The Effect of Nicotine on the BOLD MRI Response in Smokers

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Introduction: Nicotine causes CNS stimulation partly through increased adrenergic and dopaminergic activity, followed by CNS depression. The purpose of this study was twofold: First, to determine the stimulant effects of nicotine on the BOLD response in visual cortex and second, to reinvestigate with an imaging method shown to be more reliable near the skull base than EPI (1) whether basal cerebral nuclei involved in craving and the sensation of pleasure could indeed be observed to respond directly to nicotine.

Methods and Materials: After approval by the local ethics board six healthy young habitual smokers (age 22±2 y, written informed consent) who consumed at least one pack of cigarettes/d were examined by fMRI between 7:00 and 10:00 a.m. before, during ascending doses of nicotine, and during maintenance nicotine infusion (0.5 μg/min x kg b.w.). For comparison, also six non-smokers were studied without nicotine application. The examination of the primary visual cortex was performed with a T2*-weighted, multi-slice blipped gradient-echo EPI sequence (TR/TE = 2000/54 ms, flip angle 70°, 2x2 mm^2 resolution in-plane, 4 mm sections) at 2-T (Siemens Vision, Erlangen, Germany). The protocol included scans of 8 minute length with oblique transverse sections parallel to the calcarine fissure each for repetitive visual stimulation (12 cycles of 10 s on/off checkerboard) and sustained visual stimulation (240 s) before and during nicotine maintenance administration, respectively. Loading of nicotine occurred in 3 sequential ascending iv doses of 0.75, 1.5 and 3.0 mg over 1 min, while a T2*-weighted FLASH scan (TR/TE = 62.5/30ms, flip angle 10°, in-plane resolution 1.6x0.8mm^2, time resolution 6 s) (1) recorded coronal sections at the level of the N. accumbens, amygdala, and thalamus for 36 minutes. A short heart rate increase was observed at 2-4 min (peak range 4-30 bpm) after nicotine doses. Serum cotinine levels after the examination ranged at 190-310 ng/ml. Evaluation of significantly activated pixels was based on cross-correlation of signal intensity time courses with a boxcar reference waveform representing the stimulus protocol shifted by 6 sec to account for hemodynamic latencies, thresholding ($p = 0.0001$), and normalization of pixel clusters as reported previously (2).

Results and Discussion: Without nicotine, the responses to both visual stimulations were the same in smokers and non-smokers. In 5 out of 6 habitual smokers nicotine resulted in a significant increase (30-110%) in the number of activated pixels, both at repetitive and sustained stimulation. One subject did not cooperate properly. At stimulation nicotine also caused a strong reduction of the temporal fMRI signal intensity in the range of 20-50 % consistent with the vasoconstrictive action of nicotine. The increased number of activated pixels reflects the stimulant activity of the drug probably mediated by dopaminergic and noradrenergic transmission. In a second part, employing coronal FLASH imaging instead of low-resolution transverse EPI to avoid the substantial magnetic susceptibility distorsions within the deep inferior brain, we did not observe activation of any of the putative limbic cortical structures with a similar regimen of nicotine administration as used by (3). In particular, no BOLD responses were detected in the N. accumbens, amygdala, cingulum, putamen, and thalamus.

References: (1) Merboldt, KD et al. (2001) Neuroimage 14:253-257. (2) Bruhn, H et al. (2001) J. Magn. Reson. Imag. 13:325-334. (3) Stein, EA et al. (1998) Am. J. Psychiatry 155:1009 - 1015.