Neural Correlates of the Affect Regulation Model in Schizophrenia Patients With Substance Use History: A Functional Magnetic Resonance Imaging Study

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Background: The lifetime prevalence of substance use disorders among schizophrenia patients is close to 50%. The negative consequences of substance abuse in schizophrenia are well documented, but the etiology of this comorbid condition remains unknown. According to the affect regulation model, schizophrenia patients abuse drugs in order to cope with their negative affects. Supporting the model, clinical studies have shown that dual-diagnosis patients have less blunting of affect and that they experience more negative affect. We hypothesized that patients with a history of substance use would have increased cerebral activations in response to aversive stimuli when compared to abstinent patients.

Method: Schizophrenia patients were divided into 2 groups: patients with (SCZ-SU group; N = 12) and without (SCZ group; N = 11) a current or past substance use disorder (alcohol, cannabis, and/or LSD). Diagnoses were made according to DSM-IV criteria. Using functional magnetic resonance imaging (fMRI), patients were scanned during passive viewing of emotionally negative pictures (International Affective Picture System). Data were gathered from September 2001 to December 2003.

Results: Subjectively, the emotional experience induced by viewing the negative pictures was rated significantly higher in the SCZ-SU group than in the SCZ group ($p = .008$). Neurally, in the SCZ-SU group, significant loci of activation were identified in the right medial prefrontal cortex (Brodmann's area [BA] 10), left medial prefrontal cortex (BA 10), right orbitofrontal cortex (BA 47), and left amygdala. No significant loci of activation were observed in the SCZ group.

Conclusions: These results suggest that the functioning of the medial prefrontal cortex, thought to be impaired in patients with prominent negative symptoms, is more preserved in dual-diagnosis schizophrenia. This relative preservation could be primary or secondary to substance use.

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Epidemiologic investigation has revealed that the lifetime prevalence of substance use disorders (SUDs) among schizophrenia patients is close to 50%.[1] This comorbidity has profound and costly implications on the course and treatment of schizophrenia. Schizophrenia patients abuse, in decreasing order, alcohol, cannabis, and cocaine.[1,2] Those drugs of abuse have a clear negative impact on the course of the pathology, which translates into a higher incidence of psychotic relapses, depressive episodes, homelessness, and unemployment, as well as legal and health problems.[2]

Khantzian[3] has proposed the self-medication model, which aims to explain the comorbidity of substance use and schizophrenia. This model hypothesizes that psychoactive substances are abused in a selective manner in order to match the pharmacologic properties of drugs of abuse with the type of symptoms experienced. In this vein, a recent review posited that negative symptoms

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would play a key role in the etiology of the schizophrenia-addiction comorbidity.[4] Further, it has been shown, in laboratory settings, that amphetamines relieve the negative symptoms of schizophrenia.[5] In another study, Kirkpatrick et al.[6] demonstrated that the deficit syndrome of schizophrenia is related to less substance use. Arndt et al.[7] also found that addicted schizophrenia patients have better premorbid adjustment levels. In addition, it has been shown that schizophrenia patients addicted to cannabis or cocaine have less severe negative symptoms.[8,9]

Among the negative symptoms, blunted affect is one of the most enduring.[10] It was viewed by Bleuler as the core symptom of schizophrenia.[10] According to DSM-IV, blunted affect is a restriction in the range and intensity of emotional expression, resulting in socio-emotional maladjustments. It is noteworthy that Dixon et al.[11] have reported that substance-abusing patients had less severe blunted affect symptoms compared to nonabusing patients at discharge from hospital. In addition, a number of studies have found that dysregulation of negative emotions is among the most frequently reported reasons for substance use in schizophrenia.[12,13]

The present functional magnetic resonance imaging (fMRI) study attempted to explore the affect regulation model of dual-diagnosis schizophrenia[14,15] from a neurobiological perspective. The affect regulation model is a variant of the self-medication hypothesis. According to this model, addicted schizophrenia patients experience more severe negative emotional states in their daily life compared to abstinent schizophrenia patients.[15] Substance use would therefore be a coping strategy to deal with those negative emotions. In this context, this study sought to examine the neural substrates underlying such a difference. To do so, we compared dual-diagnosis patients with abstinent schizophrenia patients while both groups of subjects were passively viewing emotionally negative pictures.

