Response Inhibition and Sustained and Attention in Heavy Smokers Versus Non-smokers

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ABSTRACT

Background: Repeated nicotine administration induces neuro-adaptations associated with abnormal dopaminergic activity. These neuronal changes may contribute to impaired inhibitory control and attention deficit. However, it remains unclear whether smokers perform worse than non-smokers on tests that involve attention and control of impulsivity. The present study examined response inhibition and sustained attention capacities in a large sample of smokers and non-smokers.

Methods: Continuous Performance Test (CPT) and Go/NoGo computerized tasks were used as a measure of response-inhibition ability and sustained attention. Three-way repeated measures analysis of covariance was used with response time, variability of response time, number of commission errors (inappropriate responses to stimuli) and number of omission errors (missed stimuli) as dependent measures. Main effects were: group (smokers and controls), condition (CPT and Go/NoGo), and block (in each condition); gender, education, and age were used as covariates.

Results and Conclusions: Smokers, as compared to the control group, made more errors of commission in the Go/NoGo task, reflecting impaired inhibition ability. However, we found no significant differences between the groups in our measure of sustained attention. Impaired response inhibition was found to co-occur with heavy smoking and therefore may be a potential target for the development of more effective cessation programs.

BACKGROUND

Tobacco smoking is one of the leading causes of preventable death in the world (1). Tobacco use not only kills approximately 440,000 Americans each year, it also causes serious health problems in the population. According to national surveys, an estimated 70.9 million Americans aged 12 or older reported current use of tobacco (2). Chronic smoking is not merely a destructive habit, but is also widely accepted as an addiction. Most chronic smokers use tobacco because they are addicted to nicotine (2). Addiction to nicotine can be described as a persistent state in which there is diminished capacity to control compulsive drug-seeking, regardless of whether it involves risk of negative consequences (3).

In order to improve characterization and treatment of this debilitating addiction, clinicians and researchers are interested in identifying behavioral patterns that may either contribute to or co-occur with smoking (4).

The subjective and physiological effects of smoking are caused by the central actions of nicotine (5), the primary constitute of tobacco. The effects of nicotine on neurocognitive function have long been held to play a role in nicotine dependence. Previous studies hypothesized that smoking may be used as a form of self-medication due to beneficial acute effects of nicotine on cognitive functioning. Nicotine has been shown to facilitate sustained attention and inhibitory control (6-9). In a prospective study, poor sustained attention and low inhibition predicted adolescent smoking (10). Nicotine has been shown to enhance visuospatial and sustain attention in both smokers and non-smokers (11-15). Nicotine has also been found to reduce omission errors and response time variability in a continuous performance test (CPT) (16) which assesses the ability to sustain attention (17).

In contrast to the findings reporting beneficial acute effects of nicotine, long-term use of nicotine has been associ-

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ated with poorer performance on a variety of neurocognitive tests (independent of gender, alcohol consumption, baseline cognitive function, age, occupational class and education) (18-20). Repeated nicotine administration induces neuroadaptations associated with abnormal dopaminergic activity in the mesocorticolimbic circuitry, resulting in altered cortical neurotransmission and excitability (21). Altered baseline dopamine levels in addicted individuals may contribute to the often-observed elevation of impulsivity in these populations and may contribute to other dopaminergic abnormalities such as attention deficit (22).

To date, several studies have demonstrated higher impulsivity in smokers; however, it is unclear if impulsivity is a consequence of drug use or a risk factor in the development of nicotine dependence. Impulsivity is traditionally defined as acting suddenly and without a plan to satisfy an immediate desire and consists of multiple faces, including risky decision making, response inhibition, and delay-reward discounting (23). Two types of behavioral measures are primarily used to examine impulsivity in humans and animals; Go/NoGo tasks to assess response inhibition and relative preference tasks to assess delay aversion (20).

Current literature reported a number of studies measuring delay discounting, in which impulsivity was higher among adult smokers versus non-smokers (24-26).

However, the results of studies on response inhibition in smokers have been inconsistent. That is, some studies have found response inhibition during a Go/NoGo task to be impaired in smokers relative to controls (27, 28), whereas other studies did not find this group difference in performance on the Go/NoGo task (29), or on other behavioral tasks measuring response inhibition (30).

This inconclusive pattern of results goes beyond impulsivity measures to another critical cognitive domain. Using several attentional tasks under drug-free condition several authors reported no significant performance differences between smokers and non-smokers (31-33). Nevertheless, two other studies, based on a young population, report significant performance decrements in smokers compared to non-smokers (28, 34).

