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Afr. J. Biomed. Res.Vol.15 (September 2012); 159 - 164

Full Length Research Paper

Effect of Nicotine on Cognitive Performance in Non-smokers in a Nigerian University Community

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ABSTRACT:

The effects of nicotine on cognition are still elusive. The aim of the present study is to determine how exposure to nicotine affects specific cognitive domains in a random population of non-smokers in the age range 18-35 years. Ninety-nine non-smokers (80 males and 19 females), with no clinically classified blood pressure (≥140/90 or ≤ 90/60 mmHg), body mass index (≥ 25 kg/m2) or depression level score participated in the study. Nicotine was administered via chewing 4 mg nicotine gum for 15 minutes (one-chew/3seconds). The cognitive domains used in this study, the neuropsychometric test instruments and the predetermined reaction time respectively include global cognitive function (mini-mental state examination *MMSE*), working memory (Two-back task, reaction time: 1 sec.) and verbal information processing (Logical reasoning task, reaction time: 4 sec.). Performance scores (PS) on cognitive tasks, before (baseline) and after administration of nicotine were analyzed using paired student's-test ($P < 0.05$). Correlations between baseline PS and magnitudes of nicotine effect were determined using Pearson product moment correlation (r). PS and the magnitudes of nicotine effect compared across 3-subgroups based on baseline PS using one-way *ANOVA*. The results showed that nicotine significantly improved PS on all the cognitive tasks but the magnitudes of the improvements increased significantly with decrease in baseline PS. The assessment of the cognitive effect of nicotine may be misleading if based exclusively on neuropsychological test scores without correlations with baseline PS. Indication for baseline dependency effect of nicotine is considered.

Keywords: *Cognitive domain; Nicotine-gum; Mini-mental state examination; Two-back task; Logical reasoning task; Reaction time; Performance scores.*

INTRODUCTION

The cognitive performance on task-directed activation of cognitive processes can be compromised by a wide spectrum of factors ranging from genetic (Lynn & Irwing 2004; Douglas *et al.*, 2006; Deary *et al.*, 2007) to environmental (Winterer & Godman, 2003), psychological (Carol, 1990; Taylor *et al.*, 2005) and physiological (Courtnot *et al.*, 2006; Starr *et al.*, 2007). In addition, pathological conditions (VanHaren *et al.*, 2007; Broyd *et al.*, 2009) and psychoactive substances (Rezvani & Levin 2001; Lawrence *et al.*, 2002; Moore *et al.*, 2007; Swan & Lessov-Schlaggar, 2007) affect cognitive processes as well.

Nicotine is a psychoactive substance (Rezvani & Levin 2001; Swan & Lessov-Schlaggar, 2007) and a major

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Date Received: April 2012
Date Accepted: July, 2012

Abstracted by:
Bioline International, African Journals online (AJOL), Index Copernicus, African Index Medicus (WHO), Excerpta medica (EMBASE), CAB Abstracts, , Global Health Abstracts, Asian Science Index, Index Veterinarius, , African Journals online

constituent of the tobacco plant *Nicotiana tabacum* (Melsens, 1844). The most popular form of nicotine consumption is cigarette smoking, which has been demonstrated to disrupt biochemical processes that may directly or indirectly compromise cognitive processes (Ceballos, 2006; Durazzo & Meyerhoff, 2007; Swan & Lessov- Schlaggar, 2007; Durazzo *et al.,* 2010). Several studies have shown that nicotine administration or smoking enhances performance in neuropsychometric tests but at the same time, other have reported inconclusive results (Heishman & Henningfield, 2000; Ernst *et al.,* 2001; Hahn *et al.,* 2002; Heishman *et al.*, 2002; Lawrence *et al*., 2002; Newhouse *et al*., 2004; Thiel *et al*., 2005; Ceballos, 2006; Giessing *et al*., 2006; Poltavski & Petros, 2006; Swan & Lessov-Schlaggar, 2007). The neural substrates and mechanisms underlying the cognitive effects of nicotine are still not well understood. Hence trying to unravel how nicotine affects brain function and complex cognitive tasks is a challenging task.

