

Alexithymia and stress-induced brain activation in cocaine-dependent men and women

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Objective: Alexithymia means a reduced capacity to identify and describe one's own feelings. Both stress and an alexithymic response to stress can contribute to relapse into drug abuse, but to our knowledge the neural processing of an alexithymic response to stress in cocaine-dependent individuals has not been examined. **Methods:** In a functional magnetic resonance imaging session, 17 male and 10 female abstinent cocaine-dependent subjects participated in script-guided imagery of neutral or stressful situations. Spatial preprocessing and statistical analysis of brain images were performed using Statistical Parametric Mapping Software (SPM2). Blood oxygen level-dependent contrasts between stress and neutral imagery were correlated voxelwise with scores on the 26-item Toronto Alexithymia Scale (TAS). **Results:** Male cocaine users demonstrated a positive correlation between TAS scores and activation in the right putamen and middle frontal cortex during stressful, compared with neutral, imagery. In contrast, no brain regions showed a negative correlation with TAS scores. Female subjects demonstrated a negative correlation between TAS scores and activation in the right amygdala, thalamus, putamen, and left frontal and bilateral temporal cortices, and no positive correlations with TAS scores during stressful, compared with neutral, imagery. **Conclusions:** Women with greater alexithymic features showed reduced left-hemispheric cortical and right-hemispheric subcortical activation during processing of stress. However, men showed an opposite correlation in the right frontal cortex and putamen, suggesting that responses to stress in the putamen (activation v. deactivation) and frontal cortex (activation v. deactivation, as well as right v. left correlations) are critically different in association with alexithymia between male and female cocaine-dependent patients.

Objectif : L'expression « alexithymie » signifie capacité réduite de définir et de décrire ses sentiments. Le stress et une réponse alexithymique à celui-ci peuvent contribuer à une rechute chez un toxicomane, mais sauf erreur, on n'a pas étudié le neurotraitement d'une réponse alexithymique au stress chez les cocaïnomanes. **Méthodes :** Au cours d'une séance d'imagerie par résonance magnétique fonctionnelle, 17 hommes et 10 femmes cocaïnomanes abstinentes ont participé à une imagerie guidée par scénario portant sur des situations neutres ou stressantes. On a procédé au prétraitement spatial et à l'analyse statistique d'images cérébrales au moyen du logiciel de cartographie paramétrique statistique (SPM2). On a établi une corrélation au moyen de voxels entre des contrastes dépendants de la concentration sanguine d'oxygène pour les images neutres et pour le stress et les résultats de l'échelle de l'alexithymie de Toronto (TAS) à 26 questions. **Résultats :** On a constaté chez les cocaïnomanes de sexe masculin un lien positif entre les résultats de l'échelle TAS et l'activation dans le putamen droit et le cortex frontal médian en présence d'images stressantes comparativement à des images neutres. Par contre, aucune région cérébrale n'a montré de lien négatif avec les résultats TAS. On a constaté chez les sujets de sexe féminin un lien négatif entre les résultats de l'échelle TAS et l'activation dans le corps amygdalien droit, le thalamus, le putamen, et le cortex frontal gauche et les cortex temporaux des deux côtés, et aucun lien positif avec les résultats de l'échelle TAS en présence d'images stressantes comparativement à des images neutres. **Conclusions :** Chez les femmes présentant des caractéristiques alexithymiques plus marquées, on a constaté une réduction de l'activation corticale dans l'hémisphère gauche et de l'activation subcorticale dans l'hémisphère droite au cours du traitement du stress. On a toutefois constaté chez les hommes un lien contraire dans le cortex frontal droit et le putamen, ce qui indique que la réponse au stress dans le putamen (activation c. désactivation) et le cortex frontal (activation c. désactivation, ainsi que corrélations droit c. gauche entre les hémisphères) présente des différences critiques reliées à l'alexithymie entre les hommes et les femmes cocaïnomanes.

