Effects of Nicotine on Hippocampal and Cingulate Activity During Smooth Pursuit Eye Movement in Schizophrenia

Jody Tanabe, Jason R. Tregellas, Laura F. Martin, and Robert Freedman

Background: *Abnormal smooth pursuit eye movement (SPEM) in schizophrenic patients is a well known phenomenon, but the neurophysiological mechanisms underlying the deficit are unknown. Nicotine temporarily improves SPEM and has been associated with reduced hippocampal hemodynamic activity in schizophrenics. Nicotine's effect on brain activity in control subjects performing SPEM has not been studied. The purpose of this work was to determine if nicotine differentially affects brain activity in schizophrenic and control subjects during pursuit eye tracking.*

Methods: *16 subjects with schizophrenia and 16 control subjects underwent functional MR imaging during SPEM after receiving placebo or nicotine gum. Four brain regions were analyzed for main effects of group, drug, and interactions: hippocampus, cingulate gyrus, frontal eye fields, and area MT.*

Results: *Nicotine reduced hippocampal activity in both groups, but the effect was greater in control subjects. A group by drug interaction was observed in the anterior cingulate gyrus, where nicotine decreased activity in control subjects and increased activity in schizophrenic subjects. There were no significant effects of group, drug, or interactions in frontal eye fields or area MT.*

Conclusions: *Nicotine may improve SPEM performance in people with schizophrenia through cholinergic stimulation of the hippocampus and cingulate gyrus. Potential mechanisms include improved inhibitory function and attention.*

Key Words: Nicotine, smooth pursuit eye movement, schizophrenia, fMRI, hippocampus, cingulate

The nicotinic cholinergic system is one of several neurotransmitter systems implicated in the pathophysiology of schizophrenia. Evidence for this involvement includes (a) a higher frequency of nicotine dependence in persons with schizophrenia (Hughes et al 1986), (b) the finding of fewer nicotinic receptors in brains of schizophrenic subjects compared to control subjects (Freedman et al 1995; Durany et al 2000), (c) the normalization of two sensory gating deficits, auditory P50 and smooth pursuit eye movements (SPEM), in schizophrenic patients by nicotine (Adler et al 1993; Olincy et al 1998), (d) the modulation of sensory gating by nicotinic agonists in animals (Stevens and Wear 1997), and (e) an association between inhibitory function and nicotinic cholinergic receptor activity in animals (Alkondon et al 1997).

Smooth pursuit eye movements enable the continuous maintenance of foveal vision on a moving target. Performance depends on a complex interaction of sensorimotor transformation, retinal and extraretinal motion processing, attention, and prediction. Parsing out specific components of the pursuit deficit could suggest the underlying neurophysiological mechanisms of the deficit in schizophrenia (Avila et al 2002). For example, increased anticipatory saccades found in people with schizophrenia and their relatives (Clementz et al 1990; Rosenberg et al 1997; Ross et al 1998) may represent a disturbance in attention or internal representation (Rosenberg et al 1997), premature anticipation (Hommer et al 1991), or inhibitory failure (Levin 1984; Rosenberg et al 1997; Ross et al 2002). While the basic neural pathways of pursuit eye movements are relatively well understood, it is not known if specific brain regions underlie this deficit in people with schizophrenia.

Nicotine is the only drug known to improve SPEM deficits in schizophrenic subjects (Avila et al 2003; Olincy et al 2003a; Sherr et al 2002). Nicotinic cholinergic receptors are widely distributed throughout the brain. The α-7 nicotinic cholinergic subtype is particularly rich in the hippocampus (Nestler et al 2001). Activation of cholinergic receptors on inhibitory interneurons is one possible mechanism by which nicotine improves pursuit eye movements. Alterations in inhibitory γ-aminobutyric acid (GABA) interneurons, particularly those in the hippocampus and anterior cingulate gyrus, have been implicated in schizophrenia (Benes and Berretta 2001). Several human neuroimaging studies have demonstrated differences in hippocampal activity at rest (Malaspina et al 2004), during smooth pursuit (Tregellas et al 2004), and during memory retrieval in schizophrenic subjects (Heckers et al 1998) compared to control subjects (for review, see Heckers 2001). Hippocampal hyperactivity in schizophrenic subjects was observed during smooth pursuit eye movements using functional magnetic resonanace imaging (fMRI) methods (Tregellas et al 2004). Nicotine was associated with a reduction in hippocampal hyperactivity in the patients (Tregellas et al 2005), supporting a hypothesis that nicotine improves smooth pursuit by improving inhibitory function in the hippocampus. It is not known if the reduction in hippocampal activity is specific to schizophrenia or represents a general effect of nicotinic cholinergic stimulation.

