University of Groningen

Effects of nicotine on pupil size and performance during multiple-object tracking in non-nicotine users

Wardhani, I. K.; Mathôt, S.; Boehler, C. N.; Laeng, B.

Published in:
International Journal of Psychophysiology

DOI:
[10.1016/j.ijpsycho.2020.09.005](https://doi.org/10.1016/j.ijpsycho.2020.09.005)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wardhani, I. K., Mathôt, S., Boehler, C. N., & Laeng, B. (2020). Effects of nicotine on pupil size and performance during multiple-object tracking in non-nicotine users. *International Journal of Psychophysiology*, 158, 45-55. <https://doi.org/10.1016/j.ijpsycho.2020.09.005>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Effects of nicotine on pupil size and performance during multiple-object tracking in non-nicotine users

I.K. Wardhani^{a,b,c,*}, S. Mathôt^b, C.N. Boehler^c, B. Laeng^a

^a Department of Psychology, University of Oslo, Forskningsveien 3A, 0373 Oslo, Norway

^b Department of Experimental Psychology, University of Groningen, Grote Kruisstraat 2/1, 9712 TS Groningen, the Netherlands

^c Department of Experimental Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium

ARTICLE INFO

Keywords:

Nicotine
Pharmacological stimulant
Multiple-object tracking
Pupillometry
Pupil size
Cognitive function

ABSTRACT

Nicotine has been commonly used in psychopharmacological studies, showing its benefits as a pharmacological stimulant on cognitive performance. In the current study, we investigated the effects of 2 mg (Experiment 1) and 4 mg (Experiment 2) of nicotine on performance on a multiple-object-tracking task. Participants were young non-smoking adults with no pre-existing attentional deficits. Nicotine and placebo were administered through nicotine and nicotine-free taste-matched chewing gum, respectively. Additionally, we compared pupil size between nicotine and placebo conditions in both experiments. Although we found that pupil size was considerably smaller in the nicotine conditions, nicotine administration did not appear to facilitate behavioural performance. We speculate that nicotine might enhance performance only for certain cognitive functions, and only for specific populations, such as nicotine-deprived smokers.

1. Introduction

1.1. Nicotine and cognitive processing

Nicotine is a pharmacological stimulant that has been commonly used in smoking cessation treatment programmes, even though the effectiveness of such treatments is disputed (e.g., Cepeda-Benito, 1993; Kim and Baum, 2015; Yudkin et al., 2004). Nicotine is also commonly studied as a cognitive-performance enhancing drug (see Keith et al., 2017, for a review). Despite the addictive and toxic nature of nicotine (Benowitz, 2009; Herman et al., 2014), several benefits of nicotine on cognitive processing have been observed, which could contribute to its continued and widespread use.

In non-clinical samples (e.g., non-smokers without pre-existing attentional deficits), improved performance on a continuous-attention task was found after participants were administered 7 mg of nicotine, as compared to placebo (Levin et al., 1998). Similarly, performance on a memory *n*-back task improved after participants were administered 1 mg of nicotine subcutaneously, as compared to placebo (Kumari et al., 2003). This improvement was accompanied by increases in blood-oxygen-level dependent (BOLD) response in frontal and parietal areas, anterior cingulate, and superior colliculus.

In clinical samples, nicotine was reported to facilitate performance amongst smokers and non-smokers with attention-deficit/hyperactivity disorder (ADHD). Compared to the placebo condition, performance on the continuous-performance task (CPT) and the Stroop task was better for smokers and non-smokers when, after having been deprived from nicotine, they were administered 21 mg/day and 7 mg/day, respectively (Levin et al., 1996a; Potter and Newhouse, 2004). Similarly, there was a notable decline in errors as well as response-time variability amongst non-smoking late adults (62–87 years old) with Alzheimer's disease after 5 and 10 mg/day of nicotine was administered (Newhouse et al., 1988; White and Levin, 1999). Amongst smokers with schizophrenia, nicotine (7, 14, and 21 mg/day through a transdermal patch) enhanced performance on a spatial memory test and a continuous-attention task, compared to the placebo condition (Levin et al., 1996b). Interestingly, in combination with the antipsychotic drug haloperidol consumed by the participants, Levin et al. (1996b) found that nicotine not only enhanced performance, but also attenuated the adverse side effects of haloperidol.

Nevertheless, other studies have failed to find beneficial effects of nicotine on cognition. For example, Ernst et al. (2001) did not find evidence for beneficial effects of 4-mg nicotine on cortical activity as recorded using positron emission tomography (PET), nor on behavioural performance during a 2-back task. Compared to ex-smokers, task

* Corresponding author at: Department of Experimental Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium.

E-mail address: intankusuma.wardhani@ugent.be (I.K. Wardhani).

performance improved only amongst abstinent smokers after nicotine administration. This indicated that performance could benefit from nicotine only when there were withdrawal and tolerance effects. This finding was strengthened by the PET scan's results showing that, in the nicotine condition, cortical activation diminished in smokers, but enhanced in ex-smokers.

Furthermore, an electroencephalographic (EEG) study showed no evidence for behavioural improvement, nor for an enhancement of the P300 ERP component, amongst non-smokers during an oddball task after they were administered with 7 mg of nicotine (Evans et al., 2014). In contrast to the previous EEG study (Evans et al., 2013), the amplitude of the P300 component decreased during an oddball task following nicotine deprivation amongst smokers. Taken together, these results suggested that the beneficial effects of nicotine on behaviour and P300 component were unique to nicotine deprivation amongst smokers and did not generalise to cognitive improvements amongst non-smokers.

This finding was supported by other studies that compared the effects of nicotine on smokers and non-smokers on various tasks. Grundey et al. (2015) assessed the effect of 15-mg nicotine on working memory (with an *n*-back task) and attention (using a Stroop interference task) in healthy non-smokers and smokers. The smokers abstained from smoking at least 6 h prior to nicotine administration. The authors found that nicotine improved working-memory performance for smokers, but not for non-smokers. Additionally, the effect of nicotine was less apparent for attentional processes. The authors concluded that nicotine did not improve cognitive performance for non-smokers, neither for working memory nor for attention. However, the nicotine-deprived smokers did benefit from nicotine, at least on a working-memory task.

In a similar vein, Ettinger et al. (2017) assessed the effect of 7-mg transdermal nicotine on a battery of interference control and response inhibition tasks amongst healthy non-smokers. The tasks included a pro- and anti-saccade task, a stop-signal task, a go/no-go task, a flanker task, a shape-matching task, a Stroop task, and a Simon task, as well as the attentional-network test (ANT) and the CPT. The authors found that nicotine led to faster responses, but only on the pro-saccade task and the CPT. Interference and inhibitory control on the other tasks did not improve; rather, nicotine even seemed to increase the interference effect on the Simon task.

To summarise, it is still unclear whether there are benefits of nicotine on cognitive processing, especially for healthy, non-smoking participants. On the one hand, some studies have shown such beneficial effects; however, when found, these effects are most pronounced for clinical and nicotine-deprived samples. On the other hand, some studies have found that healthy non-smokers without pre-existing attentional deficits do not benefit from nicotine on cognitive tasks.

1.2. Nicotine and acetylcholine: its relationship with cognitive processing and pupillary responses

One route through which nicotine could effect cognitive processing is through its relationship with acetylcholine (ACh). Nicotine is the prototypic nicotinic acetylcholine receptor (nAChR) agonist (Kumari et al., 2003; Luttrell and Vogel, 2014; Rezvani and Levin, 2001). It mimics and binds to a subset of acetylcholinergic receptors. Nicotine uptake into the body varies from one person to another due to variations in genetic make-up, such as the diverse expression of the *CHRNA4* gene (Espeseth et al., 2010). This gene is known to interact with medium to high load processing in visual search and multiple-object-tracking tasks (Espeseth et al., 2010). This demonstrates that nicotinic and cholinergic neurotransmission are involved in cognitive processing.

Acetylcholine is a chief neurotransmitter that is found throughout the nervous system, such as in ganglia, neuromuscular connections, and central and autonomic nervous systems (Whitehouse, 2014). In the central nervous system (CNS), the function of acetylcholine and its interaction with nicotine is more complex because it involves excitation of acetylcholine and inhibition of muscarinic receptors, or vice versa, at

the same time (Kimura, 2000). In general, acetylcholine contributes to brain plasticity (Perry et al., 1999; Sarter and Bruno, 1999), arousal and alertness (Perry et al., 1999), and sustaining attention as well as learning and memory (Hasselmo and Giocomo, 2006). Damage to the cholinergic system is associated with learning and memory deficits in Alzheimer's disease (AD), and treatment usually involves nicotine to stimulate acetylcholine release (e.g., Levin et al., 1998; White and Levin, 1999). The association between augmented acetylcholine release and attention is also found in the prefrontal cortex during performance under a challenging and detrimental sustained-attention task (Kozak et al., 2006).

