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Original article

Acute administration of nicotine does not enhance cognitive functions

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Chronic smokers often claim that smoking improves their cognitive abilities, such as concentration. However, scientific evidence to support this claim is scarce. Previous studies gave inconclusive results, and some of them had significant methodological flaws. Therefore, the aim of this study was to test whether smoking a single cigarette affects performance across several cognitive domains. It included a group of 22 occasional smokers aged 19–29 years. Attention, working memory, and visuospatial reasoning were assessed using a within-subjects design with a control setting. There were two separate testing sessions two days apart. Half the group started with experimental and the other half with control setting. In the experimental setting, the participants completed the first block of tasks, smoked one cigarette (with a nicotine yield of 0.5 mg), and then completed the second block of tasks. In the control setting, the procedure was the same, except that the participants had a glass of water instead of a cigarette. Repeated measures ANOVA showed no significant effects of cigarette smoking on either reaction time rates or accuracy on any of the three cognitive domains. These results suggest that, at least among young, occasional smokers, smoking does not affect cognition and the claims of its improvement are probably a result of some sort of cognitive bias.

KEY WORDS: attention; mental rotation; nicotine; smoking; working memory

Smokers often claim that in addition to relaxing effects, smoking improves their cognitive abilities (1–3). Some earlier studies suggest that smoking indeed improves cognitive performance, but many of them had flawed design (4). For example, the participants were smokers who were tested after a certain period of deprivation, and their performance was then compared with the performance on the same tasks after smoking. Since abstinence symptoms can cause emotional, physical, and cognitive difficulties (5), it cannot be determined whether improved performance after smoking reflected the actual effect of nicotine or only the participants' normal performance, once the abstinence symptoms were removed. Some studies lacked ecological validity, as nicotine was not smoked but administered through the transdermal or intranasal route, and their findings are not comparable with the smoking studies due to huge variations in nicotine doses (4).

Nicotine activates nicotinic acetylcholine receptors (nAChRs) (6), which are highly represented in the cortical and subcortical areas of the brain. By binding to specific cellular and substrate nAChR subtypes, nicotine modulates the activity of different types of neurons in the neuronal network (7). In addition to facilitating the release of acetylcholine, nicotine also facilitates the release of dopamine, serotonin, glutamate, and other neurotransmitters involved in cognitive processes, including attention, working memory, and visuospatial reasoning (5).

Attention processes are strongly linked to acetylcholine signalling in the prefrontal cortex (PFC). Nicotine has been shown to increase acetylcholine activity in the PFC, which suggests that it might have a positive effect on attention (7, 8). One study showed that nicotine enhanced reaction time (9) and another accuracy of response (10) in the rapid visual information processing (RVIP) task. Furthermore, nicotine seems to de-activate certain brain regions that need to be de-activated to successfully solve the RVIP task (8) and therefore to facilitate focusing of cognitive resources on a specific task. Similar effects were reported for the continuous performance task (11, 12), vigilance, and selective attention. However, these effects varied significantly with the type and difficulty of the tasks (13, 14). Studies in clinical populations are particularly interesting, as they showed a promising potential of nicotine for therapeutic purposes by improving performance in patients with ADHD (12) and schizophrenia (15).

As for working memory, a large number of nicotine receptors were found in the hippocampus, which suggests that nicotine could also influence memory (16). Several studies conducted mostly on rodents confirmed this hypothesis (17, 18). The most significant improvements after nicotine treatment were seen in spatial working

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memory tasks (e.g. radial labyrinth). Although this effect has repeatedly been confirmed in animals, the results are rather inconsistent in humans (3, 9, 19–22). However, these studies were conducted on deprived smokers, and it is impossible to exclude abstinence symptoms as the confounding factor. Ernst et al. (23) compared smokers and former smokers (who had not smoked for 6.5 years before entering the study) and found no effect of nicotine in former smokers. They also monitored brain activity during task solving and found that smokers had higher activity in the right hemisphere, while non-smokers had higher activity in the left hemisphere, which suggests that chronic exposure to nicotine or withdrawal from nicotine affects cognitive strategies used to perform a memory task.

