Hypofrontality and Negative Symptoms in Major Depressive Disorder

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The purpose of the current study was to compare regional cerebral blood flow (rCBF) in patients with major depressive disorder (MDD) to that of healthy subjects and to examine the relationship between rCBF, depressive symptoms (DS) and negative symptoms (NS) in these patients. **Methods:** Eleven psychiatric inpatients with diagnosed (MDD) and 15 normal control subjects were administered the scale for the assessment of negative symptoms (SANS) and the modified Hamilton rating scale for depression with items descriptive of NS excluded (HRSD-DS). Each patient underwent a SPECT scan using ^{99m}Tc-HMPAO at rest. Cortical and subcortical regions of interest (ROIs) were symmetrically defined in each hemisphere. Cortical-to-cerebellar perfusion ratios were established quantitatively using ADAC software. **Results:** Subjects in the MDD group had significantly lower rCBF in the frontal cortex and cinglulate gyrus (MANOVA, $p = 0.038$) due to differences in dorsolateral prefrontal cortex bilaterally (right $F = 7.69$, $p = 0.01$; left $F = 8.41$, $p = 0.01$) in the right orbitofrontal cortex ($F = 6.79$, $p = 0.02$) and in the cingulate gyrus ($F = 5.34$, $p = 0.03$). The MDD group also had lower rCBF in the posterior cortical structures (MANOVA, $p = 0.072$), which was due to decreased perfusion in the right parietal cortex ($F = 7.54$, $p = 0.01$). There were negative correlations between the SANS total score and rCBF in both the left dorsolateral prefrontal cortex (Pearson's correlation coefficient $r = .-67$, $p < 0.05$) and the left anterior temporal cortex ($r = -0.71$, $p < 0.01$) in MDD patients. Additionally, there were positive correlations between HRSD scores and rCBF in the left anterior temporal ($r = 0.71$, $p < 0.01$), left dorsolateral prefrontal ($r = 0.70$, $p < 0.01$), right frontal ($r = 0.82$, $p < 0.01$) and right posterior temporal ($r = 0.74$, $p < 0.01$) cortices. Cerebral blood flow was not correlated with either mini-mental state examination scores or age. **Conclusion:** This preliminary study replicates the finding of hypofrontality in MDD and indicates that decreased perfusion is associated specifically with negative symptom severity. These results support the hypothesis that, in MDD, negative symptoms and symptoms of depression are distinct phenomena and underscore the importance of negative symptom evaluation in neuroimaging studies of MDD and other disorders.

Key Words: technetium-99m-HMPAO SPECT; regional cerebral blood flow; depression; negative symptoms; dorsolateral prefrontal cortex; temporal cortex

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Over the last 15 yr, pathophysiological investigations of depression have increasingly made use of functional brain imaging technologies, specifically, PET and SPECT. Several studies have measured regional cerebral glucose metabolism (rCMRglc) and regional cerebral blood flow (rCBF) in patients with major depressive disorder (MDD) relative to control subjects (*1–11*), patients with different types of depression (*12,13*) and patients with other affective disorders (*14–17*).

The studies comparing MDD patients and control subjects yielded inconsistent results both when patients were studied at rest and under activation conditions (*2–11*). Global CBF in MDD patients has been reported to be either reduced (*5,7–9*) or not different relative to control values (*10,17*). Lower values of rCBF in MDD patients than in control subjects have been observed in the left cerebral hemisphere (*18*), left dorsolateral prefrontal cortex (*2,3,12,19*), left prefrontal cortex (*20*), paralimbic regions (*19,21*), bilateral temporal regions (*20*) and anterior parietal regions (*9*). The most consistent findings involved differences in the left prefrontal rCBF. Nevetheless, several reports showed no abnormalities or higher values of rCBF or rCMRglc (*10,17,22*).

