

importance of considering depressive symptoms as one contributing factor.

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References

1. Clark DM, Teasdale JD: Diurnal variation in clinical depression and accessibility of memories of positive and negative experiences. *J Abnorm Psychol* 1982; 91:87-95
2. Coyne JC, Gotlib IH: The role of cognition in depression: a critical appraisal. *Psychol Bull* 1983; 94:472-505
3. Glass RM, Uhlenhuth EM, Weinreb H: Imipramine reversible cognitive deficit in outpatient depressives. *Psychopharmacol Bull* 1978; 14:10-13
4. Riskind JH, Rholes WS, Eggers J: The Velten mood induction procedure: effects on mood and memory. *J Consult Clin Psychol* 1982; 50:146-147
5. Sternber DE, Jarvik ME: Memory functions in depression. *Arch Gen Psychiatry* 1976; 33:219-224
6. Weingartner H, Cohen RM, Murphy DL, et al: Cognitive processes in depression. *Arch Gen Psychiatry* 1981; 38:42-47
7. Gass CS, Russell EW: Differential impact of brain damage and depression on memory test performance. *J Consult Clin Psychol* 1986; 54:261-263
8. Hamilton M: Development of a rating scale for depression. *J Neurol Neurosurg Psychiatry* 1967; 23:56-62
9. Russell EW: A multiple scoring method for the assessment of complex memory functions. *J Consult Clin Psychol* 1975; 43:800-809
10. Stukenberg KW, Dura JR, Kiecolt-Glaser JK: Depression screening scale validation in an elderly community dwelling population. *Psychological Assessment: A Journal of Consulting and Clinical Psychology* 1990; 2:134-138
11. Beck AT, Beck RW: Screening depressed patients in family practice: a rapid technique. *Postgrad Med* 1972; 81-85
12. Derogatis LR, Spencer PM: *The Brief Symptom Inventory Administration, Scoring and Procedures Manual-I*. Baltimore, Johns Hopkins University, 1982

Spontaneous Remission of Post-Stroke Depression and Temporal Changes in Cortical S₂-Serotonin Receptors

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A patient with post-stroke depression following infarction of the left basal ganglia is described. The patient's depression remitted during a 6-week double-blind treatment trial while receiving placebo medication. Cortical S₂-receptor binding that was measured using ¹¹C-N methyl spiperone and positron emission tomography (PET), increased in the left temporal cortex by more than 25% during the treatment trial. The change in serotonin receptor binding and its relationship to the improvement in mood observed in this patient are consistent with previously published data demonstrating a correlation between serotonin receptor binding in the left temporal cortex and severity of symptoms of depression.

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In recent studies, we have reported that post-stroke major depression is more frequent following lesions of either the left frontal cortex or left basal ganglia (particularly the caudate nucleus) than any other lesion location.^{1,2} In addition, cortical S₂-serotonin receptors, measured in noninjured areas of the temporal and parietal cortex using positron emission tomography (PET) and ¹¹C-N methyl spiperone (NMSp), were differentially affected, depending on whether the stroke was present in the right or left hemisphere.³ Right, but not left, hemisphere strokes were associated with an increase in the

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ratio of ipsilateral-to-contralateral (stroke to nonstroke) cortical S₂-serotonin receptor binding, compared to age-comparable normal controls. Furthermore, the ratio of ipsilateral-to-contralateral NMSP receptor binding in the temporal cortex of patients with left hemisphere stroke was significantly correlated with severity of depressive symptoms (the lower the binding ratio, the higher the depression score). Neither of these lateralized phenomenon could be explained by interhemispheric differences in lesion size or location, background demographic or clinical characteristics of the patients, or medication exposure.

Based on these findings, we postulated that up-regulation of ipsilateral S₂-serotonin receptors following right hemisphere stroke may play a role in preventing depression or facilitating its resolution, while loss of cortical receptors or failure to up-regulate these receptors in the left hemisphere may lead to the onset of depression in patients with left-sided lesions. In light of this hypothesis, we present the following case to illustrate longitudinal changes in NMSP binding temporally related to alterations in mood state.