Mesocorticolimbic regions are involved in the processing of drug reward[16] and aversion,[17,18] and hypoactivity in the mesocorticolimbic system is thought to underlie the negative symptoms of schizophrenia.[19,20] In healthy volunteers, negative emotions have been shown to elicit cerebral activations in the medial prefrontal cortex, the orbitofrontal cortex, the amygdala, and the ventral striatum.[21–24] In schizophrenia patients, these brain regions have been reported to be underactive in similar experimental settings.[25,26] These regions have also been shown to be involved in the addiction process.[27–29] Based on these findings, we hypothesized that schizophrenia patients with a substance use history would experience stronger emotional reactions during the passive viewing of negative pictures than abstinent schizophrenia patients. We further hypothesized that, relative to abstinent patients with schizophrenia, schizophrenia patients with a substance use history would show increased cerebral activations in the brain regions involved in the processing of negative pictures.

MATERIALS AND METHOD

Subjects

Based on DSM-IV criteria, all subjects were diagnosed with schizophrenia, and they were further divided into 2 groups: patients with and without a history of substance use. The local scientific and ethics committees approved the study. Data were gathered from September 2001 to December 2003.

Twelve patients with a substance use history versus 11 patients with no such history participated in the study after signing a detailed written informed consent form. The schizophrenia–substance use (SCZ-SU) group and the schizophrenia without substance use (SCZ) group were matched for sociodemographic data: age, sex, age at onset, years of education, and lifetime tobacco consumption (Table 1).

Patients in the SCZ-SU group were diagnosed with 1 or more of the following SUDs: alcohol abuse (2 subjects), alcohol dependence (3 subjects), cannabis abuse (4 subjects), cannabis dependence (6 subjects), and lysergic acid diethylamide (LSD) abuse (1 subject). Patients were diagnosed with either a current SUD (last 12 months) (8 subjects) or a past SUD (4 subjects).

Patients were stabilized on treatment with 1 antipsychotic medication or more. Patients with a substance use history received medications in the following doses, expressed as mean ± SD: haloperidol 6.7 ± 2.9 mg (3 subjects), zuclopenthixol (IM) 100 mg (1 subject), risperidone 4.8 ± 3.1 mg (4 subjects), olanzapine 16.3 ± 7.5 mg (4 subjects), and quetiapine 300 ± 250 mg (2 subjects). Patients in the SCZ group received haloperidol 10 mg (1 subject), zuclopenthixol (IM) 150 mg (2 subjects), clozapine 225 mg (1 subject), risperidone 4 ± 2.1 mg (7 subjects), and olanzapine 23.3 ± 5.8 mg (3 subjects).

The possible effects of antipsychotic medication on cerebral activity were considered by using a dose equivalency estimation to 100 mg/day of chlorpromazine.[30] A 2-tailed independent sample t test found no significant difference between the 2 groups (SCZ-SU: mean = 35.7, SD = 84.4; SCZ: mean = 51.2, SD = 140.3) ($t = 0.29$, $df = 21$, $p = .77$).

Psychiatric Assessments

Psychiatric assessments included the Positive and Negative Syndrome Scale (PANSS),[31] the Calgary Depression Scale for Schizophrenia (CDSS),[32] and the Rating Scale for Emotional Blunting (RSEB).[10] Criteria for entry into the study were a diagnosis of DSM-IV schizophrenia, with no concomitant Axis I or Axis II disorders other than substance abuse. Patients with medical or neurologic diseases were not included in the study. There

Table 1. Population Characteristics and Demographics for Patients With Schizophrenia With (SCZ-SU) and Without (SCZ) Substance Use Disorders

Characteristic	SCZ-SU Group (N = 12)	SCZ Group (N = 11)
Age, mean (range), y	25.5 (21–40)	28.7 (20–46)
Sex, N		
Male	8	8
Female	4	3
Age at onset, mean (range), y	21.7 (17–25)	22.1 (17–35)
Years of education, mean	10.4	10.4
Tobacco consumption, N	11	9
SUD diagnoses (abuse/dependence), N		
Cannabis	9	0
Alcohol	5	0
LSD	1	0
No. of SUD diagnoses, mean (range)[a]	2.6 (1–6)	0
Addiction score, mean (range)[b]	4.1 (3–5)	1.5 (1–2)
No. of psychoactive substances tried (excluding tobacco), mean	3.6	1.5
"Hard drug" tried, N[c]	5	0
Positive urine drug screens (mainly cannabis)		
N	5	1
No. of positive screens, range	1–6	1
Psychotic relapses/toxic psychoses/ hospitalizations secondary to drug intake		
N	9	0
No. of occurrences, range	1–4	0
Legal problems, N	4	0
Detoxifications/intoxications, N[d]	2	0

