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ORIGINAL INVESTIGATION

Medications influencing central cholinergic pathways affect fixation stability, saccadic response time and associated eye movement dynamics during a temporally-cued visual reaction time task

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Abstract
Rationale Anticholinergic medications largely exert their effects due to actions on the muscarinic receptor, which mediates the functions of acetylcholine in the peripheral and central nervous systems. In the central nervous system, acetylcholine plays an important role in the modulation of movement.
Objective This study investigated the effects of over-the-counter medications with varying degrees of central anticholinergic properties on fixation stability, saccadic response time and the dynamics associated with this eye movement during a temporally-cued visual reaction time task, in order to establish the significance of central cholinergic pathways in influencing eye movements during reaction time tasks.
Methods Twenty-two participants were recruited into the placebo-controlled, human double-blind, four-way crossover investigation. Eye tracking technology recorded eye movements while participants reacted to visual stimuli following temporally informative and uninformative cues. The task was performed pre-ingestion as well as 0.5 and 2 h post-ingestion of promethazine hydrochloride (strong centrally acting anticholinergic), hyoscine hydrobromide (moderate centrally acting anticholinergic), hyoscine butylbromide (anticholinergic devoid of central properties) and a placebo.
Results Promethazine decreased fixation stability during the reaction time task. In addition, promethazine was the only drug to increase saccadic response time during temporally informative and uninformative cued trials, whereby effects on response time were more pronounced following temporally informative cues. Promethazine also decreased saccadic amplitude and increased saccadic duration during the temporally-cued reaction time task.
Conclusion Collectively, the results of the study highlight the significant role that central cholinergic pathways play in the control of eye movements during tasks that involve stimulus identification and motor responses following temporal cues.

Keywords Saccadic response time · Temporally informative cue · Temporally uninformative cue · Anticholinergic · Eye movement dynamics · Fixation stability

Introduction

It is estimated that up to 40% of the general population ingests a medication with anticholinergic properties on a daily basis (Wang 2013). Even though anticholinergic medications can possess potent adverse effects, they are not a class of drug that is restricted to prescription use only. Instead, many countries permit oral medications with anticholinergic properties to be accessed over-the-counter (OTC) by the general public. Anticholinergic medications largely exert their effects due to actions on the muscarinic (M) receptor. M receptors carry out the functions of acetylcholine in the peripheral nervous system (PNS) and central nervous system (CNS) (Birdsall and Hulme 1983). In particular, in the CNS, acetylcholine plays an important role as a

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neuromodulator of movement (Aosaki et al. 2010; Klawans and Rubovits 1974; Picciotto et al. 2012). Given that medications that act on the M receptor can interfere with cholinergic neurotransmission, thereby affecting voluntary and involuntary movement (Naicker et al. 2016), it is of interest to establish the significance of central cholinergic pathways in motor control.

Reaction time (RT) tests are useful measures of fine motor control that assess the speed of central processing involved in generating muscle activity (Blokland et al. 2001; Tandonnet et al. 2003). With regard to the oculomotor system, the speed of eye movement responses can be assessed in terms of RT. Centrally acting medications including benzodiazepines, anticonvulsants and potent anticholinergics have been found to increase the RT of saccades (Oliva et al. 1993; Reilly et al. 2008). As such, visual RT assessments involving stimuli detection and motor response can provide for a sensitive means of detecting the subtle effects of medications on central motor pathways. RT is composed of central (pre-motor RT) and peripheral (motor RT) components, where impairments to CNS processes prolong RT potentially due to increases in pre-motor RT (Zwierko 2008; Zwierko et al. 2010). Conversely, CNS functions such as alertness improve RT, whereby exciting the alerting system enables a faster and more efficient response to sensory stimuli (Bueno and Ribeiro-do-Valle 2012; Matthias et al. 2010; Maunsell 2015).

Alertness refers to a state of readiness to receive and respond to information that influences arousal (Geva et al. 2013; Matthias et al. 2010; Thiel and Fink 2007). In an experimental setting, the effects of alertness on RT can be gauged by comparing responses to target detection following a warning (temporally informative cue) versus target detection without a warning (temporally uninformative cue) (Amado et al. 2011; Martella et al. 2011; Thiel and Fink 2007). Temporally informative cues increase readiness, thereby decreasing pre-motor RT and enabling a quicker execution of motor response (Tandonnet et al. 2003; Thiel and Fink 2007; Weinbach and Henik 2012) and, as such, would be more sensitive to central pharmacological effects compared to temporally uninformative cued RT trials.