Moderate levels of nicotinic cholinergic receptors, with a significant portion of the α4β2 subtype (Chattopadhyay et al 2005), are found in the cingulate gyrus, a region also implicated in the smooth pursuit pathway (Berman et al 1999; Schmid et al 2001; Tanabe et al 2002). Several studies have shown that nicotine modulates cingulate gyrus activity with concomitant improvements in attentional performance (Jacobsen et al 2004; Lawrence et al 2002). Given these findings, it is possible that attentional facilitation may partly explain nicotine's beneficial effect on pursuit eye movements (Depatie et al 2002).

The purpose of this study was to extend previous work to a placebo-controlled, case-controlled, crossover design to com-

From the Departments of Radiology (JT) and Psychiatry (JT, JRT, LFM, RF), University of Colorado Health Sciences Center; and the Denver Veterans Affairs Medical Center (LFM, RF), Denver, Colorado.

Address reprint requests to Jody Tanabe, M.D., University of Colorado Health Sciences Center, Campus Box A034, 4200 E. 9th Avenue, Denver, CO 80262; E-mail: jody.tanabe@uchsc.edu.

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pare the effects of nicotine on brain activity in schizophrenic subjects to that of control subjects during smooth pursuit eye movements. We postulated that nicotine improves the pursuit deficit in people with schizophrenia by reducing hippocampal hyperactivity (e.g. improving inhibitory function) and increasing frontal and cingulate gyrus activity (e.g. improving attention). We tested for the effects of drug and group using anatomically defined regions-of-interest (ROIs): hippocampus, cingulate gyrus, frontal eye fields, and area MT.

Methods and Materials

Subjects

16 subjects with DSM-IV schizophrenia (n = 15) or schizoaffective disorder, depressive type (n = 1) and 16 control subjects participated in this study. Subjects were recruited from the Denver Veterans Affairs Medical Center and the Denver Metro Area Mental Health Clinics. Control subjects were recruited from the Denver metro area via an email advertisement and word of mouth. Capacity to participate was informally assessed through the consent process. Participants were required to describe the procedures associated with the study as well as the most common and most serious side effects of nicotine. They were also assessed for their ability to follow directions during the gum chewing procedure. Diagnoses were confirmed using the Structured Diagnostic Interview for DSM-IV or the Diagnostic Interview for Genetic Studies (Nurnberger et al 1994) and severity of symptoms was assessed using the Positive and Negative Syndrome Scale (Kay et al 1987). One subject was neuroleptic-naive, one subject was taking a typical, 13 subjects were taking atypical, and 1 subject was taking both typical and atypical neuroleptics. There were no differences in age, education, gender, or smoking or nicotine dependence. A medical history was gathered from and physical exam performed on all subjects to ensure that no subjects suffered from known cardiac atherosclerotic disease, uncontrolled hypertension, diabetes, or neurologic illness. Three subjects with schizophrenia were taking cholesterol or lipid lowering agents. One subject with schizophrenia was taking an antihypertensive medication.

Smokers were asked to abstain from smoking for 6 hours prior to scanning. They were monitored for two hours prior to magnetic resonance (MR) scanning to ensure non-smoking status. Carbon monoxide levels were measured to verify subjects had not smoked recently. If carbon monoxide levels exceeded 14 ppm, the subject was asked to return on another day after abstaining for 6 hours prior to the scan. Only one individual had an elevated carbon monoxide level and he returned 7 days later. All volunteers provided written, informed consent approved by the Colorado Multiple Institutional Review Board.