[a]Number of times that an SUD diagnosis was reported in the medical record.
[b]Scored on a scale from 1 to 5 using the Alcohol Use Scale and the Drug Use Scale[33]; 1 = abstinent and 5 = dependence with institutionalization.
[c]In all instances, the hard drug tried was cocaine.
[d]Detoxifications were instances in which the patient was hospitalized for the purpose of detoxification treatment. Intoxication information was retrieved from the patients' charts based on observations by psychiatrists on the ward. Intoxication criteria were based on DSM-IV substance-related disorders criteria.
Abbreviations: LSD = lysergic acid diethylamide, SUD = substance use disorder.

was no direct evaluation of withdrawal or intoxication symptoms, but a trained team (clinician, radiologist, and trained personnel) able to detect the majority of acute withdrawal or intoxication symptoms evaluated the patients prior to scanning. In addition, 1 month prior to the scan session, none of the SCZ-SU patients were regular users, defined as daily or "binge" consumption.

Through chart review, the patients' medical records were screened for DSM-IV diagnoses of SUD, established by psychiatrists on the ward. Other data were also gathered and considered: toxic psychoses, psychotic relapses/hospitalizations secondary to drug intake, positive urine screenings, detoxifications, drug intoxications, legal and health problems associated with drug abuse, and the number and types of substances ever consumed (including "hard drugs"). Based on these complementary data, the patients' substance use history was scored on a scale from 1 to 5 (1 = abstinent, 2 = use without impairment [occasional], 3 = substance abuse, 4 = substance dependence, 5 = dependence with institutionalization), using the Alcohol Use Scale and the Drug Use Scale.[33] An interrater agreement was performed between A.M.-M. and S.P. to validate the substance use scores, using a consensual approach. Patients were divided into 2 groups (SCZ-SU vs. SCZ), according to the SUD diagnoses and the substance use scores (patients scoring 1 or 2 were in the SCZ group, and patients scoring > 2 were in the SCZ-SU group) (Table 1).

Behavioral Procedures

Blood-oxygen-level-dependent (BOLD) signal changes were measured during 2 experimental conditions, i.e., a negative emotional condition and a neutral emotional condition. During the negative condition, a series of 44 emotionally laden negative pictures (plane crash, snake, spider, shark, angry face, sad face, mutilation, accident, burn victim, dead body, dying man, aimed gun, electric chair, etc.) were presented to the subjects, whereas in the neutral condition, subjects saw a series of 44 emotionally neutral pictures (tourist, rocks, boat, leaves, outlet, towel, spoon, mug, basket, fan, iron, shoes, fork, umbrella, lamp, plate, chair, etc.). The 2 categories of pictures were selected from the International Affective Picture System (IAPS).[34] They were matched as much as possible in terms of visual complexity.

The mean ± SD affective valence was 2.66 ± 1.58 for the negative pictures and 5.74 ± 1.47 for the neutral pictures. The mean arousal level was 6.11 ± 2.14 for the negative pictures and 2.97 ± 2.08 for the neutral pictures. During the run, 4 blocks of negative pictures and 4 blocks of neutral pictures were presented to the subjects. The blocks were presented in an alternating manner (1 block negative, then 1 block neutral, then 1 block negative, then 1 block neutral, etc.). Each picture was presented for a period of 2.88 seconds, and each block, which lasted 31.68 seconds, comprised 11 pictures. Blocks were separated by resting periods of 14.4 seconds, during which subjects viewed a blank cyan screen. Subjects were instructed to look carefully at each of the 88 pictures presented to them during the run. To assess the subjective responses of the subjects to the stimuli, immediately at the end of the run, subjects were asked to rate verbally on a visual analog subjective rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotional reaction ever felt in one's lifetime) the intensity of emotional reaction felt during the viewing of the negative IAPS pictures.