Since spatial reasoning mainly activates the right brain (24–34) and since nicotine increases right brain activity as well, nicotine might also influence visuospatial reasoning. Several animal and human studies have investigated this effect of nicotine on spatial working memory (17, 18, 35, 36) and yielded inconsistent results. Studies of nicotine effects on visuospatial reasoning, in turn, remain few and inconclusive. In an EEG study, Iwaki et al. (37) reported minimal improvement in the reaction time and the number of correct answers between the experimental (cigarette smoking) and control setting (a break without smoking) in 12 study participants. However, the lateralization (greater right hemisphere activity) was significantly higher after the experimental treatment. Neumann et al. (38) also explored possible sex differences, and found that, contrary to Iwaki et al. (37), nicotine prolonged reaction times in the mental rotation tasks, which was even more pronounced in women than men. They suggested that men are more resistant to the effect of nicotine due to their general superiority in mental rotations.

Mental rotations are the most complex type of spatial abilities, involving many different areas of the brain, and various cognitive processes. It is very likely that attention has an important role in these processes (39), especially the ability to maintain attention over a longer time. Therefore, it seems plausible that nicotine affects performance on mental rotation tasks through attention-allocating processes (11–13).

In summary, given the inconsistencies and methodological flaws of earlier research, it is still not clear which, if any, of the cognitive functions are affected by nicotine. Therefore, the aim of this study was to exclude withdrawal/abstinence symptoms as a confounding factor by testing the effects of smoking one cigarette in a group of occasional smokers without withdrawal symptoms. Furthermore, we tested their performance in three cognitive domains: working memory, attention, and spatial reasoning. We chose these domains in an attempt to differentiate between direct effects of nicotine on certain complex cognitive processes (such as spatial reasoning, measured here via mental rotations) and its potential indirect effects (e.g. by enhancing underlying cognitive processes, such as attention and working memory).

PARTICIPANTS AND METHODS

Participants

The study included 22 participants (20 women and two men) aged 19–29 years (mean±SD=22.2±2.35). They were tested individually, after signing an informed consent. The procedure followed the Ethical Code of Conduct of the Croatian Psychological Association and the guidelines of the Declaration of Helsinki. All participants were occasional smokers, who smoked less than one cigarette a day. Fifteen smoked up to 15 cigarettes a month, and seven smoked one to five cigarettes a week. Sixteen smoked exclusively during a night out, and six also smoked in stressful situations (e.g. exams). At the first meeting, participants filled a socio-demographics background questionnaire, and their anonymity was ensured by replacing personal information with a unique code. All participants declared that they were healthy.

Study design

The protocol for each testing session was the same: in the first session the participants completed the first trial (pretest), then had a short break during which they smoked one cigarette (experimental setting) or drank a glass of water (control setting) and then completed the second trial (posttest). In the second session, two days later, they did the same tasks again, but if they had smoked a cigarette during the first session, now they had to drink water (Figure 1). All the participants were given the same brand of cigarettes, which yields 0.5 mg of nicotine and 6 mg of tar. This amount of nicotine was selected because these occasional smokers were not used to larger amounts and we wanted to avoid the risk of inducing adverse side effects.

We opted for a within-subject design in which all participants were exposed to all conditions, so that individual differences would not distort the results. Each participant served as his/her own baseline. Furthermore, within-subject designs have greater statistical power than between-subjects designs (takes fewer participants to show a significant effect if there is one). The reason for this is that repeated measures ANOVA separates individual variance from the rest of the error variance. Thus, the total variance in the within-subject analysis is comprised of treatment variance, between-subjects variance, and error variance. By separating between-subjects variance, we reduced the amount of error variance in the equation, allowing for greater internal validity of the study. To avoid a potential limitation of a repeated measures design and of the learning effect (enhanced performance is expected on subsequent trials of most cognitive tests), we counterbalanced the order of sessions for all participants.
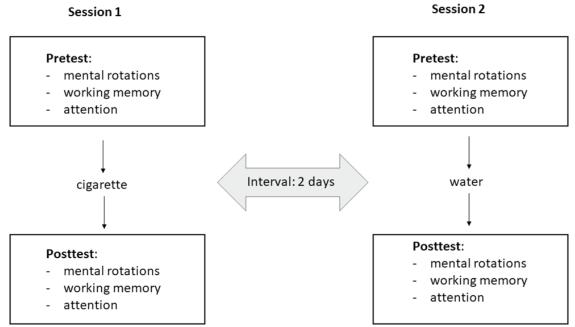
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Figure 1 Experimental design

Testing

We used E-prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, USA) (40) to run the tests and collect participants' responses.

