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Investigating the impact of nicotine on executive functions using a novel virtual reality assessment

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Abstract

Aims Nicotine is known to enhance aspects of cognitive functioning in abstinent smokers but the effects on specific areas of executive functions, and in non-smokers are inconclusive. This may be due in part to the poor sensitivity of tests used to assess executive functions. This study used a new virtual reality assessment of executive functions known as JEF (the Jansari assessment of Executive Functions) to address this issue.

Design 2x2 design manipulating group (smokers and never-smokers) and drug (nicotine [4mg for smokers; 2mg for never smokers] vs placebo gum).

Setting School of Psychology; University of East London

Participants 72 participants (aged 18 to 54). 36 minimally-deprived (2 hr) smokers and 36 never-smokers.

Measurements Components of executive function were measured using the virtual reality paradigm JEF, which assesses eight cognitive constructs simultaneously as well as providing an overall performance measure.

Results Univariate ANOVAs revealed that nicotine improved overall JEF performance, time-based prospective memory and event-based prospective memory in smokers ($p < 0.01$) but not in never-smokers. Action-based prospective memory was enhanced in both groups ($p < 0.01$) and never-smokers out-performed smokers on selective thinking and adaptive thinking ($p < 0.01$).

Conclusions. Overall executive functioning and prospective memory can be enhanced by nicotine gum in abstinent smokers. That smokers were only minimally deprived suggests that JEF is a sensitive measure of executive functioning and that prospective memory is particularly susceptible to disruption by abstinence.

Introduction

Nicotine is thought to play a significant role in the maintenance of smoking behaviour through its effect on psychological functions (1). Nicotine is a cholinergic agonist, which mimics the action of acetylcholine, a neurotransmitter associated with effortful cognitive processes (2). Nicotine also acts on the mesolimbic dopaminergic reward system (3), which is associated with both increased pleasure and reduction of negative affect (4,5). Individuals may smoke to obtain certain effects (e.g. pleasure, stimulation) or remove unwanted effects (e.g. negative affect, tiredness). In addition to its effects on mood nicotine's effect on cognition may also contribute to smoking addiction. In nicotine-dependent smokers, nicotine abstinence results in pronounced cognitive impairments (6,7), and this effect has been observed as early as 30 minutes post cigarette (8). These impairments are typically reversed following the smoking of one or two cigarettes (6).

Although it is widely agreed that nicotine withdrawal leads to cognitive decrements, there is less agreement over the precise effects of nicotine on cognition. Smokers often report that smoking aids them in memory and concentration (9). If nicotine does have an absolute facilitative effect on cognition this might to some extent explain why individuals initiate the habit. In addition, this enhancement effect might also represent another potential form of smoking reinforcement. Subjective reports, although interesting, cannot provide objective evidence as to whether or not smoking enhances cognitive performance in addition to reversing withdrawal deficits.

Nicotine has been shown to improve sustained attention in non-deprived smokers and non-smokers (11,12). However, findings relating to the impact of nicotine on working memory (WM) have been less consistent. Nicotine's effect on WM has included enhancement (13), impairment (14), or no effects (15).

Myers, Taylor, Moolchan and Heishman (12) found no effects of nicotine nasal spray on WM performance in deprived and non-deprived smokers. Kleykamp et al, (14) attempted to determine the effects of nicotine on working memory, attention and executive function using the n-back task and the Attention Network Task (ANT) that assesses alerting, orienting, and executive function aspects of attention. They found no effects of nicotine on their cognitive measures in never smokers in a within

participant design using 0mg, 2mg and 4mg nicotine gum (although there was a dose related effect of nicotine on heart rate)(14).

A review carried out by Heishman, Kleykamp and Singleton (6) examined the effect of nicotine on various aspects of cognitive performance in 41 double-blind placebo controlled studies between 1994 and 2008 in non smokers and smokers not experiencing withdrawal. Meta-analyses revealed significant positive effects of nicotine on fine motor abilities, overall accuracy and response times for alerting and orienting attention consistent with their earlier review. Meta-analyses also confirmed significant effects of nicotine on working memory RT and accuracy of episodic memory performance; findings that, the authors suggest, capture true performance facilitation effects rather than withdrawal relief and reflect the use of more sophisticated cognitive measures. The authors conclude that these findings provide indirect evidence that nicotine's performance enhancing effects may indeed contribute to the initiation of smoking (6) in contrast to their earlier conclusions that nicotine was unlikely to be a contributing factor in starting smoking (6).