The variability in physiological baseline activity is a well-documented feature of biological systems, including the brain (Furusawa & Kaneko, 2000; Sato *et al.,* 2003). It is not known how such variability in brain baseline activity may influence the cognitive effects of nicotine. To address this important issue, in this study we have examined how baseline cognitive ability influences the magnitude of nicotine-induced changes in cognitive performance. To this end, we have used a battery neuropsychometric including working memory (*Two-Back task*), verbal information processing (*Logical reasoning task*) and global cognitive function (*Mini-mental state examination*) in a random population of non-smokers in the age-range 18-35 years.

MATERIALS AND METHODS

Selection and screening of participants

Ninety-nine non-smokers (80 males and 19 females) in the age-range 18-35 years (mean ± SEM, 23.38 ± 0.26) participated in the study. Participants recruited through poster advertising from Ahmadu Bello University's community, Zaria provided written informed consent for participation in the study. The selection and screening of participants occurred in two phases. Phase I consisted in selecting 150 participants from a total of 267 that responded to the advertisement. The criteria for inclusion were the age range of 18-35 years, a non-smoker history and no history of using common psychoactive substances (e.g. cannabis or caffeine). Phase II essentially consisted in screening the selected subjects for eligibility to participate in the study. The screening included a questionnaire and clinical examinations conducted in two stages (baseline screening on the day prior to the actual investigation and an additional screening on the day of the experiment). The baseline screening was designed to identify and exclude subjects with systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, body mass index ≥ 25 kg/m2 or ≤ 20 kg/m2, with history of gastrointestinal ulcer (contraindication for nicotine gum) or with neurological or psychiatric disorders. The additional screening on the day of the experiment aimed to identify and exclude subjects with moderate or severe depression level scores (via www.IME-I v2.3: 0-8 for normal depression range, 9-18 for mild depression, 19-28 for moderate depression, and > 28 for severe depression) or with body temperature outside the (36 to 38) ^{0} C range. Participants who passed the screening procedure were requested to refrain themselves from any form of physical activity for at least 24 hours prior to the day of the experiment.

Experimental design

Subjects were trained on three neuropsychometric test (NT) procedures: the *Two-Back task* for working memory, the *Logical reasoning task* for verbal information processing and the *Mini-mental state examination* for global cognitive function. Experiments were repeated on a daily basis between 9 am and noon for 30 days. Subjects had to refrain from eating for at least 3 hours prior to testing and they rested for 30 minutes in a quiet room they became familiar with during the baseline screening procedure. The experimental procedure consisted of an initial baseline assessment of performance on the three NTs mentioned above. The subject then received 2 pieces of nicotine chewing gum (***Nicorette:*** *manufactured by Pharmacia Limited, Ramsgate Road, Sandwich, Kent, UK.*), each containing 2mg of nicotine. The NTs were repeated 1 hour after the administration of the nicotine gum.

Nicotine administration

Subjects were asked to chew 2 pieces of nicotine gum, each containing 2mg of nicotine. The procedure was as follows: subjects first rinsed their mouth with distilled water and then chew the gums for 15-30 minutes at an approximate frequency of one chew every 3 seconds to allow enough time for the nicotine to penetrate the oral mucosa and being absorbed into the bloodstream. The peak venous plasma levels of nicotine achieved using this procedure matches those resulting from smoking a typical commercial American cigarette (Benowitz *et al.,* 1988).

Neuropsychometric test procedures

The choice of the three NT procedures used in this study was based on previous reports of sensitivity to acute nicotine administration in human studies (Heishman *et al.,* 1994; Decker *et al.,* 1995; Snyder & Henningfield, 1989; Mendrek *et al.,* 2006; Schrimsher *et al.,* 2009).

***Two-Back Task*:** Two-back task is a version of the *N*-Back task for the assessment of working memory. The two-back task used for this study was adapted from *Ernst et al.* (2001) with modified numbers of "target" and "non-target" letters. It is a computer-based identity monitoring (letters) paradigm; the task requires subjects to remember

Series of letters continuously updated. The letters appear in the middle of a computer screen, one at a time, for 500 ms, at intervals of 1 second (predetermined reaction time). The subject is instructed to press a "target" button whenever a letter is repeated with one intervening letter. When any other letter appears, the subject must press a "non-target" button. The test lasts for 2 minutes, comprising 80 trials (performance scores (PS) = 1-80) with varied numbers of target and non-target letters. Accuracy score was the critical variable assessed. Errors consisted of either errors of commission (pressing a target button for a non-target letter) or errors of omission (pressing a non-target button for a target letter).

