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Smoking status as a potential confound in the BOLD response of patients with schizophrenia

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Abstract

BACKGROUND—Functional magnetic resonance imaging (fMRI) studies comparing schizophrenia patients and controls may have been confounded by the vascular effects of heavier long-term cigarette use in patients.

METHODS—The blood oxygen level dependent (BOLD) response to a simple sensorimotor task was compared between schizophrenia patient with a smoking history (mean 33 pack years) and carefully matched patient non-smokers and control non-smokers.

RESULTS—Group differences in activation magnitude and spatial extent were non-significant.

CONCLUSIONS—Typical smoking histories in schizophrenia patients do not significantly confound fMRI results in simple sensorimotor tasks when patient demographics are carefully controlled.

Keywords

Schizophrenia; Functional Magnetic Resonance Imaging; Cigarette; Nicotine; Atherosclerosis; Vascular Disease

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1. INTRODUCTION

The hundreds of FMRI studies of schizophrenia are marked by a diversity of findings (Callicott, 2003). Whereas FMRI studies have examined short-term pharmacological effects of nicotine, only one report has examined the long-term cumulative history of cigarette use as a potential confound in FMRI studies of schizophrenia (Friedman et al., 2008). Smoking history contribute to diversity of study results yet has rarely been taken into consideration. A high proportion of schizophrenia patients smoke and many smoke heavily (Goff et al., 2005) presenting a potential for confounding FMRI studies.

Long-term cigarette use has many effects which may globally impact the blood oxygen level dependent (BOLD) signal. Smoking accelerates atherosclerosis (Ingall et al., 1991; McGill et al., 1997; Whisnant et al., 1990) which may reduce the cerebrovascular response underlying the BOLD signal (D'Esposito et al., 2003; Ogawa et al., 1993). The cerebrovasculature of smokers is less responsive to the vasodilator CO₂ compared to nonsmokers (Rogers et al., 1984) and this is relevant to FMRI studies (Bandettini and Wong, 1997; Cohen et al., 2004). Compared to controls, the BOLD response to a simple sensory-motor task in patients with cerebrovascular disease was reduced by 30% even in the unaffected hemisphere (Pineiro et al., 2002). Smoking damages the vascular endothelium (Hanna, 2006; Wiesmann et al., 2004), which may impair an active amplification (Iadecola, 2004) of the blood flow response important in FMRI. Thus, with respect to the BOLD signal, atherosclerosis may be a passive structural impediment and endothelial damage may cause a functional impairment. Also, chronic smoking decreases baseline cerebral blood flow (Kubota et al., 1983; Rogers et al., 1983) which may reduce the BOLD response (Murata et al., 2006). Finally, long-term smoking increases hematocrit (Aitchison and Russell, 1988; Isaka et al., 1993) which increases the BOLD contrast (Gustard et al., 2003; Levin et al., 2001). In summary, the chronic effects of cigarette smoking may confound FMRI studies of schizophrenia.

To date no published FMRI study has examined the interaction of chronic smoking history with schizophrenia in a large dataset. The present specific aim was to compare schizophrenia patient smokers (PS) to patient non-smokers (PN) and to control non-smokers (CN) on a simple auditory-motor task. A simple non-cognitive task allows for examination of the potential effects of the long-term consequences of lifetime cigarette smoking history (Hahn et al., 2007; Jacobsen et al., 2002; Salmeron and Stein, 2002) and gives equivalent behavioral responses between patients and controls (see Results). We hypothesized that comparisons between controls and patients would depend on patient smoking status.

2. EXPERIMENTAL MATERIAL AND METHODS

2.1 Subjects

Data were obtained from the MIND Consortium (MCIC) schizophrenia study at the Universities of Iowa (UI) and New Mexico (UNM). Consent was obtained according to institutional guidelines. Diagnosis was through a Structured Clinical Interview for DSM-IV disorders. Patient exclusion criteria were: neurological/psychiatric disease (except schizophrenia), head injury, epilepsy, neurosurgery, substance abuse. Control subjects were free of medical, neurological, psychiatric, and addiction problems.

