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Regional cerebral glucose metabolism in late-life depression and Alzheimer disease: A preliminary positron emission tomography study

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ABSTRACT **Eight subjects with late-life depression, eight subjects with probable Alzheimer disease, and eight healthy age-matched controls were studied using 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography in the resting state with their eyes open and ears unoccluded. The depressed subjects showed widespread reductions in the regional cerebral metabolic rate for glucose in most major neocortical, subcortical, and paralimbic regions that were significantly different from control values ($P < 0.01$). The metabolic decrements in the depressed group were comparable in magnitude to those seen in the Alzheimer disease group. These data demonstrate widespread nonfocal decline in glucose metabolism in late-life depression that is comparable to the hypometabolism seen in Alzheimer disease. These findings have pathophysiological implications in major depressive disorder in the elderly.**

Depressive illness is one of the most common mental disorders in the elderly (1, 2). It typically presents as a pervasive disturbance of mood associated with neurovegetative and cognitive signs and symptoms such as disturbance of sleep and appetite, crying spells, fatigue, anhedonia, and loss of attention, concentration, and memory (1, 2). The prevalence of major depressive illness—the most severe form of the disorder—is estimated to be ≈1% in studies of noninstitutionalized elderly subjects (3). The prevalence of dysthymic disorder and depressive symptoms—less severe but clinically significant forms of depression in the same population—is 2–3 and 10–15%, respectively (3). Depression in the elderly is often associated with functional and economic loss, physical illness, institutionalization, and a high rate of suicide (1, 2). Despite these staggering consequences, late-life depression remains one of the most underdiagnosed and undertreated conditions in the elderly (1, 2).

While the structural basis of late-life depression has been investigated using computerized tomography and magnetic resonance imaging (4–9), there have been very few studies aimed at elucidating the physiologic basis of late-life depression (10, 11). Cerebral blood flow has been examined using the xenon-133 inhalation technique and single photon emission computed tomography (SPECT) in a mixed sample of elderly and younger subjects with major depression and in a small group of subjects with late-life depression (10, 11). Global reduction in blood flow, in the major neocortical regions, has been reported to occur in these subjects when compared to healthy age-matched controls (10). However, given the technical limitations of the xenon-133 technique, only cortical blood flow was examined by this method (10). The question of subcortical, paralimbic, and cerebellar physiological activity in subjects with late-life depression remains unanswered (10). Semiquantitative estimates of blood flow have been obtained using 99^{m}Tc-hexamethylpropyleneamine-oxime (Tc-HMPAO) SPECT (11). Focal reductions in Tc-HMPAO uptake have been reported in the frontal lobes with normal uptake in other major neocortical regions (11). Subcortical HMPAO activity was not reported in this study of elderly subjects with major depressive illness (11).

Positron emission tomography (PET) using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}FDG PET) provides a reliable *in vivo* method of examining glucose metabolism in both cortical and subcortical regions of the brain. Glucose metabolism closely parallels neuronal activity and regional measures of absolute regional cerebral glucose metabolism [regional cerebral metabolic rate for glucose (rCMRglc)] can be obtained using this technique (12). ^{18}FDG PET has been used to examine cerebral glucose metabolism across a broad spectrum of neuropsychiatric conditions (13–17). Measurements of absolute rCMRglc in neocortical, subcortical, and limbic regions using high-resolution scanners have made it possible to examine cerebral physiology in various disease states and to compare rCMRglc between healthy controls and subjects with specific disorders (13–17).