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Introduction

Alexithymia is a personality trait whereby individuals have a reduced capacity to identify and describe their own feelings. Alexithymic individuals manifest bland or flattened affect, are preoccupied with somatic symptoms, emphasize communication through action and nonverbal behaviour, avoid close interpersonal relationships and tend to be socially conforming.¹ This dysfunction of affect regulation contributes to a variety of physiological and mental disorders.²

One hypothesis about the cause of alexithymia is that autonomic responses are exaggerated and prolonged in alexithymic individuals when they experience emotionally provoking situations.^{3,4} These dysregulated physiological responses over many years may result in untoward health effects. Empirical evidence for this hypothesis has been mixed, however, with some studies showing increased physiological arousal in alexithymic individuals under affect-laden situations and others showing the opposite pattern of response (see Neumann et al⁵). Moreover, sex differences have not received careful attention in these studies of alexithymia and physiological and neural responses to stress.

A neurological basis of alexithymia has been suggested in patients with brain lesions. For instance, cerebral commissurotomy is associated with alexithymia.^{6,7} Alexithymia also occurs more often in patients with stroke who had a lesion in the right rather than the left hemisphere.⁸⁻¹⁰ More recently, a functional magnetic resonance imaging (fMRI) study compared responses to emotional pictures in 2 groups of men with high versus low scores on the Toronto Alexithymia Scale (TAS). Compared with the nonalexithymic men, the alexithymic men demonstrated less activation in the left medial frontal-paracingulate cortex to negative stimuli and more activation in the anterior cingulate, medial frontal cortex and middle frontal gyrus to positive stimuli.¹¹ Kano et al¹² compared alexithymic and nonalexithymic men with respect to their brain responses to facial stimuli in a positron emission tomography (PET) study.¹² The alexithymic men exhibited lower regional cerebral blood flow (rCBF) in the right inferior frontal, middle frontal and inferior parietal cortices. Furthermore, rCBF in the right frontal cortices correlated negatively with TAS scores across subjects. Thus, a wide range of brain areas can be involved in mediating the altered affective processing of alexithymic individuals, with the right hemisphere perhaps playing a more dominant role than the left hemisphere.

The current study addresses the neural substrates underlying emotional-distress processing in cocaine-dependent individuals with varying levels of alexithymia. Alexithymia is a potential risk factor for substance use disorders.¹³⁻¹⁹ For instance, patients with cocaine dependence had higher alexithymia scores compared with healthy control subjects.²⁰ In a study of 46 inpatients with alcohol abuse or dependence, the total TAS score was significantly higher among those who relapsed after discharge than among those who did not, even when depressive symptoms were taken into account.¹⁵ Stress also contributes to substance abuse and

relapse.²¹ Our earlier imaging study employing script-guided imagery showed that, compared with healthy controls, cocaine-dependent patients failed to activate the anterior cingulate and other paralimbic regions during stress imagery, suggesting dysregulation of control under emotional distress in these patients.²² Instead, cocaine-dependent patients demonstrated greater craving-related activation in the dorsal striatum, a region that has been implicated in reward processing and obsessive-compulsive behaviours. The current study addresses how alexithymia might alter neural responses to stress in abstinent cocaine-dependent individuals as a first step in understanding how both of these factors might contribute to relapse. Furthermore, because of sex differences in the neural correlates of emotional-distress processing that we have identified,²³ we examined how alexithymia may modulate brain activation during stress separately in men and women. Given that there have been relatively few neuroimaging studies of affect processing in alexithymic subjects, we felt that it was premature to focus on specific brain regions of interest, but broadly hypothesized that limbic brain activation would correlate with levels of alexithymia.