This study will investigate the effects of OTC anticholinergic medications on fixation stability, saccadic response time and the dynamics associated with eye movement during a temporally-cued visual RT task. Participants reacted to visual stimuli following temporally informative and uninformative cues while an eye tracker collected eye movement data. Participants performed the RT task pre-ingestion as well as 0.5 and 2 h post-ingestion of medications that possessed varying degrees of central anticholinergic properties. Promethazine hydrochloride, hyoscine hydrobromide and hyoscine butylbromide were the medications tested. Although promethazine is a first-generation antihistamine, it is well recognised for its strong central anticholinergic properties due to the ease in which it penetrates the blood-brain barrier (BBB) and interacts with central M receptors (Liu and Farley 2004). Hyoscine hydrobromide also possesses central anticholinergic properties as it is a tertiary anticholinergic; however, its central properties are not considered to be as potent as promethazine (Corallo et al. 2009; Renner et al. 2005). Hyoscine butylbromide is an anticholinergic that is considered to be devoid of central properties as it is a quaternary ammonium compound (Tytgat 2007). It was hypothesised that promethazine, and to a lesser extent hyoscine hydrobromide, would decrease fixation stability, increase saccadic response time and influence the dynamics associated with this eye movement due to central anticholinergic properties. On the contrary, it was predicted that hyoscine butylbromide would not significantly influence saccadic response time or any other performance measure during the task, thereby attesting to the significance of central cholinergic pathways in influencing eye movements during a temporally-cued visual RT task.

Methods

Participants

Twenty-two healthy participants (mean age 24 ± 6 years, ten females) volunteered for this study. Medical history questionnaires were completed prior to enlistment to ensure that participants were free from CNS disorders and not taking medications that would affect outcome measures in this study. Since the tasks in this study were dependent on the integrity of the visual system, clinical assessments of vision were performed prior to each testing session. In particular, the visual contrast sensitivity grating test, Snellen chart and the confrontation visual field exam were used to examine visual contrast sensitivity, visual acuity and peripheral vision, respectively. Participants with prescription glasses or hard contact lenses were excluded as these aids compromise the reliability of eye tracker measurements. Participants were instructed to avoid alcohol and coffee and to not participate in moderate- to high-intensity physical activity for at least 5 h prior to testing. The Institutional Human Research Ethics Committee approved all experimental protocols, and written participant consent was obtained prior to commencement of testing sessions.

Experiment design and drug intervention

A human, placebo-controlled, double-blind, four-way crossover study was conducted. Participants attended one testing session per week (at least 7 days apart) for 4 weeks. Each testing session was approximately 4 h in duration. During each session, participants reacted to visual stimuli following temporally informative and uninformative cues while an eye tracker measured eye motion. Data were collected pre- and post-ingestion of therapeutic doses of the drug interventions. The drugs tested were 25 mg promethazine hydrochloride,

300 mg hyoscine hydrobromide, 20 mg hyoscine butylbromide and a placebo. The order of drug ingestion was randomly determined, and the task was performed pre-ingestion and 0.5 and 2 h post-ingestion, in accordance with peak drug plasma concentration times. The drugs were commercially compounded into standard opaque capsules using Avicel® as the filler. Placebo capsules contained only the Avicel® filler.

Visual RT task

Participants performed a temporally-cued visual RT task (Fig. 1), which was based on procedures embedded in the Attention Network Test (see Naicker et al. 2016). At the start of each trial, the participant's gaze was fixed on a cross presented in the centre of a PC (55-cm ASUS LED monitor) placed 65 cm in front of the participant. Participants were then presented with a visual warning (temporally informative cue) or no warning (temporally uninformative cue), prior to the appearance of target stimuli. Warning cues induced a state of alertness before the participant reacted to stimuli. Temporally informative cues (center cue or double cue) alerted the participant that target appearance would be imminent but provided no information as to where the target would appear. To the contrary, temporally uninformative cues (no cue) provided no information about the target. The order of appearance for all forms of temporally-cued trials was counterbalanced. Each participant performed a total of 108 trials, which consisted of 36 double cue, 36 center cue and 36 temporally uninformative (no cue) trials.

During the performance of the RT task, fixation stability, saccadic response time and the dynamics associated with this eye movement were analysed. Missed trials during the performance of no cue, center cue and double cue RT trials were also determined by subtracting the number of correctly reacted to trials from the total number of trials. Vertical coordinates of eye data and respective time points were used to calculate the coefficient of variation, saccadic response time, amplitude, duration and velocity (Fig. 2). The coefficient of variation of eye movement was defined as the ability to maintain a steady visual gaze while the eyes remained on the fixation cross and thus provided a measure of fixation stability during the performance of the visual RT task. Saccadic response time was defined as the time that it took the eye to start moving in response to the visual target appearing on the monitor. Saccadic amplitude described the size of the eye movement made to the visual target from the fixation cross. Saccadic duration was defined as the length of time that it took the eye to move from the fixation cross to the visual target, and saccadic velocity described the rate of change of eye movement from the fixation cross to the visual target.