To our knowledge, there have been no reported studies of cerebral glucose metabolism using PET in subjects with late-life depression. We therefore designed a study to examine global and regional glucose metabolism in neocortical, subcortical, and paralimbic structures in subjects with late-life depression and to compare them to similar measures obtained from healthy age-matched controls. Additionally, we were interested in comparing rCMRglc in late-life depression to glucose metabolic patterns in subjects with probable dementia of the Alzheimer type (DAT)—a condition where widespread reductions in rCMRglc have been demonstrated (13). In an earlier study of subjects with late-onset depression using [^{123}I]iodoamphetamine SPECT, we demonstrated a low cerebral/cerebellar uptake ratio of the radiotracer that improved after treatment of the depressed state (18). Based on this observation (18) and the diverse clinical and biological aberrations that characterize major depressive disorder (1, 2), we hypothesized that subjects with late-life depression would show widespread reductions in glucose metabolism in the neocortical and paralimbic regions of the brain. Based on basic and clinical studies that demonstrated that limbic and paralimbic regions and their connections are involved in the regulation of emotions and affect (19–21), we also hypothesized that the paralimbic regions would show greater decrements in rCMRglc in subjects with major depression than the

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Abbreviations: DAT, dementia of the Alzheimer type; PET, positron emission tomography; ^{18}FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; rCMRglc, regional cerebral metabolic rate for glucose; SPECT, single photon emission computed tomographic scanning; Tc-HMPAO, 99^{m}Tc-hexamethylpropyleneamineoxime.

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neocortical regions. We additionally hypothesized that the metabolic decrements in the neocortical regions in subjects with late-life depression would be significantly lower than those in healthy controls but less marked than neocortical decrements in rCMRglc observed in subjects with DAT. This hypothesis was based on earlier PET and neuropathological studies that showed widespread neocortical involvement in DAT with paralimbic hypometabolism occurring primarily in cases with superimposed behavioral aberrations (13). While resting FDG PET studies in DAT have been reported (17, 22, 23), we reexamined rCMRglc in our DAT group primarily to compare glucose metabolic patterns between two groups with considerable clinical and biological overlap (1, 2). A preliminary report of our study is presented here.

SUBJECTS AND METHODS

Our sample comprised eight subjects with late-life depression (six women and two men), eight healthy age-matched controls (three women and five men), and eight subjects with probable DAT (three women and five men). The depressed subjects met DSM-III-R criteria for unipolar major depressive disorder (24) with Hamilton depression rating scale scores (HRSD) of 15 or greater on a 17-item scale [HRSD scores, 22 ± 6 (mean ± SD)] (25). Four of the eight depressed subjects had their first episode of depression after age 60 and one subject additionally displayed psychotic features. Diagnosis of unipolar major depression was based on comprehensive history and mental status examinations performed by a board-certified psychiatrist using DSM-III-R criteria (A.K.). All eight depressed subjects were cognitively intact, based on mental status examinations and histories obtained from both subjects and informed caregivers. Their mean Folstein Mini Mental State Exam Scores (MMSE) (26) was 28.6 ± 1.3 (mean ± SD; range 26–30). Depressed subjects and controls were free of major medical/neurologic illness such as diabetes, stroke, heart disease, malignancies, gastrointestinal, renal, and liver disease, significant head injury, and seizures. They had normal laboratory indices including complete and differential blood counts, electrolytes, hepatic, renal screen, and thyroid indices. Computerized tomography/magnetic resonance imaging scans of the head were interpreted as normal for age in all subjects from the three groups. Three of the depressed subjects and two controls had essential hypertension well controlled at the time of the study. Five of the depressed subjects were free of psychotropic medication for a week before the study, and the other three were medication free 72 h prior to the study. These three subjects were previously on low doses of benzodiazepines with half-lives of 12–24 h. Follow-up data are available on six of the eight depressed subjects. Four of them responded totally to antidepressant therapy whereas the other two were partial responders. Twelve months after the PET study, there was no evidence of clinical dementia in any of these six subjects. All the DAT subjects were cognitively impaired for at least 12 months prior to the study and met National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable DAT (27). They had mild-moderate dementia as demonstrated by their MMSE scores [20 ± 4.95 (mean ± SD); range, 12–25] and were free of significant other medical neurologic illness (27). The aforementioned laboratory values were also normal in all the DAT subjects.