Methods

We recruited 27 cocaine-dependent patients (17 men, mean age 35.9 [standard deviation {SD} 8.3] yr and 10 women, mean age 36.5 [SD 6.2] yr) who had been abstinent for at least 2 weeks and had repeated drug-free urine tests while in an inpatient unit. The male and female patients had a mean total score of 63.2 (SD 13.8) and 68.1 (SD 10.4), respectively, on the 26-item TAS (TAS-26,^{24,25} $p = 0.34$; 2-tailed, 2-sample t test). According to the research criteria suggested by Taylor et al,²⁶ 3 of the male and 2 of the female patients who had a total score greater than 74 were considered to be alexithymic. Ten of the male and 3 of the female patients had a total score lower than 64 and were, thus, nonalexithymic. As reported previously, these male and female subjects did not differ in other demographic characteristics including age, ethnic origin, education, total number of days of cocaine use in the month before admission, total number of years of cocaine use, lifetime prevalence of post-traumatic stress disorder, lifetime prevalence of major depression and childhood trauma, including sexual abuse.²³ The 2 groups also did not differ in hematocrit level, which has been shown to affect blood-oxygen level-dependent (BOLD) signals.²⁷ All subjects provided informed written consent before the study, in accordance with the study protocol approved by the Yale Human Investigation Committee.

The subjects participated in script-guided stress imagery,²⁸ while BOLD signals of their brain were acquired in a 1.5-T GE Signa imager (repetition time [TR] 1500 ms, echo time [TE] 45 ms, flip angle 85°, field of view 20 cm, matrix 64 × 64, slice thickness 6 mm and interslice gap 1 mm; 220 images were acquired in each trial). Two scripted imagery trials each covered neutral and stressful events based on individual real-life scenarios. Stress and neutral trials were interleaved within a study, and the order in which they were presented

was counterbalanced across subjects. Each trial comprised baseline (1.5 min), imagery (2.5 min) and post-imagery (1.5 min) periods. Subjects rated their anxiety level, imagery vividness and cocaine craving on a 10-point Likert scale before and after each trial. Heart rate was recorded every 10 seconds throughout each trial. Spatial preprocessing and statistical analyses of brain images were performed using Statistical Parametric Mapping Software (SPM2; Wellcome Department of Imaging Neuroscience, University College London, London) (www.fil.ion.ucl.ac.uk/spm/software/spm2/). Images of each individual subject were corrected for slice timing and realigned (motion corrected). Images were then normalized to an MNI (Montreal Neurological Institute) echo-planar imaging template with affine registration followed by nonlinear transformation, resampled with trilinear interpolation and written in $4 \times 4 \times 4 \text{ mm}^3$ isotropic voxels. Finally, images were smoothed with a Gaussian kernel (10 mm at full width at half maximum).

In a general linear model, brain activation was contrasted for individual subjects between stressful and neutral imagery, each with its own baseline subtracted.²⁹ Regressors modelling these different epochs were convolved with a canonical hemodynamic basis function to model corresponding changes in BOLD contrast signal. Low-frequency signal drifts were removed by using a high-pass filter (cutoff 1/128 s). A first-order autoregressive model corrected serial autocorrelation. The general linear model estimated the component of variance that could be explained by each of the regressors. At the group level, voxelwise linear correlation with individual TAS scores was performed for the whole brain separately for men and women. We implemented a statistical height threshold of uncorrected $p = 0.001$ and an extent threshold of 20 voxels. Conversion of the MNI to the Talairach coordinates³⁰ was accomplished using a linear algorithm,³¹ and Brodmann areas were then identified based on the nearest grey matter approach, using the Talairach Daemon (<http://ric.uthscsa.edu/projects/talairachdaemon.html>). Other details of the methods were as described previously.²³

Results

Both male and female subjects showed increases in heart rate and in anxiety and craving ratings during stressful, compared with neutral, trials.²³ Moreover, these increases as well as the imagery vividness rating (both for stress and neutral trials) did not differ between male and female subjects.²³ The changes in heart rate, imagery vividness, anxiety and cocaine craving ratings did not correlate with individual TAS scores, either for male ($p > 0.30$ in each case) or for female ($p > 0.15$ in each case) subjects.

For male subjects, TAS scores correlated positively with activation in the right putamen and right middle and superior frontal cortex (Brodmann area [BA] 8) during stressful trials, compared with neutral trials (Fig. 1). No brain regions showed a significant negative correlation with TAS score. For female subjects, TAS scores during stressful trials, compared with neutral trials, correlated negatively with

activation in the following areas: right middle and superior temporal cortex (BA 21 and 38), left frontal cortex (BA 6), left superior temporal cortex (BA 38), left inferior frontal cortex (BA 47), right thalamus, right amygdala, parahippocampal gyrus (BA 35), and right putamen and claustrum (Fig. 2). On the other hand, no brain regions showed a significant positive correlation with TAS score. These results are summarized in Table 1.