All in all there seems to be paucity of large sample comparative research reporting performance in cognitive tasks addressing the psychological constructs of impulsivity and sustained attention in chronic heavy smokers. The purpose of this study is to identify behavioral patterns that co-occur with heavy smoking and, therefore, may be potential targets for the development of more effective cessation programs. Our study was designed to compare performance on the CPT and the Go/NoGo task on a large cohort of non-deprived, heavy smokers versus a group of non-smokers controls.

We hypothesized smokers to show worse performance accounted for by both predate neurocognitive characteristics influencing maintenance of smoking, and long-term negative effects of nicotine.

METHODS

SUBJECTS

One hundred fourteen males and females who smoke at least 20 cigarettes per day were included in our study. Subjects were recruited from the general population by advertisement for a clinical trial of smoking cessation intervention and will be the focus of future publications. Exclusion criteria included any psychiatric or neurological disorder, any psychotropic medications, current alcohol dependence or any substance abuse except nicotine, history of significant brain malformation or neoplasm, head injury, cerebral vascular events or prior brain surgery.

The study was approved by the Helsinki committee of Beer Yaakov Mental Health Center and the Israeli Ministry of Health. All subjects signed an informed consent. Subjects underwent a clinical interview including full demographics, medical history, and smoking habits information. The computerized neurocognitive test that is the focus of the present report was implemented after the interview and before any intervention. Subjects smoked their last cigarettes prior to the beginning of the testing session within one hour of commencement.

The control group included 68 healthy volunteers who were recruited from non-smoking medical personnel and healthy volunteers. The project was approved by the Helsinki Committee of Beer Yaakov Mental Health Center and all subjects gave written informed consent. Inclusion criteria were no current or history of smoking. Exclusion criteria for the control group were the same as for the smokers group.

NEUROPSYCHOLOGICAL ASSESSMENT

The Go/NoGo task primarily reflects the ability to suppress a very potent (but not yet initiated) response. It has been previously reported that Go/NoGo performance is multidimensional, reflecting various inter-related cognitive and emotional functions (35). In order to investigate pure response-inhibition deficits, we used a simple situation and controlled for confounding factors. We applied a computerized special task that included both the CPT and the go/no-go (AnimaScan Ltd, Ashdod, Israel, 2000) as described herein and previously (28, 36, 37).

TASK DESCRIPTION

Subjects were requested to respond to red squares (Go event) by immediate button press, but to withhold responses to black squares (NoGo event). To ensure comprehension of the task instructions, participants carried out a practice with 30 stimuli that familiarized them with the task. Also, they were given feedback at the end of the practice session, showing their accuracy of performance. Subjects were trained until they achieved a 100% correct performance level. All stimuli were briefly displayed in random order, against a white background centrally on the computer screen, 100 ms each, at a rate of one stimulus per 2000 ms. A total of 300 stimuli were divided into two successive conditions, each of which contained 150 stimuli. The CPT is a condition with frequent (80%) NoGo events and the subjects were instructed to detect and generate a response to rare Go stimuli (20% frequency). The Go/NoGo is a condition with frequent go (80%) events, and the subjects were instructed to withhold responding to rare NoGo stimuli (20%). The whole experimental task lasts for 10 min, and each condition (either CPT or Go/NoGo) continues for 5 min without a pause between them. The performance of each patient is measured during two blocks in each condition [the CPT condition includes both block 1 (75 stimuli) and block 2 (76–150 stimuli); the Go/NoGo condition includes both block 3 (151–225 stimuli) and block 4 (226–300 stimuli)]. The order of task conditions was constant for each examinee. It was found that this specific construction of the task might help to investigate the inhibition ability in situations involving performance shifting (38, 39) from rare Go stimuli (as in the CPT) to frequent go events (in the Go/NoGo).

TASK MEASURES

Errors of commission occur when the subject incorrectly responds to black squares; such a response is considered to be a measure of impulsivity. Errors of omission occur when the subject omits pressing the button when a red square appears; such a response is considered to be a measure of inattention. Reaction times to Go events were computed for trials in which the participants responded within 2100 ms of stimulus onset. Failures to respond to a Go event within a period of more than 2100 ms of stimulus onset or implausibly early, i.e., less than 250 ms after red stimuli onset were considered errors of omission. Errors of commission were defined as responses that occurred within 2100 ms of a NoGo stimulus onset. Slow response time or variable response time may be a consequence of distraction by external or internal stimuli resulting in fluctuations in processing speed throughout the task. Performance is measured by both speed and accuracy and the speed-accuracy tradeoff may help to elucidate the impairment of inhibitory function during the task performance. Quick and inaccurate responses may point to an impulsive behavior whereas slow and inaccurate responses may occur due to a lapse in attention.