Smoking was quantified in pack years (packs of cigarettes smoked per day × number of years; National Cancer Institute). A matched case-control design was used. Forty-five subjects were placed into triplets, each with one control non-smoker (CN), one patient non-smoker (PN), and one patient smoker (PS), for a total of 15 members per group (Table 1). Each triplet controlled for MRI scanner (Friedman et al., 2007), age, medication history (Kane et al., 2003) and years since diagnosis. For example, a single triplet consisted of one CN, one PN, and one PS, of the

same age, scanned on the same MRI machine, and in which the PN and PS had similar medication and disease histories. The PS group had a mean history of 16.9 pack years. This analysis was based on an opportunistic sampling of subjects in the MCIC study which had few control smokers and precluded inclusion of an appropriately-matched control smoker group.

2.2 MR Imaging

Scanning was as follows: New Mexico 1.5T - Siemens Sonata, 6 triplets (18 subjects); Iowa 1.5T - GE Genesis Signa, 2 triplets; Iowa 3T - Siemens Trio, 7 triplets. EPI functional images used a single-shot sequence [TE = 30 ms (3T), 40 ms (1.5T); TR = 2000 ms; FOV = 22 cm; matrix size = $64 \times 64 \times 27$ axial slices].

2.3 Task

All subjects performed an auditory-motor task using a prototypical block-design fMRI paradigm (Aguirre and D'Esposito, 2000; Buxton, 2003) such as the simple sensorimotor tasks previously used in fMRI studies of schizophrenia (Braus et al., 2002; Callicott, 2003; Kircher and Thienel, 2005; Muller et al., 2002; Tost et al., 2005). Subjects alternated 16 second ON periods of tapping their right thumb on an input device in time to auditory tones with 16 second OFF periods of rest. Subjects did 14 ON/OFF cycles.

2.4 Image Processing and Statistical Analyses

Images were preprocessed using AFNI software (Cox, 1996).¹ Data was normalized to the MNI template (Statistical Parametric Mapping, Wellcome Trust Functional Imaging Lab). The voxelwise hemodynamic response function (HRF) corresponding to the 32-second ON/OFF cycle was determined using FMRISTAT (Worsley et al., 2002). The mean percent signal change from 4 to 20 seconds into the task, encompassing the peak hemodynamic response (Cohen, 1997), was used as a single measure of percent signal change (PSC) per voxel.

A priori regions of interest (ROIs) for this auditory-motor task were the right cerebellum (CBLM), the left sensorimotor cortex (SMC), and bilateral auditory (AUDT) and supplementary motor areas (SMA) (Maldjian et al., 2003). Within these ROIs, further analysis included only voxels showing a significant overall voxelwise activation of $p < 0.05$ using parametric and cluster-size thresholds (Forman et al., 1995).

The average PSC and the volume of activation (VOL) were measured per ROI per subject. Two mixed model MANOVAs were performed using group means. The dependent variables were PSC among the four ROIs for one MANOVA and VOL among the four ROIs for the second. Group (CN, PN, and PS) and gender were fixed effects and triplet was a random effect. Because short term antipsychotic treatment can increase fMRI activation (Snitz et al., 2005) and atypical vs. typical antipsychotics are associated with normalization of brain imaging (Davis et al., 2005), the analysis was repeated using only the 11 (of 15) triplets (Table 1) for which both PN and PS were on atypical antipsychotics. Scanner, age, and medication history were controlled for within each triplet.

3. RESULTS

There were no significant group differences in age ($p = 0.91$), years since diagnosis for patients ($p = 0.25$), gender (Pearson Chi-Square significance = 0.26), or medication type for patients (Pearson Chi-Square significance = 0.13) (Table 1). There were no significant behavioral differences between groups in either accuracy ($p = 0.77$) or reaction time ($p = 0.83$). The

¹Data from 5 subjects were excluded due to motion. After excluding these subjects, 45 subjects in 15 appropriately matched triplets remained in the study.

MANOVA model for PSC and VOL showed no main effects or interactions of gender so gender was removed from the model. The MANOVA model showed no significant group differences for either PSC or VOL in any of the ROIs. Non-significant results were also found using only 11 of the 15 matched triplets for which both the PS and PN were on atypical antipsychotics (Table 1). Group means are shown in Figure 1.

