Effect of Varenicline on BOLD and Neural Networks in Awake animals

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Introduction

Tobacco dependence is the most preventable cause of death and is a chronic, relapsing disorder in which compulsive tobacco use persists despite known negative health consequences. All currently available cessation agents (nicotine, varenicline and bupropion) have limited efficacy and are associated with high relapse rates, revealing a need for more efficacious, alternative pharmacotherapies (Dwoskin et al 2009).Varenicline is a partial nicotinic receptor agonist/antagonist that is prescribed for smoking cessation, but an important question is how the agonist and antagonist properties of varenicline contribute to its effectiveness. We used functional Magnetic Resonance Imaging (fMRI) to study the Blood Oxygenation Level Dependent (BOLD) response and neural networks related to first time exposure of the different doses of varenicline in awake animals.

Methods

The fMRI study was performed on a Bruker Biospec 4.7 T/40 cm horizontal scanner. Before imaging, all the adult male Sprague-Dawley rats (N=20) were acclimated to a restraint system that incorporates surface and volume coil electronics and allows us to image conscious animals (King et al 2005). To assess the effect of the first dose of varenicline in naïve animals, 8 animals received a dose of varenicline (0.4 mg/kg), 6 animals received a dose of varenicline (0.04mg/kg), all intravenously (IV) administered during the functional image data collection.

High-resolution anatomical images were obtained using fast spin echo pulse sequences (echo time, 48 ms; repetition time, 2000 ms; field of view, 30 mm; 1.2 mm slice thickness; 256 x 256 data matrix; RARE (rapid acquisition relaxation enhanced) factor, 8). Next, BOLD fMRI images were continuously acquired over 30 minutes to include a 5 minute baseline and 25 minutes after varenicline administration IV over 1 minute. The functional images were obtained with a fast spin echo pulse sequence (field of view, 30 mm; 1.2 mm slice thickness; echo time, 56 ms; repetition time, 2000 ms; 64 x 64 data matrix; RARE factor, 16). fMRI image data analysis employed Analysis of Functional NeuroImages(AFNI) software to correct motion artifact, to register, segment and analyze the data. The correlation analysis and percent change in BOLD activation was calculated on a pixel-by-pixel basis by comparing the average values obtained during the 5min before and 25min after the challenge dose. The threshold p-value was 0.0267.

Results

The top figure shows 8 anatomical regions of interest: PFC- prefrontal cortex; ACG- anterior cingulate gyrus; NAcc- nucleus accumbens; SEP- septum; VP- ventral pallidum; HP- hippocampus; VC- visual cortex; and VTA- ventral tegmental area. The lower figure shows BOLD activation in response to the first dose 0.4mg/kg and 0.04mg/kg varenicline challenge. The BOLD activation in response to the first dose of 0.4mg/kg varenicline is much more robust than that observed with 0.04mg/kg.

Discussion

Elucidation of the mechanisms underlying different doses of varenicline in awake naïve animals may assist in understanding the action of this partial nicotinic receptor agonist/antagonist in patients. The brain areas that were activated by varenicline include those of the limbic system that are involved with addiction, and cortical areas associated with cognition. The involvement of the limbic system is consistent with varenicline's proven efficacy as a smoking cessation drug.

References: (1) Dwoskin et al. Biochem Pharmacol. 78(7):732-43 2009. (2) King et al. J Neurosci Methods.148 (2):154-60. 2005.
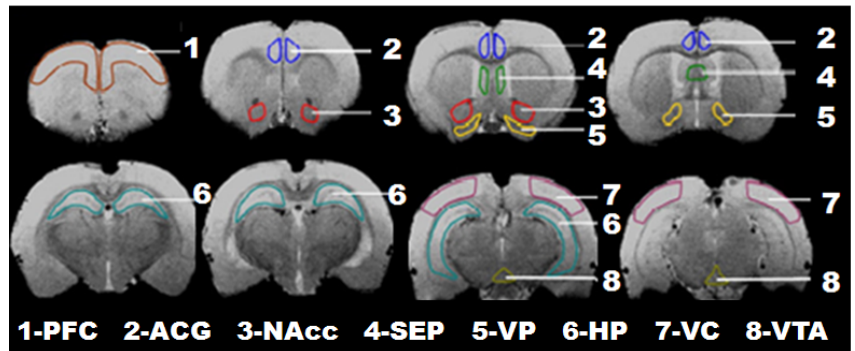
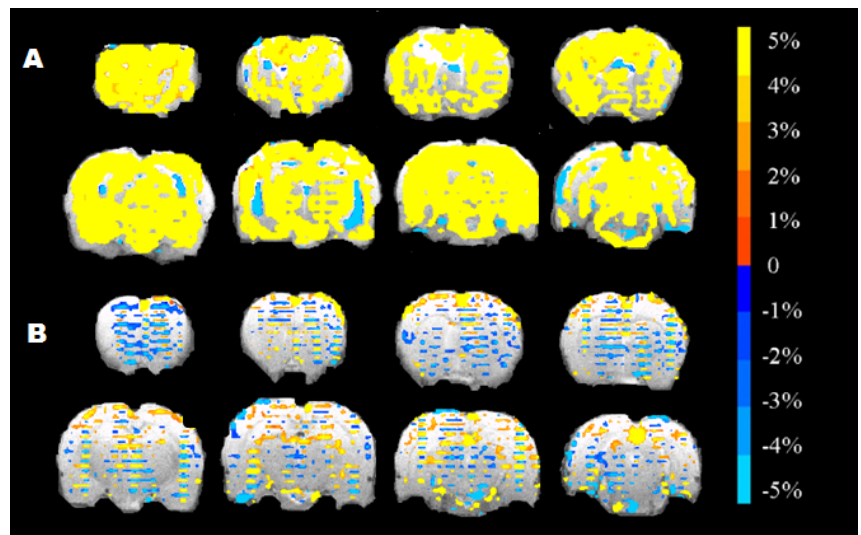**Figure1:** High-resolution anatomical images and 8 anatomical regions of interest

Figure2: Functional BOLD change maps were overlaid on their anatomical images. Panel A shows BOLD activation in response to the first dose 0.4mg/kg varenicline challenge. Panel B shows BOLD activation in response to the first dose 0.04mg/kg varenicline challenge