The inconsistency in previous research findings could be related to several factors, including demographic considerations, e.g., age and gender (*23–25*), medication status [specifically neuroleptic status (*26, 27*)] and other methodological and statistical considerations (*9*). Since several reports indicate that rCBF abnormalities may be symptom-specific and not disease-related (*12,28*), one major factor that can influence rCBF in MDD is heterogeneity of depressive symptomatology (*29*). We were particularly interested in the role of negative symptoms (NS) in MDD (*30–32*) and their relationship to rCBF. Athough NS such as avolition, amotivation, poverty of speech and thought and blunted affect have been recently measured in MDD, their association with rCBF abnormalities has not been investigated (*30*). We expected NS to be associated with hypofrontality in MDD as has been shown for schizophrenia (*33,34*) and Alzheimer's disease (dementia) (*35,36*).

The purpose of this study was to replicate the findings of hypofrontality in hospitalized MDD patients and to assess the relationship between rCBF abnormalities, NS and other symptoms of depression.

MATERIALS AND METHODS

Subjects

Subjects included 11 right-handed patients (7 women and 4 men) hospitalized in the acute adult psychiatric unit and recruited from a sample of 23 patients participating in a study of NS in depression (*30*). All subjects gave informed consent and underwent complete physical, neurological and psychiatric evaluations and met DSM-IV criteria for unipolar MDD. All subjects had a complete blood count, routine chemistries and thyroid function tests within normal limits with negative RPR results. Exclusion criteria included previous history of head trauma resulting in a loss of consciousness, history of seizures or alcohol/substance abuse over the 6-mo period preceding hospitalization, ongoing medical illness and abnormal thyroid functions and RPR test results. At the time of assessment, all 11 of the MDD subjects were receiving psychotropic medications, specifically antidepressants and benzodiazepines. MDD patients were compared to 15 normal control subjects (6 men and 9 women; 14 right-handed, 1 left-handed) recruited from full-time hospital staff. Exclusion criteria for the control group were the same as for the MDD subjects, but also included history of psychiatric illness requiring psychotropic medications.

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Testing Procedures

A single rater tested all the MDD subjects and administered the 17-item Hamilton rating scale for depression (HRSD) (*37*), the scale for assessment of negative symptoms (SANS) (38), the positive and negative symptom scale (PANSS) (*39*), and the mini-mental state examination (MMSE) (*40*) to them within the first 3 days of their hospitalization. We derived a corrected Hamilton score (HRSD-DS) that excluded items #7, 8 and 13 in an attempt to index DS severity independent of negative symptom severity as described previously (*41*). Items #7 (work/interest), #8 (psychomotor retardation) and #13 (energy) were combined in the HRSD-negative symptom (HRSD-NS) scale (*30,41*). Psychometric ratings of the control subjects were not performed; we assumed that the control subjects would test in the normal range as was reported previously (*30*).

Scanning Procedures

The subjects were scanned within 48 hr of psychiatric ratings administration (medications unchanged during that time) using a single-head ADAC (ADAC Laboratories, Milpitas, CA) SPECT camera with a low-energy, high-resolution collimator (FWHM 7.5 mm at 10 cm depth). They received 740 MBq ^{99m}Tc-HMPAO (Ceretec, Amersham, Ltd., UK) intravenously while sitting with their eyes open in a dimly lit room. Acquisition began 20–60 min postinjection and lasted 45 min during a 360° rotation of the gamma camera in a 128 × 128 matrix. The data were prefiltered with a Gaussian filter (cutoff frequency 0.42, filter order 18).

Data Analysis

Reconstructions were done in the transaxial, coronal and sagittal planes. The transaxial plane was reconstructed parallel to the canthomeatal line. The SPECT data, which consisted of transaxial, coronal and sagittal image sets, were then viewed on a video-display terminal. Images were analyzed by two readers who were blind to the patients' identities. Cortical and subcortical regions of interest (ROIs) were symmetrically defined in each hemisphere on transaxial images. Cerebellar ROIs were selected in the middle portion of each cerebellar hemisphere. Cortical-to-cerebellar perfusion ratios were established semiquantitatively using ADAC software in 20 ROIs.

