4-mg, and Placebo 250-mg starch tablet in a five-way crossover, double-blind study. Following each dose the participants were subjected to take a series of test of cognitive functions and psychomotor performances at defined interval. A certain amount of washout period was also maintained for each drug. The test battery included PennCNP—Full Battery Test, Psychology Experiment Building Language, Stanford Sleepiness Scale, and Brief Mood Introspection Scale. The test results These test results were analyzed by one-way and two-way ANOVAs. In general, antihistamines didn't show any statistically significant deviation from that of placebo. However, slight improvement was observed in word memory test (Both immediate

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PUBLIC INTEREST STATEMENT
This research investigated the modulating effects of antihistamines—Loratadine, Fexofenadine, Meclizine, and Chlorpheniramine on cognitive (executive function, memory, attention, emotion regulation), mood, psychomotor performance, and sedation in healthy human volunteers. Antihistamines are pharmaceutical drugs widely used in relieving allergic symptoms. When histamine is overdosed among people suffering from seasonal allergic reactions, sedation and neurocognitive impairment is observed. Sedative effects can also contribute to impairment of cognitive and psychomotor performance. Right choice of antihistamine will maximize the productivity; minimize the losses of working hours and daytime in school and workplaces that will eventually result to contribute the economic growth. Right options of antihistamines for the people needed sharp motor functioning to work in a factory with life threatening machineries could be chosen in a wide flexibility. Choosing a better antihistamine will as well help them to avoid the interference of precise psychomotor function due to the sedative effect of antihistamine.
and delayed) by Chlorpheniramine; although it increased the reaction time in visual object learning test. Fexofenadine also increased performance in delayed word memory test. Meclizine showed significant reduction (p < 0.05) of reaction time in line orientation task. The subjects receiving Loratadine reported slightly unpleasant mood then control group. This study will contribute to choose antihistamine rightly maximizing the productivity; minimizing the losses of working hours and daytime in school and workplaces. Right options of antihistamines will make wider flexibility for the people needed sharp motor functioning to work in factory with life-threatening machineries achieving less sedation and psychomotor unimpairment.

Subjects: Bioscience; Food Science & Technology; Health and Social Care

Keywords: antihistamine; cognitive performance; psychomotor performance; mood; sleep

1. Introduction

Antihistamines are drugs that antagonize the effects of histamines. They are widely used in relieving allergic symptoms. They have adverse effects in the central nervous system (Gengo, 1996). They are mostly used to provide symptomatic relief from allergic symptoms caused by histamine release (Dridi, Ben Attia, Reinberg, & Boughattas, 2005). Sedative effects exerted by antihistamine impair cognitive, psychomotor performance (Marshall & Colon, 1993), working memory (Van Ruitenbeek, Vermeeren, & Riedel, 2010), learning (Vuurman, van Veggel, Sanders, Muntjewerff, & O’Hanlon, 1996), emotion (Arnone, Horder, Cowen, & Harmer, 2009), executive function (Tamura et al., 2010), attention (Conen, Theunissen, Vermeeren, & Ramaekers, 2011), and psychological functioning (Gauci, King, Saxarra, Tulloch, & Husband, 1999), mainly through histamine H1 receptors (H1Rs) (Watanabe, Timmerman, & Yanai, 2001). Allergic rhinitis interferes with our quality of living, because of its discomforts. Antihistamines are widely used in treating various allergic diseases. They can cross the blood–brain barrier and block histaminergic receptors and other neurotransmitters (e.g. serotonin, choline, noradrenaline) in the brain, and as a consequence produce sleepiness, drowsiness, fatigue, and sedation (Passalacqua et al., 1996; Snyder & Snowman, 1987), which lead to cognitive and psychomotor impairment (Hindmarch, 1995; Kay, 2000). There are three generation of antihistamine, first-generation antihistamines penetrate readily into the brain by crossing blood–brain barrier, in which they occupy 50–90% of the H1Rs (Tagawa et al., 2001) and impairs cognitive and psychomotor performance and have a sedative effect also (Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004). Second-generation antihistamines also impair cognitive and psychomotor performance but have a low sedative effect (Bender, Berning, Dudden, Milgrom, & Tran, 2003; Kay & Harris, 1999) compared to first-generation. Third-generation antihistamines don’t impair cognitive and psychomotor performances (Hindmarch, Shamsi, & Kimber, 2002) and do not have any sedative effects (Hindmarch, 2002).