Mental rotation task

Participants were first shown a fixation cross (for 500 ms) which was then followed by a letter (F, G, L, N, P, or R), which was either rotated, mirrored, or rotated and mirrored. They had to press "1" on the keyboard if the letter was mirrored, "0" if the letter was just rotated or shown normally (Figure 2). The letter would stay on the screen for no more than ten seconds (or less if the participant responded sooner) after which the next item was loaded. The task had 50 items and lasted about two minutes.

Working memory task

We used a modified version of Experiment 1 described by Vogel et al. (41). Participants were briefly shown red
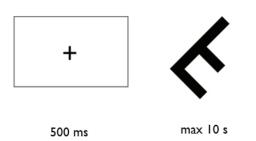

Figure 2 An item in the mental rotations task: letter F is both mirrored and rotated

and blue rectangles at various angles. They had to memorise the position of the rectangles indicated by the arrow and then, when the next picture was shown, respond if the two pictures were identical or if they differed. Participants were first shown a fixation cross (400 ms) with an arrow indicating on which side of the screen they should focus, followed by the first picture with rectangles (300 ms), then again a fixation cross (500 ms), and then the second picture with rectangles (Figure 3). The participants had to press "1" if the second picture was the same as the first one or "0" if the pictures were different. The second picture was displayed for no more than 10 seconds. The task had 96 items and lasted about four minutes.

Attention task

Participants were first shown a fixation cross (1 s), then a letter of the alphabet (1 s), then again a fixation cross (1 s), and then a letter (1 s). They had to press "1" if the second letter was letter "X" which was preceded by letter "A". If any other combination of letters appeared on the screen, participants had to press "0" (Figure 4). Two sets of letters were separated by a pause, which lasted either 1500 ms, 2000 ms, or 2500 ms. The durations of the pause were randomised. The task had 45 items and lasted for about three and a half minutes.

Statistical analysis

All data analyses and statistical procedures were carried out with the IBM SPSS Statistics v. 25 (Armonk, NY, USA). We used the repeated measures ANOVA to analyse reaction time and accuracy (dependent variables) in relation to setting (experimental vs. control) and trial (pretest vs. posttest). The rationale for this procedure was that we
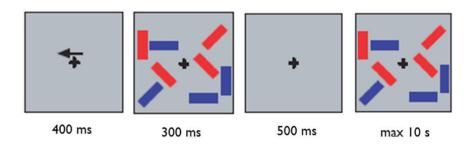
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Figure 3 An item in the working memory task

Figure 4 An item in the attention task

expected a significant main effect of trial (i.e. better performance at posttest as compared to pretest), but also wanted to test for an interaction effect between setting and trial. If there was an enhancing effect of smoking on performance, then the pretest-posttest increase in participants' scores would be significantly larger in the experimental setting as compared to the control setting.

First we ran it for the female participants only and then included the responses of the two male participants and repeated the analysis. As this inclusion did not change the results, their data were kept in the analysis.

RESULTS

Mental rotation

ANOVA showed no significant effects of cigarette smoking (vs. water) on either reaction times (ms) or on the number of correct answers (Figures 5 and 6, Table 1). Participants were significantly faster at posttest, regardless of whether they drank water or smoked a cigarette during the break, but did not significantly improve the number of correct answers (Table 1).

Working memory

Regardless of the setting (experimental or control), participants were significantly faster (ms) and had significantly more correct answers in the posttest than in pretest (Figures 7 and 8, Table 2). However, there were no significant differences between settings (experimental vs. control) and no significant interaction (setting x trial) (Table 2).

