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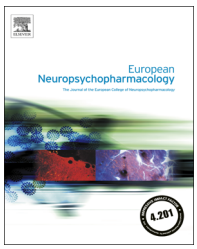

The effects of nicotine on cognition are dependent on baseline performance

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Abstract
Since cholinergic neurotransmission plays a major role in cognition, stimulation of the nicotinic acetylcholine receptor may be a target for cognitive enhancement. While nicotine improves performance on several cognitive domains, results of individual studies vary. A possible explanation for these findings is that the effect of nicotine administration may be dependent on baseline cognitive function, where subjects with a suboptimal cognitive performance may benefit from nicotine, while subjects who already perform optimally may show a decline in performance after nicotinic stimulation. We conducted a double-blind randomised placebo-controlled crossover trial, examining the effects of placebo, 1, and 2 mg of nicotine on cognition in young (n=16, age 18–30 years) and healthy elderly (n=16, age 60–75 years) subjects. We hypothesised that the elderly would benefit more from nicotine compared to young subjects, as normal ageing is associated with decreases in cognitive function. Attention, working memory, visual memory, information-processing speed, psychomotor function, stereotypy, and emotion recognition were assessed. Compared to the young volunteers, the elderly performed significantly worse on psychomotor function and emotion recognition in the placebo condition. Nicotine had no effect in the young volunteers and decreased performance on

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working memory and visual memory in the elderly. Contrary to our hypothesis, the effect of nicotine was dependent on baseline performance in both the groups, with subjects with lower baseline performance benefiting from nicotine administration, while those with higher baseline performance performed worse after nicotine administration. This suggests that subjects with lower cognitive performance, irrespective of age, may benefit from nicotine.

1. Introduction

Cholinergic neurotransmission plays an important role in the peripheral and central nervous system. In the latter, it is an important modulator of cognition (Sarter and Parikh, 2005). Increased age is associated with a decreased availability of the nicotinic acetylcholine receptor (nAChR) (Mitsis et al., 2007, 2009), which may contribute to the decline of cognitive function (such as attention, executive function, memory, visuospatial function and cognitive speed) that is associated with normal ageing (Christensen, 2001; Drag and Bieliauskas, 2010). Decreases in nAChR's are also implicated in several pathological states associated with decreased cognitive functioning, such as neurodegenerative disorders (e.g. Alzheimer's disease) and schizophrenia (Dani and Bertrand, 2007; Quisenaerts et al., 2013a, 2013b). Stimulation of the cholinergic neurotransmission with cholinesterase inhibitors has been shown to ameliorate cognitive impairment in Alzheimer's disease (Birks, 2006; Rolinski et al., 2012), suggesting that the cholinergic system is a valid target for cognitive enhancement.

Nicotine, present in tobacco smoke, is an agonist of the nAChR, and as such may improve cognition (Heishman et al., 2010). Of the several subtypes of the nAchR, the $\alpha4\beta2$ and the $\alpha7$ nAchR appear to be the most important in cognitive functioning (Levin et al., 2006). In a meta-analysis of studies in healthy adult smokers and non-smokers, it was shown that nicotine improved attention, motor function, and short-term episodic memory (Heishman et al., 2010). Although the aforementioned meta-analysis showed that nicotine globally enhanced several domains of cognition, the results of individual studies are conflicting (Newhouse et al., 2004; Quisenaerts et al., 2014). Newhouse et al. (2004) suggest that the effects of nicotine may be dependent on baseline functioning, where the effect of nicotine is best described with an inverted U-shape, similar to the effects of stimulants (Cools and D'Esposito, 2011), where only those subjects with suboptimal cognitive performance may benefit from nicotine.

Following this line of thought, nicotine may be particularly effective in populations with decreased cognitive performance. Indeed, a study on patients with minimal cognitive impairment (MCI) showed that nicotine improved attention, memory, and psychomotor speed (Newhouse et al., 2012). So far, only two studies have addressed the effects of nicotine in a normal elderly population. White and Levin (2004) found that 10 mg of transdermal nicotine improved attention and clinical global impression score in patients with age-associated memory impairment, whereas another study in healthy elderly non-smokers, found that 5 mg transdermal nicotine improved verbal memory, but not short-term memory, concentration, and orientation (Min et al., 2001).

To assess the effects of nicotine on the cognitive performance of healthy elderly subjects, we conducted a clinical trial comparing the effect of the administration of 0, 1, and 2 mg oromucosal nicotine spray on several cognitive measures in healthy elderly and young volunteers. We hypothesised that the administration of nicotine would improve cognitive function in healthy elderly subjects, since we expected lower baseline cognitive functioning due to age-related decreases in cognitive performance. We expected that nicotine would have no or negative effects in healthy young subjects, since they already have an optimal cognitive performance relatively to elderly.

2. Experimental procedures

2.1. Study population

Healthy young (aged 18–30 years) and healthy elderly volunteers (aged 60–75 years) were eligible for the study. Additional inclusion criteria were: a body mass index between 18 and 30 kg/m^2 and the use of an effective contraceptive method by the female participants. The exclusion criteria were: smoking or the use of nicotine based products during the last 3 months, significant history of/or current psychiatric, somatic, or neurological illness, pregnancy or breast feeding, clinically significant abnormalities in lab values/physical examinations/vital signs/ECG, clinically significant recent or current acute illness, the use of any prescription irrespective of over-the-counter or herbal medication, and substance abuse. The consumption of alcohol, methylxanthine containing beverages or foods, quinine, grapefruit, grapefruit juice, Seville oranges and any poppy seeds were not permitted from 48 h before drug administration until discharge from the unit. Smoking was not allowed during the study and subjects were not allowed to do any strenuous exercise (from 7 days prior to the first study drug administration) until after study completion.

SGS Clinical Research Unit, Antwerp, Belgium, recruited the participants. A written informed consent form was obtained from every participant after full explanation of trial procedures. After screening each subject for eligibility, 16 young and 16 elderly

Table 1 Mean demographic and clinical variables (standard deviation).

Variable (unit)	Young	Elderly
Age (years)	22.6 (3.03)	62.9 (2.71)
Gender (male:female)	4:12	8:8
Education (years)	13.9 (1.03)	12.9 (1.89)
Education (level)		
Low (%)	12.5	18.75
Average (%)	62.5	56.25
High (%)	25	25

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