Functional imaging of conditioned nicotine administration in an animal model of ADHD

W. Chen[1], J. R. DiFranza[2], W. Huang[1], and J. A. King[1]

[1]Center for Comparative Neuroimaging,Psychiatry, University of Massachusetts Medical School, Worcester, MA, United States, [2]Department of Family Medicine and Community Health, University of Massachusetts Medical School

Introduction

Nicotine is similar to other drugs that support place conditioning (e.g. psychostimulants and opioids) in terms of its actions on the brain's reward circuitry, namely the mesocorticolimbic dopamine system [1, 2]. Individuals with Attention Deficit Hyperactivity Disorder (ADHD) smoke at higher rates than the general population. Meanwhile, recent studies suggest that nicotine administration may improve symptoms and executive functioning deficits associated with ADHD (e.g., attention, working memory, response inhibition) [3]. Furthermore, nicotine has been studied as a possible treatment for attention deficit disorder [4, 5, and 6]. Individuals with ADHD may have more difficulty quitting smoking [7, 8]. The current study used functional imaging to map brain activation produced by a conditioned nicotine cue in a genetic model of ADHD, the Spontaneously Hypertensive Rat (SHR).

Methods

Two groups of male rats (250-350g), SHR (n=4) and its parent strain the Wistar-Kyoto (WKY, n=4), were first acclimated for three days by being restrained and placed for 60 minutes in a mock scanner with recorded scanner sounds to reduce physiologic stress and motion artifact during imaging (King et al 2005). The Conditioned Place-Preference (CPP) apparatus was a plexiglass box (30x10x12.5inch) divided into a blue light side (black and white stripes paired with a blue light) and a yellow light side (black paired with yellow light). For five days each animal was given four intraperitoneal (IP) injections (3 saline and 1 nicotine) daily with a 20 minute lag in between, two on each side of the apparatus. All animals received 1 saline and 1 nicotine injection with the blue light and two saline injections with the yellow light. This ensured equal exposure to each chamber, with both paired with two injections. On the sixth day, the restrained animals were placed in a Bruker Biospec 4.7 T/40 cm horizontal scanner. 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, Blood Oxygenation Level Dependent (BOLD) fMRI images were continuously acquired over a 14 minute period. After a 3 min baseline, the animal was exposed to the nicotine paired blue light. 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 analysis employed Analysis of Functional NeuroImages software (NIH, Bethesda, MD) to register, segment and analyze the data. BOLD activation maps were generated using a statistical threshold of $P < 0.05$.

Results

With the drug-paired blue light presentation, the preliminary results indicate that the SHRs have less cortical activity compared to WKY rats. Functional maps obtained from the BOLD analysis also suggested a broader and more intensive neural response in these conditional animals, especially in the hippocampus and the frontal association cortex (Figure 1).

Discussion

In our prior experiments using this apparatus, the SHR demonstrated much stronger conditioned place preference than the WKY. Through Pavlovian conditioning processes, the blue light might have become a conditioned stimulus that gained motivational salience [9]. That the SHR showed much less cortical activation than the WKY suggests a deficit in the processing of reward cues. Through the use of awake animals we were able to conduct the first study of drug-reward cue processing using fMRI in an animal model. We plan to use fMRI to compare food and drug reward cue processing in humans and in animal addiction models with the addition of molecular studies in the animals. Our ongoing studies are examining control animals that were exposed to the blue light without it being paired with nicotine.
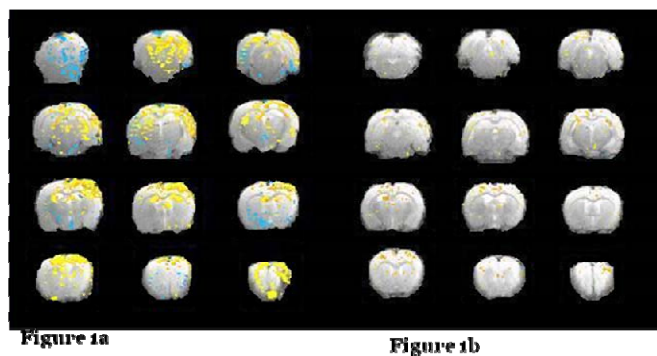

Figure1: Functional activation maps of BOLD intensity changes related to presentation of a drug-paired blue light were overlaid on anatomical images. Figure 1a represents BOLD activation of a WKY rat conditioned to the light while figure 1b represents a compared SHR rat.

References

[1] Pich, et al. Science 1997; 275: 83–6
[2] Picciotto MR. Drug Alcohol Depend 1998; 51: 165–72.
[3] Levin ED, et al. Psychopharmacology (Berl) 2006; 184:523–539
[4] Levin ED, et al. *Psychopharmacology (Berl)* 1996; 123:55-63.
[5] Potter AS, Newhouse PA. Psychopharmacology (Berl) 2004; 176:182-94.
[6] Shytle RD, et al. World J Biol Psychiatry 2002; 3:150-5.

[7] Pomerleau OF, et al. J Subst Abuse 1995; 7:373–378
[8] Humfleet GL, et al. Nicotine Tob Res 2005; 7:453–460. [9] Goldberg S.R, et al. Science 1981; 214, 573–575