The pervasiveness of acetylcholine throughout the nervous system suggests that it does not only play an important role in cognitive processing, but also in the regulation of peripheral organs and basic physiological processes. In the autonomic nervous system (ANS), acetylcholine helps to control many involuntary body functions, and it also interacts with psychopharmacological substances. A key function, which is more easily observable, is an interaction between acetylcholine receptors and acetylcholine agonists (e.g., nicotine) that constrict pupils through the parasympathetic pathway (Beatty and Lucero-Wagoner, 2000; Mathôt, 2018; McDougal and Gamlin, 2008; Wang and Munoz, 2015). A pupil constriction after smoking cigarettes with low nicotine content (e.g., 1 mg) has been shown by some studies (e.g., Erdem et al., 2015; Lie and Domino, 1999). Conversely, when acetylcholine receptors bind with an acetylcholine antagonist (e.g., atropine), a signal is sent through the sympathetic pathway to dilate pupils (Beatty and Lucero-Wagoner, 2000; McDougal and Gamlin, 2008).

Other pupillary parameters (e.g., amplitude, maximum constriction velocity and acceleration) have also been used to signal abnormalities in the neurotransmitter system involving acetylcholine. For example, Prettyman et al. (1997) and Stergiou et al. (2009) compared the resting pupil size and pupil light response (PLR) of patients with AD and Parkinson's disease (PD) to those of typical participants. They found that patients with AD and PD had reduced pupil size and diminished PLR. These studies corroborated the use of pupillometry to help reveal internal, physiological states.

2. Current study

As discussed above, some previous studies have suggested that nicotine has general, beneficial effects on cognition (e.g., Kumari et al., 2003; Levin et al., 1998). However, all of these studies tested the cognitive effects of nicotine using variants of continuous-performance tasks that demanded convergent and selective attention. Most of them also compared the performance between smokers and non-smokers.

In the present study, we conducted two experiments to test the effect of nicotine for non-smokers using a divided-attention task instead of a task for continuous performance. To measure divided attention, we used a multiple-object-tracking (MOT) paradigm (Pylyshyn and Storm, 1988). While it is possible that other processes also play a role (Cowan, 2011; Meyerhoff et al., 2017), the MOT paradigm is believed and has been used to test divided attention because participants are required to allocate their attentional resources to multiple sets of input (Alnæs et al., 2014). In the task, participants track several items moving randomly and report the location of a target by answering yes or no to the probe. We predicted that response times would be faster and accuracy would be higher, after administration of nicotine, as compared to placebo. We further predicted that this effect would be observed for all task difficulty levels, as manipulated through the number of objects to be tracked simultaneously.

Finally, we tested the effect of nicotine on changes of pupil size. As described before, acetylcholine binds with nicotine as an acetylcholine agonist and the interaction between them should result in pupil constriction. Thus, we predicted that pupil size would be smaller after the administration of nicotine, as compared to placebo, despite the use of a relatively low dosage. Pupillometry is also a very promising, non-

invasive tool that can provide continuous measure of cognitive processing through pupillary changes (Alnæs et al., 2014; Laeng et al., 2012). Therefore, we predicted that pupil dilation during the MOT trials would increase as a function of task difficulty; we did not have predictions about whether the effect of difficulty on pupil dilation would interact with nicotine administration.

2.1. Ethics statement

Approval of the current study was obtained from the Department of Psychology's Research Ethics Committee at the University of Oslo (ref. number: 1730636). Participants read the experiment information and signed an informed consent at the beginning of the experiment. Participants were treated according to the Declaration of Helsinki. Each participant was debriefed at the end of the final session.

3. Experiment 1

3.1. Method

3.1.1. Participants

Prior to data collection of both experiments, eligibility criteria of participation were set due to the nicotine treatment. Participants ought not to be users of any types of nicotine products, such as cigarettes, e-cigarettes, vapour device, chewing tobacco, and pouched tobacco. To avoid negative side effects, we excluded participants who were pregnant, breastfeeding, on a medical prescription or medically-restricted diet, or clinically diagnosed with heart attack, heart disease, heart rate irregularities, allergies, high blood pressure, asthma, diabetes, ulcers, thyroid, dentures, depression, and anxiety during data collections (American Society of Health-System Pharmacists, 2013). To avoid interference in the eye-tracking recording, participants were requested to use no eye makeup (e.g., eyeliner, mascara, dark eyeshadow).

Thirty-one participants volunteered in the experiment. Data from two participants were excluded from the analysis due to a technical failure and erroneous keypresses in one session. Therefore, the analyses included 29 university students in Oslo, Norway, recruited through social media ($M_{age} = 24.69$ years, $SD = 3.26$, age range = 19–34 years, $n_{women} = 19$). Participants' visual acuity was normal or corrected-to-normal (by contact lenses). Completion in both sessions was compensated with a NOK 300 (~€30) gift card.

3.1.2. Design, materials, and apparatus

We had a 2 (Drug: placebo vs. nicotine) $\times$ 3 (Load: two vs. three vs. four) within-participants design. Drug was manipulated by administering nicotine chewing gum as well as regular chewing gum as placebo. A third person allocated each type of the chewing gum in two separate opaque and covered containers that were identical and labelled with a unique letter. The experimenter was blind to the chewing gum identity and participants were naïve to the purpose of the experiment and to the nicotine treatment. The blind labels remained until data collection and statistical analyses were completed. The order of drug manipulation was randomised using the balanced permutations technique (www.randomization.com), such that a number of participants took chewing gum from Container A, for example, and another from Container B in the first session. In the second session, participants took chewing gum from a container that was not assigned to them in the first session.

We administered placebo and 2 mg of nicotine using the Extra® peppermint and Nicorette® fresh mint chewing gum, respectively. Both types had identical off-white colour and similar flavour. Relative to other studies with human (e.g., Levin et al., 1996b) or animal subjects (e.g., Ortega et al., 2013), we administered low dosage of nicotine to avoid causing adverse side effects such as nausea, dizziness, and sore throat in non-smoking participants. More importantly, nicotine has psychoactive effects following the Yerkes-Dodson principle (Newhouse et al., 2004), in which nicotine could cause improvement in cognitive

processing performance at low-to-medium dosages. However, performance impairment would occur at a higher dosage of nicotine.

All participants did a partial-report variant of multiple-object tracking (MOT) task (Pylyshyn, 2004; Pylyshyn and Storm, 1988). Eye events and pupil diameter were recorded binocularly by the SMI RED500® remote eye-tracker running on iViewX 2.8 (60 Hz sample rate). The pupil recording resolution of individual measurements was better than 0.01 mm. The task was created with Java and presented using Experiment Centre®3.2.17 (SMI®, Berlin, Germany) on a flat Dell P2213 VGA LCD monitor (47 $\times$ 29.40 cm, display resolution = 1680 $\times$ 1050 pixels). Stimuli consisted of 12 animated circles ($r = 29$ pixels, RGB: 182, 91, 48) with a minimum distance of 2 pixels between circles, positioned onto a grey background (RGB: 128, 128, 128). The size of the display area was 800 $\times$ 800 pixels. The motion was presented at a rate of 30 frames per second with a speed of 8.5 pixels per frame. Targets were cued at the beginning of each trial for 4000 ms and tracking time was 6000 ms (Fig. 1). During tracking, all stimuli moved in a random, independent, and non-overlapping fashion. After the animation stopped, one stimulus was highlighted with a 50% probability that it would be one of the targets. Participants' task was to decide as quickly and accurately as possible if the specific highlighted stimulus was one of the targets by pressing a corresponding button on the keyboard for a "yes" or a "no" answer.

In each Drug condition, there were 72 trials of MOT task that were divided into four blocks. Each block comprised six two-, six three-, and six four-target trials of which the presentation order was pseudo-randomised. The block always begun with the presentation of targets in three gradual levels (i.e., two-target trial followed by three-, then four-target trial). The order of the trials in the rest of the block was fully randomised. The entire order of trials in the first block was then repeated in the second, third, and fourth blocks. There were no practice trials preceding the task.