Logical Reasoning Task: The logical reasoning task used for the assessment of verbal information processing in this study was adapted from *Ernst et al.* (2001) with reference to *Baddeley* (1968). It is a computer-based 3 minutes exercise in transformational grammar and measures verbal information processing. It comprises 32 trials, each of which presents a letter pair such as "VX" or "XV" and below the letter pair, a statement (e.g., V does not precede X) that correctly or incorrectly describes the alphabetical order of the letters. The participant is required to determine in 4 second (predetermined reaction time), whether the statement is true or false by pressing a "Yes" or "No" button respectively (PS = 1-32). Accuracy score was the critical variable assessed. Errors consisted of either errors of commission (pressing a "Yes" button for a false statement) or errors of omission (pressing a "No" button for a true statement). Two sessions were performed for each participant and the average of the two sessions was the variable of interest.

Mini-mental State Examination (MMSE): The MMSE is a popular test for rapid evaluation and global assessment of cognitive function (Folstein *et al.,* 1975). It is a paper and pencil neuropsychometric test lasting 5-10 minutes consisting of 11 questions with maximum PS of 30. It assesses primarily language and memory skills and is influenced by age, socio-economic status and level of education (Aggarwal & Kean, 2010). The possibility of obtaining a false positive or a false negative score due to the subject's level of education and/or age (Aggarwal and Kean, 2010) was controlled for during the initial selection phase of the study participants. All participants had formal education and were still in their undergraduate studies.

Data Analysis

Two main issues were addressed in the interpretation of the results. 1) The effects of acute administration of nicotine on performance on the three NTs? 2) Baseline cognitive ability and the magnitude of the nicotine effect on performance? Data were analysed using descriptive statistics, paired t-test, ANOVA, Student Newman Kuels (*post hoc)* test and Pearson product moment correlation (*r*) as appropriate at $P \leq 0.05$ for all comparisons. Data reported as mean ± SEM

RESULTS

Table 1 shows the characteristic of all participants in the study. It has been shown that clinically classified BMI (i.e. ≥ 25 kg/m2 or ≤ 20 kg/m2), body temperature (i.e. > 380C hyperthermia or < 360C hypothermia) and blood pressure (i.e. ≥ 140/90 mmHg hypertension or ≤ 90/60 mmHg hypotension) can all affects cognitive performances and therefore it was important to use subjects yielding mean values (computed for the entire population) that were not within any clinically classified range. Furthermore, moderate to severe mental depression and belonging to a polygamous (but not monogamous) family type also affects cognitive performances. The mean value of the mental depression level test scores for the total population in the study was 9.33±0.55 (mean ± SEM), indicating only mild depression. The monogamous family type was the predominant one in the study, with 72.5% of participants in the male group and 94.74% in the female group being monogamous.

Tables 2, 3 and 4 respectively show the performance scores (PS) before and after administration of nicotine by gender and subgroups of baseline PS on the NTs of working memory (*two-back task*) verbal information processing (*logical reasoning task*) and global cognitive function (*mini-mental state examination*). Paired student's t-test revealed that PS was significantly improved after administration of nicotine in the male

group, the total population for all three NTs ($P< 0.05$). Within subgroups, the improvement of PS was significant mainly, in subgroups with lower baseline PS (i.e. ≤ 70 and 71-75 for two-back task; ≤ 15 for logical reasoning task and 26 and 27-28 for MMSE). In the female group, there were no significant differences in PS after administration of nicotine. Pearson product moment correlations of the magnitudes of the nicotine improvement of PS and of baseline PS on the *two-back task, logical reasoning task and mini-mental state examination*, revealed significant negative correlations in the male group (r = -0.52; -0.50 and -0.73 respectively; $P<0.01$) and in the total population (r = -0.48; -0.45 and -0.73 respectively; $P<0.01$). ANOVA comparing the magnitude of the nicotine improvement of PS across the three subgroups in each of the NTs showed significant differences. Student Newman Kuels revealed that, all the mean values were significantly different across subgroups.