Eye movement recording

The GP3 eye tracker (Gazepoint®, sampling rate 60 Hz) was used to record eye movement characteristics during the performance of the temporally-cued visual RT task. The eye tracker was used in a room where lighting and temperature conditions were controlled. It was placed at a 65-cm distance away from the participant, in front of a 55-cm ASUS LED monitor (screen resolution; 1920 × 1020). The eye tracker

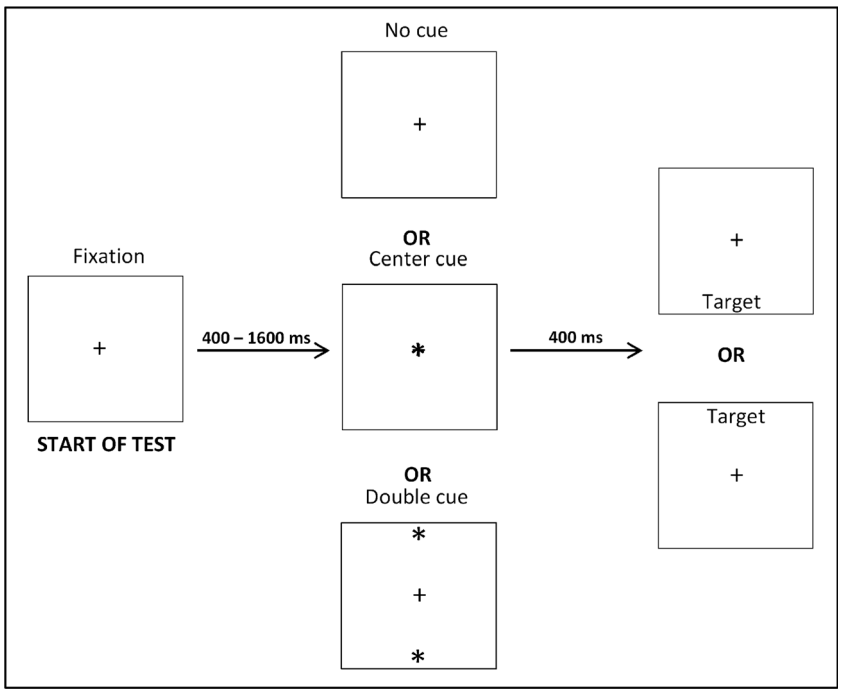

Fig. 1 Eye movement data were collected while participants performed a visual RT task which involved reacting to target stimuli following temporally informative (center cue and double cue) and uninformative (no cue) trials. The visual RT test commenced with the participant's visual gaze on a fixation cross for a random duration between 400 and 1600 ms. After this, temporal cues (no cue, centre cue or double cue) appeared for a period of 100 ms. A visual target then appeared 400 ms after temporal cues, at a visual angle of 10° above or below the fixation cross

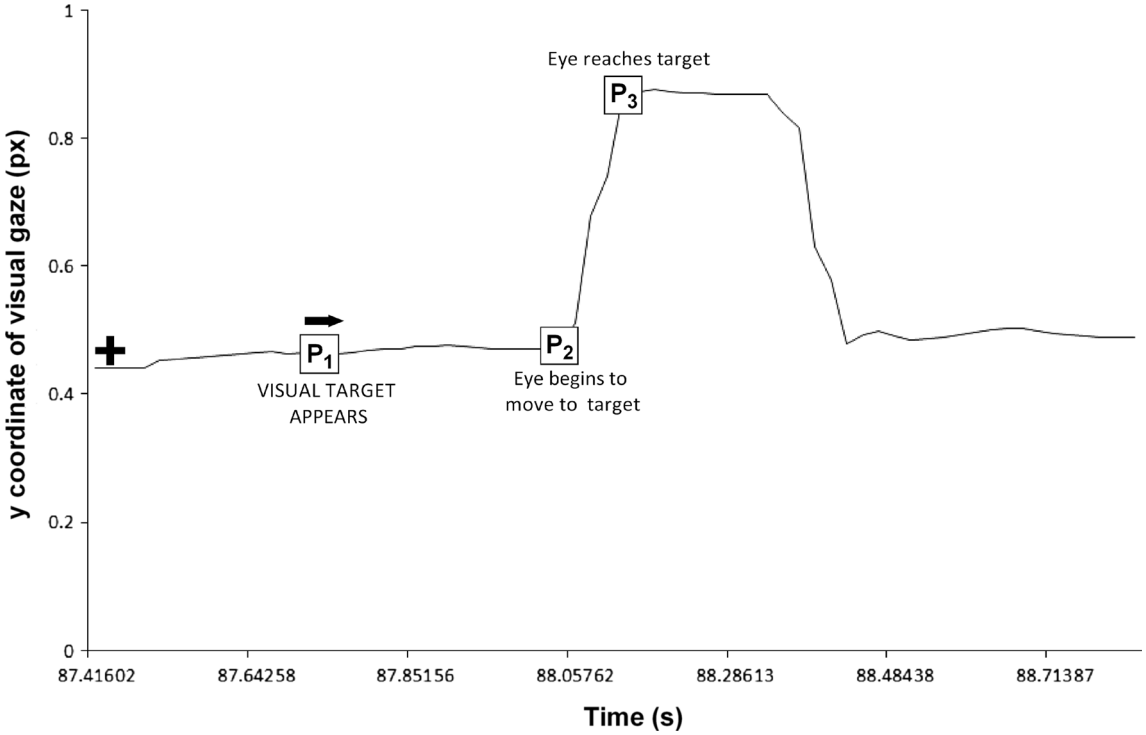

Fig. 2 Graphical representation of vertical coordinates of raw eye data during the performance of a visual RT trial. The illustration depicts visual gaze while it remained on the fixation cross as well as movements of the eye that occurred following appearance of the visual target. Vertical coordinates of raw eye data corresponding to time points 0.25 s before the visual target appeared (P1) were used to calculate the coefficient of variation of eye movement while visual gaze remained on the fixation cross. Time points corresponding to P1 and P2 were used to calculate saccadic response time. Vertical coordinates of raw eye data and respective time points corresponding to P2 and P3 were used to determine saccadic amplitude, duration and velocity