Many studies showed certain effects of some antihistamines on human cognitive and psychomotor performance (Jauregui et al., 2013; Kay & Harris, 1999). Few studies also suggested that some antihistamine does not influence certain cognitive and psychomotor performance (Gupta, Kapoor, Gillani, Kapoor, & Gupta, 2004; Hindmarch, Shamsi, Stanley, & Fairweather, 1999).

Computerized neuropsychological (CNP) tests have been used in behavioral research for last two decades (Schlegel & Gilliland, 2007). Though many different test batteries have been developed and new batteries are introduced every year for clinical screening, but standardized psychometric measures are not yet available (Zygouris & Tsolaki, 2015). Paper and pencil-based neuropsychological tests are not fit in present time. PennCNP (The University of Pennsylvania Computerized Neuropsychological Test Battery) is suitable for evaluation of human behavior and performance. However, neuropsychological evaluation can provide information concerning normal brain functioning and allows monitoring the cognitive status of an individual, especially throughout older age (Canini et al., 2014). Therefore, its results are extremely important to trace a variety of normal
functioning in the aging population. CNP also used for neurobehavioral evaluations of brain disorders. Application of neuropsychological batteries in psychiatric research has been initially slow, but more recently; it has become combined into efforts to understand the association of neural systems central nervous system (Censits, Danielragland, Gur, & Gur, 1997; Gur et al., 2001).

The main focus of this study is to explore the effect of antihistamines on common brain functions. Since these antihistamines may widely distribute in many brain areas and influence the activities associated with that particular area. Researches that have been conducted so far on this issue are very much tedious, imprecise, and insufficient as well. More specifically, no similar study has been conducted on Bangladeshi population till now. Therefore, specific and precise behavioral effects of antihistamines on human volunteers (Bangladeshi population) are still necessary to be investigated. We investigate the effects of antihistamines—Loratadine, Fexofenadine, Meclizine, and Chlorpheniramine on cognitive performance (emotion, attention, memory, executive function) and psychomotor performance on healthy human volunteers. This study also investigated activity of antihistamines on mood and alertness.

2. Methods

2.1. Participants

All of the participants (age: 18–24) which are situated in Chittagong district. Sample size of the study was total participants 100 (both male and female). These samples were selected by convenient sampling from the target population.

2.2. Procedure

This study was conducted on 100 participants. These participants were selected by convenient sampling method from targeted population (education level 14) that means undergraduate students which are situated in Chittagong district. Background of the volunteers was initially checked by university infirmary’s chief medical officer for their physical conditions and exposure to other drugs and stress. The participants were given consent of participant sheet to be approved. After approval, a questionnaire for measuring sleepiness was provided to the volunteers. The volunteers took antihistamines randomly after returning back the questionnaire. The participant took it at bedtime and attended the computerized test in next day morning at 8 in psychological Laboratory, University of Chittagong. Their blood pressure and pulse rate were measured by a physician when they entered the laboratory first. Then they started the computerized neuropsychological test batteries in PennCNP (The University of Pennsylvania Computerized Neuropsychological Test Battery). After completing the test battery, they attended PEBL test. When participants completed the task, their blood pressure and pulse rate were measured once again by a physician. Finally, they were given a questionnaire for measuring mood. A Personal Information Form was used to collect information like—sex, age, educational background, and handiness in CNP test batteries. The whole process illustrated in Figure 1.

After collecting data from 100 participants, data were analyzed by proper statistical method.

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**Figure 1.** Flow chart of the current experiments (on test day).

- Participants
  - Participants were asked to take a drug on the day before coming
  - Participants took a drug
  - Measured Sleepiness
  - Wait for 1/2 hours depending of drug
  - Participated in PennCNP test
  - Participated in PEBL test
  - Measured Mood

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2.3. Preparation of drugs and placebo
Inert placebo tablet (250-mg tablet made of starch) was used in this experiment. Chlorpheniramine maleate 4-mg Tablet (Histacin from Jayson pharma), Loratadine 10-mg Tablet (Oradin SK + F), Fexofenadine 120-mg Tablet (Fexo from Square Pharmaceuticals Ltd.), and Meclizine 50-mg Tablet (Vomec from Beximco Pharmaceuticals Ltd.) were given to the participants. Participants were not informed about the type of drug was given.