After the MOT task, a paper-and-pencil questionnaire that we developed was handed out to each participant as a manipulation check. Data from the questionnaire were collected to measure participants' subjective assessments of: (1) concentration level; (2) mood states; (3) chewing gum identity (with or without active ingredient); (4) confidence level in estimating the chewing gum identity; (5) the similarity between the two chewing gum types. Participants were asked to give response to Questions 1 and 2 only in the first session. In their second sessions, participants completed the five questions. Question 2 was an open-ended question and other questions stored responses in a Likert scale ranging from 1 to 10 (see Supplementary Materials).

3.1.3. Procedure

Data collection was divided into two sessions and only one chewing gum of either type was taken in each session (Fig. 1). At least three days elapsed in between the sessions, such that the nicotine would have been fully eliminated from the body since the previous session. In this experiment, there were on average $M_{day} = 8.72$ days ($SD = 10.2$, range = 3–42 days) in between the sessions. Participants were required to refrain from eating or drinking, including water, at least 15 min before the start of each session. Oral consumption of food or drinks could change the neutral pH level in the mouth and, consequently, it could inhibit the absorption of nicotine through the lining of mouth (American Society of Health-System Pharmacists, 2013).

Upon arrival, each participant was ushered into the experiment room. There was only one participant at a time. In every session, each participant was instructed to take chewing gum from Container A or B according to the random assignment. Participants had to chew the gum three times and place it between the cheek and the mouth gums or at the palate every 1 min (Nicorette, n.d.). This process was to be repeated for 30 min to let the nicotine be completely absorbed into the bloodstream. The experimenter placed a digital timer for participants to keep track of the time.

To let time pass during chewing, participants did a filler perceptual

Fig. 1. Procedure and Trial Sequence of the MOT task in Experiment 1.

Note. The experiment's procedure is illustrated in magenta and cyan boxes. The trial sequence of the MOT task is illustrated in grey boxes. In the task, targets were cued in orange colour during target assignment. Arrows in the tracking phase indicate random movements. Pupil responses were recorded only during the MOT task. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

task that was unrelated with the main experiment. After 30 min elapsed, participants ejected the chewing gum into a provided plastic cup and were seated in front of the computer monitor. Participants used a head rest to remain in a stable posture during the eye recording. The head placement yielded a stable 60-cm distance between the screen and the cornea. The testing room was illuminated in constant and standard indoor lighting level throughout the experiment in both sessions for all participants. This illumination (188 lx) allowed pupils to maintain an average size of about 4.7–5.2 mm at rest.

3.2. Data processing and analyses

Our datasets in readable formats and the data processing files are stored online (<https://osf.io/hk5uq/>). We analysed participants' response accuracy, response latency, and pupil size. Additional self-reports were collected to assess subjective level of concentration and estimate of chewing gum type. Traditional NHST and Bayesian statistical analyses were executed using JASP (JASP, 2018). Our verbal interpretations of the Bayes factor (BF) refer to the general interpretations as reported by Wetzels et al. (2011) and Jarosz and Wiley (2014). For example, a BF of 12 means that the data provides strong evidence for the alternative hypothesis.

3.2.1. Subjective assessments

We analysed responses from Questions 1 (concentration level) and 3 (estimate of chewing gum type). Responses from other questions were not further analysed due to its peripherality in answering the research questions. Question 1 was treated as an interval scale that ranged from 1 (*very distracted*) to 10 (*very focussed*). A paired-samples *t*-test was conducted to examine participants' subjective measure of concentration. Responses to Question 3 were treated as a dichotomous variable whereby "*with active ingredient*" was scored 1 and "*without active ingredient*" was 0. A binomial test was conducted to examine the portion of correct estimate.

3.2.2. Response accuracy and latency

The average accuracy in the MOT task was calculated separately for each level of conditions. Each trial was either a target or a non-target trial. Participants had to press the "M" key for a "yes" response if the highlighted disk was a target. If not, they had to press "B" for a "no"

response. Correct responses were scored 1 and incorrect responses 0. Participants' response latency was recorded since the onset of the probe until a keypress indicating a response. A 2 (Drug: placebo vs. nicotine) $\times$ 3 (Load: 2 vs. 3 vs. 4) repeated-measures ANOVA (RM ANOVA) was conducted to analyse response accuracy and latency.

3.2.3. Pupil size

The binocular pupillary data resulted in 600 samples (i.e., 60 samples/s in a 10-s epoch) of pupil size per participant per trial of the MOT task. The trial epoch of interest for pupil diameter was during the tracking (from 4000 to 10,000 ms), in which pupil diameter from both left and right eyes was averaged into a single measure. Pupil size data during the epoch of interest were averaged first across samples (i.e., time points), then across trials, resulting in a single value for each participant. A 2 (Drug: placebo vs. nicotine) $\times$ 3 (Load: 2 vs. 3 vs. 4) RM ANOVA was conducted to statistically analyse pupil size during target assignment and tracking.

3.3. Results

For significant results, the exact *p*-values and descriptive statistics are reported in the text. Other exact *p*-values are shown in Table 1. The Greenhouse-Geisser method was used as a sphericity correction. Bayes factors (BF) reported here are generated as BF inclusion values from the tables of analysis of effects across matched models. All models were compared to the best model.

3.3.1. Subjective assessments

Subjective concentration level. In the placebo condition, concentration level was lower ($M = 7.552$, $SD = 1.804$) than in the nicotine condition ($M = 8.190$, $SD = 1.312$), $t(28) = -2.066$, $p = .048$, Cohen's $d = -0.384$, $BF_{10} = 1.247$. According to the Bayes factor, there was weak evidence in favour of the alternative model in comparison to the null model, suggesting little differences in the concentration levels between placebo and nicotine conditions.

Estimate of chewing gum type. Results revealed that 24 participants (83%) correctly estimated the type of the chewing gum (i.e., with or without active ingredients) they took in the second session, $p < .001$, $BF_{10} = 150.694$. The Bayes factor suggested extremely strong evidence in favour of the alternative model compared to the null model, showing

Table 1
Results Summary of Experiments 1 and 2.

Components	Experiment 1			Experiment 2		
	NHST	Effect size	Bayesian	NHST	Effect size	Bayesian
Accuracy						
Drug	0.895	0.001	0.167	0.337	0.033	0.304
Load	0.003	0.192	83.964	<0.001	0.775	2.582e+19
Drug x load	0.156	0.064	0.348	0.314	0.040	0.258
Latency						
Drug	0.233	0.050	0.545	0.898	0.001	0.168
Load	0.219	0.053	0.095	<0.001	0.659	26.892
Drug x load	0.475	0.020	0.106	0.466	0.027	0.113
Baseline pupil size						
Drug	0.008	0.227	1.309e+6	0.001^a	0.673 ^a	29.835^a
Load	<0.001	0.392	0.210	–	–	–
Drug x load	0.218	0.053	0.117	–	–	–
Tracking pupil size						
Drug	0.014	0.197	71,956.987	0.001	0.325	1.041e+10
Load	<0.001	0.503	7.506	<0.001	0.617	2.585
Drug x load	0.155	0.064	0.118	0.423	0.030	0.118

Note. NHST = null hypothesis significance testing. Numbers in the NHST columns represent the p -values and in the Bayesian column the Bayes factors ($BF_{incl.}$). Bold fonts accentuate significant values below 0.05 and substantial/large BF. Effect size is represented by the partial eta-squared.

^a Results from paired-samples t -test and the Cohen's d effect size.

that more participants estimated the chewing gum type correctly.

3.3.2. Response accuracy and latency

Response accuracy. Results showed a main effect of Load, $F(1.904, 53.299) = 6.671, p = .003, \eta^2_p = 0.192, BF_{incl.} = 83.964$ (Fig. 2). Accuracy in Load 2 ($M = 0.946, SD = 0.226$) was higher than accuracy in Load 3 ($M = 0.914, SD = 0.281$) and Load 4 ($M = 0.907, SD = 0.290$). Main effect of Drug ($F(1, 28) = 0.018, \eta^2_p = 0.001, BF_{incl.} = 0.167$) and the interaction effect of Drug $\times$ Load ($F(1.984, 55.565) = 1.927, \eta^2_p = 0.064, BF_{incl.} = 0.348$.) were insignificant, $p_s > 0.155$, null model was the best model.

Response latency. Results indicated that there were no significant Drug ($F(1, 28) = 1.487, \eta^2_p = 0.050, BF_{incl.} = 0.545$) and Load ($F(1.93, 54.053) = 1.566, \eta^2_p = 0.053, BF_{incl.} = 0.095$) main effects, or a Drug $\times$ Load interaction effect, $F(1.167, 32.681) = 0.584, \eta^2_p = 0.020, BF_{incl.} = 0.106$. All $p_s > 0.218$, null model was the best model (Fig. 2).

