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Short communication

# Donepezil increases contrast sensitivity for the detection of objects in scenes

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## HIGHLIGHTS

- A single dose of donepezil facilitates signal detection.
- Cholinergic stimulation facilitates signal detection under difficult perceptual conditions.
- Cholinesterase inhibitors might improve perception in patients with Alzheimer disease.

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## ABSTRACT

We assessed the effects of donepezil, a drug that stimulates cholinergic transmission, and scopolamine, an antagonist of cholinergic transmission, on contrast sensitivity. 30 young male participants were tested under three treatment conditions: placebo, donepezil, and scopolamine in a random order. Pairs of photographs varying in contrast were displayed left and right of fixation for 50 ms. Participants were asked to locate the scene containing an animal. Accuracy was better under donepezil than under scopolamine, particularly for signals of high intensity (at higher levels of contrast). A control experiment showed that the lower performance under scopolamine did not result from the mydriasis induced by scopolamine. The results suggest that cholinergic stimulation, through donepezil, facilitates signal detection in agreement with studies on animals showing that the pharmacological activation of cholinergic receptors controls the gain in the relationship between the stimulus contrast (intensity of the visual input) and visual response. As Alzheimer disease is associated to depletion in acetylcholine, and there is evidence of deficits in contrast sensitivity in Alzheimer, it might be interesting to integrate such rapid and sensitive visual tasks in the biomarkers at early stage of drug development.



## 1. Introduction

Alzheimer's disease (AD) is characterized by alterations in memory, attention and visual perception. Patients with AD exhibit impairments on multiple visual tasks [1]; contrast sensitivity and masking being the most prevalent [2]. Impaired contrast sensitivity has been documented in AD using different paradigms [3,4]. For instance, Risacher et al. [5] assessed visual contrast sensitivity in patients with mild cognitive impairment (MCI) and patients with AD using a frequency doubling paradigm. They found that both AD and MCI showed marked deficits including increased exam time and reduced general sensitivity. With photographs of scenes Neargarder and Cronin-Golomb [6] reported that the ability of patients with AD to detect a change in a scene was influenced by visual characteristics of the target, especially by low contrast images.

Some of visual deficits in AD may arise from degeneration of a basal forebrain structure, the nucleus basalis of Meynert, which is accompanied by loss of cortical cholinergic innervation [7,8]. Evidence suggests that degeneration of this nucleus may underly

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the decline in functions like perception, memory, and attention observed in dementia [9,10]. The nucleus of Meynert provides the principal cholinergic input of the cortex [11]. The primary visual cortex (V1) is a major target of cholinergic projections, and its neuronal information processing is known to be modulated by acetylcholine (ACh) in many species [12–15]. ACh modulates the contrast sensitivity, and signal-to-noise ratio of responses in the visual cortex, to enhance the detectability of a visual stimulus. For instance, Soma et al. [15] examined whether ACh influences behavioral contrast detectability in rats. They measured the contrast sensitivity to a grating stimulus in freely behaving animals. They showed that donepezil (a cholinesterase inhibitor) improved the contrast sensitivity at spatial frequency peak, especially in the difficult detectability condition. They suggested that ACh plays a role in enhancing contrast sensitivity at sensitive spatial frequency ranges. In anesthetized macaque monkeys Soma et al. [14] reported that micro-iontophoretic administration of ACh induced facilitatory effects on the visual responses of V1 neurons to sinusoidal gratings varying in contrast.

In the present study we compared the effect of donepezil and scopolamine in humans in a categorization task using photographs of scenes. The task was performed on randomly mixed sequences of photographs at different contrast reductions. Pairs of scenes were simultaneously displayed left and right of fixation. Participants were asked to decide if the left or the right scene contained a target (an animal). As ACh plays an important role in visual processing, particularly in contrast perception, we expected donepezil to improve categorization and scopolamine to impair categorization.

## 2. Method

### 2.1. Participants

30 healthy males (age: 23.1 ± 2.4 years) were recruited. They were tested for general physical, cognitive, and mental functions. A standard biological examination, urinary toxic research, and ECG were performed to eliminate abnormal medical conditions. Written informed consent was obtained. The experimental procedures were approved by the local ethic committee. All participants had normal vision. Tobacco smokers were excluded. Subjects were paid for their participation.