2.4. Measuring instruments
The University of Pennsylvania Computerized Neuropsychological test battery was used in the original study (PennCNP). The PennCNP comprises four computerized neuropsychological test batteries (executive function, memory, attention, and emotion regulation). In the study of the effect of anti-histamines on cognitive and psychomotor performance, it has been made of a series of subjective and objective tests and examinations are given below:

(1) PennCNP—Full Battery Test.
(2) PEBL (Psychology Experiment Building Language).
(3) Stanford Sleepiness Scale (SSS).
(4) Brief Mood Introspection Scale (BMIS).

2.4.1. Motor Praxis (MPraxis)
The Motor Praxis (Gur et al., 2001) was designed as a measure of sensory-motor function. During the MPraxis test, the participant needed to move the computer mouse cursor over an ever-shrinking green box and clicked on it once each time it appeared on a different location on the test page.

2.4.2. Penn Facial Memory Test (CPF)
The Penn Facial Memory Test (Gur et al., 2001) is designed as a measure of facial memory. It consisted of 20 target faces and 20 non-target faces. The task trial was followed by immediate and delayed recognition trials, during which subjects were presented with the target faces mixed with 20 new faces. New faces were presented at each delayed. The participant’s task was to decide whether they have seen the face before by selecting any one of a four-point scale: “definitely yes,” “probably yes,” “probably no,” and “definitely no,” The total number of true-positive responses and median reaction time for true-positive response were selected as cognitive performance measures.

2.4.3. Penn Word Memory Test (CPW)
The Penn Word Memory Test (Gur et al., 1993) was designed as a measure of word memory. It consisted of 20 target words and 20 non-target words. The task trial was followed by immediate and delayed recognition trials, during which subjects were presented with the target faces mixed with 20 new words. Procedure for administration and scoring of the task were identical to those for the facial recognition task.

2.4.4. Penn Continuous Performance Test—Number and Letter Version (PCPT-NL)
The Penn Continuous Performance Test—Number and Letter Version (Kurtz, Ragland, Bilker, Gur, & Gur, 2001) was designed as a measure of visual attention and vigilance in human. In this test, a series of red vertical and horizontal lines were flashed in a digital numeric frame-like as resembling a digital clock. The test was divided in two parts: one set of trials where the participant was looking for complete numbers and another was looking for complete letter followed by 3 min. Total number and letter of true-positive responses and median reaction time for true-positive response were selected as cognitive performance measures.
2.4.5. Penn’s Computerized Finger—Tapping Task (CTAP)

The Penn’s Computerized Finger—Tapping Task (Lezak, 2004) was designed as a measure of manual dexterity (Halstead, 1947; Reitan & Wolfson, 1993). In this task, participants used their dominant hand and non-dominant hand. The task consisted of 10 trials where five trials were dominant hand and another five trials were for the non-dominant hand. A total mean score of the dominant and non-dominant hand were selected as psychomotor performance.

2.4.6. Penn Conditional Exclusion Task (PCET)

The Penn Conditional Exclusion Task (Kurtz, Ragland, Moberg, & Gur, 2004; Kurtz, Wexler, & Bell, 2004) is a measure of abstraction in executive function. It is form of the “Odd Man Out” model (Flowers & Robertson, 1985) where participants decide what object out of four objects did not belong with the other three. This test has three criteria for choosing an object, namely line thickness, shape, and size, respectively. The participants conducted 48 trials to find out 10 consecutive answers in each criterion. Total number of correct responses, median reaction time for correct response and error rate were selected as cognitive performance measures.

2.4.7. Visual Object Learning Test (SVOLT)

The Visual Object Learning Test (Glahn, Gur, Ragland, Censits, & Gur, 1997) was designed as a spatial analogy of the California Verbal Learning Test is measure of visual object learning and memory. It consisted 20 three-dimensional Euclidean shapes that were learning stimuli for both immediate and delayed recalls (delayed recall = SVOLTD). The total response, number, and median reaction time of true-positive responses were selected as cognitive performance measures for short- and long-term memory.