In relation to executive functions specifically, to date there have been few published reports on the effects of nicotine. In the Heishman et al. (6) review it was not possible to determine the effect of nicotine on executive function and complex cognition as there were insufficient effect sizes to conduct a meta-analysis. The authors also noted that there were no studies that met the inclusion criteria that investigated learning or executive functions, such as decision-making and planning and that there were no studies that related laboratory tasks to real-world performance.

In verbal fluency tasks, thought to tap executive aspects of retrieval strategies, inhibitory functioning and memory monitoring, nicotine has been shown to both improve (16) and have no effect on performance in smoking groups (17). In non-smokers, however, nicotine has been shown to have no effect on task performance (18). On the basis of an attention scale measurement Poltavski and Petros (19) split male non-smokers into two groups, high and low attentiveness. Nicotine administration in the high attentiveness group led to poorer performance on the Wisconsin Card Sort Test (20). This finding suggests that in areas assessed by the

WCST such as strategic planning, set shifting and mental flexibility (21, 22) nicotine may in fact impair rather than enhance performance.

Prospective Memory, or the forming of a delayed intention (23, 24) is thought to incorporate strategic processing in areas of intention formation and intention execution. In a number of recent studies nicotine has been shown to improve prospective memory performance in minimally deprived (2 h) smokers (25, 26) and non-smokers (25). These findings suggest that nicotine can significantly improve performance when task conditions engage strategic and effortful processing and stretch cognitive resources In Heishman et al.'s review (6) it was not possible to determine the effect of nicotine on long-term prospective memory, as there was an insufficient effect size to conduct a meta-analysis. Recent studies have also pointed to nicotine enhancing inhibitory processes in memory (27, 28).

In a recent review Evans and Drobes (29) pointed to evidence suggesting that the absolute effects of nicotine on cognition might only become apparent in environmentally complex real-life activities. In a study of non-smoking pilots nicotine was shown to improve performance in complex flight simulation tasks in comparison to placebo (30). Multiple aspects of cognition are involved in complex flight performance, including attention and memory, and involve high cognitive loads. Unfortunately Mumenthaler et al. (30) were unable to provide a way of measuring the effects of nicotine on the various different cognitive domains involved.

To address the fact that traditional assessments of cognitive performance lack ecological validity and sensitivity, Jansari, Agnew, Akesson, & Murphy (31) have developed a virtual reality assessment known as JEF (Jansari assessment of Executive Functions[1]). JEF examines a range of executive functions concurrently, namely planning, prioritization, selection, creative-thinking, adaptive thinking, time-based prospective memory, event-based prospective memory and action-based prospective memory. Performance is assessed independently for each cognitive construct and in addition an average performance score across all constructs is also

[1] In previous papers, the JEF was known by a different acronym JAAM; however, the assessment is unchanged between the different studies

provided; this provides the researcher with an overall understanding of the participant's level of executive functions as well as a breakdown of performance on individual elements. JEF was originally developed to assess executive functions in a sample of brain injured participants showing significantly lower performance than age and IQ-matched healthy controls (31), but importantly has also been used in non brain-damaged populations to explore the impact of ecstasy (32), alcohol (33) and cannabis (34).

In summary, findings on the absolute facilitative effects of nicotine on cognitive performance are inconsistent and present a complex picture displaying improvements, null effects and decrements in abstinent and non-deprived smokers as well as non-smokers. The use of JEF responds directly to the gap in the literature with specified cognitive constructs that can capture isolated elements of executive functioning that reflect theories of fractionated executive processes (35). This study compares the effects of nicotine on abstinent smokers and non-smokers using a sensitive ecologically-valid measure of executive functions.

Method

Design

A between participants design was used with smoking group (smoker versus never-smoker) and gum type (nicotine versus placebo) as the independent variables. The dependent variables were scores on the various JEF constructs.

Participants

72 participants were recruited, 36 (21 female) smokers and 36 never-smokers (18 female), a sample size that is comparable to other studies exploring the effects of nicotine on cognition in smokers and non-smokers (6, 25). Participants were recruited via Internet advertising (Gumtree) and university e-mailing (70% were students). Never-smokers had smoked fewer than 20 cigarettes in their lifetime while smokers smoked at least 10 cigarettes a day and smoked their first cigarette within one hour of waking. The University of East London Ethics Committee approved the research.