3.3.3. Pupil size

During target assignment. The trace of pupil size throughout the MOT task was plotted in Fig. 3. Results suggested that pupil size during target assignment in the nicotine condition ($M = 4.553, SD = 0.782$) was significantly smaller than in the placebo condition ($M = 4.681, SD = 0.827$), $F(1, 28) = 8.232, p = .008, \eta^2_p = 0.227, BF_{incl.} = 1.316e+6$ (Drug as the best model).

The main effect of Load on pupil size during target assignment was

also significant, $F(1.928, 53.981) = 9.372, p < .001, \eta^2_p = 0.392$. Pupil size in Load 2 was smaller ($M = 4.594, SD = 0.798$) than pupil size in Load 3 ($M = 4.621, SD = 0.816$) and Load 4 ($M = 4.636, SD = 0.807$). In contrast, the Bayesian test did not show evidence for the effect of Load on pupil size during target assignment, ($BF_{incl.} = 0.202$). There was no significant Drug $\times$ Load effect on pupil size during target assignment, $F(1.841, 51.535) = 1.574, p = .218, \eta^2_p = 0.053, BF_{incl.} = 0.119$.

During tracking. Results showed a significant main effect of Drug ($F(1, 28) = 6.874, p = .014, \eta^2_p = 0.197, BF_{incl.} = 71,956.987$ (Drug + Load as the best model)). Pupil size in the nicotine condition ($M = 4.733, SD = 0.831$) was smaller than pupil size in the placebo condition ($M = 4.856, SD = 0.894$).

Main effect of Load was also significant ($F(1.760, 49.289) = 28.383, p < .001, \eta^2_p = 0.503$). Pupil size was larger in a higher tracking load (Load 2: $M = 4.742, SD = 0.855$; Load 3: $M = 4.806, SD = 0.874$; Load 4: $M = 4.835, SD = 0.865$). However, the Bayesian test showed only positive, but smaller, effect of Load on tracking pupil size, ($BF_{incl.} = 7.506$). Meanwhile, the Drug $\times$ Load effect on tracking pupil size was not significant, $F(1.983, 55.519) = 1.930, p = .155, \eta^2_p = 0.064, BF_{incl.} = 0.118$.

3.3.4. Discussion

In Experiment 1, we recorded participants' self-report and examined their pupil size, response accuracy, and response latency between the nicotine (2 mg) and placebo conditions on a MOT task. From the self-report assessment, results showed a very small difference in the

Fig. 2. Response Accuracy and Latency in Experiment 1.

Note. Load on the x axis is the number of targets to be tracked. A significant main effect of Load on response accuracy was observed.

Fig. 3. Pupil size in placebo and nicotine (2 mg) conditions of Experiment 1.

Note. The figure above depicts pupil trace from the onset of target assignment (time = 0) to the offset of tracking period (time = 10 s) in Experiment 1. The vertical dashed lines indicate the onset of the stated phases. The grey area shows a period in which pupil size wiggled into constriction, likely caused by changes in the stimulus field. The coloured shadings surrounding the pupillary traces represent 95% within-subject CI.

subjective concentration rating although 83% of the participants discerned the chewing gum identity. This result might indicate that the potential awareness of the nicotine manipulation did not have an effect on subjective concentration rating, or even behavioural performance. The discernment of the chewing gum identity is further discussed in [Section 6](#) General Discussion.

Results from both NHST and Bayesian analyses suggested that pupil size in the nicotine condition was smaller than pupil size in the placebo condition. This finding was in line with our hypothesis. Tracking load as a function of cognitive effort also had an effect on pupil size. As hypothesised, pupil size in the lower tracking load was smaller than pupil size in the higher tracking load. At the start of the tracking period, pupils constricted as a result of the onset of visual movement ([Fig. 3](#)). Later in time, pupil dilations throughout the tracking period reflected attentional effort deployed by the participants.

The effect of tracking load on baseline and tracking pupil size was especially striking according to the NHST, but not the Bayesian (see [Table 1](#) for comparison). One explanation for this is the tendency of Bayesian statistics to favour the null hypothesis against the alternative hypothesis when the effect size is small. Conversely, in this case, the NHST will still reject the null hypothesis if the sample size is reasonably large, such as in the current study.

On the behavioural level, no beneficial effects of nicotine were observed. Administered with 2 mg of nicotine, participants' performance on the MOT task was not more efficient (i.e., faster and more accurate) than performance in the placebo condition. Tracking load appeared to have a very strong effect on response accuracy, wherein responses were more accurate in the lower than higher tracking load. No difference by tracking load in response latency was observed.

Some limitations of the current experiment include (1) a short baseline epoch during target assignment, (2) pseudo-randomised trial orders and few experimental trials per participant in each session, and (3) the use of a self-report measure that was not psychometrically tested. These limitations will be addressed one by one. First, the baseline epoch should be in the prestimulus period, such that effects elicited following a stimulus presentation is not interfered by the prestimulus effects and vice versa. However, in the current experiment, there was a tracking-load effect already in the baseline epoch, showing an overlap between the baseline and stimulus epochs. Second, the pseudo-randomised trial orders might result in a preparatory effect that, in turn, would be manifested in a better performance. If this were the case, then higher accuracy and/or faster response should be attributed mainly to the preparatory or anticipatory activity. Additionally, the few trials in the current experiment might result in a low signal-to-noise ratio. Third, the

use of a self-report scale that was not validated and checked for its reliability might measure other psychological aspects not as intended. For these reasons, a second experiment was conducted.

4. Experiment 2

We conducted Experiment 2 to address the potential methodological issues in Experiment 1 (see [Section 3.3.4](#) Discussion). In the current experiment, we constructed a baseline epoch prior to the target onset, added more experimental trials that were fully randomised to improve the signal-to-noise ratio, and used the computerised Abbreviated Profile of Mood States (Abbreviated POMS; [Groves and Prapavessis, 1992](#)) to have a validated measure of participants' current mood states. Unless mentioned otherwise in the following sections, the design and other materials and apparatus of Experiment 2 remained the same as in Experiment 1.

4.1. Method

4.1.1. Participants

In the current experiment, we applied the same exclusion criteria as before for the participants. Thirty-two participants volunteered in this experiment. Data from three people were removed from the analyses: one participant felt sick in the first session and did not complete the whole experiment, one person did not return for the second session, and a technical problem occurred in one participant's second session. The final analyses included 29 participants ($M_{age} = 24.9$ years, $SD = 5.06$, age range = 19–43 years, $n_{women} = 16$). Participants' visual acuity was normal or corrected-to-normal (by contact lenses). Completion in both sessions was compensated with a NOK 300 (~€30) gift card. Two participants were compensated with a NOK 400 (~€40) gift card each because they experienced sickness after chewing the gum in the first session and rescheduled to complete the whole experiment.

4.1.2. Design, materials, and apparatus

In Experiment 2, we doubled the nicotine dosage to discern if there would be a different effect on the measured variables that could be attributed to the dosage. Nicotine of 4 mg was administered using Nicotinell® ice mint chewing gum and its taste-matched chewing gum as the placebo. Both types were identical in colour, shape, size, and flavour. We presumed the chewing gum would be less distinguishable by the participants.

We used OpenSesame ([Mathôt et al., 2012](#)) to recreate the MOT task and generate the stimuli. Eye events and pupil diameter were recorded

using the SMI RED250 remote eye-tracker running on iViewX 2.7 (60 Hz sample rate) during the task. The pupil recording resolution of individual measurements was better than 0.01 mm. Each trial started with a 2000-ms fixation dot that was used as the baseline pupil diameter (Fig. 4). All stimuli were presented in orange (RGB: 255, 140, 0) for 1000 ms, then targets were cued by the green colour (RGB: 0, 255, 0) for another 1000 ms. Subsequently, all stimuli appeared identical again in orange for 1000 ms before the animation. Tracking time was 10,000 ms, rendering each trial to last for 15,000 ms. The next trial would start immediately after a response was made and blocks were interspersed with a break period (see <https://osf.io/q7hfk/> for the task demonstration). Participants responded to the task by pressing one of the designated response keys. Other key functions were disabled, such that the next trial started only when one of the response keys was pressed and other keys would not be recorded.

In each Drug condition, there were 168 trials of MOT task divided into seven blocks (eight two-, eight three-, and eight four-target trials in every block). Participants were shown their average response time (ms) and success rate (%) in the block they had just completed. The next block was started by pressing the space bar. Trial orders were fully randomised. Participants had three practice trials preceding the experimental trials.