Image Acquisition and Analysis

Echo-planar images (EPI) were acquired on a 1.5-Tesla system (Magnetom Vision, Siemens Electric; Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 seconds in an inclined axial plane, aligned with the anterior commissure–posterior com-

missure (AC-PC) axis. These T2*-weighted functional images were acquired using an EPI pulse sequence (time of echo [TE] = 44 ms, flip = 90°, field of view [FOV] = 215 mm, matrix = 64 × 64 pixels, voxel size = 3.36 × 3.36 × 5 mm). Following functional scanning, high-resolution data were acquired via a Tl-weighted 3-dimensional volume acquisition obtained using a gradient echo pulse sequence (TE = 44 ms, flip = 12°, FOV = 250 mm, matrix = 256 × 256 pixels, voxel size = 0.94 mm^3).

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology; London, United Kingdom). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces.[35] These inhomogeneities can create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions.[36] To correct for such artifacts, a mask was applied to the slices of the mean EPI image that presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized into an MRI stereotactic space[37] using this masked mean image. Images were then convolved in space with a 3-dimensional isotropic Gaussian kernel (12-mm full width at half maximum [FWHM]) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

For the statistical analysis, the time series of the images were convolved with the delayed box-car function, which approximates the activation patterns. Effects at every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM t), subsequently transformed to the unit normal distribution (SPM Z).

A "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the negative pictures and that associated with the viewing of the emotionally neutral pictures (negative minus neutral). This fixed-effects model produced individual contrast images, which were used as raw data for the implementation of a "random-effects model," which takes into account intersubject variance and permits population-level inferences.[38] Within such a random-effects model, and using these individual contrast images, 1-sample t tests were used to measure, voxel by voxel, the mean BOLD response produced by the negative minus neutral contrast for each group of subjects. In addition, 2-sample t tests were carried out, voxel by voxel, to directly compare the mean BOLD response between the 2 groups of subjects (SCZ-SU group minus SCZ group and SCZ group minus SCZ-SU group) with regard to the negative minus neutral contrast.

An a priori search strategy was used, and a small volume correction (SVC) was performed in the brain regions of interest (ROIs) defined a priori. The search volume corresponding to the ROIs was defined a priori, using SVC and box volume function in SPM99, and based on the neuroanatomic boundaries of these regions noted in the MR reference image (Montreal Neurological Institute template) and the Talairach and Tournoux[37] atlas. For this a priori search, a probability threshold for multiple comparison of a corrected $p < .05$ was used. Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis.

The a priori search strategy encompassed areas of the medial prefrontal cortex (mPFC) (Brodmann's areas [BAs] 9 and 10),[21,25,39–42] the orbitofrontal cortex (OFC) (BAs 47 and 11),[25,39,42,43] the amygdala,[21–25,42,44] and the ventral striatum (VS).[18,22,23,41,45] These mesocorticolimbic regions were chosen based on findings in previous functional neuroimaging studies of both aversion[18,21,23,25,39] and alcohol/drug addiction.[29,40–43,45]

The search strategy encompassed the following ROIs (Talairach coordinates [TAL]): right and left superior frontal gyri (BA 10: x = ±15, y = 60, z = 8; search box x = 12, y = 10, z = 32), right and left medial frontal gyri (BA 10: x = ±4, y = 58, z = 6; search box x = 2, y = 15, z = 28), right and left medial frontal gyri (BA 9: x = ±3, y = 43, z = 26; search box x = 5, y = 5, z = 19), right and left OFC (BA 47: x = ±36, y = 33, z = –12; search box x = 30, y = 25, z = 23), right and left OFC (BA 11: x = ±24, y = 45, z = –21; search box x = 44, y = 25, z = 16), and right and left amygdala (x = ±21, y = 0, z = –18; search box x = 8, y = 4, z = 12). The search for activations in VS included the putamen, caudate nucleus, and nucleus accumbens. Search box was x = 30, y = 50, z = 32; center located at x = 18, y = –5, z = –8 for the right striatum and x = –18, y = –5, z = –8 for the left striatum.

For psychiatric data (e.g., PANSS), statistical analyses were conducted using the Statistical Package for the Social Sciences, version 10.0. Considering the limited sample size of this study, comparisons between the 2 groups were performed using the Mann-Whitney U test, a nonparametric test equivalent to the independent samples Student t test, which is based on rankings of the data. Significance tests were 2-tailed, and the α level for rejecting the null hypothesis was set at .05.