Discussion

Alexithymia was correlated predominantly with activity in the right hemisphere during stressful, compared with neutral, emotional processing in both men and women, although in opposite directions. This finding is broadly consistent with earlier studies documenting activity mostly in the right hemisphere during an affective processing task.³² Women with

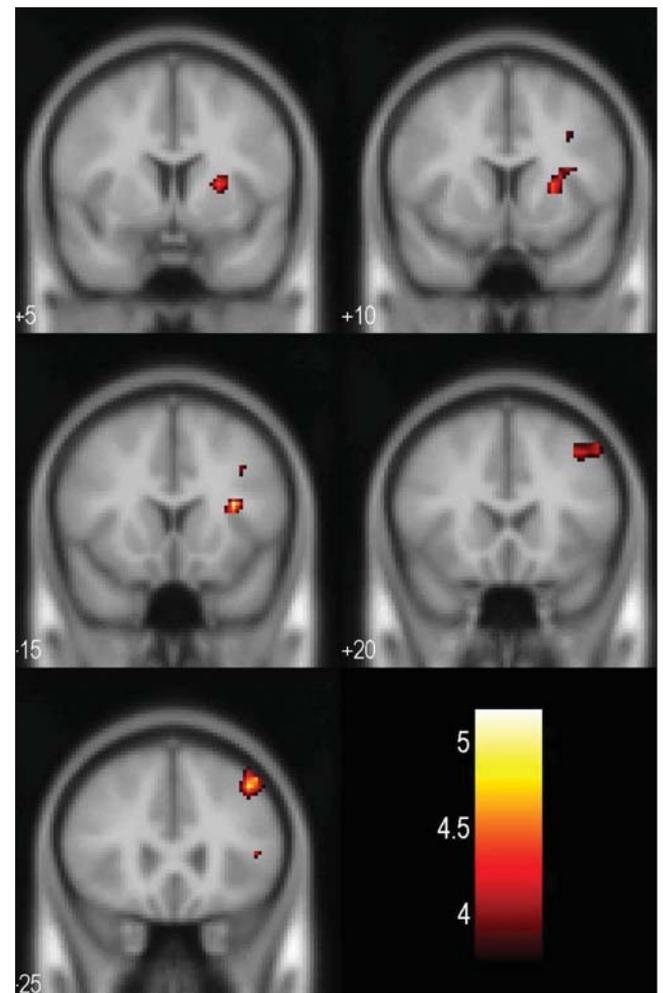


Fig. 1: Brain regions that show significant positive correlation between total Toronto Alexithymia Scale score and stress minus neutral contrast in male cocaine users. Areas of activation were superimposed upon a structural image shown in coronal sections. Adjacent sections are 5 mm apart. Coloured voxels reflect the t value of the correlation.

greater alexithymic features showed reduced activation in left-hemispheric cortical and right-hemispheric subcortical regions during stress processing, whereas men with greater alexithymic features showed an opposite correlation of increased activation in the right frontal cortex and putamen.

