Cholinergic enhancement decreases spatial spread of visual responses in human primary visual cortex

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Background

- Animal physiology studies suggest that the neurotransmitter acetylcholine (ACh) modulates lateral interactions in early visual cortex:
  - Injecting ACh into marmoset V1 resulted in a shorter preferred length of neurons by decreasing spatial summation area (Roberts et al., 2004)
  - Increasing ACh levels with cholinergic agonists suppressed spread of intracortical excitatory activity in slices of rat visual cortex (Kimura et al., 1999)
- Functional MRI Blood Oxygenation Level-Dependent (BOLD) signal that is correlated with an increase in neural activity (relative to baseline) for a given stimulus is classified as positive BOLD, and the signal that is correlated with a decrease in such activity is classified as negative BOLD (Shmuel et al., 2006)

Purpose:

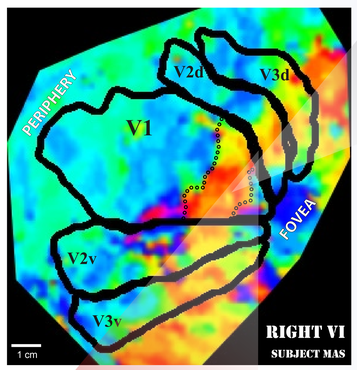
To determine the effects of increasing synaptic acetylcholine in humans on the amount of visual cortex activated by visual stimulation.

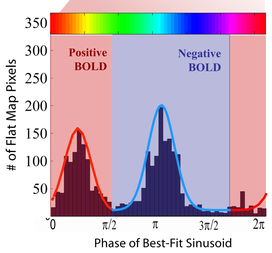
Methods

Analysis:

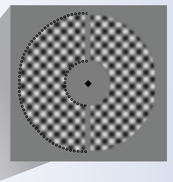
- fMRI was used to measure the BOLD responses in human primary visual cortex (area V1) to passive visual stimulation. Early visual areas V1, V2., and V3 were defined in each subject using standard phase-encoded retinotopic mapping techniques.

A 0.05 Hz sinusoid (same frequency as the stimulus cycle) was fit to the fMRI time series for each voxel within V1, and a phase was assigned to each voxel corresponding to the temporal delay of the response relative to the stimulus cycle. The spatial distribution of response phases were displayed on flat maps of visual cortex:





The distribution of response phases was fit with two Gaussian curves, and the parameters of the best-fit curves were used to define phase windows for positive and negative BOLD within each session.



Subjects viewed a contrast-reversing checkerboard annulus (with diameter subtending 3-9 degrees of visual angle) that was presented in a block-alternation design, with periods of 9.6s of continuous stimulus presentation alternating with 9.6s of a blank screen (uniform gray except for the fixation point). Subjects were instructed to continuously maintain fixation.

- Voxels with positive BOLD responses were clustered within V1 with boundaries corresponding to the inner and outer edges of the stimulus annulus (see schematic outline above and to the left). This band of positive responses in V1 was flanked on either side by regions displaying negative BOLD, and the locations of the boundaries between the positive and negative BOLD regions provided a measure of the spatial spread of the visual response.

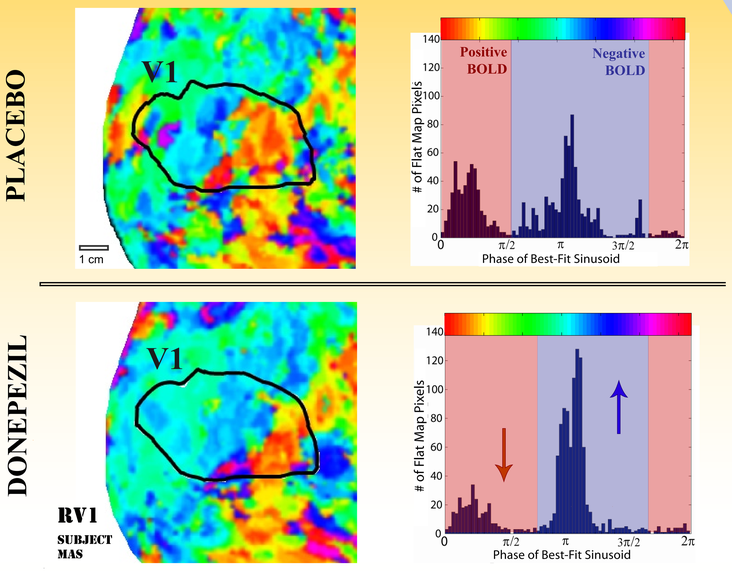
- The response phases had a bimodal distribution within V1. One population of voxels showed increased activity during visual stimulus presentation (positive BOLD response to the stimulus), and the second population was less active during stimulus presentation than during the blank screen control (negative BOLD response to the stimulus).