allows for a 21° × 10° movement area, with a ±13° depth of visual angle. Participants positioned their head on a chin rest during the performance of the RT task, to ensure that head movement was restricted and that the visual angle was the same between sessions and participants. The eye tracker measured where the participant was looking (visual gaze) using the corneal-reflection, pupil-centre system. This technique determines eye characteristics through reflection of infrared light on the retina and cornea.

Statistics

Outcome measures were presented as change scores to reflect how each subject's physiological response changed following the ingestion of each drug. Change scores were calculated by subtracting each subject's pre-ingestion data from corresponding 0.5 and 2 h post-ingestion data. A one-way ANOVA was applied to placebo data to establish whether eye movement variables inherently varied between testing sessions (from pre-ingestion to 0.5 and 2 h post-ingestion).

A two-way repeated measures ANOVA was applied to the coefficient of variation of eye movement change scores to examine the interaction between drug (promethazine, hyoscine hydrobromide, hyoscine butylbromide and placebo) and time post-ingestion (0.5 and 2 h). A repeated measures three-way ANOVA was applied to change scores corresponding to missed RT trials, saccadic response time and associated eye movement variables to examine the interaction between drug, time post-ingestion and temporal cues (no cue, center cue and double cue). In circumstances where a main effect was established, multiple comparison tests using the Bonferroni method were performed. Results were only reported as significant when the drug intervention was different compared to placebo. This was to minimise pairwise comparisons as not every pairwise comparison had physiological relevance (e.g. responses to hyoscine hydrobromide 2 h post-ingestion compared to responses of promethazine 0.5 h post-ingestion). IBM® SPSS® Statistics (version 22, IBM Corp, Armonk, NY) was used to conduct statistical analyses, where alpha levels were set at 0.05.

Results

The coefficient of variation of eye movement, saccadic response time, saccadic amplitude, saccadic duration and saccadic velocity were unaffected during the placebo trials from pre-ingestion to 0.5 and 2 h post-ingestion. In addition to these measures, the number of missed trials during the placebo trials was also unaffected from pre-ingestion to 0.5 and

2 h post-ingestion. As such, all measures of eye movement assessed in this study remained consistent in the absence of the drug interventions.

Number of missed RT trials

The drug interventions did not influence the number of missed trials during no cue, center cue or double cue RT trials (Fig. 3).

Coefficient of variation of eye movement

A significant main effect of drug was identified for the coefficient of variation of eye movement change scores ($F(3, 168) = 3.827$, $p = 0.011$). Post hoc analysis showed that promethazine (0.017 ± 0.036) caused significantly greater influences to the coefficient of variation of eye movement compared to hyoscine hydrobromide (0.005 ± 0.027), hyoscine butylbromide (0.006 ± 0.013) and placebo (−0.001 ± 0.016). The Bonferroni multiple comparison test revealed that during the performance of the visual RT task, promethazine significantly increased the coefficient of variation of eye movement, 2 h post-ingestion compared to placebo ($F(3, 84) = 3.547$, $p = 0.020$, Fig. 4).

Saccadic response time

A significant difference in the main effect of drug was identified for saccadic response time change scores ($F(3, 504) = 20.001$, $p < 0.001$), where post hoc analysis found that promethazine (0.006 ± 0.031 ms) caused a significantly greater increase in response time compared to hyoscine hydrobromide (−0.009 ± 0.025 ms), hyoscine butylbromide (−0.009 ± 0.022 ms) and placebo (−0.018 ± 0.025 ms). Bonferroni multiple comparisons revealed that promethazine significantly increased mean saccadic response time ($F(3, 84) = 3.331$, $p = 0.045$) 2 h post-ingestion during no cue trials (Fig. 4). Bonferroni multiple comparisons also found that compared to placebo, promethazine increased mean saccadic response time 0.5 ($F(3, 84) = 3.670$, $p = 0.026$) and 2 h ($F(3, 84) = 7.692$, $p < 0.001$) post-ingestion during center cue trials as well as 0.5 h ($F(3, 84) = 3.730$, $p = 0.008$) post-ingestion of double cue trials (Fig. 5).

Saccadic amplitude

A significant main effect for the factor drug was identified for saccadic amplitude change scores ($F(3, 504) = 3.148$, $p = 0.025$), where post hoc analysis found that promethazine (−0.092 ± 1.122°) caused a significant reduction in saccadic amplitude compared to placebo (0.125 ± 1.147°). Bonferroni multiple comparisons determined that promethazine significantly decreased median saccadic amplitude ($F(3, 84) = 4.873$, $p = 0.035$) compared to placebo, 2 h post-ingestion during no cue trials (Fig. 6). The drug interventions did not influence saccadic amplitude during center cue and double cue trials.

