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Brain Activity in Cigarette Smokers Performing a Working Memory Task:

Effect of Smoking Abstinence

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Running Title: Brain Activity in Smokers

Abstract is 200 words; text is 4,406 words; 4 figures; 2 tables

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Abstract

**Background.** When nicotine-dependent human subjects abstain from cigarette smoking, they exhibit deficits in working memory. An understanding of the neural substrates of such impairments may help to understand how nicotine affects cognition. Our aim, therefore, was to identify abnormalities in the circuitry that mediates working memory in nicotine-dependent subjects after they initiate abstinence from cigarette smoking.

**Methods.** We used BOLD fMRI to study eight smokers while they performed a letter version of the N-Back working memory task under satiety (≤ 1.5 h abstinence) and abstinence (≥ 14 h abstinence) conditions.

**Results.** Task related activity in the left dorsal lateral prefrontal cortex (DLPFC) showed a significant interaction between test session (satiety, abstinence) and task load (1-back, 2-back, and 3-back). This interaction reflected the fact that task-related activity in the satiety condition was relatively low during performance of the 1-back task, but greater at the more difficult task levels, whereas task-related activity in the withdrawal condition was relatively high at the 1-back level and did not increase at the more difficult task levels.

**Conclusion.** We conclude that neural processing related to working memory in the left DLPFC is less efficient during acute abstinence from smoking than at smoking satiety.
INTRODUCTION

Working memory is a limited-capacity system, responsible for the maintenance and manipulation of online information, that contributes to a wide range of cognitive operations \{Baddeley 1996 11712 /id; Baddeley 1996 11053 /id; Ragland 2002 11711 /id\}. Acute abstinence from smoking has deleterious effects on working memory in nicotine-dependent subjects, and smoking reverses these effects (e.g., Snyder & Henningfield 1989; Blake & Smith 1997). In an investigation of how working memory load interacts with smoking abstinence, we used a parametric, letter version of the N-Back Task to test a group of smokers (n = 15) that included the subjects studied here with functional magnetic resonance imaging (fMRI). They showed significantly longer response latencies when abstinent (13-16 h) than when at smoking satiety (Mendrek et al., 2005; in review), and mean response latency increased with memory load, up to the 3-back level. In the abstinence condition, however, peak latency was observed at the 2-back level, and dropped (though not significantly) at the 3-back level. This result, in conjunction with the fact that error rates were especially high at the 3-back level during abstinence (26% during abstinence vs. 18% during satiety) suggested that smokers reach maximum memory load capacity (and put forth maximum effort) at lower levels of task difficulty while in abstinence. Because of the fundamental role of working memory in cognition, impairments in this function can contribute to the symptoms that follow abrupt cessation of cigarette smoking. Knowledge of the biological bases for such deficits may help in the development of treatments to facilitate smoking cessation.

Neuroimaging techniques, such as fMRI and positron emission tomography (PET), have been used to assess the neural substrates associated with the cognitive effects of nicotine and abstinence from nicotine in dependent subjects. A general conclusion from studies of smokers
and non-smokers is that nicotine, administered by various routes, can increase task-related