After the MOT task, we asked participants to complete the Abbreviated POMS questionnaire and to indicate the type of the chewing gum taken that day. Additionally, in the second session using the same questionnaire, participants were asked to rate the similarity in the taste between the two chewing gum types. Self-report assessments were recorded using OpenSesame on the same computer monitor as for the MOT task.

4.1.3. Procedure

There were on average $M_{day} = 7.83$ days ($SD = 5.31$, range = 3–24 days) in between the sessions. Participants read art history books as a filler task while chewing. The testing room was different from Experiment 1 and the illumination level (358 lx) allowed pupils to maintain an average size of about 4.6–4.8 mm.

4.2. Data processing and analyses

4.2.1. Subjective assessments

We analysed responses from Question 1 (a subset of the Abbreviated POMS questionnaire that was related with concentration level) and Question 2 (estimate of chewing gum type). For Question 1, one subscale that explicitly asked about concentration level was Confusion (CON) and this subscale was highly correlated ($r_s > 0.52$) with the Anger (ANG), Tension (TEN), and Depression (DEP) subscales (Grove and Prapavessis, 1992). To measure their self-reported concentration level, we summed the total scores in these four subscales. Higher scores in these subscales indicated lower concentration level. A paired-samples *t*-test was conducted to compare participants' scores that were correlated with concentration level in placebo and nicotine conditions.

For Question 2, responses were recorded in both sessions. This resulted in estimate of chewing gum type in the placebo as well as the nicotine conditions. Responses were first analysed using a binomial test to examine the proportion of correct and incorrect estimates. Further, we tested for the independence of the responses in two conditions (placebo vs. nicotine) using the chi-squared contingency tables.

4.2.2. Response accuracy and latency

Due to the faulty response operation in Experiment 1, we improved the key function in Experiment 2. Participants had to press either "P" or "Q", which were located on the opposite halves of the keyboard, for a "yes" or "no" answer, respectively. Other data processing and analyses were the same as in Experiment 1.

4.2.3. Pupil size

Binocular pupillary data resulted in 900 samples (i.e., 60 samples/s in a 15-s epoch) of pupil size per participant per trial in the MOT task. The trial epoch of interest for pupil diameter was during the tracking (from 5000 to 15,000 ms), in which pupil diameter from both left and right eyes was averaged into a single measure. Pupil size data during the epoch of interest were averaged first across samples (i.e., time points), then across trials, resulting in a single value for each participant. In

Fig. 4. Trial sequence of the MOT task in Experiment 2.

Note. The fixation phase was used as the baseline period. After displaying all of the stimuli, targets were cued in green colour during target assignment. The stimuli were displayed again in a uniform colour before moving randomly (arrows in the tracking phase indicate random movements). A stimulus was finally probed and participants indicated whether the probed stimulus was one of the targets or not. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Experiment 2, baseline pupil size was analysed using a paired-samples *t*-test comparing the placebo and nicotine conditions. Tracking pupil size was statistically analysed using a 2 (Drug: placebo vs. nicotine) $\times$ 3 (Load: 2 vs. 3 vs. 4) RM ANOVA.

4.3. Results

The reporting procedure of the analysis results in Experiment 2 is the same as in Experiment 1.

4.3.1. Subjective assessment

Subjective concentration level. Results suggested that the concentration-related scores in the placebo condition ($M = 9.966$, $SD = 7.998$) were significantly lower than the nicotine condition ($M = 15.069$, $SD = 10.849$), $t(28) = -2.555$, $p = .016$, Cohen's $d = -0.474$. Significantly lower scores indicated that participants were more concentrated in the placebo than the nicotine condition. Nevertheless, the Bayes factor suggested anecdotal evidence for the difference in the concentration level between the two groups, $BF_{10} = 3.014$.

Estimate of chewing gum type. It was shown that in the placebo condition, 24 participants (83%) correctly estimated the identity of chewing gum, $p < .001$, $BF_{10} = 150.694$. In the nicotine condition, there were also 24 participants (83%, $p < .001$, $BF_{10} = 150.694$) correctly estimating the chewing gum identity.

A chi-squared test with a contingency table revealed that responses in the placebo condition had no association with those in the nicotine condition, $\chi^2(2, N = 29) = 2.193$, $p = .139$, BF_{10} (independent multinomial, rows fixed) = 1.173. Three of the participants who estimated correctly in the first session did not estimate correctly in the second session. Three participants estimated correctly in the second session, although not in the first session. Two participants did not estimate correctly in both sessions.

4.3.2. Response accuracy and latency

Response accuracy. There was a significant main effect of Load, $F(1.990, 55.708) = 96.573$, $p < .001$, $\eta^2_p = 0.775$, $BF_{incl.} = 2.582e+19$ (Load as the best model). Accuracy was lower as tracking load increased (Load 2: $M = 0.930$, $SD = 0.256$; Load 3: $M = 0.875$, $SD = 0.330$; Load 4: $M = 0.831$, $SD = 0.375$). However, main effect of Drug ($F(1, 28) = 0.954$, $\eta^2_p = 0.033$, $BF_{incl.} = 0.304$) and a Drug $\times$ Load effect ($F(1.806, 50.567) = 1.171$, $\eta^2_p = 0.040$, $BF_{incl.} = 0.258$) were non-significant, $p > .313$ (Fig. 5).

Response latency. Results suggested that there was a significant main effect of Load, $F(1.777, 49.751) = 54.175$, $p < .001$, $\eta^2_p = 0.659$, $BF_{incl.} = 26.892$ (Load as the best model, Fig. 5). Response times were faster in a smaller tracking load (Load 2: $M = 714.407$, $SD = 383.643$; Load 3: $M = 755.799$, $SD = 413.213$; Load 4: $M = 803.217$, $SD = 443.994$). However, there were no significant Drug ($F(1, 28) = 0.017$, $p = .898$, $\eta^2_p = 0.001$, $BF_{incl.} = 0.168$) and Drug $\times$ Load effects ($F(1.920, 53.773) =$

0.764 , $p = .466$, $\eta^2_p = 0.027$, $BF_{incl.} = 0.113$).

4.3.3. Pupil size

During baseline period. The trace of pupil size throughout the MOT trials was plotted in Fig. 6. Results indicated that pupil size in the nicotine condition ($M = 4.399$, $SD = 0.676$) was significantly smaller than pupil size in the placebo condition ($M = 4.597$, $SD = 0.603$), $t(28) = 3.625$, $p = .001$, Cohen's $d = 0.673$, $BF_{10} = 29.835$.

During tracking. Results indicated a significant effect of Drug, $F(1, 28) = 13.475$, $p = .001$, $\eta^2_p = 0.325$, $BF_{incl.} = 1.041e+10$ (Drug + Load as the best model). Pupil size in the nicotine condition ($M = 4.412$, $SD = 0.665$) was smaller than pupil size in the placebo condition ($M = 4.597$, $SD = 0.617$).

A significant main effect of Load was also observed, $F(1.251, 35.024) = 45.040$, $p < .001$, $\eta^2_p = 0.617$. Pupil size was larger as tracking load increased (Load 2: $M = 4.457$, $SD = 0.645$; Load 3: $M = 4.508$, $SD = 0.650$; Load 4: $M = 4.550$, $SD = 0.646$).

Nevertheless, unlike the NHST, Bayesian analysis revealed that the data provided only weak evidence for Load, $BF_{incl.} = 2.585$. The Drug $\times$ Load effect was not significant, $F(1.911, 53.506) = 0.864$, $p = .423$, $\eta^2_p = 0.030$, $BF_{incl.} = 0.118$.

4.3.4. Discussion

In Experiment 2, we recorded participant's self-report and compared their pupil size, response latency, and response accuracy between the nicotine (4 mg) and placebo conditions during an MOT task. We increased twofold the nicotine dosage to observe if effects of nicotine on cognitive processing could be attributed to the higher dosage. In terms of the participants' estimate of chewing gum type, the trend was the same as in Experiment 1: 83% of participants estimated correctly the type of chewing gum in the placebo and nicotine conditions. Discernment of the chewing gum identity is further discussed in Section 6 General Discussion.

In terms of the self-reported concentration level, there was a discrepancy between the NHST and Bayesian analysis results. The NHST showed significantly higher concentration level in the placebo than in the nicotine condition. However, the Bayesian analysis suggested that the difference was anecdotal, similar to the result in Experiment 1 (see also Section 3.3.4 Discussion).