Table 1:
Characteristics of the subjects selected for the study

		Female	Male	Total
Sample size (n)		19	80	99
Family type	Monogamy	18 (94.74%)	58 (72.5%)	76
	Polygamy	1	22	23
Age (years)		21.90 ± 0.44	23.74 ± 0.29 *	23.38 ± 0.26
Blood pressure (mmHg)	SBP	113.42 ± 1.71	114.94 ± 0.60 *	114.65 ± 0.58
	DBP	73.68 ± 1.14	72.81 ± 0.62 *	72.98 ± 0.55
	MABP	86.93 ± 1.22	86.85 ± 0.52 *	86.87 ± 0.48
Pulse rate (beats/minutes)		72.68 ± 1.29	72.38 ± 0.94 ns	72.43 ± 0.79
Height (meters) (m)		1.64 ± 0.02	1.71 ± 0.01 *	1.69 ± 0.01
Weight (kilogram) (kg)		59.00 ± 2.34	65.34 ± 1.05 *	64.12 ± 0.99
Body mass index (BMI) (Kg/m^2)		22.01 ± 0.81	22.45 ± 0.35 *	22.37 ± 0.32
Body temperature (^{0} Celsius)		36.43 ± 0.08	36.44 ± 0.14 *	36.44 ± 0.11
Depression level Scores		8.65 ± 1.22	9.48 ± 0.62 *	9.33 ± 0.55

*P < 0.05 (male vs. female) (unpaired Student's t-test); no significant difference (ns); Systolic Blood Pressure (SBP); Diastolic Blood Pressure (DBP); Mean Arterial Blood Pressure (MABP)

Table 2: Performance scores on the neuropsychological test for working memory (*two-back task*) before and after nicotine administration by gender and baseline PS

Neuropsychological Tests		**Two-Back Task (1 second reaction time)**			
Ranges of Baseline scores		≤ 70	71-75	76-80	Total
Sample Size (n)		13	63	23	
Male	Before	68.73±0.38‡ (n=11)	72.92±0.20‡ (n=47)	76.68±0.20 ns (n=22)	73.38±0.31‡ (n=80)
	After	73.36±1.03	74.81±0.38	77.23±0.39	75.28±0.31
	Difference	4.64±1.07	1.89±0.39	0.55±0.35	1.90±0.32
	Magnitude of differences (%)	6.77±1.59	2.62±0.54	0.71±0.45	2.67±0.45 (r = -0.52; $P<0.01$)
Female	Before	70.00±0.00ns (n=2)	73.25±0.32 ns (n=16)	79.00±0.00● (n=1)	73.21±0.48 ns (n=19)
	After	71.00±2.00	74.31±0.64	80.00±0.00	74.26±0.68
	Difference	1.00±2.00	1.06±0.79	1.00±0.00	1.053±0.68
	Magnitude of differences (%)	1.43±1.59	1.50±1.09	1.27±0.00	1.48±0.94 (r = -0.35; P=0.14)
Within subgroup Total	Before	68.92±0.35‡ (n=13)	73.00±0.17‡ (n=63)	76.78±0.22 ns (n=23)	73.34±0.27‡ (n=99)
	After	73.00±0.93	74.68±0.32	77.35±0.39	75.08±0.29
	Difference	4.08±1.00	1.68±0.35	0.57±0.33	1.74±0.29
	Magnitude of differences (%)	6.00±1.48	2.34±0.49*	0.74±0.43*†	2.44±0.40 (r = -0.48; $P<0.01$)

‡ $P<0.05$ (before vs. after nicotine administration); *$P<0.05$ vs. ≤70; †$P<0.05$ vs. 71-75; Pearson product moment correlations (r) (baseline PS and magnitude of differences); ● Sample size is fewer than two (statistics not obtainable); no significant difference between before vs. after nicotine administration (ns)

Table 3
Performance scores on the neuropsychological test for verbal information processing (*logical reasoning task*) before and after nicotine administration by gender and baseline PS