Saccadic duration

A significant difference in the main effect of drug was found for saccadic duration change scores ($F(3, 504) = 7.708$, $p < 0.001$), where post hoc analysis revealed that promethazine (0.008 ± 0.023 ms) caused a significant greater increase in saccadic duration compared to hyoscine hydrobromide (−0.003 ± 0.020 ms), hyoscine butylbromide (−0.003 ± 0.025 ms) and placebo (0.001 ± 0.019 ms).

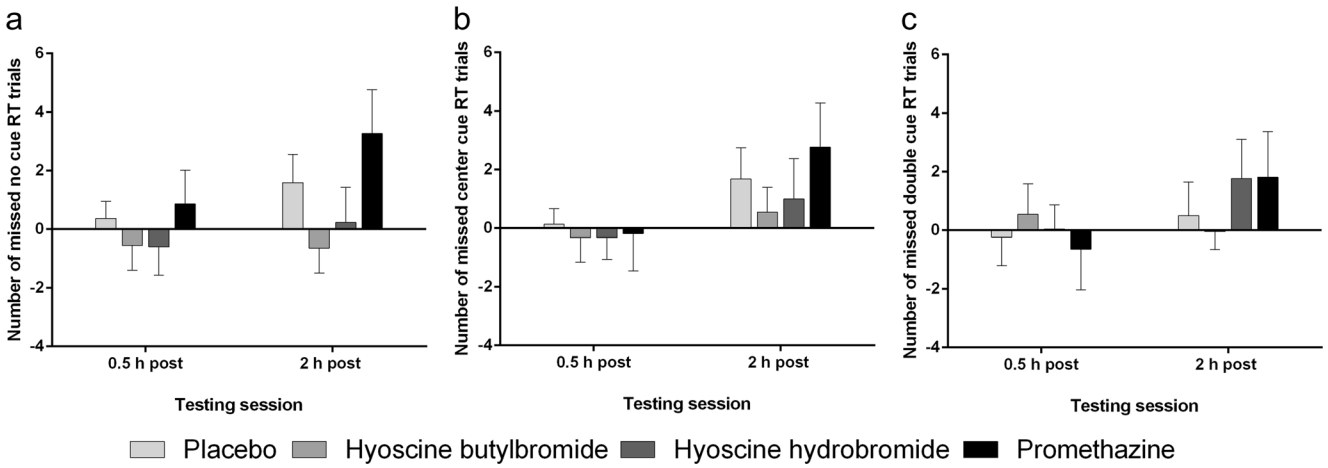

Fig. 3 The effects of placebo, hyoscine butylbromide, hyoscine hydrobromide and promethazine on the number of missed no cue (**a**), center cue (**b**) and double cue (**c**) visual RT trials. Data represent change scores 0.5 and 2 h following ingestion, where post-ingestion data were subtracted from the corresponding pre-ingestion data. Positive change scores indicate an increase in the number of missed RT trials following ingestion of the drug intervention. *Error bars* represent one standard error of the mean

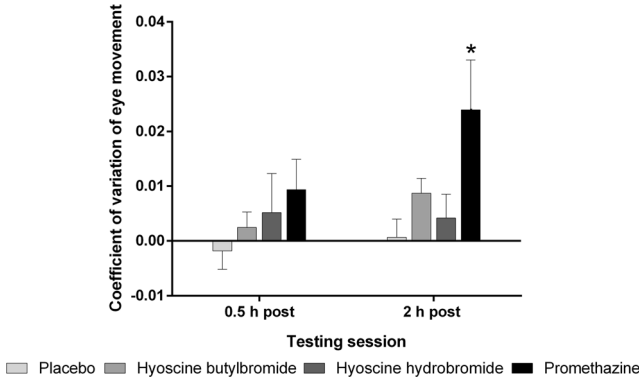

Fig. 4 The effects of placebo, hyoscine butylbromide, hyoscine hydrobromide and promethazine on the coefficient of variation of eye movement during the performance of the visual RT task. Data represent change scores 0.5 and 2 h following ingestion, where the post-ingestion coefficient of variation data was subtracted from the corresponding pre-ingestion data. Positive change scores indicate an increase in the coefficient of variation of eye movement following ingestion of the drug intervention. *Error bars* represent one standard error of the mean. *Asterisk* indicates that the coefficient of variation during the intervention was significantly different compared to placebo ($p < 0.05$)

Bonferroni multiple comparisons established that following the ingestion of promethazine, mean saccadic duration significantly increased ($F(3, 84) = 4.222$, $p = 0.049$) compared to placebo, 2 h post-ingestion during center cue trials (Fig. 6). The drug interventions did not influence saccadic duration during no cue and double cue trials.

Saccadic velocity

The drug interventions had no effect on saccadic velocity during no cue, center cue and double cue trials (Fig. 6).