2.4.8. Penn’s Logical Reasoning Test (SPVRT)

The Penn Logical Reasoning Test (Gur, Gur, Obrist, Skolnick, & Reivich, 1987) is the short version of the Penn Verbal Reasoning Test (PVRT) is a measure of verbal intellectual ability in human volunteer. The short PVRT has been developed at the University of Pennsylvania Neuropsychiatry Department. It was a multiple choice task in which the individual participant must answer eight questions which age-appropriate verbal analogy problem (R. C. Gur, J. D. Ragland, P. J. Moberg, T. H. Turner, et al., 2001).

2.4.9. Penn Emotion Recognition Task (ER40)

The Penn Emotion Recognition Task (Gur et al., 2002; Kohler, Turner, Gur, & Gur, 2004; Kohler et al. 2004) is a measure of emotion recognition. Participants were shown a series of 40 faces and it was a multiple choice task. It was taken from the University of Pennsylvania Emotion Recognition Task, 96 faces version, balanced for equality and intensity of emotion, age, gender, and ethnicity (Kohler et al. 2004).

2.4.10. Letter-N-back (LNB2)

The Letter-N-Back has been designed the Neuropsychiatry Department at the University of Pennsylvania (Ragland et al., 2002). It is measure of attention and working memory. In this task, participants were asked to give attention to flashing letters on the computer screen, one at a time, and to press the spacebar according to three different principles or rules: the 0-back, the 1-back, and the 2-back. Total number of correct responses, median reaction time for correct response, and reaction time of 0-Back, 1-Back, and 2-Back were selected as cognitive performance measures.

2.4.11. Penn Abstraction Inhibition and Working Memory Task (AIM)

The Penn Abstraction Inhibition and Working Memory Task is a measure of abstraction and concept formation, with and without working memory (Glahn, Cannon, Gur, Ragland, & Gur, 2000; Gur et al., 2001). It is divided into two separate question types, which the participant practices before starting the task. During the first question type, the participant sees two pairs of stimuli on the top of the page (adjusted to the left and to the right) and one single stimulus on the mid-bottom of the page. His/her task is to decide with which pair the stimulus on the bottom best belongs. The participant then clicks with the mouse on the pair he/she thinks fits the bottom stimulus the best and receives
immediate feedback for his/her answer. Total number and median reaction time of true-positive responses of without working memory and with working memory were selected as cognitive performance measures.

2.4.12. Judgment of Line Orientation (CJOLO)
The Judgment of Line Orientation (Benton, Hannay, & Varney, 1975) is measure of Spatial orientation abilities based on the original paper-based task. Participants are shown a pair of lines on top of the screen and asked to click with the mouse on the letter label of the matching lines arranged in a coordinate array on the mid-bottom of the screen. Total number of correct responses and median reaction time for correct response were selected as cognitive performance measures.

2.4.13. Penn Emotion Discrimination Task (EDF40)
The Penn Emotion Discrimination Task (Erwin et al., 1992) is measure of emotion discrimination. Participants were shown 40 pairs of faces, one pair at a time. Each pair of faces consists of two pictures of the same person with or without a subtle, computer-generated difference in emotion expression, which might or may not represent a difference in the intensity of the emotion between the two faces. For each pair, the participant had to decide which face expressed the given emotion more intensely or whether they are equally emotional. Total number of correct responses, median reaction time of emotion discrimination and total number of correct response and median reaction time of happy and sad were selected as cognitive performance measures.

2.4.14. Change Detection Task
Psychology Experiment Building Language (PEBL) is a system designed for creating psychology and neuroscience experiments and tests. The change detection task measure the attention perception, motor, and executive function of brain. It is developed by Mueller, S.T. in 2011. In this test, participants have to press the space button as quickly as possible every time when she/he identify the changing object then click this object on the mouse. This test has given feedback “Correct” or “Incorrect” when click this object. After taking feedback, press the space button to start the next trial. The changing pattern has four ways that is changes in presence, location, size, and color of random circles among background field of circles was presented on the monitor in 20 trials.