RESULTS

Psychiatric Data

On a clinical level, the Mann-Whitney U test was performed to differentiate the psychiatric profile of the patients in the 2 groups (Table 2). While SCZ-SU patients showed significantly less severe negative symptoms on

Table 2. Comparative Psychiatric and Behavioral Data for Patients With Schizophrenia With (SCZ-SU) and Without (SCZ) Substance Use Disorders

Measure	SCZ-SU Group (N = 12) Mean	SCZ-SU Group (N = 12) SD	SCZ Group (N = 11) Mean	SCZ Group (N = 11) SD	Mann-Whitney U	p Value
Subjective report of emotional reaction[a]	5.8	2.8	2.2	2.1	23.5	.008
Blunted affect[b]	10.6	2.1	19.7	2.8	33.5	.044
PANSS						
Positive	22.6	5.1	21.4	7.7	61.5	.781
Negative	20.6	8.9	27.5	8.8	39.0	.095
General	44.0	11.9	47.9	8.1	48.0	.267
Total	87.2	21.3	96.7	18.2	51.0	.355
Depression[c]	5.3	4.4	6.0	4.6	59.5	.684

[a]Emotional reaction was induced by presenting negative pictures from the International Affective Picture System and was rated by patients on a visual analog scale from 0 (absence of any emotional reaction) to 8 (strongest emotional reaction ever felt in one's lifetime).
[b]Blunted affect was assessed with the Rating Scale for Emotional Blunting.[12] Possible scores range from 0 to 32; a higher score means more severe negative symptoms.
[c]Depression was assessed with the Calgary Depression Scale for Schizophrenia.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

the RSEB (p = .044), no differences were noted using the PANSS negative subscale. For positive symptoms (PANSS) (p = .781) and depression (CDSS) (p = .684), no significant differences were detected.

Self-Report Data

In keeping with one of our hypotheses, it was shown that the emotional experience induced by viewing the negative pictures was rated significantly higher in the SCZ-SU group (mean = 5.8, SD = 2.8) than in the SCZ group (mean = 2.2, SD = 2.1, p = .008) (Table 2).

fMRI Results

One-sample t tests (negative minus neutral contrast). In the SCZ-SU group, significant loci of activation were identified in the right mPFC (BA 10), left mPFC (BA 10), right OFC (BA 47), and left amygdala (Figure 1). Regarding the VS, activations close to significance were found, especially in the left putamen (Table 3). No significant loci of activation were observed in the SCZ group.

Two-sample t tests (negative minus neutral contrast). Exploratory analysis was conducted to investigate potential differences between the 2 groups in brain regions other than our a priori ROIs. When the SCZ group was subtracted from the SCZ-SU group, significant loci of activation were found in 2 areas of the left mPFC (BA 10), as well as in the right parahippocampal gyrus (BA 28). (Table 4 and Figure 2). When the SCZ-SU group was subtracted from the SCZ group, no significant locus of activation was detected.