FIGURE 1. Noncontrast CT scan showing irregular area of low density involving the head of the left caudate nucleus, anterior limb of the left internal capsule (upper arrow), and putamen (lower arrow)



CASE REPORT

The patient was a 60-year-old right-handed black female admitted to the stroke unit of the University of Maryland Hospital (Baltimore, MD) in September 1987 with sudden weakness of the right hand and leg. On admission, she was alert, mildly anxious, cooperative, and orientated to time, place, and person. There was no evidence of dysarthria or aphasia. Cranial nerve examination was normal. She had a right hemiparesis with grade II (mild) weakness of the tongue and face and grade V (severe) weakness of both the upper and lower extremities. Sensory examination was normal bilaterally. She had right-sided hyperreflexia and a positive right plantar response. The remainder of the physical examination was normal. Family history was negative for neurological or psychiatric disorders, and her past medical history revealed only remote past alcohol abuse.

Routine laboratory studies (including urinalysis, blood count, serum electrolytes, blood glucose, serum B₁₂ and folate, coagulation profile, serum lipids and triglycerides, and rheumatoid and syphilis serology) were all within normal ranges. An EEG performed 1 day after admission showed frequent 2-5 Hz waves in the left anterior quadrant consistent with a lesion in that region. X-ray computed tomography (CT) performed the same day revealed an area of low density in the region of the head of the left caudate nucleus (Figure 1), which was later confirmed by magnetic resonance imaging (MRI) as a comma-shaped lacunar infarct involving the head of the left caudate and extending into the anterior limb of the internal capsule and putamen.

TABLE 1. Psychiatric examination scores for one patient with post-stroke depression

Measure	Pre-Treatment Depressed State	Post 6 Weeks Treatment Euthymic State
Present State Exam	21	0
Hamilton Depression Rating Scale	16	0
Johns Hopkins Functional Inventory	3	3
Social Functioning	36	36
Social Ties Checklist	5	5
Mini-Mental State Exam	18	24

TABLE 2. PET measurements of ¹¹C-N methyl spiperone (NMSP) binding to S₂-serotonin receptors in noninjured cortex before and after treatment of one patient

	Stroke Hemisphere/Non-Stroke Hemisphere Binding Ratio	
	NMSP Study 1: Pre-Rx (Depressed)	NMSP Study 2: Post-Treatment (Euthymic)
Frontal Cortex	0.92	1.20
Temporal Cortex	0.92	1.17
Parietal Cortex	0.91	1.12

Eight days following the stroke, the patient was observed to be sad, expressing self-deprecatory thoughts, feelings of hopelessness, and a wish to be dead. Informed consent was obtained, and the patient was enrolled in the Stroke Data Bank of the University of Maryland Hospital, a 6-week double-blind post-stroke depression treatment study,⁴ and the PET imaging study. A baseline detailed neuropsychiatric examination, including the Present State Examination (PSE)⁵ (modified to elicit primarily depressive and anxiety symptoms), the Hamilton Depression Rating Scale (HDRS),⁶ the Mini-Mental State Examination (MMSE),⁷ the Johns Hopkins Functional Inventory (JHFI)⁸ (a measure of activities of daily living), and a neuropsychological battery,⁹ were performed.

The psychiatric interview revealed that the patient had symptoms meeting DSM-III criteria for major depression (excluding the 2-week symptom duration criteria).¹⁰ Fifteen days after the comprehensive psychiatric and neuropsychological assessment, and 2 days prior to the initiation of treatment (hospital day 23), a NMSP PET scan measurement of cortical S₂-serotonin receptor binding was performed,³ followed a day later by a PET scan of regional cerebral glucose metabolism using ¹⁸F-fluoro-2-deoxy-D-glucose (FDG).¹¹ Following completion of the baseline PET studies, 25 days after the onset of the acute stroke symptoms and 17 days after the onset of the major depression, the double-blind treatment study¹² was started.