2.4.15. Stanford Sleepiness Scale (SSS)
The Stanford Sleepiness Scale (SSS) is developed by Dement (1972), a great way to quickly assess how alert or sleepy of a person’s feeling and discover the patterns of alertness by recording your “degree of sleepiness” at different times throughout the day. Using the seven-point scale below pick what best represents how participant are feeling and note the corresponding number on the chart. The scoring test–retest reliability was 0.88 and validity of mean SSS using the Wilkinson addition and vigilance tests was reported at correlation of 0.68.

2.4.16. Brief Mood Introspection Scale (BMIS)
The original version of the Brief Mood Introspection Scale (BMIS) was developed by (Mayer & Gaschke, 1988). This version was used to measure mood of the respondents in the present study. The BMIS scale is a freeware mood scale consisting of 16 mood-adjectives to which a person responds. The scale can yield measures of overall pleasant–unpleasant mood, arousal–calm mood, and it also can be scored according to positive-tired and negative-calm mood.

2.5. Data analysis
IBM SPSS Statistics 19 program, GraphPad Prism 6 and Microsoft Excel program (2013 version) was be used for analyzing the data. Collected data were presented in tables, graphs, and charts. Simple statistical tools, such as one-way ANOVA (and non-parametric) two-way ANOVA, Newman–Keuls comparison, and Tukey’s multiple comparisons were used to interpret findings of the study. Emphasis was also being given on qualitative with quantitative data.
3. Results

3.1. Effect on cognitive performance

Table 1 summarizes the effect of the antihistamines on the cognitive performances of the volunteers (Target identification and target location).

3.2. Immediate and delayed recall word memory test

In immediate word memory test, a one-way ANOVA was conducted to compare the effect of antihistamines between subjects and placebo on immediate recall word memory test. There was no significant effect of immediate recall word memory test on antihistamines at the $p < 0.05$ level for five conditions [$F(4, 88) = 0.44, p = 0.78$]. There was a significant effect of reaction time in immediate recall word memory test on antihistamines at the $p < 0.05$ level for the five conditions [$F(4, 88) = 2.39, p = 0.06$]. Neuman–Keuls multiple comparisons test showed that placebo group ($M = 1,319, SD = 264.9$) spent significantly ($p < 0.05$) higher time than the Chlorpheniramine Maleate group ($M = 1,043; SD = 246.7$) (Figure 2). In delayed word memory test, there was no significant effect of antihistamines on correct response in delayed recall word memory test at the $p < 0.05$ level for five conditions [$F(4, 82) = 0.26, p = 0.90$]. There was a significant effect of antihistamines on reaction time
Table 1. Effect of the antihistamines on the cognitive performances of the volunteers