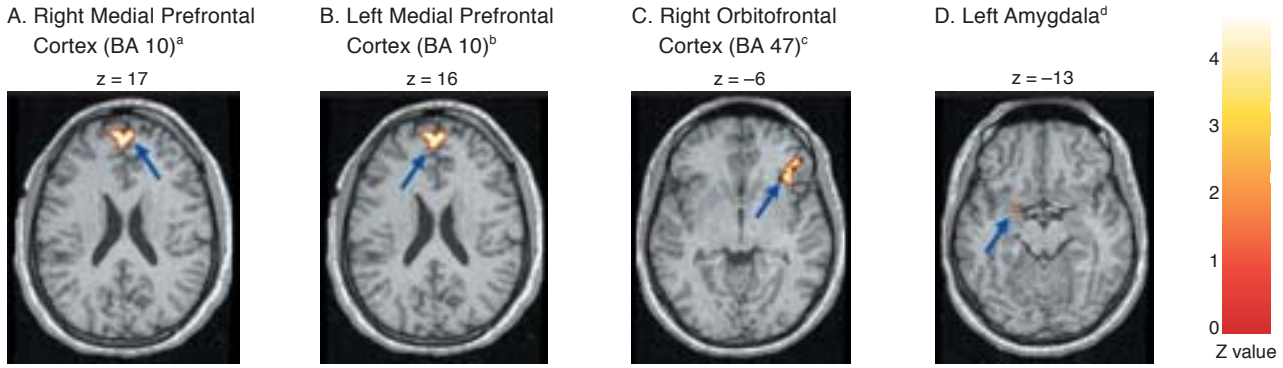
A posteriori correlational analyses between ROIs. Our ROIs have been repeatedly shown to be interconnected in both animals and humans.[28,46] Therefore, it was of interest to determine if loci of activation in these brain regions were functionally correlated. Since the left mPFC was identified as significantly activated in both the 1-sample and 2-sample t tests (Table 3 and Table 4), this ROI was our starting point. When evaluating Pearson correlation coefficients at a stringent statistical threshold of $p < .001$ uncorrected, we found that activated voxels in the left mPFC (BA 10) correlated positively with activated voxels in the right mPFC (BA 10) (TAL: x = 15, y = 56, z = 11; 6 voxels; p = .0001). In addition, when the threshold was decreased ($p < .05$ uncorrected) to allow for exploratory analyses, it was observed that voxels activated in the left mPFC correlated positively with voxels activated in the right OFC (BA 47) (TAL: x = 42, y = 32, z = –7; 5 voxels; p = .003) and the left lateral OFC (BA 47) (TAL: x = –45, y = 17, z = –1; 10 voxels; p = .0001 and TAL: x = –36, y = 41, z = –5; 17 voxels, p = .008). A positive correlation was also noted between voxels in the left mPFC and voxels in the right ventral putamen (TAL: x = 27, y = 6, z = –5; 19 voxels; p = .004).

A posteriori correlational analyses between fMRI data and self-report data. Pearson correlational analyses were conducted between self-report ratings of negative images and BOLD signal increases found in the ROIs. In the SCZ-SU group, a significant ($p < .001$) positive correlation was found in the right OFC (BA 47) (x = 42, y = 24, z = –9; voxels = 9; Z = 3.67; p = .0001).

DISCUSSION

This study was conducted to test the hypotheses that (1) schizophrenia patients with a substance use history would experience stronger emotional reactions during the passive viewing of negative pictures than abstinent schizophrenia patients and (2) relative to abstinent schizophrenia patients, schizophrenia patients with a substance use history would show increased cerebral activations in the brain regions involved in the processing of negative pictures. Subjectively, the emotional reaction induced by the negative pictures was rated higher in the SCZ-SU group than in the SCZ group. Neurally, in the SCZ-SU group, passive viewing of the negative pictures was associated with significant loci of activation in the mPFC (BA 10), right OFC (BA 47), and left amygdala, whereas no significant activation was noted in the SCZ group. When the SCZ group was subtracted from SCZ-SU group, significant loci of activation were found in the left mPFC (BA 10), while the reverse contrast (SCZ minus SCZ-SU) produced no significant locus of activation. In addition, positive correlations were found between the left mPFC (BA 10) and the right mPFC (BA 10), the OFC (BA 47), and the right ventral putamen. Finally, significant positive correlations were found in the SCZ-SU

Figure 1. Statistical Activation Maps in the Schizophrenia–Substance Use Group for the Negative Minus Neutral Contrast (1-sample t test)



[a]Z = 3.21, p = .021 corrected.
[b]Z = 3.45, p = .009 corrected.
[c]Z = 3.14, p = .041 corrected.
[d]Z = 2.60, p = .048 corrected.

Table 3. BOLD Cerebral Activation in Patients With Schizophrenia and Substance Use Disorders (1-sample t test; negative minus neutral contrast)

Region	Brodmann's Area	Voxel	Talairach Coordinates x	y	z	Z Score	p[a] Value
Right medial prefrontal cortex	10	11	3	56	17	3.21	.021
Left medial prefrontal cortex	10	6	–3	59	16	3.45	.009
Right orbitofrontal cortex	47	28	39	29	–6	3.14	.041
Left amygdala	…	5	–21	–1	–13	2.60	.048
Left putamen	…	7	–21	0	3	2.13	.070

[a]Corrected for multiple comparisons.
Abbreviation: BOLD = blood-oxygen-level-dependent.