Preparation of nicotine and placebo gums

2mg and 4mg Nicorette freshmint nicotine gums were used respectively for never-smokers and smokers along with Wrigleys Extra peppermint regular chewing gums. The gums were wrapped in an extra piece of regular chewing gum to hide their appearances, and two drops of Tabasco pepper sauce were used to hide the nicotine taste. This has been used effectively in previous research (37).

Tasks

JEF (31) is a virtual reality assessment that involves the participant playing the role of an office assistant. Participants read the scenario, which describes their role and they are shown how to navigate around the environment after being given time to practice using the assessment. The participant is given a list of tasks to complete for the office manager who they are informed is out of the building for the day. In addition to these tasks the participant is also handed a number of memos during the assessment relating to additional tasks or events. In this respect, the tasks reflect those that would naturally occur in a typical working environment, and rely on

working memory and task switching. Executive Function is assessed through eight cognitive constructs: *Planning*, *Prioritisation*, *Selection*, *Creative Thinking*, *Adaptive Thinking* and three types of *Prospective Memory (Action-Based, Event-Based and Time-Based)*. Participants are required to carry out two tasks for each construct and their performance on each task is assessed through predetermined criteria and a corresponding three-level scoring system. Participants receive a score of 0, 1 or 2 for each task depending on how successful they are at meeting the requirements of the task criteria. As an example, for the *Planning* construct the participant is required to group the manager's list of tasks in a practical and sensible manner and to also arrange the tables and chairs for the members of the meeting. Scoring was conducted on the full completed set of anonymised (numerically coded) data by the test administrator. Performance is scored manually against a strict protocol on a proforma for which previous studies have demonstrated an inter-rater reliability ranging between 0.956 and 1.0 for scoring on individual constructs.

In total, the JEF task takes approximately 40 minutes to complete. The scores for the tasks are then summed and a percentage score calculated for each construct. An overall performance score is calculated as the mean average of the eight construct percentage scores.

Procedure

Smokers were asked to abstain from smoking for two hours prior to testing consistent with Rusted & Trawley (25). The assessment was administered in a quiet laboratory in isolation. Smokers and never-smokers were randomly allocated to a nicotine or placebo group according to the order in which they were recruited to the study (quasi-randomization approach). Smokers in the nicotine group were given 4mg nicotine gum. Never-smokers in the nicotine group were given a 2mg gum, because higher doses of nicotine have been shown to have adverse effects on non-smokers (38). Participants were asked to follow the Nicorette manufacturer's instructions (Nicorette ActiveStop Freshmint 2mg and 4mg gum) when chewing the nicorette and placebo gums. Participants chewed the gum until the taste became strong, rested it between the gum and cheek for several minutes, and then chewed the gum again for several minutes. Participants repeated this chewing procedure for 20 minutes before testing to allow for maximum blood sera levels of nicotine to be attained through the buccal

mucosa (39). Studies that used similar placebo preparation and chewing procedures reported that compared with a placebo condition, the 2mg gum can increase plasma nicotine levels by approximately 4.6 ng/mL, and the 4mg gum can increase plasma nicotine levels by approximately 8.5 ng/mL (40). A cigarette, by way of comparison, can increase plasma nicotine levels by approximately 14 ng/mL (41). During the 20-minute chewing period participants completed the WTAR IQ Test. Participants then carried out the JEF assessment and removed the gum upon completion of the assessment. Participants were reminded of their right to withdraw at anytime throughout the testing session. Never-smokers tolerated the gum very well with only a handful reporting any side effects (mild nausea/light-headedness) and none withdrawing or having to be excluded.

Results

As can be seen from Table 1, groups were well matched in terms of age and IQ.