Comparing the baseline pupil size, we found that pupil size was smaller in the nicotine than placebo condition. The same trend was also observed in the pupil size during tracking. This finding was in line with our hypothesis. Similar to Experiment 1, pupils constricted as a result of the onset of visual movement (Fig. 6). Pupils would then dilate during tracking, reflecting attentional effort. Additionally, there was a discrepancy in the effect of tracking load on tracking pupil size. In contrast to the Bayesian analysis result, the NHST result showed that pupil size increased proportionally with the tracking load. This result had the same pattern as in Experiment 1 (see also Section 3.3.4 Discussion).

Fig. 5. Response accuracy and latency in Experiment 2.

Note. Load on the x axis is the number of targets to be tracked. Significant main effects of Load on response accuracy and response latency were observed.

Fig. 6. Pupil Size in Placebo and Nicotine (4 mg) Conditions of Experiment 2. Note. The figure above depicts pupil trace from the onset of fixation (time = 0) to the offset of tracking period (time = 15 s) in Experiment 2. The vertical dashed lines indicate the onset of the stated phases. The grey area shows a period in which pupil size wiggled into constriction, likely caused by changes in the stimulus field. The coloured shadings surrounding the pupillary traces represent 95% within-subject CI.

On the behavioural level, we discovered that 4-mg nicotine did not facilitate performance on the MOT task. Tracking load appeared to have very strong effects on response accuracy and latency. We found that responses were more accurate in the lower than higher tracking load. Response latency, in contrast, increased as tracking load was higher. There was no discrepancy in the results shown by NHST and Bayesian analysis for response accuracy and latency.

5. Results summary

Table 1 summarises the results of ANOVAs and *t*-tests to analyse response accuracy and latency as well as baseline and tracking pupil size. In both experiments, response accuracy was only affected by Load. The Bayesian analyses also suggested decisive evidence that accuracy would differ under different Load levels. For response latency, there was a significant effect of Load in Experiment 2, but not in Experiment 1. The Bayesian analysis result complemented the NHST result by suggesting strong evidence for the effect of Load on response latency.

For baseline pupil size, results indicated a clear and extremely strong effect of Drug. In Experiment 1, the baseline pupil size was during target assignment, thus there was an effect of Load as shown by the NHST. However, the Bayesian analysis did not show evidence for an effect of Load on baseline pupil size. In Experiment 2, the *t*-test result indicated a notable difference in baseline pupil size affected by Drug. For tracking pupil size, there were significant main effects of Drug and Load as shown by the NHST in both experiments. However, the Bayesian analyses in both experiments indicated very strong evidence only for Drug, but not for Load.

6. General discussion

The current study aimed to investigate the effect of nicotine on pupil size and behavioural performance during a multiple-object-tracking (MOT) task. Participants were non-nicotine users without pre-existing attentional deficits; by selecting these participants, we eliminated withdrawal and tolerance effects that are associated with impaired performance (Benowitz, 2009). Drug intake was manipulated using a relatively low dosage of nicotine (2 mg in Experiment 1 and 4 mg in Experiment 2), using a taste-matched chewing gum as a placebo control. Participants' response accuracy, response latency, and pupil size were measured during the MOT task wherein they were allowed to move their eyes.

First, we hypothesised that response accuracy would be higher in the nicotine condition than in the placebo condition, and that this effect

would persist under an increased tracking load. However, this hypothesis was not supported by our results: Participants' response accuracy was affected only by tracking load, and not by nicotine administration.

Second, we hypothesised that response times (RTs) would be faster in the nicotine condition than in the placebo condition, and that this effect would persist under an increased tracking load. Again, this hypothesis was not supported by our results: RTs were not affected by nicotine administration. Tracking load did affect RTs, as expected, although mostly, or only, in Experiment 2.

Third, we hypothesised that baseline (pre-trial) pupil size would be smaller in the nicotine condition than in the placebo condition, and that this difference would persist while participants were performing the tracking task. This hypothesis was supported by our results. Moreover, the results demonstrated that nicotine had a prolonged effect on pupil constriction, at least as long as our experiments lasted.

Our finding of smaller pupil size in the nicotine condition is consistent with previous findings (Erdem et al., 2015; Lie and Domino, 1999). This may show an interaction between nicotine and acetylcholine in the parasympathetic pathway that contracts the iris sphincter muscle, resulting in pupil constriction. However, this does not preclude the possibility that there were simultaneous nicotinic-cholinergic effects also in the central nervous system, which was not observable in our study, that could have contributed to the pupil constriction.

Fourth, we hypothesised that pupil size, as measured during the tracking task, would increase with increasing tracking load. This hypothesis was roughly supported by our results, although according to a Bayesian analysis, the evidence for this effect was only anecdotal.

Taken together, our findings show that there is a clear effect of low-dosage nicotine on the physiological level as reflected by the changes in pupil size. Smaller pupil size in the nicotine condition shows that nicotine administered via chewing gum is absorbed by the nervous system. However, such presence of nicotine in the nervous system does not enhance the cognitive performance of non-smokers, at least not as measured through response accuracy and latency on a MOT task. This null result is inconsistent with several previous studies that have observed beneficial effects of nicotine on attention (e.g., Kumari et al., 2003; Levin et al., 1998; Levin et al., 1996a; Levin et al., 1996b; Newhouse et al., 1988; Potter and Newhouse, 2004; White and Levin, 1999). There are several possibilities to explain this discrepancy. These possibilities are discussed below.

First, one possibility is that the nicotine dosage in our experiments (2–4 mg) was too low to result in a measurable effect on behaviour; other studies have administered 7–21 mg of nicotine per day. There are two caveats here, however. First, the beneficial effects of a higher

nicotine dosage largely comes from studies of nicotine-replacement therapy (NRT). The NRT involves patients with prolonged nicotine dependence, in which case nicotine is associated with relief of withdrawal and craving (Carpenter et al., 2013). Second, a low nicotine dosage (12 µg/kg body weight) administered subcutaneously to healthy non-smoking participants was found to improve response accuracy and load-specific latency in a memory *n*-back task (Kumari et al., 2003). Taken together, it is unclear what the minimum dosage of nicotine would be in order to observe behavioural benefits, if indeed such benefits exist.

Second, nicotine may mostly, or even only, improve performance for participants who are nicotine-dependent, or who suffer from cognitive deficits (e.g., Ernst et al., 2001; Evans et al., 2014). In experiments involving smokers as participants, the participants are usually deprived of nicotine (or cigarettes) for a night prior to the experiment. During the experiment, participants are then tested just before and right after they have received nicotine, thus providing relief from withdrawal. A positive effect of nicotine is then usually observed. One problem with this design is that it does not show clearly whether the enhancing effect of nicotine is a manifestation of withdrawal relief or a direct cognitive improvement. Poor performance during the deprivation period is likely due to participants feeling restless and having impaired concentration. After the nicotine intake, the negative side effects are alleviated, such that concentration and performance are better. This is known as the paradoxical relaxing-arousing effect of nicotine amongst smokers (Kumari et al., 2003), wherein participants feel calm and their attention increases.

Further, in clinical and smoker samples, nicotine may work differently at the neural transmission level as explained by the bivalent model of nicotine reinforcement (Valentine and Sofuoglu, 2018). According to the bivalent model, nicotine effects are driven by positive reinforcement (in nucleus accumbens) and negative reinforcement (in prefrontal cortex), both received by the $\alpha 4\beta 2$ and $\alpha 7$ nAChR. The positive reinforcement pathway centres around the rewarding effect of nicotine that mediate continued self-administration amongst nicotine-dependent users. For the relevance of the current discussion, we will focus on the negative reinforcement pathway. Via the negative reinforcement, nicotine enhances cognitive performance by alleviating impaired functioning, such as cognitive deficits, withdrawal effect, and craving/stress, as described previously. The mechanism of negative reinforcement is also observed in the inter-network connectivity level, showing differences between nicotine-abstinent and -satiated conditions (e.g., Lerman et al., 2014). Therefore, it is possible that beneficial effects of nicotine is observed amongst nicotine-dependent participants, but not amongst nicotine-independent participants.