Subjects/Pharmacology:

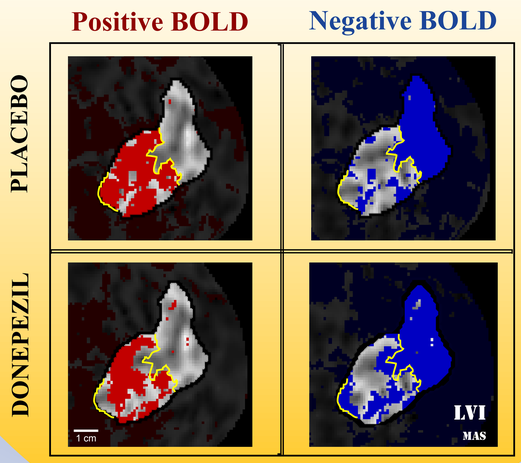
- Five healthy human volunteers participated in this study. We administered the Alzheimer's medication donepezil (Aricept®), a cholinesterase inhibitor, in order to increase levels of synaptic ACh across the brain. Subjects received either 5 mg of Aricept or placebo three hours before each of the functional imaging sessions.
- Most subjects participated in four fMRI sessions (two drug and two placebo), a retinotopic mapping session, and a functional localizer session to map out areas of the visual cortex most responsive to the stimulus. The effects of cholinergic enhancement were determined in scanning sessions that were separate from the retinotopic mapping sessions.
- Experiments were randomized with respect to drug/placebo order and were double blind.

Single Subject Results

Relative to placebo, donepezil decreased the number of positive BOLD and increased the number of negative BOLD voxels in V1:

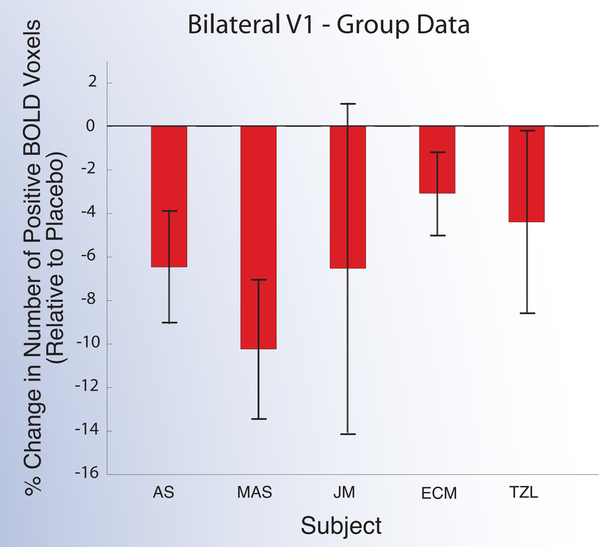


Cholinergic enhancement with donepezil decreased spatial spread of positive BOLD visual response for both the central and peripheral boundaries of the stimulus representation:



Group Results

Donepezil decreased spatial spread of positive BOLD voxels in all five subjects:



Conclusions

- Cholinergic enhancement with donepezil **reduced the spatial spread of visual responses** in primary visual cortex across all subjects.
- Stimulus representation boundaries receded:
  - Inner annulus border *away from* fovea
  - Outer annulus border *towards* fovea

References

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Roberts MJ, Zinke W, Guo K, Robertson R, McDonald JS, Thiele A. (2005) Acetylcholine dynamically controls spatial integration in marmoset primary visual cortex. J Neurophysiol 93:2062-72.

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