The psychometric test scores within the MDD group and all perfusion ratios were found to be normally distributed using Lilliefors' test (*42*). Accordingly, group differences in perfusion means were compared using omnibus MANOVA. The ROIs were analyzed in three groups according to their anatomical location: (a) frontal cortex and cingulate gyrus; (b) temporal, parietal and occipital cortex; and (c) basal ganglia and thalamus. The relationships between rCBF and clinical symptoms within the MDD group tested using the Pearson correlation method. Due to the exploratory nature of this study, rCBF of all 20 ROIs (38 correlations) needed to be assessed for possible relationships between NS and rCBF. We performed correlation analyses both with and without Bonferroni correction for multiple comparisons.

RESULTS

Descriptions of the MDD subjects with with respect to age, sex and medication regimen are presented in Table 1. The clinical ratings for all subjects are presented in Table 2. The two groups did not differ significantly on these items, although all patients in the MDD group were receiving psychotropic medications. In addition, scores on HRSD, PANSS and SANS are presented for the MDD patients, who, in addition to symptoms of depression, manifested negative symptoms as reported previously (*30*). A preliminary analysis indicated no significant correlations between rCBF and either age ($r<0.54$, ns) or MMSE scores ($r<0.52$, ns).

TABLE 1
Age, Sex and Medication Regimens of 11 Patients with Major Depressive Disorder

Patient no.	Age (yr)	Sex	Medication
1	55	F	None
2	47	M	Sertaline 50 mg/day
3	41	F	Venlafaxin 150 mg/day, diphenylhydramine 50 mg/day
4	40	F	Fluoxetine 40 mg/day
5	55	M	Fluoxetine 20 mg/day; lorazepam 3 mg/day
6	40	F	Fluoxetine 20 mg/day, lorazepam 1 mg/day
7	48	F	Fluoxetine 20 mg/day; clonazepam 1 mg/day
8	47	M	Paroxetine 20 mg/day;
9	48	M	Nortryptilline 150 mg/day
10	54	F	Venlafaxine 150 mg/day
11	34	F	Fluoxetine 20 mg/day; lorazepam 2 mg/day

The results of MANOVA analyses of ROI-to-cerebellum rCBF ratios between MDD and control groups are shown in Table 3. The multivariate analyses of rCBF in the frontal cortex were significant ($p = 0.038$). Compared to the control subjects, MDD patients had lower relative perfusion in the right orbitofrontal ($p < 0.02$) and dorsolateral prefrontal cortex ($p < 0.01$) bilaterally and in the cingulate gyrus 2 ($p < 0.05$). The multivariate analyses of rCBF in the posterior cortical structures indicated that perfusion differences between MDD patients and control subjects approached statistical significance ($p = 0.072$). Univariate analyses of variance revealed that this finding was the result of perfusion differences in the right parietal cortex ($p = 0.01$). The MANOVAs of rCBF in subcortical structures showed no differences between the groups.

Table 4 shows correlation analyses between rCBF values and cumulative psychometric scale scores. HRSD-DS scores showed positive correlation with rCBF in all ROIs, particularly in the right frontal and posterior temporal regions and in the left anterior temporal and parietal regions ($p < 0.01$). In contrast to HRSD-DS scores, SANS scores showed a trend toward negative correlation with the rCBF in most of the ROIs and specifically in the left dorsolateral prefrontal ($p < 0.05$) and the left anterior temporal cortices ($p < 0.01$). These results,

TABLE 2
Age and Clinical Ratings (MMSE, HRSD, PANSS, and SANS) for MDD and Control Subjects

	MDD group (n = 11)			Control group (n = 15)		
	Range	Mean	s.d.	Range	Mean	s.d.
Age, yr	34–55	45.76	6.86	28–42	36.11	8.27
MMSE	21–30	27.53	2.90	29–30	29.92	0.34
HRSD	21–35	27.53	5.07		—	
HRSD-DS	14–29	21.61	5.31		—	
HRSD-NS	5–9	6.69	1.25		—	
PANSS-G	40–69	50.00	9.23		—	
PANSS-N	16–32	23.38	5.17		—	
PANSS-P	7–20	12.38	3.88		—	
SANS	8–17	13.92	2.17		—	

MMSE = mini mental state examination; PANSS = positive and negative symptom scale; SANS = scale for the assessment of negative symptoms; HRSD = Hamilton rating scale for depression; HRSD-DS = Hamilton rating scale for depression, depression subscale. HRSD-NS = Hamilton rating scale for depression, negative symptom subscale; MDD = major depressive disorder.