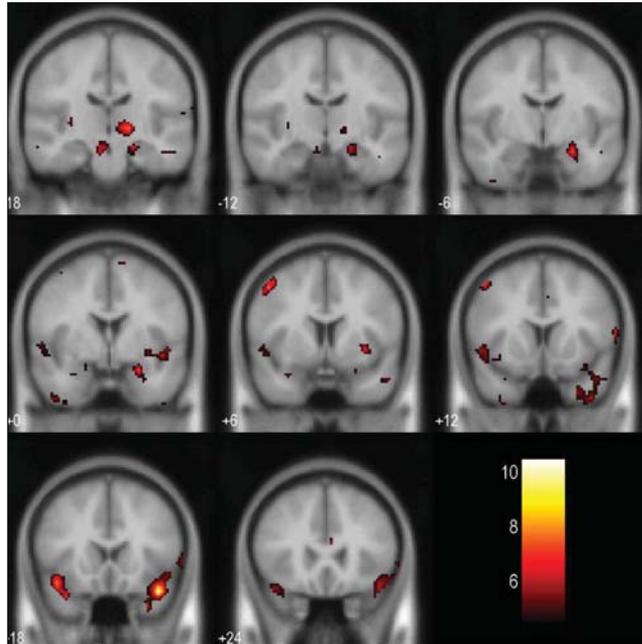


Fig. 2: Brain regions showing significant negative correlation between total Toronto Alexithymia Scale scores and stress minus neutral contrast in female cocaine users. Areas of activation were superimposed upon a structural image shown in coronal sections. Adjacent sections are 6 mm apart. Coloured voxels reflect the *t* value of the correlation.

Specifically, male and female cocaine-dependent patients showed critically different activation in response to stress in the putamen (activation v. deactivation) and frontal cortex (activation v. deactivation, as well as right v. left correlations) in association with alexithymia. This contrast suggests fundamental sex differences in the neural correlates of alexithymia. It is possible that women with greater alexithymic features are less able to generate and perceive emotion, whereas men with greater alexithymic features are able to generate emotion that they control and do not express. More important for these analyses, alexithymia appears to have a stronger effect on neural processing in female than male cocaine-dependent patients, and this association involves different brain regions and inverse associations from those previously described in non-substance-abusing populations. On the other hand, because we did not compare men and women directly in their association between alexithymia and specific regional brain activations, the sex differences that we presented here should be taken as descriptive in nature.

For instance, one hypothesis about how alexithymia is associated with adverse health effects is that alexithymic individuals show impairment when integrating the verbal capacity of the left hemisphere and the appraisal and regulatory capacity of the right hemisphere.³³ An alexithymic tendency to mislabel somatic sensations in conjunction with the failure of the frontal cortex to downregulate amygdaloid responses to emotional stimuli can then perpetuate and amplify dysregulated somatic sensations. Our current findings did not show an association between activity in verbal frontal areas (inferior frontal cortex [BA 44/45]³⁴ or medial frontal cortex [BA 6]³⁵) and alexithymia. Moreover, at least in women, alexithymia is associated with less rather than more activation in the limbic circuitry during stressful, compared with neutral, emotional tasks.

Table 1: Brain regions correlated with Toronto Alexithymia Scale scores in response to stressful minus neutral imagery

Group, correlation	Cluster <i>p</i> value (corrected)	* <i>F</i> ²	Cluster size (voxels)	Voxel <i>z</i> score	Talairach coordinate			Side	Identified region and Brodmann area
					x	y	z		
Men									
Positive	0.045	0.53	29	3.68	20	4	7	Right	Putamen
	0.049	0.54	28	3.68	34	20	50	Right	Superior and middle frontal G, BA 8
Negative	†None above threshold								
Women									
Positive	†None above threshold								
Negative	0.000	0.79	92	3.76	45	4	-25	Right	Middle temporal G, BA 21
				3.76	24	12	-35	Right	‡Superior temporal G, BA 38
	0.019	0.80	20	4.33	-43	4	42	Left	Frontal G, BA 6
	0.000	0.78	68	4.13	-32	12	-24	Left	Superior temporal G, BA 38
				3.65	-36	24	-20	Left	‡Inferior frontal G, BA 47
	0.001	0.80	33	4.14	10	-27	-2	Right	Thalamus
	0.001	0.79	35	3.97	20	-7	-18	Right	Amygdala
	0.012	0.77	22	3.85	17	-19	-15	Right	‡Parahippocampal G, BA 35
			3.61	27	1	-4	Right	Putamen	
				38	-3	-7	Right	‡Claustrum	

BA = Brodmann area; G = gyrus.
 *Averaged across all voxels in the cluster.
 †Threshold: *p* = 0.001 uncorrected, extent = 20 voxels.
 ‡Less than 8 mm from the voxel with peak activation.

The current results thus did not provide support for this hypothesis.