DATA ANALYSIS

Data was analyzed using SAS 9.2. T-test, Mann Whitney or X2 were used to compare between smokers and controls on demographic characteristics. Three-way repeated measures ANCOVA was used to evaluate differences between smokers and controls in task performance (omissions, commissions, RT, and RT variability). Main effects were group (smokers and controls), condition (CPT and Go/NoGo), and block (1-4). Gender, education, and age were used as covariates. Spearman correlations were calculated between response time and errors of omission and errors of commission, correcting for gender, education, and age, in order to examine differences between groups in speed-accuracy trade-off characteristics in each group. Spearman correlations were calculated between errors of omission and errors of commission to distinguish between "attention" and "inhibition" within the study population. Preplanned pairwise comparisons were examined by contrast t-tests.

RESULTS

STUDY POPULATION

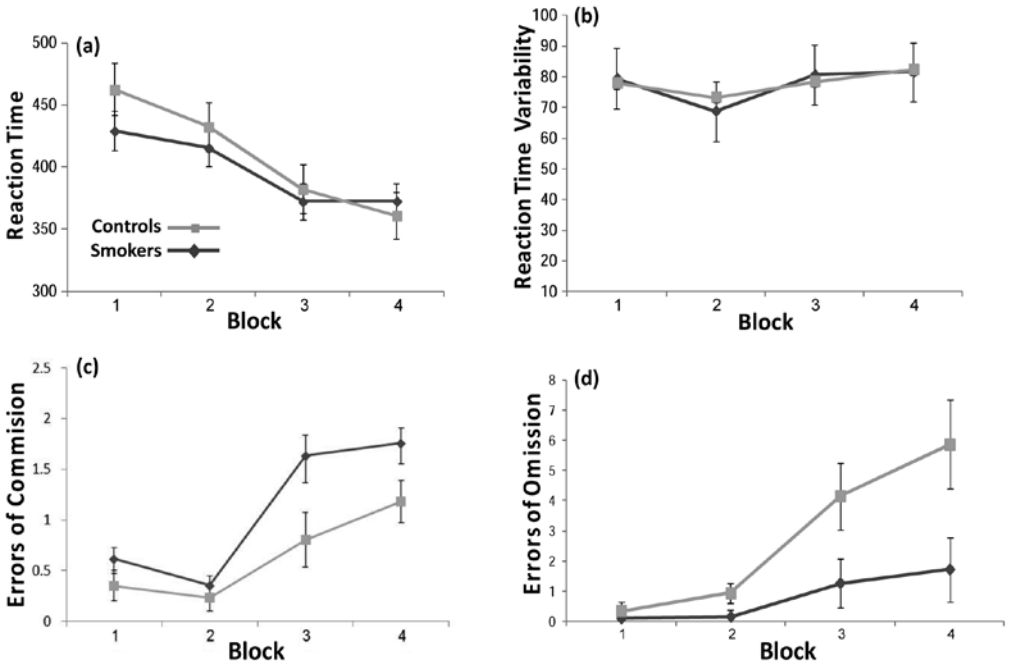
Table 1 presents descriptive statistics for each study group. Since group differences were present, age, gender, and education were entered as covariate in all analyses.

Table 1. *Descriptive statistics of smokers and controls*

Measure	Study group		Statistic†
	Smokers	Controls	
Gender (male/female)	(73/49)	(50/18)	X^2=3.58 p=0.058
Age (mean ± STD)	50.1±10.88	37.2±9.36	P<0.0001
Education[1] (median)	2	3	P<0.0001
Cigarettes/ Day	29±10.3	NR	
Pack Years (mean ± STD)	45±22.7	NR	
FTND[2] (mean ± STD)	7±1.69	NR	

†Chi-square / t-test / Mann-Whitney; [1]1:Primary education, 2:High-school education, 3:Academic education; [2]Fagerström Test for Nicotine Dependence (n=99)

Fig 1. *Adjusted means (and standard errors) of performance on the CPT and the Go/no-go in smokers and controls*



Mean reaction time (a), reaction time variability (b), number of commissions (c) and number of omissions (d) (with standard errors) in the CPT task (blocks 1,2) and the Go/NoGo task (blocks 3,4) in smokers compared with controls. All means adjusted for age, gender and education.