TABLE 3
MANOVA Analyses of ROI-to-Cerebellum Ratios in Patients with Major Depressive Disorder (n = 11) and Control Subjects (n = 15)

ROI	MDD		Controls		F	p
	Mean	s.d.	Mean	s.d.		
			Frontal cortex and cingulate gyrus*			
Cingulate 1	0.85	0.09	0.90	0.09	1.98	ns
Cingulate 2	0.84	0.09	0.93	0.10	5.34	.03
R. Orbital frontal	0.67	0.12	0.76	0.12	6.79	.02
R. Frontal	0.81	0.12	0.84	0.12	3.52	ns
R. Dorsolateral prefrontal	0.84	0.10	0.94	0.09	7.69	.01
L. Orbital frontal	0.62	0.12	0.71	0.13	3.20	ns
L. Frontal	0.83	0.06	0.85	0.14	1.87	ns
L. Dorsolateral prefrontal	0.83	0.10	0.94	0.09	8.41	.01
			Temporal, parietal and occipital cortices†			
R. Anterior temporal	0.74	0.10	0.79	0.10	0.02	ns
R. Posterior temporal	0.68	0.05	0.67	0.10	0.26	ns
R. Parietal	0.74	0.05	0.85	0.10	7.54	.01
R. Occipital	0.73	0.06	0.75	0.08	0.19	ns
L. Anterior temporal	0.76	0.10	0.77	0.08	1.90	ns
L. Posterior temporal	0.65	0.06	0.64	0.06	0.19	ns
L. Parietal	0.74	0.80	0.80	0.09	2.87	ns
L. Occipital	0.74	0.05	0.75	0.09	0.05	ns
			Subcortical structure‡			
R. Thalamus	0.81	0.10	0.78	0.10	0.39	ns§
R. Basal ganglia	0.82	0.10	0.88	0.09	2.40	ns
L. Thalamus	0.81	0.10	0.78	0.10	1.13	ns
L. Basal ganglia	0.83	0.04	0.85	0.07	0.71	ns

*Wilks' Λ = 0.418; F = 2.793; DF = 8,17; p = 0.038.
†Wilks' Λ = 0.462; F = 2.328; DF = 8,17; p = 0.072.
‡Wilks' Λ = 0.847; F = 0.902; DF = 4,21; p = 0.481.
§ns = not significant.

however, were not statistically significant after Bonferroni correction for 38 multiple comparisons (alpha level <0.002).

DISCUSSION

The results of this study indicate that normalized rCBF in acutely ill inpatients with unipolar MDD is lower in the orbitofrontal and dorsolateral prefrontal cortices as well as in the right parietal cortex but not in the cingulate gyrus and temporal cortex compared to normal control subjects. Of note, it was NS but not DS severity that was negatively correlated with rCBF in the left dorsolateral prefrontal cortex and in the left anterior temporal cortex. The severity of DS was positively correlated with rCBF in the right frontal and bilateral temporal cortices. The results of this study should be considered exploratory in view of the small sample size and a large number of analyses, which increase the probability of a Type 1 error. However, the fact that neither age (*23,24*) nor cognitive impairment were significantly correlated with rCBF in any ROIs underscores the magnitude of correlations between rCBF and negative and depressive symptoms.

Although rCBF and rCMRglc findings in patients with depression are contradictory, our finding of low relative rCBF in dorsolateral prefrontal and orbitofrontal cortices is consistent with the most reproducible finding of the previous studies. Most studies reported decreased perfusion in the left dorsolateral prefrontal cortex for unipolar and bipolar depressed patients (*2,4,12*), although bilateral decrease in perfusion in the dorsolateral prefrontal cortex was reported by Sackeim et al. (*9*) and Pardo et al. (*43*). Decreased perfusion in the inferior frontal cortex was reported by Buchsbaum et al. (*44*), Sackeim et al. (*9*) and Pardo et al. (*43*). It should be noted, however, that several studies did not reveal hypofrontality in MDD (*10,17*). Increased