Attention

In both the experimental and control settings, participants were significantly faster (ms) in the posttest than pretest (Figure 9). Neither the main effect of the setting (experimental vs. control) nor the interaction (setting x trial) were significant (Table 3). The number of correct answers hit the ceiling (accuracy was at 96 % in the pretest of the first session and 97.8 % in subsequent trials; Figure 10), so there were no significant effects of either treatment, trial, or their interaction. Figure 6 also shows that one participant consistently had a lower accuracy, so the analysis was repeated without that participant, but that exclusion did not change the results.

DISCUSSION

The main aim of this study was to test the assumption that smoking of a single cigarette would improve attention, working memory, and visuospatial reasoning, and our results showed no such effect.

Table 1 Mental rotations: repeated measures analysis of variance with setting (experimental vs. control) and trial (pretest vs. posttest) as sources of variance and reaction time and accuracy as dependent variables

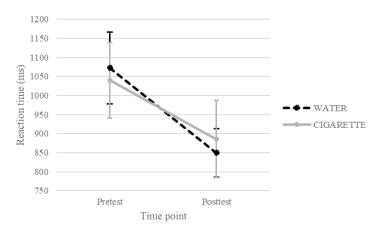|	Reaction time				Accuracy			
Variable	F	df	P	Partial η^2	F	df	P	Partial η^2
Trial (A)	26.832	(1, 21)	0.000**	0.561	0.017	(1, 21)	0.897	0.001
Setting (B)	0	(1, 21)	0.985	0.000	0.738	(1, 21)	0.400	0.034
A*B	0.787	(1, 21)	0.385	0.036	0.631	(1, 21)	0.436	0.029

*P<.05; **P<.01

Figure 5 Mental rotation: mean reaction time (ms) for each experimental setting (N=22)
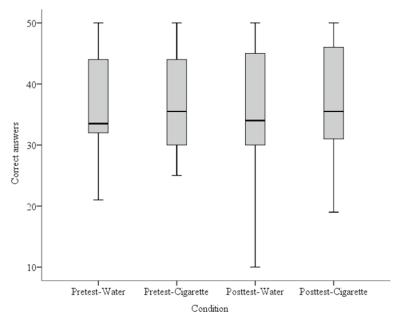

Figure 6 Mental rotation: number of correct answers for each experimental setting (N=22)
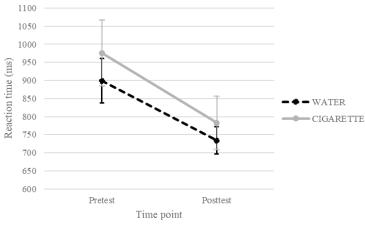

Figure 7 Working memory: mean reaction time (ms) for each experimental setting (N=22)

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Table 2 Working memory: repeated measures analysis of variance with setting (experimental vs. control) and trial (pretest vs. posttest) as sources of variance and reaction time and accuracy as dependent variables

Variable	Reaction time				Accuracy			
	F	df	P	Partial η²	F	df	P	Partial η²
Trial (A)	31.119	(1, 21)	0.000**	0.597	6.777	(1, 21)	0.017*	0.244
Setting (B)	0.511	(1, 21)	0.482	0.024	0.304	(1, 21)	0.587	0.014
A*B	0.210	(1, 21)	0.651	0.01	0.210	(1, 21)	0.571	0.016

*P<0.05; **P<0.01

Table 3 Attention: repeated measures analysis of variance with setting (experimental vs. control) and trial (pretest vs. posttest) as sources of variance and reaction time and accuracy as dependent variables

Variable	Reaction time				Accuracy			
	F	df	P	Partial η²	F	df	P	Partial η²
Trial (A)	12.573	(1, 21)	0.002*	0.374	2.967	(1, 21)	0.100	0.124
Setting (B)	0.77	(1, 21)	0.39	0.035	0.884	(1, 21)	0.358	0.040
A*B	0.354	(1, 21)	0.558	0.017	1.067	(1, 21)	0.313	0.048

*P<0.05; **P<0.01

In the majority of earlier studies, the route of nicotine administration was subcutaneous (injection), transdermal (patch), buccal (nicotine chewing gum), or intranasal (spray). These routes deliver higher nicotine doses than smoking. In other words, the lack of effect in this study may be related to the route (smoking) and dose (0.5 mg) of nicotine administered. Declarations on most cigarette brands on the market state that they yield from 0.1 to 1.1 mg of nicotine, which has been confirmed by independent reports (42). The nicotine dose used in this study may have been too low to cause any effect (3, 43). Another possible explanation for the lack of differences between cigarette vs. control setting is that the control setting (water drinking) may have had an expectancy effect. But again, this would only suggest that the effect of one cigarette, contrary to popular belief, is no greater than that of a placebo.