Over the 6 weeks of the study, the patient was evaluated every 2 weeks with the HDRS, MMSE, and JHFI. At the end of the treatment period, the entire neuropsychiatric and neuropsychological battery was readministered, and a second NMSP PET scan was performed. The double-blind treatment code was subsequently broken and the patient was found to be taking placebo. During the hospitalization, the patient was also treated with anticoagulants: intravenous heparin in the first week, and low-dose aspirin thereafter.

Scores on each of the instruments administered to the patient during the 6-week treatment period are shown in Table 1. By the second week, the patient showed a clear reduction in depressive symptoms. Over the course of treatment, her MMSE score and scores on six of nine subtests of the neuropsychological battery improved, and diagnostic criteria for major depression were no longer met.

The FDG PET study demonstrated pronounced hypometabolism in the ipsilateral (left) frontal and temporal cortices, caudate and thalamic nuclei, and contralateral (right) cerebellum. The mean decrease in metabolic rate, expressed as a ratio of matched regions in the left and right hemispheres, was approximately 20%. The relative concentration of S₂-receptor binding in the frontal, temporal, and parietal cortex was estimated by calculating the ratio of binding in symmetrical regions of the left compared to right hemisphere. In a group of age-comparable normal controls, the mean \pm SD asymmetry ratio for these regions, calculated 70–90 min after injection of NMSP, was 1.0 ± 0.11 .³ Over this time interval, the binding of NMSP previously had been shown to be sensitive to changes in receptor binding and not blood flow.^{13,14} The changes in the binding ratios between the first and second PET study are shown in Table 2. Over the course of 6 weeks,

the increase in cortical binding ratio was 28% in frontal, 25% in temporal, and 21% in parietal cortex. The patient was re-evaluated clinically at 3 months, 6 months, and 2 years following her stroke and continued to be euthymic.

DISCUSSION

This case of a 60-year old woman with no previous history of depression who developed a major depression following infarction of the basal ganglia, demonstrated changes in cortical S₂-serotonin binding that were associated with the resolution of her depressive disorder. The increase in the ratio of left to right hemisphere NMSP binding in frontal, temporal, and parietal regions coincided with both the remission of the patient's major depressive episode and improvement in cognitive function. The increase in receptor binding could not be attributed to a direct effect of antidepressant medication because the patient received placebo.

There are methodological limitations that complicate the interpretation of this study. We cannot conclude that the observed changes in NMSP binding relate solely to the resolution of the depression. Other stroke-related variables may have contributed to it, including direct effects of the basal ganglia lesion, interactions of other neurotransmitter systems with S₂-serotonin sites, or recovery from non-mood-related neurological deficits. Receptor changes may occur in all patients in the subacute phase of recovery from stroke. Although we do not have data currently, it will be critical to examine whether or not S₂-serotonin receptor binding increases in patients with left hemisphere lesions whose depressions do not resolve. It is, however, unlikely that the change in binding ratio was due to a test-retest measurement error. Repeat NMSP PET studies performed in two non-depressed stroke patients (scans 1 and 2 separated by 1 year) demonstrated cortical NMSP binding ratio changes of less than 5% in both patients (Mayberg, unpublished data). The change in binding in the case reported here was 25% over a 6-week period—greater than two standard deviations above the single study ipsilateral-to-contralateral ratio obtained in normal control subjects (1.0 ± 0.11). Lastly, although the patient met symptom and duration criteria for major depression, the abbreviated course of her illness (approximately 3–4 weeks) was somewhat atypical of post-stroke major depressions, which characteristically last about 1 year.⁴ Although a short duration of depression may suggest an adjustment disorder (DSM-III), we have previously noted that spontaneous remission of major depression within 6 months is more likely to occur with subcortical or brain stem

infarcts than cortical lesions.¹⁵ The basal ganglia lesion location in this patient and her clinical course are consistent with these previous observations. Furthermore, minor depression using DSM-III criteria for dysthymic disorder¹⁰ is unlikely to be associated with cognitive impairment, which is more often a concomitant of post-stroke major depression.⁹