Brain activation in subcortical and temporal regions was strongly associated with alexithymia in female cocaine-dependent patients, and those with greater alexithymic features demonstrated less activation in several brain regions related to depressive mood, emotional embarrassment and autobiographical recall of previously stressful emotions. The amygdala is implicated in the emotional dysregulation of patients with a mood disorder (see Drevets³⁶), and we found that women with greater alexithymic features had less activation in the right amygdala during stressful, compared with neutral, imagery. This association is consistent with earlier studies reporting a correlation between subjective feelings of fear and distress and rCBF in the right amygdala during anxiety provocation among patients with social anxiety disorder, specific phobias and post-traumatic stress disorder.^{37,38} Women with greater alexithymic features also showed less activation in the left inferior frontal cortex or Brodmann area 47, a brain region activated during emotional embarrassment.³⁹ Finally, women with greater alexithymic features had less bilateral temporal activation, suggesting that they were less engaged in autobiographical recall during stress, perhaps reflecting an inability to recall previously stressful emotions.^{40,41} Note, however, that our female subjects did not appear to experience less anxiety or vivid imagery during the task, suggesting that alternative explanations for these regional brain activations should be explored in future studies.

The interpretation of our findings in men should be tempered by their weaker statistical significance, but they suggest a different set of psychological as well as neural processes in association with alexithymia in men compared with women. The greater activation of the right frontal cortex may reflect a greater effort in men with greater alexithymic features to exercise control over memory-related affect processing during stressful, compared with neutral, imagery.^{42,43} This regulatory control may channel emotional responses into physiological changes rather than verbal and facial expressions.^{44,45} However, as indicated earlier, male and female cocaine users did not differ in their change in heart rate during stressful, compared with neutral, imagery. This negative finding suggests that alexithymia did not uniquely determine the change of physiological and subjective measures during emotional distress and that other factors (such as antisocial personality and factors related to chronic cocaine use) needed to be considered in explaining the greater frontal activation in association with alexithymia in cocaine-dependent men.

The greater activation associated with alexithymia in men in the right putamen during stress is broadly consistent with earlier studies implicating the striatum in emotional motor responses.^{46,47} However, the putamen is involved in processing a wide range of often conflicting dimensions of emotion including disgusted^{48,49} and happy⁵⁰ facial expressions, recall of sad⁵¹ and stressful⁵² life events, pain,⁵³ generation of smiles in response to visual comics,⁵⁴ processing emotionally positive but not negative words⁵⁵ and responses to increasing

intensities of fear, disgust and happiness.⁵⁶ As an example of this complexity, a meta-analysis of emotional activation studies using PET and fMRI found that the basal ganglia was activated in 70% of happiness-induction studies and 60% of disgust-induction studies.³² The diverse affect-processing tasks that activate the basal ganglia suggest the importance of accounting for sex and personality traits in studies of emotion.⁵⁷

This study also has several limitations. First, it has a very modest sample size, particularly for comparing sex differences. However, the sex differences were quite striking and, most important, reflected differences in correlations that were both statistically significant and in the opposite directions. Second, we only had a single measure of self-reported alexithymia. Future studies will need to rate this construct with a broader range of self-report as well as possible observer-rated scales based on techniques such as structured rating of self-descriptions.⁵⁸ Third, the TAS scores showed a more limited range than found in some other studies of alexithymia and showed no sex differences. Some previous work concerning non-substance-abusing individuals found higher TAS scores in males.⁵⁹ These differences probably reflect the limited data available on alexithymia in this population and are consistent with the rates of other mood and affect-related disorders such as depression, which shows no difference between male and female substance abusers, whereas other community populations show significantly more depressed women than men.^{60,61} The current findings should thus also be considered as specific to patients with cocaine dependence and not be generalized to other subject populations.

In conclusion, the current study demonstrated that alexithymia is an important personality trait in modulating brain responses during emotional imagery. Moreover, alexithymia appears to modulate affect processing differently in male and female cocaine abusers and merits consideration as an important covariate in future studies of the brain's responses to stress as precipitants of relapse into drug abuse.

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