Discussion

This study determined whether fixation stability, saccadic response time and associated eye movement dynamics are influenced by medications with varying degrees of central anticholinergic properties during a temporally-cued RT task. Participants reacted to visual stimuli following temporally uninformative and informative cued trials while an eye tracker recorded eye movement data. The visual RT task was performed pre-ingestion as well as 0.5 and 2 h post-ingestion of promethazine, hyoscine hydrobromide, hyoscine butylbromide and a placebo. The main findings of the study were that (1) promethazine decreased fixation stability during the performance of the RT task, (2) promethazine increased saccadic response time following temporally informative and uninformative cues, and (3) promethazine decreased saccadic amplitude and increased saccadic duration during the temporally-cued RT task.

Drug effects on fixation stability

Promethazine was the only drug to increase the coefficient of variation of eye movement, implying that following its ingestion, fixation stability decreased while gaze remained on the fixation cross during task performance. The effects of promethazine on fixation stability are potentially due to its central anticholinergic effects. Cholinergic neurotransmission is believed to play a role in the generation of neural activity that occurs in prepositus hypoglossi (PH)—the neural structure responsible for maintaining eye stability during fixations (Navarro-Lopez et al. 2004; Navarro-López et al. 2006). The action of acetylcholine on M receptors is proposedly involved

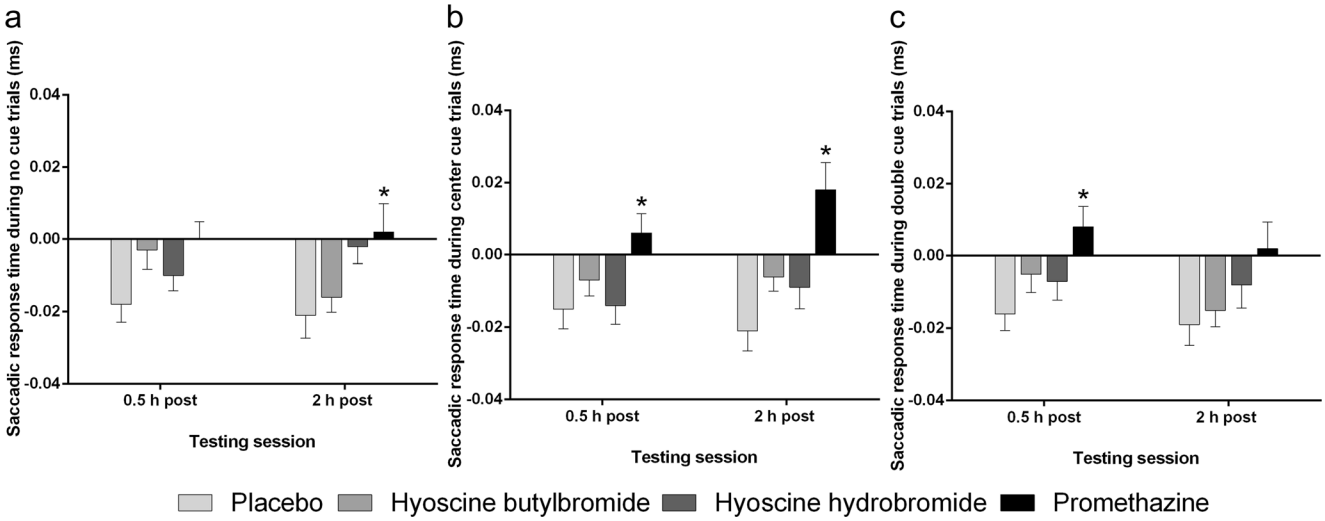

Fig. 5 The effects of placebo, hyoscine butylbromide, hyoscine hydrobromide and promethazine on saccadic response time during the performance of no cue (**a**), center cue (**b**) and double cue (**c**) trials. Data represent change scores 0.5 and 2 h following ingestion, where post-ingestion saccadic response time data were subtracted from the corresponding pre-ingestion data. Positive change scores indicate an increase in saccadic response time following ingestion of the respective drug intervention. *Error bars* represent one standard error of the mean. *Asterisks* indicate that saccadic response time measured during the intervention was significantly different compared to placebo ($p < 0.05$)