A third possibility concerns the attentional function that is targeted by nicotine, namely the selective and divided attention. Although the two functions seem to share common processing mechanisms (Hahn et al., 2008b), they have different levels of intensity and cognitive demands (Hahn et al., 2008a). Unlike selective attention that engages attentional focussing and filtering, divided attention requires additional attentional resources to be distributed, possibly over multiple foci of attention (Alnæs et al., 2014; Cavanagh and Alvarez, 2005; Hahn et al., 2008a). Thus, one can speculate that cognitive demands are higher in the MOT paradigm, and as these demands increase, the facilitatory effect of nicotine diminishes. This diminution is demonstrated by the null effect on accuracy and RTs shown in this study and also in Hahn et al. (2008a). In contrast, nicotine appears to improve mainly the ‘monofocal’ feature of attention required by a sustained-attention task (Man-cuso et al., 1999). However, further studies are necessary to confirm this speculative mechanism and to refine our understanding of the nicotine benefits on some aspects of cognitive performance in healthy and typical participants.

One possible limitation of the present study is that the majority of participants could discern the active ingredient in the chewing gum. At the beginning of both experiments, the experimenter instructed

participants to take chewing gum from a container. At the end of each experimental session, participants were asked to indicate whether they took chewing gum with or without an active ingredient. The nicotine treatment in the experiment was unknown to the participants until debriefing, although they might have derived from the exclusion criteria that the active ingredient was nicotine. However, we did not observe a difference on the behavioural performance when participants were administered with nicotine or placebo. Therefore, we believe that discerning an active ingredient in chewing gum or a nicotine treatment in a multiple-object-tracking task would have very little to no effect on performance.

7. Conclusion

We investigated the effect of nicotine on pupil size and behavioural performance in a multiple-object-tracking task. Nicotine was administered via chewing gum to healthy non-smoking adults with no pre-existing attentional deficits. Compared to a placebo condition, we found that pupil size was smaller after the nicotine administration. Our finding confirmed previous studies showing pupil constriction after the nicotine intake, presumably due to a contraction of the iris sphincter muscle by an interaction between nicotine and acetylcholine receptors. However, in contrast with many previous findings, we did not observe a benefit of nicotine on the behavioural level.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

We declare that there is no conflict of interest amongst the authors.

Acknowledgement

We thank the Department of Psychology, University of Oslo, for the summer research fellowship given to the first author, such that we could conduct the second experiment in the present study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpsycho.2020.09.005>.

References

- Alnæs, D., Sneve, M.H., Espeseth, T., Endestad, T., van de Pavert, S.H.P., Laeng, B., 2014. Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. *J. Vis.* 14 (4), 1–20. <https://doi.org/10.1167/14.4.1>.
- American Society of Health-System Pharmacists, 2013. Nicotine gum. Retrieved January 10, 2018, from <https://medlineplus.gov/druginfo/meds/a684056.html>.
- Beatty, J., Lucero-Wagoner, B., 2000. The pupillary system. In: Cacioppo, J.T., Tassinari, L.G., Berntson, G.G. (Eds.), *Handbook of psychophysiology* (pp. 142–162). Cambridge University Press.
- Benowitz, N.L., 2009. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *The Annual Review of Pharmacology and Toxicology* 49, 57–71. <https://doi.org/10.1146/annurev.pharmtox.48.113006.094742>.
- Carpenter, M.J., Jardin, B.F., Burris, J.L., Mathew, A.R., Schnoll, R.A., Rigotti, N.A., Cummings, K.M., 2013. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs* 73 (5), 407–426. <https://doi.org/10.1007/s40265-013-0038-y>.
- Cavanagh, P., Alvarez, G., 2005. Tracking multiple targets with multifocal attention. *Trends Cogn. Sci.* 9 (7), 349–354. <https://doi.org/10.1016/j.tics.2005.05.009>.
- Cepeda-Benito, A., 1993. Meta-analytical review of the efficacy of nicotine chewing gum in smoking treatment programs. *J. Consult. Clin. Psychol.* 61 (5), 822–830. <https://doi.org/10.1037/0022-006X.61.5.822>.
- Cowan, N., 2011. The focus of attention as observed in visual working memory tasks: making sense of competing claims. *Neuropsychologia* 49 (6), 1401–1406. <https://doi.org/10.1016/j.neuropsychologia.2011.01.035>.