	Never-smoker Nicotine N = 18	Never-smoker Placebo N = 18	Smoker Nicotine N = 18	Smoker Placebo N = 18	F (3,68)	p
Age	27.94 (7.76)	28.94 (11.50)	24.88 (4.12)	27.73 (8.27)	0.79	0.50
IQ	112.5 (6.86)	112.7 (8.43)	112.3 (9.56)	111.2 (9.09)	0.11	0.96

Table 1
Participant Demographics showing mean Age and IQ as a function of group (standard deviations in parentheses)

Planning, selective thinking, creating thinking, adaptive thinking, time-based PM and event-based PM were negatively skewed. Levene's test was significant (< 0.02) for creative thinking, selective thinking, time-based PM, event-based PM and overall total, reflecting, in each case, larger variance in the smoker/placebo group. To reduce negative skewing, the offending variables were reflected and square root transformed before being subjected to univariate analyses of variance (ANOVA). This reduced the skewing but did not correct the violation of homogeneity thus a more stringent α level of 0.01 was adopted to minimize the risk of Type I errors. The group x gum type interaction is of primary interest here, this was therefore tested first in each case;

where significant interactions were observed, post-hoc t-tests were conducted for smokers and never-smokers to clarify the nature of the interaction. Main effects are only reported in the absence of a significant interaction in a model that excludes the interaction term.

Figure 1 shows JEF performance scores across the eight individual cognitive constructs and overall average performance as a function of smoking group (smoker vs never-smoker) and gum type (nicotine vs placebo). Exact figures (group means and SDs) are also provided in Table 2. For overall total JEF score, there was a significant smoking group x gum type interaction. Post-hoc t-tests confirmed that the superior performance in the nicotine versus placebo group was statistically significant in smokers ($t(34) = 4.4$, $p < .0001$) but fell short of the adjusted level of significance in never-smokers ($t(34) = 2.12$, $p = .04$).

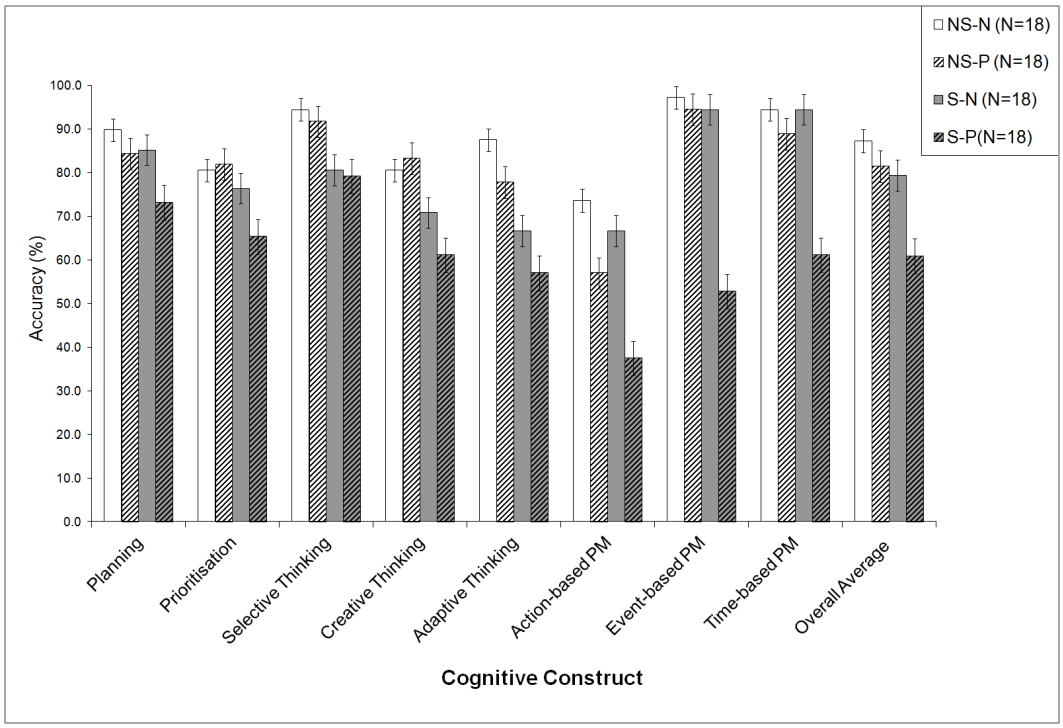

Figure 1:

JEF performance scores as a function of group and cognitive construct (error bars represent one standard error). NS-N = Non-smoker Nicotine, NS-P = Non-smoker Placebo, S-N = Smoker Nicotine, S-P = Smoker Placebo