### 2.2. Experimental design

The study followed a randomized, placebo-controlled, double-blind, cross-over design to test the acute effect of donepezil, an inhibitor of acetylcholinesterase, and of scopolamine, an antagonist of muscarinic receptors. In the inclusion session, participants were tested to verify the lack of exclusion criteria. Then all subjects participated to 3 sessions, in a double placebo manner: (i) one session with a double placebo of donepezil (oral tablet) and scopolamine (subcutaneous injection); (ii) one session with donepezil (5 mg, oral tablet) and placebo of scopolamine (subcutaneous injection); (iii) one group with placebo of donepezil (oral tablet) and scopolamine (0.4 mg, subcutaneous injection). The order of drug administration was randomized between all subjects and the three pharmacological sessions. The three sessions were separated by a wash-out period of 1 month considering donepezil (half life 70 h, [16]). Donepezil, scopolamine, or placebo were administrated in the morning at 9 a.m. The testing session started 3 h later. The parameters monitored were blood pressure, alertness, and all side effects, every 2 h during the first 12 h and 24 h after taking the drug. The two placebos were formulated as identical galenic formulation of, respectively, donepezil and scopolamine. Participants received domperidone (3 × 20 mg/d) to avoid digestive adverse effects for 3 days prior to pharmacological sessions.

### 2.3. Control experiment

As scopolamine induces a mydriasis a control experiment assessed the effect of mydriasis on contrast perception. 13 new young male participants were included. They were all students in physics, working on laser, who consulted regularly in ophthalmology to check for any accident due to the use of laser. They were all healthy and had normal vision. During their consultation in ophthalmology they received a local mydriatic treatment (1 drop of mydriaticum and 1 drop of neosynephrine in each eye). They were tested 1 h later.

### 2.4. Stimuli

The stimuli were displayed on a 30 inches (Dell) screen connected to a computer (Dell). Participants responded on a box containing two keys. The stimuli were photographs of natural scenes taken from a large commercial CD database (Corel). They were displayed on a black background (0.23 cd/m2). Half of the scenes contained an animal (the target) and the other half (distractors) contained no animal. Animal targets included fish, birds, mammals, insects, and reptiles. Distractors included landscapes, trees, flowers, various objects, monuments, and means of transportation. The angular size of the pictures was 15° vertically × 10° horizontally. The original colored photographs were converted in 256 grey levels and then processed using adobe photoshop CS (version 8.01) to generate new versions of each image in which the original contrast (C) of the photograph was divided by 2, 4, 8, 10 and 16. The procedure is described in Mace et al. [17]. When luminance of the original image was divided by 2 the new image had 50% residual contrast of its original photograph. When it was divided by 4, 8, 10 and 16, the new image had 25%, 13%, 10% and 6% of the contrast of its original photograph. As compared to simpler psychophysical stimuli maximum local contrasts in natural images seldom reach 100% and nearly 90% of the photograph had less than 3% of the maximal local contrast values above 90% Michelson contrast. In original images, only 41% of the mean pixel based contrast values were above 10% Michelson contrast. This proportion was reduced to 5.9%, 0.82%, 0.26% and 0.02% in the C 1/4, C 1/8 C/10 and C 1/16 conditions. Examples are displayed in Fig. 1.

### 2.5. Procedure

Following a central fixation cross displayed for 500 ms a pair of scenes was presented for 50 ms simultaneously left and right of fixation. The center of each image was located 10° from central fixation. A two alternative forced choice paradigm was used. Participants were asked to press the left or the right key depending on the spatial location of the scene containing an animal. They were told that, for the lowest levels of contrast, they would have the feeling of seeing just a flash but that, even for those levels of contrast, a target animal was always present left or right of fixation and they were encouraged to guess. Prior to the experiment participants were adapted to the luminance of the background for 10 min. They were tested in a dark room. The experimental session was composed of 180 images randomly taken, by software, from a pool of about 1200 images per level of contrast (C, C/2, C/4, C/8, C/10 and C/16). There were 30 scenes (15 targets on the right and 15 targets on the left) for each of the 6 levels of contrast. The experience lasted about 10 min. The inter-trial interval was fixed at 2 s. Participants were given 20 practice trials.