RESPONSE TIME

Mean reaction time was not significantly different between smokers and control (F(1,166)=0.4, p=0.52) (Table 2 and Fig. 1a).

However, there was a significant main effect of condition (F(1,510)=123.16, p<0.0001) and block (F(1,510)=15.53, p<0.0001), reflecting a shorter reaction time on the Go/NoGo task compared with the CPT task and a significant decrease in response time between the second and the first block on each condition.

Significant interactions between group and block (F(1,510)=5.39, p=0.02) and between group and condition (F(1,510)=5.28, p=0.022) were found. Pairwise comparisons revealed a significantly shorter response time for both smokers and controls on the Go/NoGo task compared with the CPT task (t(510)=7.51. p<0.001 and t(510)=8.26, p<0.001 respectively). However, only the control group showed decreased response time between the second and the first block on the Go/NoGo task (t (510)=2.89, p=0.004).

Table 2. *Adjusted means (and standard errors) of performance on the CPT and the Go/NoGo in smokers and controls:*

		CPT		Go/NoGo			
Test measures	Group	Block1	Block2	Block3	Block4	F	P
Reaction time	Smokers	429.01 (15.77)	415.38 (14.98)	372.22 (14.72)	372.6 (14.3)	0.41	0.524
	Controls	462.39 (21.01)	432.41 (19.87)	382.28 (19.5)	360.94 (18.95)		
Reaction time variability	Smokers	79.4 (7.47)	68.83 (7.35)	80.73 (7.35)	81.61 (7.24)	0.04	0.96
	Controls	78.08 (9.9)	73.35 (9.74)	78.48 (9.74)	82.35 (9.59)		
Errors of commission	Smokers	0.62 (0.11)	0.358 (0.09)	1.64 (0.2)	1.76 (0.15)	8.34	0.004*
	Controls	0.35 (0.15)	0.23 (0.13)	0.8 (0.27)	1.18 (0.21)		
Errors of omission	Smokers	0.1 (0.21)	0.16 (0.24)	1.27 (0.8)	1.72 (1.06)	6.57	0.01*
	Controls	0.35 (0.28)	0.94 (0.32)	4.15 (1.11)	5.86 (1.47)		

VARIABILITY OF RESPONSE TIME

Variability of reaction time was not statistically different between groups (F(1,166)=0.04, p=0.96) (Table 2 and Fig. 1b).

There were no significant main effect of block or for the interactions between group and block and between group and condition. However, there was a significant main effect of condition (F(1,510)=6.05, p=0.01) and a significant interaction between block and condition (F(1,510)=4.97, p=0.02), resulting from a higher variability of the response time in the Go/NoGo task compared with the CPT task. Pairwise comparisons highlighted that there was less variability on the second block of the CPT t(510)=2.26, p=0.02), but no such difference between blocks emerged on the Go/NoGo task.

ERRORS OF COMMISSION

The smokers group showed significantly more errors of commissions (F(1,166)=8.34, p=0.004) (Table 2 and Fig. 1c). The interaction between group and condition was significant (F(1,510)=4.79, p=0.029). Pairwise comparisons revealed significantly more errors of commission for the smokers in the Go/NoGo task (t(510)=2.93, p=0.0036) but not in the CPT task (t(510)=1.5, p=0.138). Errors of commission in the Go/NoGo task compared with the CPT task were higher in both groups. The main effect of condition was significant (F(1,510)=67.88, p<0.0001). There was no significant main effect of block and no interaction between group and block. A significant interaction of block with condition (F(1,510)=7.19, p=0.0076), showing a significant decrease in errors of commission for the second block on CPT performance t(510)=2.53, p=0.011) and a non significant increase in errors of commission for the second block on Go/NoGo performance, was present.

ERRORS OF OMISSION

The smokers group showed fewer errors of omission. The main effect of group was significant (F(1,166)=6.57, p=0.01). (Table 2 and Fig. 1d) The interaction between group and condition was significant (F(1,510) =4.38, p=0.0369). Pairwise comparisons revealed significantly fewer errors of omission for the smokers in the Go/NoGo task (t(510)=2.39, p=0.017) but not in the CPT task, although marginally significant (t(510)=1.68, p=0.09). Mean errors of omission in the Go/NoGo task compared with the CPT task was higher in both groups (F(1,510)=15.98, P<0.0001). There was a significant main effect of block (F(1,510)=4.45, p=0.35), showing an increase of errors of omission from the first to the second block on each condition (on the CPT t(510)=3.06, p=0.002; on the Go/NoGo t(510)=1.68, p=0.09). No interaction between group and block and no interaction of block with condition were found.