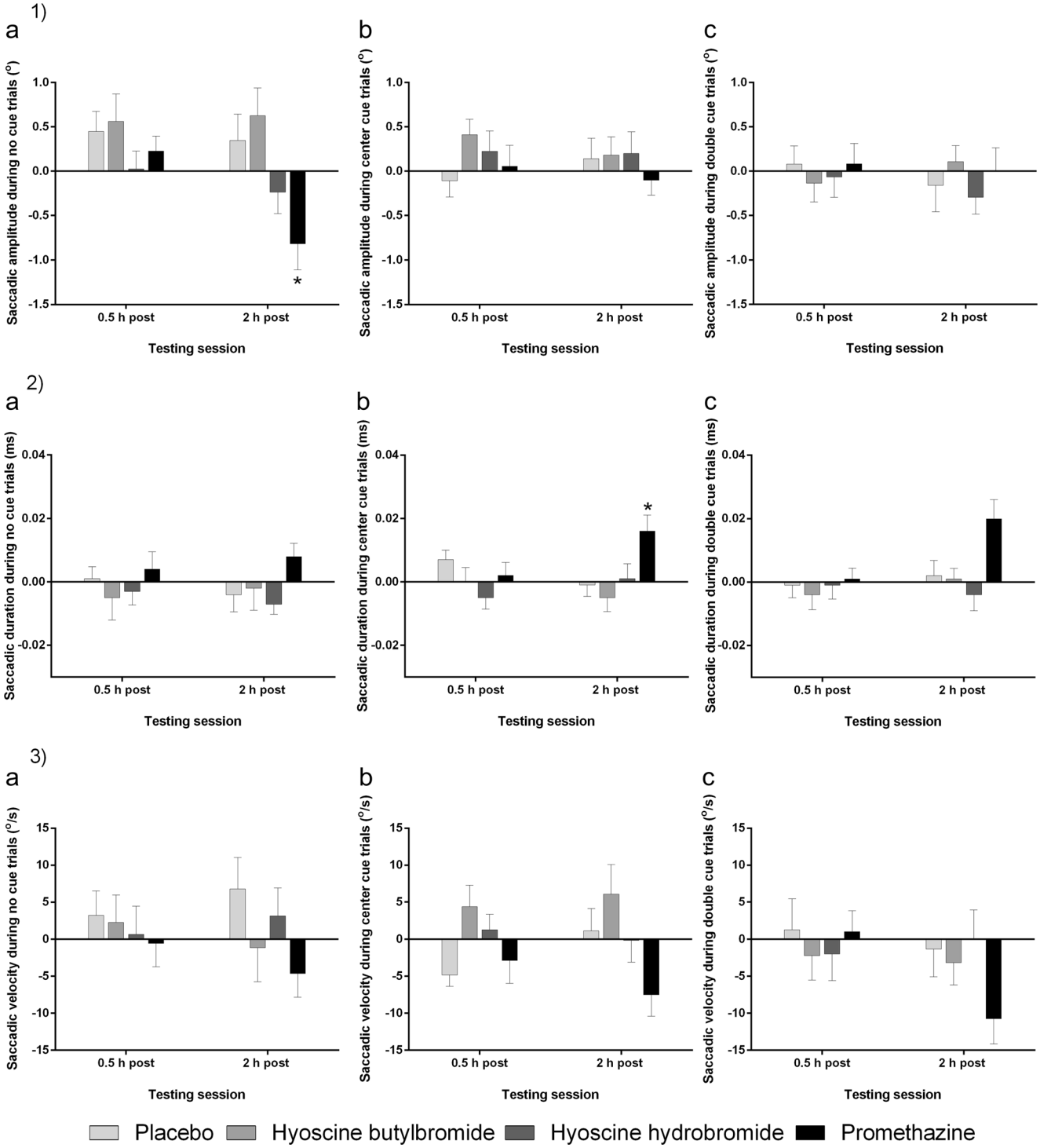

Fig. 6 The effects of placebo, hyoscine butylbromide, hyoscine hydrobromide and promethazine on (*1*) saccadic amplitude, (*2*) saccadic duration and (*3*) saccadic velocity during the performance of no cue (**a**), center cue (**b**) and double cue (**c**) visual RT trials. Data represent change scores 0.5 and 2 h following ingestion, where the post-ingestion saccadic amplitude, duration and velocity data were subtracted from the corresponding pre-ingestion data. Positive change scores indicate an increase in the respective saccadic performance measure following ingestion of the drug intervention. *Error bars* represent one standard error of the mean. *Asterisk* indicates that saccadic performance measure assessed during the intervention was significantly different compared to placebo ($p < 0.05$)

in the generation of correct eye position signals following quick eye movements (Navarro-Lopez et al. 2004). In line with the effects of promethazine on fixation stability, in vivo studies have reported that the potent central anticholinergic, atropine, causes visual instability after rapid eye movements due to the pharmacological blockade of M receptors (Navarro-Lopez

et al. 2004). In addition, the injectable form of hyoscine hydrobromide has also been found to impair visual stability during fixations (Oliva et al. 1993; Reilly et al. 2008).

Drug effects on saccadic response time during temporally uninformative and informative cued trials

Promethazine was the only drug to increase saccadic response time during task performance. RT is composed of pre-motor and motor components (Zwierko et al. 2010). Pre-motor RT involves central processes such as stimulus identification, interpretation and preparation of the response, whereas motor RT is the peripheral physical response (Zwierko et al. 2010). As such, impairments to response time elicited by central-acting drugs are more likely due to influences on pre-motor RT as opposed to motor RT. CNS functions such as alertness can also strongly affect RT (Matthias et al. 2010; Oliva et al. 1993; Thiel and Fink 2007). Temporally informative cues induce a phasic change of alertness, thereby decreasing pre-motor RT and improving RT (Karataş and Günendi 2010; Matthias et al. 2010; Pauletti et al. 2014; Vidal et al. 2015). Thus, temporally informative cued RT trials manipulate the central component of RT and therefore would be more sensitive to central drug effects.