TABLE 4
Pearson's Correlation Coefficients Between rCBF Values and Psychometric Scale Scores for Patients with Major Depressive Disorder (n = 11)

ROI	Psychometric scale/correlation coefficients	
	HRSD-DS	SANS
Cingulate 1	.24	−.27
Cingulate 2	.18	−.36
R. orbital frontal	.49	−.34
R. frontal	.82†	−.00
R. dorsolateral prefrontal	.23	−.11
L. orbital frontal	.12	−.48
L. frontal	.16	.00
L. dorsolateral prefrontal	.20	−.67*
R. anterior temporal	.08	.24
R. posterior temporal	.74†	−.37
R. parietal	.43	−.15
R. occipital	.52	−.47
L. anterior temporal	.70†	−.75†
L. posterior temporal	.00	−.02
L. parietal	.71†	−.50
L. occipital	.49	−.38
R. thalamus	.05	−.15
R. basal ganglia	.02	.18
L. thalamus	.10	−.20
L. basal ganglia	.21	−.29

*p < 0.05.
†p < .01.
HRSD-DS = Hamilton rating scale for depression, depression subscale; SANS = scale for assessment of negative symptoms.

perfusion in the frontal cortex was also observed (*22*). We did not observe reductions in the rCBF in the limbic system as reported by some researchers (*4,19*). We also observed a rCBF reduction in the right parietal cortex that has not been reported previously. These findings are inconsistent with previous reports of decreased perfusion in the temporal cortex or cingulate gyrus (*2,4,12,14,17*).

The cause of these discrepancies is uncertain. Possible explanations include statistical considerations, sample characteristics with respect to diagnosis, illness severity and medication status (*9*). One other set of factors to be considered is the variation between patients in different research studies with regard to specific symptom subgroups associated with depression. Specifically, NS severity in patients with schizophrenia was negatively correlated with rCMRglc in the left dorsolateral prefrontal cortex (*33,34*) and NS were reported to be present in patients with MDD (*30–32*). As shown in Table 4, correlation coefficients between NS and DS and rCBF in MDD indicate that those basic neurobiological processes that effect the relationships between blood flow and DS and blood flow and NS are distinct from each other. NS severity is negatively correlated with rCBF in most ROIs, including the left dorsolateral prefrontal cortex ($r = -0.67$, $p < 0.05$). Our study results suggest that hypofrontality in MDD is related to negative rather than depressive symptom severity.

Our results indicate that rCBF in the left dorsolateral prefrontal cortex and in the left anterior temporal cortex was positively correlated with severity of depressive symptoms. Several studies reported similar findings. Rosenberg et al. (*22*), Silfverskiold et al. (*45*) and Drevets et al. (*46*) reported increased rCBF in depressed patients compared to normal control subjects. Positive correlation between DS severity and rCBF in the left dorsolateral prefrontal cortex is consistent with reports of increased rCBF in MDD subjects and corresponding decreases in rCBF with resolution of DS after positive response to ECT (*17*). In a related report, Ho et al. (*47*) demonstrated increased rCMRGlc in depressed unmedicated men during non-REM sleep. These findings correspond to the clinical observation that depressed patients are frequently involved in intensive thinking, ruminations, guilt and anger such that depression might be seen generally as an active and tortured process. Such a hyperarousal theory of depression (*47,48*) is consistent with the positive correlation between severity of depressive symptoms and rCBF found in ours and in previous studies (*22*).

Our study findings are confounded by the patients' medication use. The effects of antidepressants on rCBF per se are unknown. RCBF and rCMRglc were found to increase, however, in the dorsolateral prefrontal cortex and the cingulate gyrus after successful antidepressant treatment of previously unmedicated patients with MDD (*49,50*). If such changes are partially due to medication effects, antidepressants could have attenuated the findings reported here (of decreased perfusion in the dorsolateral prefrontal cortex), which might have been even more markedly decreased in the absence of medication. Similarly unknown are the effects of benzodiazepines on rCBF. Lorazepam (a benzodiazepine) was reported to consistently decrease the whole brain cerebral glucose metabolism and rCMRglc in healthy subjects (*51*). The lorazepam effects on rCMRglc were strongest in the thalamus and the occipital cortex and not in the dorsolateral prefrontal and temporal cortices (*51*), which were the brain areas most prominently affected by negative and depressive symptoms in our study. Therefore, the psychiatric symptoms measured in our study reflect brain function in the presence of the medication, and the opposite relationship between depressive versus negative symptoms and rCBF may still be valid.