We have previously hypothesized that the pathophysiology of depression following left hemisphere stroke might be mediated, in part, by monoaminergic dysfunction resulting from ischemic injury to the ascending noradrenergic or serotonergic pathways. Since fibers of these two systems pass through the ventral aspect of the striatum as they ascend to the frontal cortex, our patient would have been at risk for injuring these pathways. The negative correlation between the S₂-serotonin binding ratio and the severity of depressive symptoms previously observed³ would suggest that as serotonin binding increased, mood improved. The change in this patient's NMSP binding ratio suggests that cortical S₂-serotonin receptor function may be directly related to changes in mood state, as predicted by our hypothesis. Although we were not able to determine whether a low NMSP binding ratio preceded or followed the onset of depression, an increase in the ratio associated with the reduction in symptoms suggests that serotonergic dysfunction is, at the least, a correlate of post-stroke depression. As the improved cognitive function was also associated with increased NMSP binding ratio, we might speculate that monoaminergic dysfunction may also be involved in the cognitive deficits seen in these depressed patients.

While depressed, the patient showed widespread hypometabolism in the ipsilateral hemisphere and contralateral cerebellum. These regional changes were consistent with those that were observed in nondepressed stroke patients with comparable lesion locations.¹⁶ Hypometabolic areas overlapped regions showing low receptor binding in the first NMSP study. Unfortunately, a follow-up FDG scan was not obtained due to radiation dosimetry limitations. Thus, it remains undetermined if there were regional changes in metabolism in association with the S₂-serotonin binding changes, reduction in depressive symptoms, and cognitive improvement. Investigation of these interactions as well as of the role of other neurotransmitter systems awaits further study.

In conclusion, the data obtained from this case study suggest that neuroreceptor function following cerebral insult is not static and may be related to changes in mood state and cognitive performance.

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References

1. Starkstein SE, Robinson RG, Price TR: Comparison of cortical and subcortical lesions in the production of post-stroke mood disorders. *Brain* 1987; 110:1045-1059
2. Starkstein SE, Robinson RG, Berthier ML, et al: Differential mood changes following basal ganglia versus thalamic lesions. *Arch Neurol* 1988; 45:725-730
3. Mayberg HS, Robinson RG, Wong DF, et al: PET imaging of cortical S₂-serotonin receptors after stroke: lateralized changes and relationship to depression. *Am J Psychiatry* 1988; 145:937-943
4. Robinson RG, Kubos KL, Starr LB, et al: Mood disorders in stroke patients: importance of lesion location. *Brain* 1984; 107:81-93
5. Wing JK, Cooper JE, Sartorius N: Measurement and classification of psychiatric symptoms. Cambridge, England, Cambridge University Press, 1975
6. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
7. Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
8. Robinson RG, Benson DF: Depression in aphasic patients: frequency, severity and clinical-pathological correlations. *Brain and Language* 1981; 14:282-291
9. Bolla-Wilson K, Robinson RG, Starkstein SE, et al: Lateralization of dementia of depression in stroke patients. *Am J Psychiatry* 1989; 146:627-634
10. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980
11. Phelps ME, Huang SC, Hoffman EH, et al: Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 1979; 6:371-388
12. Lipsey JR, Robinson RG, Pearlson GD, et al: Nortriptyline treatment of post-stroke depressions: a double-blind study. *Lancet* 1984; 1:297-300
13. Wong DF, Wagner HN Jr, Dannals RF, et al: Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science* 1984; 226:1393-1396
14. Wong DF, Gjedde A, Dannals RF, et al: Quantification of dopamine and serotonin receptors in living human brain: equilibrium binding kinetics, III (abstract). *J Nucl Med* 1987; 28:611
15. Starkstein SE, Robinson RG, Price TR: Comparison of spontaneously recovered versus nonrecovered patients with post-stroke depression. *Stroke* 1988; 19:1491-1496
16. Mayberg HM, Starkstein SE, Sadzot B, et al: Patterns of remote hypometabolism (FDG-PET) in subcortical strokes differentiates grey and white matter lesions (abstract). *J Cereb Blood Flow Metab* 1989; 9(suppl 1):621