Promethazine is a strong central-acting anticholinergic, and thus, its impairing effects on saccadic response time during temporally uninformative and informative cued trials were expected. In addition, the more pronounced effects of promethazine on saccadic response time following temporally informative cues further highlight the central impairing nature of the drug. Investigations that have assessed the effects of central anticholinergics on saccadic response time have found that hyoscine hydrobromide (injectable form) prolongs RT potentially due to increases in pre-motor RT that occur due to actions on central M receptors (Oliva et al. 1993). Nevertheless, there are limited studies which have assessed the effects of medications with varying central anticholinergic properties on saccadic response time following temporally informative and uninformative cues on a task of this nature.

Even though the noradrenergic system is linked with alertness, cholinergic neurotransmission can still play a role in alertness as central structures that control the alerting system are connected to areas of the brain innervated by cholinergic pathways (Callejas et al. 2005; Tales et al. 2011). In addition, it is believed that an interactive relationship exists between cognitive systems (Callejas et al. 2004; Fuentes and Campoy 2008), and as such, drug influences on central cholinergic pathways could still affect the alerting system. In addition to influences on cholinergic pathways, promethazine also acts on central H_1 receptors, and thus, the involvement of histaminergic pathways in the effects of promethazine on saccadic response time cannot be dismissed. Nevertheless, promethazine did not influence the number of missed RT trials during task performance. As such, it appears that promethazine did not compromise the ability to initiate a motor response in reaction to a stimulus. Since recent studies suggest that the neurophysiology of sedation is unrelated to that of motor control (Baumann-Birkbeck et al. 2014; Kavanagh et al. 2012; Naicker et al. 2013), it is unlikely that histaminergic pathways contributed to the effects of promethazine on saccadic response time.

Drug effects on saccadic amplitude, duration and velocity

Similar to results on saccadic response time, promethazine was also the only drug to influence the dynamics associated with this eye movement. Promethazine decreased saccadic amplitude during no cue trials and increased saccadic duration following center cue trials. The superior colliculus (SC) not only is directly involved in motor control but also plays a critical role in the modulation of eye movements (Lo et al. 2008; Sparks 2002). The SC receives signals from various cortical structures and sends out signals to pre-motor regions that are implicated in the generation of these eye movements (Sparks 2002; Sparks and Hartwich-Young 1989). The basal ganglia is a cholinergic structure that connects to the SC through subcortical circuits (Krauzlis et al. 2013; Redgrave and Coizet 2007; Redgrave et al. 2010). The basal ganglia play an important role in the regulation of voluntary movement, including eye movements (Hikosaka et al. 2000; McHaffie et al. 2005). A balance between acetylcholine and dopamine in the basal ganglia is believed to be imperative for motor control (Aosaki et al. 2010; Klawans and Rubovits 1974; Naicker et al. 2016; Snyder 1976), and thus, the effects of promethazine on eye movements are potentially the result of its influences on central cholinergic pathways. The resultant effects of promethazine on eye movement are consistent with a study which found that the central muscarinic anticholinergic, hyoscine hydrobromide (injectable form), decreases saccadic amplitude and increases saccadic duration (Oliva et al. 1993; Reilly et al. 2008). However, contrary to what was expected, promethazine did not influence saccadic velocity during the temporally-cued visual RT task. Nevertheless, saccadic velocity is generally considered to be more sensitive to fatigue and sedative drugs (Di Stasi et al. 2013; van Steveninck et al. 1999). Thus, promethazine's actions on central H_1 receptors may not be potent enough to influence vertical eye movement velocity, thereby further implying that the effects of promethazine on eye movements are more likely due to influences on cholinergic rather than histaminergic pathways.

Experimental considerations

It could be argued that changes in pupil dynamics may have influenced some results with promethazine, such as fixation

stability. However, although promethazine is expected to increase pupil diameter due to its actions on the M receptor, pupil diameter data on healthy young subjects have been collected which dispute this (Naicker et al. 2016). Pupil diameter at rest and during a cognitively active state was assessed pre- and post-ingestion of 25 mg promethazine, where pupil diameter was not influenced by promethazine during resting or cognitively active conditions. It was proposed that this could be due to its non-selectivity for the M receptor. As such, it is unlikely that mydriasis plays a role in effects on fixation stability. Experimental findings should not be generalised past the methods of the study. Results could differ according to populations, drug dosages and other characteristics of the study. As such, caution should be exercised when interpreting results beyond the context of the study. The implications of the findings of this study should be also be investigated further by determining consequences on real-life scenarios. Future studies would benefit from further assessments on ocular function that would assist in distinguishing whether central or peripheral cholinergic pathways are responsible for the movement dysfunction caused by OTC anticholinergic medications.

Conclusion

Overall, the results of this study convey that OTC medications with strong central anticholinergic properties can influence fixation stability, saccadic response time and the dynamics associated with this eye movement during a temporally-cued visual RT task. Subsequently, these findings highlight the significant role that central cholinergic pathways play in the control of eye movements during tasks involving stimulus identification and motor responses following temporally informative and uninformative cues.

Compliance with ethical standards The Institutional Human Research Ethics Committee approved all experimental protocols, and written participant consent was obtained prior to commencement of testing sessions.

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