	Never-smoker Nicotine	Never-smoker Placebo	Smoker Nicotine	Smoker Placebo	F, p Inter-action (df=3,68)	F, p Group Main (df=1,69)	F, p Gum Main (df=1,69)
Planning	89.82 (17.27)	84.26 (16.63)	85.18 (22.06)	73.15 (25.65)	0.44, 0.51	1.87, 0.18	4.27 0.04
Prioritisation	80.56 (18.30)	81.94 (11.52)	76.39 (20.06)	65.22 (22.89)	2.03, 0.16	5.64, 0.02	1.24, 0.27
Selective Thinking	94.44 (10.69)	91.67 (12.13)	80.56 (26.51)	79.17 (24.63)	0.02, 0.88	**6.77, 0.01**	0.28, 0.60
Creative Thinking	77.78 (24.08)	83.33 (22.69)	70.83 (31.21)	61.06 (40.40)	1.14, 0.29	3.39, 0.07	0.01, 0.93
Adaptive Thinking	86.11 (19.60)	77.78 (24.08)	66.67 (33.21)	56.94 (25.45)	0.01, 0.91	**10.27, 0.002**	2.48, 0.12
Action-based PM	76.39 (24.96)	56.94 (26.85)	66.67 (38.35)	37.50 (31.21)	0.45, 0.51	4.04, 0.05	**11.23, 0.001**
Event-based PM	97.22 (11.79)	94.44 (13.71)	94.44 (13.71)	51.39 (35.84)	**12.94, 0.001**	-	-
Time-based PM	94.44 (10.69)	88.89 (17.62)	94.44 (13.71)	61.11 (33.46)	**6.34, 0.01**	-	-
Overall Average	87.27 (6.94)	82.42 (6.82)	79.41 (12.94)	60.60 (12.72)	**8.28, 0.005**	-	-

Table 2:

Mean (SD) JEF performance scores as a function of group and cognitive construct. Main effects are only reported in the absence of a significant interaction ($\alpha = 0.01$).

In relation to the individual cognitive constructs, as can be seen from Table 2, ANOVA revealed a significant interaction for event-based and time-based prospective memory. Follow up post-hoc t-tests confirmed significantly better performance in the nicotine versus placebo group for event-based and time-based

prospective memory in smokers ($t(26.06) = -4.68$, $p < .001$ and $t(26.46) = -3.91$, $p = .001$ respectively) but not in never-smokers ($t(34) = -.82$, $p = .42$ and $t(31.20) = -.98$, $p = .34$ respectively).

In the absence of significant interactions for the remaining cognitive constructs, main effects were explored. As can be seen from Table 2, never-smokers out-performed smokers across all cognitive constructs with statistically significant group differences emerging for selective and adaptive thinking. The only main effect of gum type that emerged in the absence of an interaction was for action-based prospective memory with superior performance under nicotine.

Discussion

The aim of this study was to explore the effects of nicotine in smokers and never-smokers on specific aspects of executive functions using the JEF. Never-smokers out-performed smokers on selective and adaptive thinking and participants receiving nicotine performed better on action-based prospective memory. Significant interactions between smoking group and gum type for overall JEF performance and event-based and time-based prospective memory reflected enhanced performance by nicotine in smokers but not in never-smokers; this is clearly visible in Figure 1 and Table 2 and is consistent with pre-existing research which demonstrates that nicotine abstinence in regular smokers results in cognitive-attentional deficits which can be reversed with acute nicotine administration (11).

Inspection of the individual executive constructs assessed here by JEF, suggest that prospective memory is particularly susceptible to abstinence-associated disruption and subsequent improvement with acute nicotine administration. In fact, nicotine was observed to improve performance in this group in all three categories of prospective memory; Action-based Prospective Memory, Event-based Prospective Memory and Time-based Prospective Memory. These results are consistent with previous findings

showing that nicotine improves memory performance when task conditions stretch cognitive resources, involve effortful processing or require strategic processing of the to-be-remembered material (6, 42, 43, 13, 26). Unlike Rusted and Trawley (25) however, in the present study, with the exception of action-based prospective memory, nicotine did not improve performance in never-smokers. These discrepancies might reflect differences in the type of prospective memory task used and/or dose and mode of nicotine administration (2mg gum for never smokers here vs. 1mg nasal spray).