Our findings of a positive correlation between DS severity and rCBF are at odds with the majority of functional brain imaging studies that have indicated that depression severity was inversely correlated with rCBF (*8,9*) and rCMRglc (*2,12*). The most likely reason for this contradiction involves our use of a rating scale that excluded items measuring NS, whereas several standardized depression rating scales used in these studies do contain several questions that assess NS severity. As reported previously, convergence between NS, apathy scales and HRSD that is due to NS items within HRSD *(52–54)* exists. In fact, HRSD can be divided into two separate subscales, HRSD-DS and HRSD-NS, which overlap minimally with each other (*51*). The NS factor had the highest loading in factor analytic studies of HRSD in patients with CVA, dementias (Galynker I, Vilkas N, Miner C, Prikhojan A, unpublished observations) and schizophrenia (*53,54*). Our findings also suggest that previously reported significant correlations between left prefrontal rCBF and severity of depression might have been driven by measures of NS severity in depression rating scales (*12*). This conclusion is supported by the findings of Rosenberg et al. (*22*) who suggested that positive correlation between depressive symptoms and CBF values in melancholic patients were related to depressed mood per se and not to associated features such as psychomotor retardation.

The effects of NS on rCBF in MDD have not been previously evaluated although there are reports of decreased perfusion and inverse correlations with NS severity in the left dorsolateral prefrontal cortex in schizophrenia (*33,34*) and Alzheimer's disease (dementia) (*36*). Correspondingly, in our study, NS are inversely correlated with rCBF in the left dorsolateral prefrontal cortex and also in the left anterior temporal cortex, another brain area implicated in the etiology of schizophrenia and dementia of the Alzheimer's type (DAT) (*55–58*). Our findings suggest this cortical region could be involved in NS etiology in MDD as well as in schizophrenia and DAT.

Whether similar functional abnormalities in the cerebral cortex appear in several neuropsychiatric disorders has been a matter of some debate. Some reports implicate different neuronal networks in different types of depression (*13*), while others have indicated similarities in prefrontal rCBF changes common to several types of depression (*12*). Interestingly, similar decreases in rCMRglc were observed in depressed subjects with Parkinson's disease, Huntington's chorea (disease) and strokes (*6,59,60*). Buchsbaum et al. (*43*) and later Cohen et al. (*3*) reported similar rCMRglc abnormalities in prefrontal cortex during a continuous performance task in patients with schizophrenia and affective disorders that did not relate to symptomatology. These results were interpreted as abnormalities in the attention network reflecting psychosis vulnerability and suggesting common pathophysiology for both disorders (*3*). On the other hand, rCBF measurements in the prefrontal cortex of schizophrenic and depressed patients and normal control subjects during the Wisconsin card sorting test revealed hypofrontality only in patients with schizophrenia suggesting that pathophysiological mechanisms of prefrontal hypoperfusion in schizophrenia may differ from those of depression (*55*). Our findings suggest that prefrontal hypoperfusion in different disorders could be related to NS severity whether the symptoms are primary, as in schizophrenia, or secondary, as in MDD.

CONCLUSION

Our study suggests that the neurobiological processes underlying the relationship between blood flow and NS seem to be

related to decreased perfusion in both the dorsolateral prefrontal and orbitofrontal cortex. This finding is similar to previous reports on rCBF, rCMRglc and NS in schizophrenia (*34*) and DAT (*36*) and suggests that mechanisms influencing NS and cerebral perfusion in the prefrontal cortex could be analogous in several disorders. Thus, our study draws attention to the importance of neurobiological processes underlying the relationship between NS, DS and, possibly, other symptom clusters and between rCBF in MDD and other psychiatric disorders.

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