Attention has previously been shown as the most susceptible to the effects of nicotine (9, 12–14). However, ours is not the first study to show no significant effect (20, 21, 44). Some authors (13, 14) suggest that the effect of nicotine on attention could be a function of task complexity, and that the best improvement is achieved in tasks of medium difficulty. Admittedly, however, our participants found this task too easy and achieved the score plateau during the first session, leaving little room for improvement. Even so, the improvement in performance would have been detected in reduced reaction times, but there was no significant effect of nicotine on those either. Future studies might address this issue by using tasks of various levels of difficulty within the same cognitive domain in order to elucidate this possibly non-linear correlation. The time needed to complete the task should also be considered. In our case, the task lasted about four minutes, but the effect of nicotine, if there is one, might become evident in longer tasks.

The only significant effect we found in the working memory test was the improvement in repeated trials. These results are consistent with some previous studies (21–23).

As there is a lack of information regarding the possible effect of nicotine on visuospatial working memory in humans, we focused specifically on this component of working memory (as participants had to memorise and recognise specific locations of rectangles in the working memory task). Some previous findings (8, 23, 37) suggest that smokers prefer visual strategies (storing and processing information in a visual or spatial form, i.e. using a visuospatial sketchpad) and ex-smokers prefer phonological strategies (storing and processing information in a form of spoken and written material, i.e. using a phonological loop). While these results suggest that smokers might have an advantage in solving complex visuospatial tasks, there is not enough evidence to confirm that or to pinpoint the neural mechanism underlying this nicotine-induced lateralisation shift. However, the notion that smokers have an increased activation of the areas in the right brain that are associated with visuospatial abilities seemed worth investigating, which is why we tested performance on a mental rotation task and a working memory task with a visuospatial component. Again, with each repetition of the task, the participants had a faster response to the stimulus, but the number of correct answers did not change.

Limitations and strengths of this study

This study had a relatively small sample size. This is not unusual in this type of research, as majority of previously published studies had about 20 participants. However, larger and gender-balanced samples would make conclusions more generalisable. Furthermore, our group of participants may have been heterogeneous regarding their smoking habits (e.g. some are exclusively "social smokers", others smoke when they work/study) and their smoking-related beliefs.

As discussed above, unlike other means of delivery (e.g. intranasal spray) smoking does not allow for a precise control of the amount of nicotine being delivered. Also,
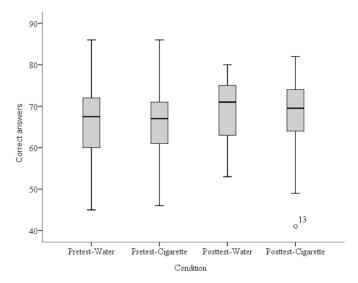
Figure 8 Working memory: number of correct answers for each experimental setting (N=22)
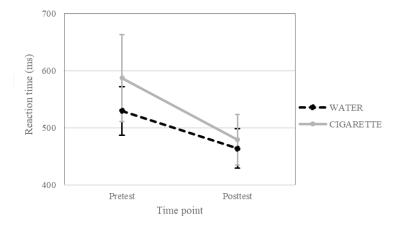

Figure 9 Attention: mean reaction time (ms) for each experimental setting (N=22)
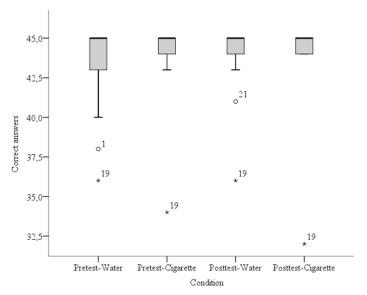

Figure 10 Attention: number of correct answers for each experimental setting (N=22)

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other ingredients (e.g. tar) in the cigarette may have interfered with the effect of nicotine. Furthermore, we did not control for the duration of the cigarette break, i.e. the participants were asked to smoke the cigarette at their usual pace. The puff rate can influence the plasma nicotine concentration, i.e. the faster the rate, the higher the nicotine concentration. In other words, administering nicotine through cigarette smoking is rather imprecise in terms of dosage. A dose-dependent study design might provide a more meaningful information regarding the specific effects of nicotine on cognition.