- Erdem, U., Gundogan, F.C., Dinc, U.A., Yolcu, U., Ilhan, A., Altun, S., 2015. Acute effect of cigarette smoking on pupil size and ocular aberrations: a pre- and post-smoking study. *Journal of Ophthalmology* 2015. <https://doi.org/10.1155/2015/625470>.
- Ernst, M., Matochik, J.A., Heishman, S.J., van Horn, J.D., Jons, P.H., Henningfield, J.E., London, E.D., 2001. Effect of nicotine on brain activation during performance of a working memory task. *Proc. Natl. Acad. Sci.* 98 (8), 4728–4733. <https://doi.org/10.1073/pnas.061369098>.
- Espeseth, T., Sneve, M.H., Rootwelt, H., Laeng, B., 2010. Nicotinic receptor gene *chrna4* interacts with processing load in attention. *PLoS One* 5 (12), 1–9. <https://doi.org/10.1371/journal.pone.0014407>.
- Ettinger, U., Faiola, E., Kasparbauer, A., Petrovsky, N., Chan, R.C.K., Liepelt, R., Kumari, V., 2017. Effects of nicotine on response inhibition and interference control. *Psychopharmacology* 234 (7), 1093–1111. <https://doi.org/10.1007/s00213-017-4542-8>.
- Evans, D.E., Maxfield, N.D., Rensburg, K.J.V., Oliver, J.A., Jentink, K.G., Drobos, D.J., 2013. Nicotine deprivation influences p300 markers of cognitive control. *Neuropsychopharmacology* 38 (12), 2525–2531. <https://doi.org/10.1038/npp.2013.159>.
- Evans, D.E., Jentink, K.G., Sutton, S.K., Rensburg, K.J.V., Drobos, D.J., 2014. 7mg nicotine patch fails to enhance p300 neural indices of cognitive control among nonsmokers. *Pharmacology Biochemistry and Behavior* 126, 77–82. <https://doi.org/10.1016/j.pbb.2014.09.001>.
- Grove, J.R., Prapavessis, H., 1992. Preliminary evidence for the reliability and validity of an abbreviated profile of mood states. *Int. J. Sport Psychol.* 23 (2), 93–109.
- Grundey, J., Amu, R., Ambrus, G.G., Batsikadze, G., Paulus, W., Nitsche, M.A., 2015. Double dissociation of working memory and attentional processes in smokers and non-smokers with and without nicotine. *Psychopharmacology* 232 (14), 2491–2501. <https://doi.org/10.1007/s00213-015-3880-7>.
- Hahn, B., Ross, T.J., Wolkenberg, F.A., Shakleya, D.M., Huestis, M.A., Stein, E.A., 2008a. Performance effects of nicotine during selective attention, divided attention, and simple stimulus detection: an fMRI study. *Cerebral Cortex* 19 (9), 1990–2000. <https://doi.org/10.1093/cercor/bhn226>.
- Hahn, B., Wolkenberg, F.A., Ross, T.J., Myers, C.S., Heishman, S.J., Stein, D.J., Kurup, P. K., Stein, E.A., 2008b. Divided versus selective attention: evidence for common processing mechanisms. *Brain Research* 1215, 137–146. <https://doi.org/10.1016/j.brainres.2008.03.058>.
- Hasselmo, M.E., Giacomini, L.M., 2006. Cholinergic modulation of cortical function. *Journal of Molecular Neuroscience* 30 (1–2), 133–135. <https://doi.org/10.1385/JMN:30:1:133>.
- Herman, A.I., DeVito, E.E., Jensen, K.P., Sofuoglu, M., 2014. Pharmacogenetics of nicotine addiction: role of dopamine. *Pharmacogenomics* 15 (2), 221–234. <https://doi.org/10.2217/pgs.13.246>.
- Jaros, A., Wiley, J., 2014. What are the ddds? A practical guide to computing and reporting bayes factors. *The Journal of Problem Solving* 7. <https://doi.org/10.7771/1932-6246.1167>.
- JASP, 2018. A fresh way to do statistics. <https://jasp-stats.org>.
- Keith, D.R., Kurti, A.N., Davis, D.R., Zvorsky, I.A., Higgins, S.T., 2017. A review of the effects of very low nicotine content cigarettes on behavioural and cognitive performance. *Preventive Medicine*. <https://doi.org/10.1016/j.ypmed.2017.06.016>.
- Kim, J.W., Baum, C.R., 2015. Liquid nicotine toxicity. *Paediatric Emergency Care* 31 (7), 517–521. <https://doi.org/10.1097/PEC.0000000000000486>.
- Kimura, F., 2000. Cholinergic modulation of cortical function: a hypothetical role in shifting the dynamics in cortical network. *Neuroscience Research* 38 (1), 19–26. [https://doi.org/10.1016/S0168-0102\(00\)00151-6](https://doi.org/10.1016/S0168-0102(00)00151-6).
- Kozak, R., Bruno, J.P., Sarter, M., 2006. Augmented prefrontal acetylcholine release during challenged attentional performance. *Cerebral Cortex* 16 (1), 9–17. <https://doi.org/10.1093/cercor/bhi079>.
- Kumari, V., Gray, J.A., Ffytche, D.H., Mitterschiffthal, M.T., Das, M., Zachariah, E., Vythelingum, G.N., Williams, S.C.R., Simmons, A., Sharma, T., 2003. Cognitive effects of nicotine in humans: an fmri study. *NeuroImage* 19 (3), 1002–1013. [https://doi.org/10.1016/S1053-8119\(03\)00110-1](https://doi.org/10.1016/S1053-8119(03)00110-1).
- Laeng, B., Sirois, S., Gredebäck, G., 2012. Pupillometry: a window to the preconscious? *Perspect. Psychol. Sci.* 7 (1), 18–27. <https://doi.org/10.1177/1745691611427305>.
- Lerman, C., Gu, H., Loughhead, J., Ruparel, K., Yang, Y., Stein, E.A., 2014. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry* 71 (5), 523–530. <https://doi.org/10.1001/jamapsychiatry.2013.4091>.
- Levin, E.D., Connors, C.K., Sparrow, E., Hinton, S.C., Erhardt, D., Meck, W.H., Rose, J.E., March, J., 1996a. Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology* 123 (1), 55–63. <https://doi.org/10.1007/BF02246281>.
- Levin, E.D., Wilson, W., Rose, J.E., McEvoy, J., 1996b. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. *Neuropsychopharmacology* 15 (5), 429–436. [https://doi.org/10.1016/S0893.133X\(96\)00018-8](https://doi.org/10.1016/S0893.133X(96)00018-8).
- Levin, E.D., Connors, C.K., Silva, D., Hinton, S.C., Meck, W.H., March, J., Rose, J.E., 1998. Transdermal nicotine effects on attention. *Psychopharmacology* 140 (2), 135–141. <https://doi.org/10.1007/s002130050750>.
- Lie, T., Domino, E.F., 1999. Effects of tobacco smoking on the human pupil. *Int. J. Clin. Pharmacol. Ther.* 37 (4), 184–188.
- Luttrell, W.E., Vogel, H.F., 2014. Nicotine. *Journal of Chemical Health and Safety* 21 (4), 39–41. <https://doi.org/10.1016/j.jchas.2014.05.006>.
- Mancuso, G., Warburton, D.M., Mélen, M., Sherwood, N., Tirelli, E., 1999. Selective effects of nicotine on attentional processes. *Psychopharmacology* 146 (2), 199–204. <https://doi.org/10.1007/s002130051107>.
- Mathôt, S., 2018. Pupillometry: psychology, physiology, and function. *Journal of Cognition* 1 (1), 16–39. <https://doi.org/10.5334/joc.18>.
- Mathôt, S., Schreij, D., Theeuwes, J., 2012. Opensesame: an open-source, graphical experiment builder for the social sciences. *Behavioural Research* 44, 314–324. <https://doi.org/10.3758/s13428-011-0168-7>.
- McDougal, D.H., Gamlin, P.D.R., 2008. Pupillary control pathways. In: Masland, R.H., Albright, T. (Eds.), *The Senses: A Comprehensive References* (pp. 521–536). Academic Press.
- Meyerhoff, H.S., Papenmeier, F., Huff, M., 2017. Studying visual attention using the multiple object tracking paradigm: a tutorial review. *Attention, Perception, & Psychophysics* 79, 1255–1274. <https://doi.org/10.3758/s13414-017-1338-1>.
- Newhouse, P.A., Sunderland, T., Tariot, P.N., Blumhardt, C.L., Weingartner, H., Mellow, A., Murphy, D.L., 1988. Intravenous nicotine in alzheimer's disease: a pilot study. *Psychopharmacology* 95, 171–175. <https://doi.org/10.1007/BF00174504>.
- Newhouse, P.A., Potter, A., Singh, A., 2004. Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology* 4 (1), 36–46. <https://doi.org/10.1016/j.coph.2003.11.001>.
- Nicorette. (n.d.). Nicorette gum: How to use. Retrieved January 10, 2018, from <https://www.nicorette.ca/products/gum/#how-to-use>.
- Ortega, L.A., Tracy, B.A., Gould, T.J., Parikh, V., 2013. Effects of chronic low- and high-dose nicotine on cognitive flexibility in c57bl/6j mice. *Behavioural Brain Research* 238, 134–145. <https://doi.org/10.1016/j.bbr.2012.10.032>.
- Perry, E., Walker, M., Grace, J., Perry, R., 1999. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends in Neuroscience* 22 (6), 273–280. [https://doi.org/10.1016/S0166-2236\(98\)01361-7](https://doi.org/10.1016/S0166-2236(98)01361-7).
- Potter, A.S., Newhouse, P.A., 2004. Effects of acute nicotine administration on behavioural inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology* 176, 182–194. <https://doi.org/10.1007/s00213-004-1874-y>.
- Prettyman, P., Bitsios, R., Szabadi, E., 1997. Altered pupillary size and darkness and light reflexes in alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 62 (6), 665–668. <https://doi.org/10.1136/jnnp.62.6.665>.
- Pylyshyn, Z.W., 2004. Some puzzling findings in multiple object tracking: tracking without keeping track of object identities. *Vis. Cogn.* 11 (7), 801–822. <https://doi.org/10.1080/13506280344000518>.
- Pylyshyn, Z.W., Storm, R.W., 1988. Tracking multiple independent targets: evidence for a parallel tracking mechanism. *Spat. Vis.* 3 (3), 179–197. <https://doi.org/10.1163/156856888X00122>.
- Rezvani, A.H., Levin, E.D., 2001. Cognitive effects of nicotine. *Biol. Psychiatry* 49 (3), 258–267. [https://doi.org/10.1016/S0006-3223\(00\)01094-5](https://doi.org/10.1016/S0006-3223(00)01094-5).
- Sarter, M., Bruno, J.P., 1999. Abnormal regulation of corticopetal cholinergic neurons and impaired information processing in neuropsychiatric disorders. *Trends in Neuroscience* 22 (2), 67–74. [https://doi.org/10.1016/S0166-2236\(98\)01289-2](https://doi.org/10.1016/S0166-2236(98)01289-2).
- Stergiou, V., Fotiou, D., Tsiptsios, D., Haidich, B., Nakou, M., Giantselidis, C., Karlovasitou, A., 2009. Pupillometric findings in patients with parkinson's disease and cognitive disorder. *International Journal of Psychophysiology* 72 (2), 97–101. <https://doi.org/10.1016/j.ijpsycho.2008.10.010>.
- Valentine, G., Sofuoglu, M., 2018. Cognitive effects of nicotine: recent progress. *Curr. Neuropharmacol.* 16, 403–414. <https://doi.org/10.2174/1570159X15666171103>.
- Wang, C., Munoz, D.P., 2015. A circuit for pupil orienting response: implications for cognitive modulation of pupil size. *Current Opinion in Neurobiology* 33, 134–140. <https://doi.org/10.1016/j.conb.2015.03.018>.
- Wetzels, R., Matzke, D., Lee, M.D., Rouder, J.N., Iverson, G.J., Wagenmakers, E.J., 2011. Statistical evidence in experimental psychology: an empirical comparison using 855 t tests. *Perspect. Psychol. Sci.* 6 (3), 291–298. <https://doi.org/10.1177/1745691611406923>.
- White, H.K., Levin, E.D., 1999. Four-week nicotine skin patch treatment effects on cognitive performance in alzheimer's disease. *Psychopharmacology* 143 (2), 158–165. <https://doi.org/10.1007/s002130050931>.
- Whitehouse, P., 2014. Acetylcholine. In: Daroff, R., Aminoff, M. (Eds.), *Encyclopedia of the Neurological Sciences* (pp. 19–21). Elsevier Science. <https://books.google.be/books?id=hjSVIwVIRUC>.
- Yudkin, P., Munafò, M., Hey, K., Roberts, S., Welch, S., Johnstone, E., Murphy, M., Griffiths, S., Walton, R., 2004. Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. *BMJ* 328 (7446), 989–990. <https://doi.org/10.1136/bmj.38050.674826>.