Neuropsychological Tests		**Logical Reasoning Task (4 seconds reaction time)**			
Ranges of Baseline scores		≤ 15	16-25	26-32	Total
Sample Size (n)		29	47	23	99
Male	Before	11.63±0.79‡ (n=24)	19.56±0.42ns (n=39)	29.77±0.53ns (n=17)	19.35±0.79‡ (n=80)
	After	17.42± 1.65	21.21± 1.02	27.88± 1.10	21.49± 0.84
	Difference	5.79± 1.84	1.64± 1.05	↓1.88± 1.19	2.14± 0.84
	Magnitude of differences (%)	76.69± 28.29	9.61± 5.40	↓5.92± 3.84	26.43±9.57 (r = -0.50; P<0.01)
Female	Before	10.40±0.25ns (n=5)	19.00±1.04ns (n=8)	26.17±0.12ns (n=6)	19.00±1.47ns (n=19)
	After	12.20± 2.33	17.38±2.54	28.17±1.74	19.42±2.00
	Difference	1.80±2.40	↓1.63±2.44	2.00±1.77	0.42±1.33
	Magnitude of differences (%)	18.00±24.00	↓8.12±13.72	7.69±6.81	3.75±8.66 (r = -0.13; P=0.61)
Within subgroup Total	Before	11.41±0.66‡ (n=29)	19.47±0.39ns (n=47)	28.83±0.52ns (n=23)	19.28±0.70‡ (n=99)
	After	16.52±1.46	20.55±0.96	27.96±0.91	21.09±0.78
	Difference	5.10±1.59	1.09±0.97	↓0.87±1.04	1.81±0.73
	Magnitude of differences (%)	66.57±24.00	6.59±5.08*	↓2.37±3.51*†	22.08±7.94 (r = -0.45; P<0.01)

‡ P<0.05 (before vs. after nicotine administration); *P<0.05 vs. ≤15; †P<0.05 vs. 16-25; Pearson product moment correlations (r) (baseline PS and magnitude of differences); no significant difference between before vs. after nicotine administration (ns)

Table 4
Performance scores on the neuropsychological test for global cognitive function (*mini-mental state examination*) before and after nicotine administration by gender and baseline PS

Neuropsychological Tests		**Mini-mental State Examination**			
Ranges of Baseline PS		≤ 26	27-28	29-30	Total
Total sample Size (n)		26	30	43	99
Male	Before	24.81±0.38‡ (n=21)	27.62±0.09‡ (n=29)	29.23±0.08ns (n=30)	27.49±0.20‡ (n=80)
	After	27.43±0.38	28.24±0.28	29.07±0.19	28.34±0.17
	Difference	2.62±0.52	0.62±0.27	↓0.17±0.19	0.85±0.22
	Magnitude of differences (%)	11.15±2.57	2.26±0.98	↓0.56±0.66	3.54±0.95 (r = -0.73, P< 0.01)
Female	Before	25.60± 0.25‡ (n=5)	28.00±0.00● (n=1)	29.31±0.13‡ (n=13)	28.26±0.40ns (n=19)
	After	27.00± 0.63	29.00±0.00	28.39±0.37	28.05±0.33
	Difference	1.40± 0.68	01.00±0.00	↓0.92±0.40	↓0.21±0.40
	Magnitude of differences (%)	5.51± 2.73	3.57±1429	↓3.12±1.36	↓0.50±1.45 (r = -0.67, P<0.01)
Within Subgroup Total	Before	24.96±0.31‡ (n=26)	27.63±0.09‡ (n=30)	29.26±0.07‡ (n=43)	27.64±0.20 ‡ (n=99)
	After	27.35±0.33	28.27±0.27	28.86±0.18	28.28±0.15
	Difference	2.39± 0.45	0.63±0.26	↓0.40±0.19	0.65±0.20
	Magnitude of differences (%)	10.06±2.17	2.30±0.95*	↓1.33±0.63*†	2.76±0.83 (r = -0.73, P<0.01)

‡ P<0.05 (before vs. after nicotine administration); *P<0.05 vs. ≤26; †P<0.05 vs. 27-28; Pearson product moment correlations (r) (baseline PS and magnitude of differences); ↓ decrease in PS; ● Sample size is fewer than two (statistics not obtainable); no significant difference between before vs. after nicotine administration (ns)

DISCUSSION

The main findings of this study are: 1) Nicotine significantly enhanced PS on the NTs of working memory, verbal information processing and global cognitive function in non-smokers 2) The magnitude of the cognitive enhancement effects of nicotine increased significantly with decrease in baseline PS. The interpretation of nicotine improvement of cognitive performance assessed by neuropsychometric test procedures therefore needs to be done with caution, taking baseline performance into consideration.