According to the multi-process theory of prospective memory, time-based tasks rely more heavily on strategic processes dependent on prefrontal systems than event-based tasks. Einstein and McDaniels (23) argue that there is a need to self-initiate retrieval of an intention in time-based tasks. In event-based tasks the introduction of external cues in the initiation phase of prospective memory means that there is less reliance on strategic processes. In the current study nicotine improved both time-based and event-based tasks and both results came with comparable small effect sizes (partial η^2 of 0.188 and partial η^2 of 0.236 respectively). These results are not consistent with Einstein and McDaniel's (23) theory where we would expect a greater effect on time-based prospective memory. The pronounced effect of nicotine on all three areas of prospective memory may be because the prospective memory tasks are competing with other distinct ongoing tasks in JEF.

More recent formulations of memory processes have underlined the role of inhibitory mechanisms in the processing of efficient remembering (44, 45, 46). That is, the suppression of irrelevant material is key in the effective processing of relevant material. Indeed, there is a growing body of evidence suggesting that nicotine can improve inhibitory control; using the retrieval-induced forgetting paradigm, Edginton and Rusted (27) and Rusted and Alvares (28) have reported positive effects of nicotine on the ability to inhibit task-irrelevant semantic information. Similarly, Powell, Dawkins and Davies (17) and Dawkins et al. (47) have observed a nicotine-induced enhancement of antisaccade performance in abstinent smokers.

In the JEF paradigm participants are required to remember a number of intentions and are then to retrieve the correct intention at a specific time or in response to the

associated cue. To our knowledge this has not been explored within the domain of prospective memory, but it is possible that nicotine serves to improve the retrieval of the relevant intention by suppressing other irrelevant intentions. An example of this can be seen in the JEF paradigm; the participant is asked to turn on the coffee machine when the first person arrives for the meeting (event-based prospective memory task), and to turn on the projector 10 minutes before the meeting begins (time-based prospective memory task). When each cue occurs during the assessment the participant is faced with a number of competing and related intentions. It is possible that in order to retrieve the relevant intention the participant must suppress the irrelevant intentions and that nicotine serves to enhance this process.

In this study nicotine did not affect performance in any of the five remaining constructs of executive functions: Planning, Prioritisation, Selection, Creative Thinking, and Adaptive Thinking. This is consistent with other studies, which have shown that nicotine has a differential effect on specific aspects of cognitive performance (18, 19, 42). These findings further suggest that the memory processes involved in prospective memory are particularly vulnerable to short periods of smoking deprivation and improvement with acute nicotine administration. It is possible however, that a longer period of smoking abstinence than used here (2 hours) may reveal significant effects in some of these other areas of cognition.

Due to the perennial problem of administering high dose nicotine to never-smokers, the present study used 4mg nicotine gum for smokers and 2mg for non-smokers, a protocol which has been used successfully elsewhere (37). It is possible that the larger effects sizes observed in smokers here may reflect this difference in dosage. Inspection of Figure 1, however reveals poorer performance in abstinent smokers (those receiving placebo) across all constructs but on no occasion did smokers receiving nicotine (4mg) out-perform never-smokers receiving nicotine (2mg) suggesting that the observed effects are driven by a restorative effect of nicotine in abstinent smokers rather than a dose effect.

Finally, main effects of smoking group were observed in the absence of an interaction for selective thinking and adaptive thinking with never-smokers out-performing smokers. Trends for better performance in never-smokers (which fell short of the

adjusted level of significance) were also seen for prioritisation and action-based prospective memory. Given the well-matched IQs across smoking groups, this pattern of findings is consistent, although not exclusively, with previous research showing that chronic smoking is associated with cerebral degeneration or brain atrophy (48, 49) and impaired executive functioning, cognitive flexibility, working memory and prospective memory (50, 51).

To conclude, the current findings support a restorative effect of acute nicotine in reversing abstinence-induced executive functioning impairments in smokers. Abstinence-induced impairments and improvement by nicotine were most apparent in all three domains of prospective memory possibly as a result of nicotinic stimulation on inhibitory control. That impairments were observed in smokers here after only 2 hours of abstinence suggests that prospective memory as assessed by JEF is particularly sensitive to nicotine deprivation. Whether such deficits are a consequence or cause of regular smoking remains to be determined.

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