4. DISCUSSION

We found that smoking status among patients with schizophrenia did not have a strong influence on BOLD activation elicited by a simple auditory-motor task in carefully matched subjects. A recent visual perception study in which the authors acknowledged a small sample size (6 per group) reported that compared to patient non-smokers, patient smokers had an increased percent signal change and a reduced volume of activation that may have been due to increased physiological noise of unknown origin (Friedman et al., 2008). The present study, with 15 subjects per group, may be more indicative of the effect of smoking status on typical FMRI studies. FMRI studies of schizophrenia show increased variability (Barch et al., 2003; Manoach et al., 2001). Conclusions from a small sample size may be biased due to genetic or environmental factors. Alternatively, although the visual task used by Friedman et al., (2008), is also a simple sensory-motor paradigm, properties of the hemodynamic response, including amplitude, are not correlated across regions, (Miezin et al., 2000). This regional heterogeneity in vascular responsiveness likely extends to the auditory cortex and may be due to vascular characteristics (Miezin et al., 2000).

Results show no significant effect of a considerable long-term smoking history (mean 17 pack years) among young (mean age 33) schizophrenia patients performing a simple sensorimotor task. This suggests that results from FMRI studies of schizophrenia in which smoking was not assessed were not biased by the global vascular effects of long-term smoking history. However, long-term nicotine exposure alters the nicotinic cholinergic system (Breese et al., 2000; Gentry and Lukas, 2002) which is involved in a broad range of cognitive processes (Lucas-Meunier et al., 2003) and is specifically implicated in schizophrenia (Martin and Freedman, 2007; Simosky et al., 2002). Thus, use of more challenging cognitive FMRI tasks might be differentially affected by long-term smoking history and introduces more potential for interactions between antipsychotic medications, such as clozapine, and an altered nicotinic system (Levin and Rezvani, 2007).

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Figure 1.

Comparisons of group means by ROI for percent signal change (upper row) and volume of activation (lower row). CN = control non-smoker; PN = schizophrenia patient non-smoker; PS = schizophrenia patient smoker; CBLM = cerebellum; AUDT = auditory cortex; SMC = sensorimotor cortex; SMA = supplementary motor area. Error bar = one standard error of the mean.

Table 1

Subject Demographics.

Pack Years*				Age (ns)				Sex (ns)				Years Since Dx (ns)				Current. Antipsych Type (ns)			
Triplet	PS	PN	CN	PS	PN	CN	PS	PN	CN	PS	PN	PS	PN	PS	PN	PS	PN		
1	34	0	0	42	39	40	M	M	F	18.9	18.6	Typ (hald)	Atyp (olan)						
2	19	4	0	34	29	33	M	M	M	16.9	9.2	Atyp (zipr)	Atyp (arip)						
3	10	0	0	24	24	25	M	F	F	10.4	5.7	Atyp (cloz)	Atyp (risp)						
4	8	0	0	30	26	29	M	M	M	6.7	5.6	Atyp (olan)	Atyp (unav)						
5	6	0	0	24	24	24	M	M	M	0.2	0.8	Atyp (risp)	None						
6	8	0	0	19	19	20	M	M	F	1.8	5.1	Atyp (olan)	Atyp (quet)						
7	7	0	0	22	22	23	M	F	F	2.1	10.0	Atyp (risp)	None						
8	19	0	0	29	23	27	M	M	M	1.1	1.9	Atyp (risp)	None						
9	17	0	0	34	39	39	F	F	F	10.5	11.6	Atyp (risp)	Atyp (arip)						
10	11	0	0	44	42	46	M	M	M	23.3	.	Atyp (cloz)	Atyp (unav)						
11	46	0	0	57	56	53	M	M	M	41.7	6.9	Atyp (flup)	Atyp (olan)						
12	11	0.7	0	26	28	27	M	F	M	6.8	9.0	Atyp (olan)	Atyp (quet)						
13	44	0	0	57	50	51	M	M	M	40.2	26.2	Atyp (unav)	Atyp (risp)						
14	3	0	0	21	23	21	F	M	F	0.1	1.6	Atyp (risp)	Atyp (arip)						
15	11	0	0	36	38	42	M	M	M	18.9	17.3	Atyp (cloz)	Atyp (arip)						
Mean	16.9	0.3	0	33	32	33				13.3	9.2								

* p < 0.001;

ns = non-significant; Pt = Patient; CR = chronic schizophrenia patient; FE = first episode schizophrenia patient; PS = patient smoker; PN = patient non-smoker; CN = control non-smoker; Typ = typical antipsychotic; Atyp = atypical antipsychotic; hald = Haldol; zipr = Ziprasidone; cloz = Clozapine; risp = Risperidone; flup = Fluphenazine; unav = unavailable; arip = Aripiprazole.