|                      | Placebo | Chlorpheniramine | Loratadine | Fexofenadine | Meclizine |
|----------------------|---------|------------------|------------|--------------|-----------|
| **Word-Memory test** |         |                  |            |              |           |
| Immediate recall     | 18.80 ± 2.48 | 19.13 ± 1.54    | 18.44 ± 2.66 | 19.20 ± 1.32 | 18.79 ± 1.32 |
| Immediate (RT)       | 1,319 ± 264.9 | 1,043 ± 246.7*  | 1,144 ± 352.3 | 1,193 ± 253.7 | 1,166 ± 242.4 |
| Delayed recall       | 18.35 ± 2.52 | 18.42 ± 2.19    | 18.26 ± 2.42 | 18.75 ± 1.94 | 18.50 ± 1.62 |
| Delayed (RT)         | 1,213 ± 178.5 | 970.3 ± 239.3*  | 1,075 ± 257.5 | 983.2 ± 291.9* | 1,081 ± 251.5 |
| **Facial memory test** |         |                  |            |              |           |
| Immediate recall     | 17.75 ± 3.77 | 17.84 ± 3.304    | 17.68 ± 2.81 | 18.40 ± 2.30 | 18.79 ± 1.65 |
| Immediate (RT)       | 1,116 ± 212.3 | 990.7 ± 254.8    | 1,115 ± 307 | 1,042 ± 249.8 | 1,016 ± 245.8 |
| Delayed recall       | 18.37 ± 1.98 | 18.39 ± 2.40    | 18.56 ± 2.18 | 18.89 ± 1.52 | 18.67 ± 1.72 |
| Delayed (RT)         | 1,109 ± 264.6 | 1,025 ± 261.9    | 1,043 ± 271.5 | 1,047 ± 297.3 | 1,028 ± 272.5 |
| **Emotion test**     |         |                  |            |              |           |
| Emotion recognition (NF) | 32.80 ± 4.65 | 32.89 ± 5.61   | 33.74 ± 2.60 | 33.35 ± 2.58 | 32.95 ± 6.78 |
| Emotion recognition (RT) | 1,697 ± 202.6 | 1,527 ± 249.9 | 1,609 ± 205.4 | 1,588 ± 224.9 | 1,488 ± 387.6 |
| Emotion discrimination (CR) | 15.89 ± 5.52 | 14.22 ± 5.01 | 16.11 ± 5.88 | 16.32 ± 6.07 | 14.95 ± 6.19 |
| Emotion discrimination (RT) | 2,289 ± 909.8 | 1,749 ± 765.4 | 217 ± 57.2 | 1,859 ± 638.7 | 1,867 ± 791.2 |
| CR of happy          | 6.85 ± 3.23 | 5.78 ± 3.03    | 7.36 ± 3.91 | 6.90 ± 4.08 | 5.94 ± 3.61 |
| RT of happy          | 2,136 ± 969.3 | 1,702 ± 836.4 | 2,191 ± 986.9 | 1,767 ± 686 | 1,895 ± 939.5 |
| CR of sad            | 9.80 ± 3.16 | 9.31 ± 3.69   | 9.36 ± 3.27 | 10.05 ± 3.65 | 9.00 ± 2.91 |
| RT of sad            | 2,274 ± 899.2 | 1,909 ± 932 | 2,156 ± 988.6 | 1,952 ± 729.2 | 1,909 ± 804.4 |
| **Change detection test** |         |                  |            |              |           |
| Reaction time        | 14,992 ± 4,954 | 13,814 ± 5,326 | 12,425 ± 6,520 | 13,025 ± 5,044 | 14,245 ± 4,125 |
| Number of times showed | 30.35 ± 17.66 | 25.55 ± 16.65 | 25.53 ± 16.59 | 26.60 ± 13.62 | 23.95 ± 7.86 |
| **Abstract inhibition** |         |                  |            |              |           |
| AI without WM (CR)   | 25.3 ± 3.01 | 25.47 ± 2.93    | 25.58 ± 3.09 | 25.90 ± 2.71 | 25.00 ± 3.49 |
| AI without WM RT     | 1,947 ± 437.3 | 1,599 ± 361.3 | 1,887 ± 602.2 | 1,806 ± 460.8 | 1,773 ± 398.8 |
| AI with WM (CR)      | 23.95 ± 3.14 | 23.00 ± 3.58    | 24.05 ± 3.34 | 23.70 ± 3.51 | 23.63 ± 3.09 |
| AI with WM RT        | 1,370 ± 324.6 | 1,157 ± 326.6 | 1,316 ± 389.1 | 1,274 ± 352.7 | 1,219 ± 354.1 |
| **Letter-N-Back**    |         |                  |            |              |           |
| Response             | 26.60 ± 4.11 | 26.74 ± 4.01    | 26.58 ± 2.65 | 27.20 ± 2.09 | 27.32 ± 2.47 |
| Reaction time        | 485.3 ± 68.90 | 503.1 ± 64.71 | 496.8 ± 99.42 | 479.3 ± 69.24 | 515.6 ± 95.70 |
| 0-Back               | 457.2 ± 34.12 | 456.4 ± 44.43 | 459.6 ± 50.19 | 464.4 ± 52.57 | 454.3 ± 45.93 |
| 1-Back               | 459.9 ± 55.61 | 486.3 ± 64.80 | 466.4 ± 68.41 | 470.4 ± 69.80 | 462.3 ± 67.17 |
| 2-Back               | 467.9 ± 50.66 | 504.6 ± 85.51 | 517.6 ± 130.3 | 488.2 ± 79.05 | 534.1 ± 105 |

(Continued)
in delayed recall word memory test at the $p < 0.05$ level for the five conditions ($F(4, 82) = 2.91, p = 0.03$). Neuman–Keuls multiple comparisons test showed that placebo group ($M = 1,213, SD = 178.5$) spent significantly ($p < 0.05$) higher time than the Chlorpheniramine Maleate ($M = 970.3, SD = 239.3$) and Loratadine ($M = 983.2, SD = 291.9$) group (Figure 3).