Table 4. BOLD Cerebral Activation in Schizophrenia Patients With Versus Without Substance Use Disorders (2-sample t test; negative minus neutral contrast)

Region	Brodmann's Area	Voxel	Talairach Coordinates x	y	z	Z Score	p[a] Value
Left medial prefrontal cortex	10	5	–6	55	–10	3.38	.0001
Left medial prefrontal cortex	10	12	–12	56	6	3.58	.0001
Right parahippocampal gyrus	28	6	18	–24	–14	3.42	.0001

[a]Uncorrected.
Abbreviation: BOLD = blood-oxygen-level-dependent.

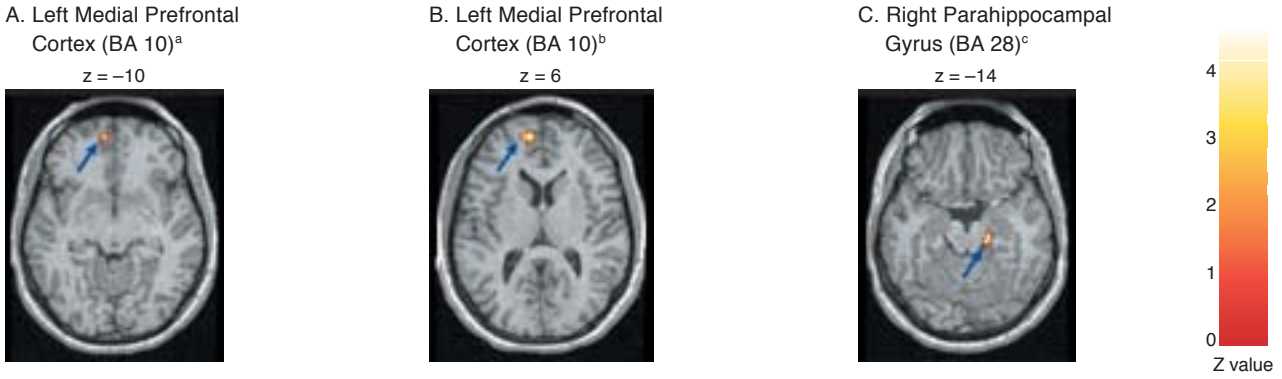
group between self-report ratings of negative pictures and BOLD signal increases in the right OFC (BA 47).

Activation of the mPFC has been found in previous functional neuroimaging studies of aversion[21,25,39] and addiction.[40–42] According to a recent meta-analysis carried out by Phan et al.,[47] this prefrontal area has been seen activated in nearly 50% of functional brain imaging studies of emotion, irrespective of the valence.[21,48–53] The mPFC receives sensory information from the body and the external environment via the OFC and is heavily interconnected with limbic structures such as the amygdala.[54,55] Lane et al.[51] and Reiman et al.[53] have postulated that the mPFC is implicated in cognitive processes such as appraisal/evaluation, experience, response, and self-representation of subjective emotional state. Here, the mPFC activation found in the SCZ-SU group might be related to emotional self-awareness.

The OFC (BA 47) receives sensory inputs (olfactory, gustatory, visceral afferent, somatic sensory, and visual) and limbic inputs from the amygdala[57] and has been found to be activated during external and/or internal induction of negative emotional states (e.g., sadness, anxiety, anger).[48–50,56,58–63] Activation of BA 47 has also been noted during voluntary emotional self-regulation.[64] These previous findings, in addition to findings in this study along with the positive correlation of activation in this area with subjective scores, make it plausible that the OFC activation found in our SCZ-SU group during the viewing of the negative pictures was related to the integration of sensory and limbic inputs about the individual's emotional state.

The amygdala activation noted in SCZ-SU subjects is in agreement with previous PET studies[52,53,65,66] and fMRI investigations[60,67,68] of negative emotions. A review by Lane[69] of experimental lesion studies in animals and clinical neuropsychological studies in humans strongly suggests the involvement of the amygdala in appraisal and evaluation of the emotional significance of external stimuli. On the basis of these findings, we could argue that the amygdala activation measured in the SCZ-SU group during the viewing of the negative pictures was related to the appraisal process of these stimuli.

Figure 2. Statistical Activation Maps Produced by the Schizophrenia–Substance Use Group Minus Schizophrenia Group During the Negative Minus Neutral Contrast (2-sample t test)



[a]Z = 3.58, p = .0001 uncorrected.
[b]Z = 3.38, p = .0001 uncorrected.
[c]Z = 3.42, p = .0001 uncorrected.