SPEED ACCURACY TRADEOFF

The correlations between number of commissions and reaction time in the Go/NoGo task (on the second block) were different in smokers compared to controls (Table 3). The number of commissions in the Go/NoGo task was negatively correlated with reaction time in both groups on the first block. However, negative correlation was found only in the smokers on the second block. On the CPT task, no correlations were found in both groups.

The correlations between number of omissions and mean reaction time in the CPT task (on the second block) were different in the smokers compared to controls. The number of omissions in the CPT task was positively correlated with reaction time in both groups on the first block. However, positive correlation was found on the second block only in smokers. On the Go/NoGo task, no significant correlations were found in both groups (Table 4).

DISSOCIATING SUSTAINED ATTENTION AND RESPONSE INHIBITION

No correlations were found between errors of omission and errors of commission in all blocks in both groups (data not shown), with the exception of block 2 of the CPT in smokers r= 0,29 ; p=0.001. No cross correlations were seen between errors of omission in the CPT

Table 3. *Spearman correlations between errors of commission and reaction time in smokers and in controls:*

		Smokers	Controls
CPT	Block1	-0.12 (0.2)	0.0008 (0.99)
	Block2	-0.04 (0.63)	-0.04 (0.73)
Go/NoGo	Block3	-0.32 (0.0005)*	-0.288 (0.03)*
	Block4	-0.376 (P<0.0001)*	-0.132 (0.33)

Table 4. *Spearman correlations between errors of omission and reaction time in smokers and in controls:*

		Smokers	Controls
CPT	Block1	0.268 (0.0046)*	0.27 (0.04)*
	Block2	0.33 (0.0003)*	-0.047 (0.72)
Go/NoGo	Block3	0.031 (0.747)	-0.177 (0.19)
	Block4	-0.08 (0.389)	-0.18 (0.172)

compared with errors of commission in the Go/NoGo (data not shown).

DISCUSSION

Our study explored smokers/non-smokers differences in the CPT and Go/NoGo tasks and tested the hypothesis that heavy smokers manifest impairments of sustained attention and response inhibition.

RESPONSE INHIBITION ABILITY

The Go/NoGo tasks require ability to withhold a response to NoGo stimuli. In this task, the less probable occurrence of NoGo events enhances an expectation that the following stimulus will be a Go stimulus, thereby promoting a tendency toward making a rapid response to Go stimuli. Therefore, this design provides a useful test for evaluation of response inhibition control and action monitoring (40), in which wrong response to the NoGo stimuli (commission error) is assumed to reflect impaired response inhibition ability (41-43).

Our results demonstrate that smokers made more commission errors and less omission errors than controls in the Go/NoGo task.

Researchers most commonly use errors of commission as indicators of impulsive responding. However, there is a support of using the omission errors as an indication of impulsivity as well. Yechiam et al., in a cognitive analysis of the Go/No-Go task have indicated that a lack of behavioral inhibition is demonstrated by both high rates of commission errors and low rates of omission errors (44). Their results demonstrated that attention to gains is positively associated with commission errors and negatively associated with omission errors. This attentional bias is characteristic of impulsivity (45).

In lines with our impulsivity hypothesis we expected smokers to show shorter RT since the time required to respond to a stimulus in impulsive subjects should be shorter (46). Contrary to our expectation, results revealed no group differences in response time or in response time variability in the Go/NoGo task. However, we found a significant negative correlation between errors of commission and reaction time in smokers. Controls exhibited this pattern only in the first Go/NoGo block, that show significant differences in strategy of building speed – accuracy tradeoff. Smokers show fast-inaccurate response style which was found previously as specific for impulsivity concept (47).