### 3.3. Judgment of line orientation task

A one-way ANOVA between subjects was conducted to compare the effect of antihistamines and placebo. There was no significant effect of correct response in line orientation task of spatial
There was no significant difference between placebo and antihistamines on the context of reaction time in line orientation task at the $p < 0.05$ level for the five conditions [$F(4, 58) = 2.848, p = 0.0318$]. Neuman–Keuls multiple comparisons test showed that placebo group ($M = 7,325, SD = 2,970$) spent significantly ($p < 0.05$) higher time than the Meclizine group ($M = 4,701, SD = 2,361$) (Figure 4).

3.4. Visual object learning test
A one-way ANOVA between subjects was conducted to compare the effect of antihistamines and placebo. There was no significant effect of total correct response time in visual object learning test of visual object learning and memory on antihistamines at the $p < 0.05$ level for the five conditions [$F(4, 72) = 2.904, p = 0.0275$]. Neuman–Keuls multiple comparisons test showed that placebo group ($M = 1,167, SD = 124.8$) spent significantly ($p < 0.05$) lower time than the Chlorpheniramine Maleate group ($M = 1,422, SD = 479.9$) (Figure 5).

3.5. Effect on psychomotor performance
A one-way ANOVA between subjects was conducted to compare the effect of antihistamines on psychomotor performance in placebo. In this study, various psychomotor performances were assessed. The result of the cognitive performance is summarized in Table 2. There was no significant effect of psychomotor performance on antihistamine, i.e. Chlorpheniramine, Loratadine, Fexofenadine, and Meclizine.
3.6. Effect on sleep
A two-way between subjects ANOVA was conducted to compare the effect of antihistamines and placebo on mood test. Five conditions were assessed to show that there was no significant sedative effect of antihistamines. It can be concluded that null hypothesis, i.e. there is no significant effect of sedation on antihistamine is accepted (Figure 6).

3.7. Effect on mood
A two-way between subjects ANOVA was conducted to compare the effect of antihistamines and placebo on mood test. Five conditions were assessed to show the effect of pleasant–unpleasant mood on antihistamine. The result reveals that one condition where \( p < 0.05 \) viz Loratadine is significant but the other four are not found to be significant. It can be concluded that null hypothesis, i.e. there is no significant effect of pleasant and unpleasant mood on antihistamine is partially accepted. Tukey’s multiple comparisons test showed that the placebo group was in a better mood than Loratadine group on the aspect of pleasant–unpleasant mood (Figure 7).

4. Discussion
Many studies showed effects of antihistamine on human cognitive and psychomotor performance (Hindmarch et al., 1999; Jauregui et al., 2013; Kay & Harris, 1999) these results are different according to the generation of drugs. On the other hand, some other studies suggested that some antihistamine does not influence certain cognitive and psychomotor performance (Gupta et al., 2004; Hindmarch et al., 1999). Our present study was conducted to test the effect of antihistamine on the cognitive and psychomotor performance in a series of cognitive tasks using PennCNP—Full Battery Test and PEBL. The aim of the study was to investigate the effects of antihistamines Loratadine, Fexofenadine, Meclizine, and Chlorpheniramine on cognitive performance (emotion, attention, memory, and executive function), mood, psychomotor performance, and sedation in healthy volunteers.
Chlorpheniramine is a first-generation antihistamine meant to be used for the temporary relief of allergic symptoms. Chlorpheniramine 4 mg showed no effect on memory performance (Millet, Dreisbach, & Bryson, 1982). Chlorpheniramine Maleate performance was better to response than the placebo in word memory test. In our current study, no significant effect of the Chlorpheniramine on the cognitive performances of the volunteers was found. Only word memory and visual object learning task have a significant effect of cognitive performance. The word memory task has a positive effect and visual object learning has negative effect. Chlorpheniramine exposed volunteers took more time to perform the visual object learning task than placebo group. As a result in Chlorpheniramine impaired effect on the visual object learning (Simons, 1996) memory was found. The finding of the study showed that there was no significant effect of Chlorpheniramine in psychomotor performance. Chlorpheniramine did increase independently and individually measured signs of sedation than other antihistamines (e.g. Fexofenadine, Meclizine). The finding of this study showed there was no significant effect of Chlorphenamine on subjective mood and sleeping rate.