In the SCZ-SU group, positive correlations were found between the left mPFC (BA 10) and other regions of the prefrontal cortex such as the right mPFC (BA 10) and the left OFC (BA 47). A positive correlation was also measured between the left mPFC (BA 10) and the right ventral striatum (putamen). This latter result is not surprising considering that the mPFC and the ventral striatum are part of the mesocorticolimbic system, and both have been found to be involved in psychotic and addictive disorders. Hypoactivity in this system is thought to underlie the negative symptoms of schizophrenia.[19,20] Furthermore, despite their diverse mechanisms of action, psychoactive substances (alcohol, amphetamines, cannabis, cocaine, hallucinogens, opiates, phencyclidine) share the common property of acutely increasing dopamine release in this system.[16,70]

To our knowledge, this is the first fMRI study that examines the neural bases of emotional processing in schizophrenia patients with substance use. Our results suggest that the functioning of the mPFC, thought to be impaired in patients with prominent negative symptoms, would be more preserved in dual-diagnosis patients. Such a result must be interpreted with caution, since the current study design does not allow us to conclude whether the patients' affective symptomatology has led them to substance use or whether drug consumption has modulated their emotional state. Thus, the current methodology cannot exclude the possibility that the differences in brain activity in response to emotional stimuli are a consequence of the substance abuse, not an antecedent. Indeed, all of the drugs used (alcohol, cannabis, cocaine, and hallucinogens) by patients included in the study exert an acute and chronic impact on emotion. Further, the addiction process has been associated with activations in our ROIs: (1) acutely, psychoactive substances activate the VS, the OFC, and/or the mPFC[16,29,70]; (2) during drug withdrawal (any psychoactive substance), a stressful reaction is elicited, which is associated with an increased glucocorticoid activity in the amygdala[28]; and (3) in the long run, drug cravings (for alcohol and cocaine, to the very least) activate the OFC and the amygdala.[29,71] In the case of the parahippocampal gyrus, the potential impact of psychoactive substances on this brain region is poorly documented.

Our findings (see Table 4) were obtained using a random-effects model, which is statistically more stringent than a fixed-effects model and takes into account intersubject variance. In so doing, the random-effects model permits population-level inferences. This study adds to the growing body of data relating negative symptoms of schizophrenia to an abnormal functioning of the prefrontal cortex. Moreover, our results strengthen the notion that the mPFC would be involved in the processing of every basic emotion (happiness, sadness, fear, etc.), as shown in a recent meta-analysis by Phan et al.[72] Our findings also provide further support to the notion that the brain regions involved in the addiction process would also be processing negative emotional responses, as has been recently shown in animals and humans.[17,22,24,73–76] It is worth mentioning that the differences in the brain activity patterns corresponding to arousal in the substance use versus non–substance use samples parallel the findings of Williams et al.[77] in paranoid versus nonparanoid patients and Fahim et al.[78] in flat affect versus non–flat affect patients, which further support the usefulness of dividing schizophrenia patients into groups when performing imaging studies.

A limitation of this study lies in the method used to evaluate substance use history. Still, 52% of schizophrenia patients in the selected sample had substance use history, a result clearly in line with the epidemiologic data showing that the lifetime prevalence of substance use disorders among patients with schizophrenia is 47%.[1] Also, this study did not include a control group of healthy volun-

teers, because the object of the study was to provide a greater understanding of the schizophrenia–substance use comorbidity. It was not the purpose of the study to differentiate the single- or dual-diagnosis patients from the general population. Furthermore, even after control for chlorpromazine equivalence, we cannot determine with certainty the extent to which the findings are attributable to the psychiatric problems themselves, the effect of medications, or the interaction of the two. In addition, patients were not directly evaluated for intoxication or acute withdrawal during the scanning session. Lastly, the heterogeneity of the SUDs in this study does not allow us to attribute findings to a specific substance.

In conclusion, our results suggest that the functioning of the medial prefrontal cortex, thought to be impaired in patients with prominent negative symptoms, is more preserved among schizophrenia patients with substance use. Whether this relative preservation is primary or secondary to substance use remains to be determined. In the future, it would be of interest to investigate other emotions (positive and negative, primary and social) in relation with specific psychoactive substances (alcohol, cannabis, cocaine) in dual-diagnosis patients, using fMRI.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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