The speed-accuracy tradeoff may help to elucidate the impairment of inhibitory function during the task performance (48). Theoretically, impulsive persons would prefer a quick, automatic selection of stimuli for responses without monitoring (49). The commission error is ignored, and the speed of performance is stressed at the expense of accuracy. Therefore, the negative correlation between number of commission errors and response time demonstrate an expression of impulsive reactions. The difference between smokers and controls only in the second block may indicate that smokers' impulsivity may become prominent over time. Our results are similar to the findings of Yakir et al. (28) and Spinella (27) but in contrast to Dinn et al. (29) and Reynolds et al. (30) who didn't find impairment in response inhibition. These discrepancies may be related to the differences in terms of sample size (23 smokers or 25 smokers, accordingly), age of subjects (mean of 18.6±1.17 or 14-18, accordingly), and substance intake (average of 5.8 or 8 cigarettes per day, accordingly). It seems feasible that significant neuroadaptations and consequent behavioral changes become evident only in later stages of more substantial nicotine consumption. However, the cross sectional design of our study and of previous studies does not directly address the key issue of whether disinhibition is a consequence of chronic use of nicotine or a risk factor in the development of nicotine dependence.

SUSTAINED ATTENTION

The study results demonstrate that smokers made a lower number of errors of omission than controls in the Go/NoGo condition. By contrast, difference in omission errors rate was not observed in the CPT task. The CPT task generally requires the ability to detect and respond to the rare Go stimuli, and missing of the Go stimuli (omission errors) is considered a measure of low vigilance /inattention (40).

We expected smokers to manifest impairments of sustained attention and, therefore, to show slower RT and higher RT variability in the CPT. Response time to target stimuli is considered a measure of alertness (50). Slow or variable response time may be a consequence of distraction by external or internal stimuli resulting in fluctuations in processing speed throughout the task. Children with ADHD have been found to have slower response time to target stimuli than normal control in several studies (50). High variability of response time has been described for groups with traumatic brain injury or attention-deficit/hyperactivity disorder (ADHD) and associated with lapses of sustained attention and low level of vigilance (51-53). In our sample, the results did not show higher RT variability or slower RT in smokers

therefore suggesting that smokers do not show impairment in sustained attention.

In our population, smokers did not differ from non-smokers in performance on CPT that assess sustained attention. These findings were in accordance with previous studies (31-33). We extend these previous results, by using a large sample and including a group of older and heavier smokers. Our results are not concordant to some previous findings (28, 34). For example in Foulds et al. (34) smokers were required to abstain from tobacco use 24 hours before the CPT was conducted and, therefore, the difference between smokers and non-smokers could be mainly attributed to the nicotine-withdrawal effect. In Yakir et al. (28) authors reported a diminished sustained attention in young female participants. Discrepancies in results may be attributed to sex-related differences in smoking populations. Another possibility, as the authors suggested, is that the results of the CPT, which was applied last, were confounded when nicotine levels among the smokers had started to decline (28).

In contrast to our expectation, the result of our study suggested no negative long-term effects of nicotine on sustained attention.

CONCLUSIONS

The major finding of our study is that heavy smokers, as compared to the control group, show high rate of commission errors in the Go/NoGo task than controls, reflecting impaired inhibition ability. In addition, in contradiction to our hypothesis, smokers did not show higher rate of omission errors on the CPT task than controls, reflecting no differences in sustained attention.

Although our study was limited to a cross-sectional study of neurocognitive functions, our findings give indirect evidence that impaired motor response inhibition ability (as measured by the Go/NoGo task) may be associated with the maintenance of smoking.

A future neuropsychological prospective cohort study that follows smokers over time may help to clarify the particular brain mechanisms underlying impaired Go/NoGo performance in smokers.

LIMITATIONS

Several limitations need to be taken into account when considering the patterns obtained here. First, the selection of the study population to include a treatment-seeking population for the smokers group did not match the controls in terms of age, gender and education. Nevertheless it seems implausible the relatively small age and education differences in these factors alone would account for such varied cognitive profile. Second, smoking and/or nicotine levels were not assessed by objective biological means, which could have influenced the results in two ways - a better performance among smokers who experienced high nicotine blood level and/or a worse performance among smokers who experienced low nicotine blood levels. Moreover, secondhand smoking among non-smokers was not assessed subjectively or objectively, and could have influenced performance in the non-smokers group if it exists.

Declaration of interests

This study is a part of first author's PhD program, Limor Dinur-Klein receives scholarship from Tel Aviv University. Dr. Kertzman is a share-holder in the Animascan which produces the neurocognitive tests battery. Dr. Rosenberg is the employee of Research Department Beer Yaakov Mental Health Center. Ms Dinur-Klein, Dr. Rosenberg, Profs. Kotler, Zangen & Dannon have no financial interests in the study

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