Task Design

Subjects performed a visual smooth pursuit task adapted from Radant and Hommer (1992) in the MR scanner. The task consisted of tracking a white dot that moved horizontally across a black background over a visual angle of 28° at a constant velocity of 16.7°/sec followed by a 700 msec fixation period at the edges. The paradigm was a block design with 4 cycles of task and rest per run. During "rest" the subject was told to "look straight ahead" at a black screen.

MR Parameters

The study was performed on a 1.5T Siemens Vision MR system (Siemens AG, Iselin, New Jersey) using a standard quadrature head coil. A high resolution 3D T1-weighted anatomical scan (repetition time (TR) = 45, echo time (TE) = 20, flip angle (FA) = 45, 256^2 matrix, 240 mm^2 field of view (FOV), 1.5 mm thick coronal slices) was acquired, followed by the functional images using gradient-echo echoplanar imaging (TR = 2500, TE = 50, 64^2 matrix, 240 mm^2 FOV, 20 axial slices angled parallel to the planum sphenoidale, 6 mm thick, 1 mm gap). Each run consisted of a 10 sec equilibration period, followed by 4 cycles of 25 sec task/25 sec rest. Two runs were acquired prior to drug administration ("pre-drug" scans) to control for any placebo effect. Subjects were then removed from the scanner and given either nicotine or placebo gum. Following drug administration subjects returned to the scanner to perform two additional runs of the smooth pursuit task ("post-drug" scans). Subjects returned the following week to repeat the procedure with either placebo or nicotine, whichever they did not receive previously.

Drug Administration

After the "pre-drug" scans, subjects were given either nicotine or placebo gum, in a counterbalanced, single-blinded design. Nicotine was administered as nicotine polacrilex (Nicorette) gum. Smokers received 6 mg (three 2 mg pieces) and nonsmokers received 4 mg (two 2 mg pieces). The pieces were pressed together with one piece of similar tasting placebo gum to maximize taste similarity between the nicotine and placebo condition. The placebo gum consisted of 3 (for the non-smokers) or 5 (for the smokers) pieces of Orbit brand peppermint gum adhered to one another to form one large piece of gum. The nicotine gum consisted of 2 (or 3) pieces of 2 mg Nicorette and 1 (or 2) pieces of Orbit brand peppermint gum adhered to one another to form one large piece of gum. Subjects were not allowed to look at the gum prior to placing it in their mouth to reduce any visual clues to the gum's identity. The adhering of the gum pieces was performed to reduce any tactile clues to the gum's identity and the use of a combination of Orbit and Nicorette in the nicotine condition was utilized to reduce any taste or olfactory clues to the gum's identity. Subjects chewed the gum for 10 minutes and were asked not to swallow their saliva but instead spit every 2 minutes into a cup. During both nicotine and placebo administration, blood pressure and heart rate were monitored. After the 10 minute gum chewing session, subjects returned to the magnet for the "post-drug" scans. Following scanning, subjects were monitored for 1 hour to ensure that any changes in blood pressure or heart rate returned to normal. During the week prior to MR imaging, all subjects were given 4 mg nicotine gum and monitored to ensure they were able to tolerate the drug safely.

fMRI Data Analysis

Preprocessing. Spatial pre-processing, model specification and estimation, and statistical inference were performed with Statistical Parametric Mapping (SPM2). The first four image volumes from each run were excluded for saturation effects. Images were motion-corrected and normalized to the Montreal Neurological Institute (MNI) template. One subject was excluded because motion exceeded 2 mm. A 4 mm full width half maximum Gaussian smoothing kernel was applied to the normalized images. The effective smoothing was approximately $7 \times 7 \times 9$ mm^3.

Model. Data were analyzed using two-stage mixed effects model (Friston et al 1999). The time series model consisted of a boxcar convolved with a hemodynamic response function. Parameter estimates of for each individual (e.g., SPM contrast images comparing "post-drug" scan to "pre-drug" scan) were then entered into the second level and analyzed using a one-way