The results of the study showed that 4 mg of nicotine improved performances on all three NTs in non-smokers. The present results are consistent with the conclusion that nicotine improves performance in non-smokers on cognitive tasks (Thiel *et al*., 2005; Levin *et al.*, 2006; Hahn *et al*, 2007, 2009). However, the results differ from reports of impaired or unimproved cognitive performances after nicotine administration in non-smokers (Heishman & Henningfield, 2000; Ernst *et al*., 2001; Newhouse *et al*., 2004). *Heishman & Henningfield* (2000) reported that nicotine improved reaction time, but not accuracy scores on working memory tasks. *Ernst et al.* (2001) performed a double-blind test of administrating nicotine (4 mg) gum or taste-matched placebo in two testing sessions to smokers, ex-smokers and non-smokers. The authors concluded that there was no significant session (i.e. nicotine or placebo) or group (i.e. history of nicotine exposure) effect in the accuracy scores on a *Logical Reasoning Task* or a *Two or Three-Back Task* or a *Two-Letter Search Task*. However, they did observe both session and group effects with respect to reaction time on the *Two-Letter Search Task* that assesses visual scanning and recognition abilities and on the *Two or Three-Back Task* for working memory. On the contrary, the results of the present study provide evidence for nicotine-induced improved performance on accuracy scores in non-smokers assessed on *Two Back Task*, *Logical Reasoning task* and *MMSE*. In addition, the results suggest that, assessment of the effect of nicotine on cognitive performance may be contingent upon the critical variable of interest (e.g. reaction time or accuracy scores).

A plausible explanation for the observed differential cognitive effects of nicotine in the aforementioned studies is that the selection and grouping of participants and the analysis of accuracy scores in *Heishman & Henningfield* (2000) or *Ernst et al.* (2001) did not take cognizance of baseline dependent differences in the influence of nicotine on PS (Perkins, 1999). Baseline dependency effect of nicotine reflects a relationship between the optimal cognitive performance at baseline and the cognitive effect of nicotine. Though, the cognitive enhancement effect of nicotine may be contingent upon individual differences in pharmacological sensitivity to nicotine, it also may be due partly to individual differences in baseline level of responding on the measure of interest. Indeed, subjects might already be performing at near or optimal performance level at baseline. Therefore, in such conditions, a further beneficial effect of nicotine should not be expected. Baseline-dependency, perhaps, is most clearly demonstrated in comparisons between groups selected on the basis of specific characteristics, for example, high versus low performance levels at baseline (Perkins, 1999). This is consistent with the "*Yerkes-Dodson Principle*" which indicates that, "performance increases with physiological or mental excitement, but only up to a point. When levels of arousal or excitement become too high, performance decreases." The process is often illustrated graphically as a curvilinear, inverted U-shaped curve which increases and then decreases with higher levels of arousal (Yerkes & Dodson, 1908). Similarly, cognitive performance in relation to nicotine stimulation can be envisaged as a curvilinear function, suggesting that, if an individual is performing sub-optimally at baseline, increased nicotinic stimulation will enhance his performance. While, if the individual is already performing at or near optimal level of performance at baseline level, increasing nicotinic stimulation will impair cognitive functioning. Thus, the beneficial effects of nicotine will be most evident in individuals with relatively lower levels of baseline cognitive performance as evident by the improved cognitive function after administration of nicotine, observed in pathological disease states characterized by cognitive impairments, such as Alzheimer's disease (AD) and attention-deficit/hyperactivity disorder (ADHD) (Newhouse *et al*., 2004; Poltavski & Petros, 2006). Accordingly, allowing for the selection and grouping of participants with different levels of baseline cognitive abilities for studies of this nature and a correlation of the baseline with the magnitude of cognitive performance after nicotine stimulation might be more informative in elucidating the cognitive effect of nicotine.

Overall, the disagreement between the results of the present study and the previous studies that reported nicotine impaired or unimproved performance on cognitive tasks in non-smokers can be explained by the concept of baseline-dependency nicotine effects (Perkins, 1999) with reference to the notion that nicotine tends to optimize rather than improve performance on cognitive tasks (Poltavski & Petros, 2006).