These shortcomings notwithstanding, we believe that the choice of occasional smokers is one of the main advantages of this study, as it overcomes the problem pertinent to chronic smokers of distinguishing between the effects of nicotine and withdrawal symptoms on cognitive performance (4). Occasional smokers have a certain tolerance for negative nicotine effects and are unlikely to suffer from withdrawal symptoms. Similarly, unlike some other routes of administration smoking adds to the ecological validity of the study – most people inhale and not inject themselves with nicotine. An additional advantage of this research is the use of a full experimental design, i.e. the pre-posttest control, contributing to a greater internal validity of the experiment.

Furthermore, ours was one of the few studies that dealt with visuospatial reasoning, and even though no significant effect of nicotine was found in this domain, it has singled out potentially relevant variables (e.g. sex differences, lateralisation, and the frequency of cigarette use in everyday life) and suggested directions for future research in this domain.

CONCLUSION

Taken together, our results suggest that the effect of cigarettes on cognition is probably subjective. People tend to believe that a cigarette shall have some beneficial effect (e.g., help them relax and/or improve their concentration). In other words, cigarettes may have a placebo effect. It is also possible that nicotine does improve performance on some tasks, but, in reality, this effect is small at best. Furthermore, cigarettes may indirectly influence cognitive performance through mood enhancement and general activation. A small number of studies dealt with these aspects, and future research should focus more on it in order to determine the potential indirect effects of nicotine. Given the inconsistency and lack of significant effect in many human studies, it seems likely that self-reported enhancement in cognitive functions is a result of various cognitive biases (such as confirmation bias and illusory correlation), at least among young, occasional smokers. Self-reports are notoriously prone to errors in judgement and such errors might have a role in maintaining the smoking habit.

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Akutna primjena nikotina ne poboljšava kognitivne funkcije

Kronični pušači često tvrde da im pušenje, između ostaloga, pozitivno utječe na kognitivne sposobnosti (npr. pomaže im u održavanju koncentracije). Je li doista tako još uvijek nemamo jednoznačan odgovor, budući da su prethodne studije ne samo dale nekonzistentne rezultate nego su bile i metodološki manjkave. Stoga je cilj ovoga istraživanja bio utvrditi utječe li konzumacija jedne cigarete na izvedbu zadataka u nekoliko različitih kognitivnih domena. U istraživanju je sudjelovala skupina povremenih pušača u dobi od 19 do 29 godina. Pomoću računalnog programa E-Prime prezentirani su zadaci koji mjere pažnju, radno pamćenje i obradu vidno-prostornih informacija. Korišten je prije-poslije nacrt, uz kontrolni i eksperimentalni uvjet. Sudionici su iste zadatke rješavali četiri puta: prije i poslije tretmana u kontrolnom uvjetu te prije i poslije tretmana u eksperimentalnom uvjetu. U kontrolnom uvjetu tretman se sastojao od čaše vode koju su sudionici morali popiti, a u eksperimentalnom uvjetu od pušenja jedne cigarete koja otpušta 0,5 mg nikotina. Stanka između kontrolnoga i eksperimentalnoga testiranja bila je dva dana. Redoslijed uvjeta bio je rotiran. Niti u jednom zadatku nije utvrđen značajan utjecaj pušenja ni na vrijeme reakcije ni na točnost rješavanja. Ovi su nalazi u skladu s hipotezom da su samoiskazi o pozitivnom utjecaju pušenja na kognitivnu učinkovitost posljedica neutemeljenih subjektivnih dojmova.

KLJUČNE RIJEČI: mentalne rotacije; nikotin; pažnja; pušenje; radno pamćenje