Loratadine is a second-generation antihistamine used to temporarily relieve the allergic symptoms of hay fever (allergy to pollen, dust, or other substances in the air) and other allergies. Loratadine 10 mg showed no effect on cognitive (Kay & Harris, 1999) and psychomotor performance (DuBuske, 2007; Hindmarch et al., 1999; Kay & Harris, 1999). Different study found that Loratadine did not impair the performance of the memory-related task (Bender, McCormick, & Milgrom, 2001; Bradley & Nicholson, 1987), attention (Valk, Simons, Struyvenberg, Kruit, & van Berge Henegouwen, 1997), executive function (Philpot, 2000), and emotion same result was also found in our study. Ratings of sleepiness on the Stanford sleepiness scale were higher following the initial administration of Loratadine than rating for Chlorpheniramine and placebo. The sleepiness ratings increased in Loratadine group but not significant enough with compared to placebo. Loratidine 10-mg dose reported more sedation and unpleasant mood \( (p < 0.05) \) than the placebo group. Finally, Loratadine did not impair cognitive, psychomotor performance, and sleepiness but affected the mood.

Fexofenadine is a third-generation antihistamine used to relieve the allergic symptoms of seasonal allergic rhinitis. Fexofenadine 120 mg caused no significant effect in psychomotor performance including sensory motor ability, finger-tapping and cognitive function, including memory tasks such as word memory, facial memory, visual object learning memory, Letter-N-back for attention and working memory. Fexofenadine performance was better in response than placebo in the word memory test. The finding of the study indicated that Fexofenadine not impaired the memory, attention, executive function, emotion, and motor ability. Rating of sleepiness on the Stanford sleepiness scale were lower score of Fexofenadine than rating for Chlorpheniramine, Loratadine, Meclizine, and placebo. The sleepiness rating was decreased in Fexofenadine group but not significant enough with compared to placebo. With compared to five groups the lowest sleepiness rating was found in Fexofenadine and sleepiness also decreases per hour gradually. The mood score exhibited that the subject who received 120-mg dose of Fexofenadine, had no sedation and no mood effect than placebo group. Finally, Fexofenadine did not impair the cognitive, psychomotor performance, sleepiness and mood but influenced reaction time to perform the word memory task.

Meclizine is a first-generation antihistamine that antagonizes the effects of natural chemical histamine in the body. The result of the Meclizine 50 mg revealed no significant impairment on the psychomotor performance. The finding also indicated no significant impairment on the cognitive performance in word memory task, facial memory task, visual object learning memory, emotion recognition, logical reasoning, letter-N-back, abstraction inhibition task, change detection task, emotion discrimination, and list learning task but only line orientation task influenced by meclizine. Rating of sleepiness on the Stanford sleepiness scale was lower than rating for Chlorpheniramine, Loratadine, and placebo. The sleepiness rating was decrease in Meclizine group but not have significant difference between Meclizine and placebo. The comparison of five groups indicated that the second lowest sleepiness rating was Meclizine and per hour gradually decrease the sleepiness. The
mood score showed that the subject who received 50-mg dose of Meclizine reported no sedation and mood effect than placebo group. Finally, Meclizine did not impair cognitive, psychomotor performance and sleepiness and mood but influenced reaction time to performing the line orientation task.

5. Conclusion
The antihistamines didn't produce any disruptive effects on aspect of psychomotor and cognitive function. The study showed slight increase in cognitive function in case of FX and MC. CM exhibited better performance output then other antihistamines in most of the tests. None of the antihistamines varied significantly (p < 0.05) from placebo in increasing cognitive and psychomotor functions.
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