This study showed that the magnitude of the cognitive enhancement effects of nicotine increased significantly with decrease in baseline PS. Pearson product moment correlations of the baseline PS and the magnitudes of the nicotine enhancement effect of PS, showed significant negative correlations that are indicative of a baseline-dependency nicotine effect (Perkins, 1999). The data suggest that the extent to which nicotine improves cognitive performance is a function of baseline cognitive ability, given that for the three NTs, the subgroups with lower baseline PS showed significant PS improvement after the administration of nicotine. In contrast, the subgroups with higher baseline PS showed either no drug effect (i.e. on the *Two-Back Task* and the *logical Reasoning Task*) or impairment of performance (i.e. on the *MMSE*). Furthermore, the impairment effect of nicotine observed in the subgroup with the highest baseline PS on the *MMSE* provides evidence that supports the notion that nicotine tends to optimize rather than improve performance on cognitive tasks (Poltavski & Petros, 2006). However, the consequences of "*ceiling effect*" cannot be overruled.

The term *ceiling effect* in this context refers to the level above which variance in PS can no longer be measured or estimated, which is a commonly encountered practical issue in gathering data in many scientific disciplines. Such a ceiling effect is often the result of constraints on data gathering instruments (Cramer & Howitt, 2004). The range of data that a particular instrument can gather may be constrained by inherent limits in the instrument's design. Ceiling effect prevents the instrument from detecting an effect or it may detect abnormally large effects due to the design of the instrument rather than to the phenomenon under observation. When a ceiling effect relates to data gathered on a dependent variable (such as PS), failure to recognize it may lead to the mistaken conclusion that the independent variable (i.e. nicotine) has no effect (Cramer & Howitt, 2004). Indeed, the analysis across the subgroups showed that although the subgroups with the highest baseline PS may be prone to ceiling effect, there were significant differences in the magnitude of nicotine-mediated PS improvement among the subgroups with lower baseline PS. The beneficial effect of nicotine was most evident in the subgroups with the lowest baseline PS. Generally, the results are indicative of baseline dependency plasticity in the magnitude by which nicotine improves cognitive performances on neuropsychometric tests of working memory, verbal information processing and global cognitive function in non-smokers.

In support of the above indications, an intrinsic functional network of the resting brain, the default network of resting brain function (DNB), has been shown to provide a framework for understanding the neural substrates and mechanisms that underlie the cognitive effects of nicotine (Hahn *et al.*, 2007, 2009). The DNB describes a default mode of spontaneous activity that widely distributes across topographically organized brain areas (Raichle *et al.*, 2001; Raichle & Snyder, 2007). DNB activity appears to represent a physiological baseline for cognitive function (Fox *et al.*, 2005; Raichle & Gusnard, 2005) and localized deactivation of the DNB activity during specific cognitive demanding tasks appears to correlate with cognitive performance (McKiernan *et al.*, 2003; Fox *et al.*, 2005; Raichle & Gusnard, 2005). Potentiating DNB deactivation optimizes cognitive performance during specific cognitive demanding tasks (Polli *et al.*, 2005; Fair *et al.*, 2008; Broyd *et al.*, 2009). It has been shown that nicotine improves cognitive performance by potentiating task-related deactivation of DNB activity (Hahn *et al.*, 2007, 2009). Accordingly, *Hahn et al.* (2007) reported that, the deactivations were induced in active task trials relative to baseline.

In conclusion, the magnitude by which nicotine improves cognitive performances on neuropsychometric tests of working memory, verbal information processing and global cognitive function in non-smokers is plastic and the plasticity appears to be consistent with the concept of "*baseline-dependency nicotine effect*". Thus, assessing cognitive effects of nicotine might be misleading, and the complexity might further increase if exclusively based on neuropsychometric test scores without correlations with baseline scores. Therefore, as a recommendation for future research, a meta-analysis of the implication of *baseline-dependency effect of nicotine* in resolving the enigmatic conclusions of studies on the cognitive effects of nicotine may be considered.

Conflict of interest

The authors declare that there is no conflict of interest in this work.

Acknowledgment

The authors are grateful to the Ahmadu Bello University Board of Research for partly funding this work.

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