Regional cerebral glucose metabolism was measured using ^{18}FDG and the Penn PET scanner with in plane and axial resolution of 6 mm (full-width half-maximum) (28). All subjects were studied in the resting state with their eyes unoccluded, ears open, and room noise minimized. ^{18}FDG (5 mCi; 1 Ci = 37 GBq) was injected intravenously, and after an uptake period of 45 min, subjects were scanned for 45 min. Slices (2 mm) were obtained parallel to the cantho-meatal line and arterial blood samples were obtained during the uptake period and scan time. rCMRglc was determined as described and expressed as mg per 100 g of brain per min (29, 30). A lumped constant of 0.52 (31) was used in the Sokoloff equation (32) to calculate CMRglc.

Only transaxial images were used for image analysis. Metabolic images were compared with anatomic sections from the Matsui and Hirano atlas of the human brain containing sections parallel to the cantho-meatal line (33). Because of individual differences in head size and shape, each PET slice was assigned a level above the cantho-meatal line based on the atlas. By using the Talaraich neuroanatomic atlas (34) as a guide, a template was developed in our laboratory that contained regions of interest appropriate for individual PET slices. Once a given PET slice was identified as corresponding to a specific level and slice on the atlas, the appropriate template was transferred to the PET image. Individual regions on the template were then enlarged, rotated, or appropriately moved to best fit the region of interest in the PET image. In every instance the atlas provided a guide to placement of the regions of interest. For rCMRglc estimates, PET slices at all levels where the brain regions were well visualized were used in the analysis. The final metabolic value for any given region (e.g., right frontal lobe) was obtained by averaging the metabolic value for this region over all the slices in which this region was identified. For whole-brain CMRglc measurements, an elliptical region of interest from the template was transferred to the PET image and appropriately modified to encircle the entire brain (gray and white matter). The final whole-brain CMRglc in each subject was obtained by averaging the whole-brain CMRglc over five PET slices at the level of the basal ganglia.

The one-way analysis of variance (ANOVA) was used to compare rCMRglc values between the three groups. The Kruskal–Wallis test was used to confirm the results of the ANOVA. Pairwise post hoc contrasts between groups adjusted for multiple comparisons were performed using the Ryan–Einot–Gabriel–Welsch procedure in the SAS Institute (Cary, NC) statistical package (SAS ANOVA). Analysis of covariance was also performed to control for imbalances in age between groups.

RESULTS

Our data (Table 1) demonstrate that our sample of subjects with major depression have widespread decrements in rCMRglc that are significantly different from rCMRglc in the healthy control group ($P < 0.01$). Whole-brain CMRglc in the depressed and DAT groups was significantly lower than in the control subjects. The decrease in rCMRglc was noted in most major neocortical (frontal, parietal, temporal, sensorimotor, and calcarine regions), paralimbic (orbitofrontal, anterior, and posterior cingulate regions), and subcortical (caudate and lenticular nuclei) regions of the brain. In the depressed group, rCMRglc in the right and left calcarine cortex, the right and left thalamus, and the left cerebellum, though lower than control values, was not significantly different ($P > 0.05$). rCMRglc in the right cerebellum, though significantly lower in the depressed group, was only marginally so ($P = 0.03$). Adjustment for age did not affect the statistical significance of these comparisons. Though rCMRglc in our DAT group was lower across all major neocortical and subcortical regions when compared to the control group, the differences were statistically significant bilaterally only in the parietal and frontal lobes and anterior cingulate regions. Additionally, rCMRglc in the left temporal, sensorimotor, and orbital regions and in the left caudate and lenticular nuclei were significantly lower in the DAT group when

Table 1. Absolute rCMRglc in all regions in the depressed, DAT, and control groups

Region	rCMRglc, mg per 100 g per min		
	Depressed	Control	DAT
Whole brain	3.18 ± 0.46*	4.80 ± 1.24	3.65 ± 1.06*
Neocortical			
R. frontal	3.03 ± 0.52*	4.61 ± 1.09	3.61 ± 1.00*
L. frontal	2.98 ± 0.57*	4.63 ± 1.03	3.26 ± 0.81*
R. Lt. temporal	3.54 ± 0.64†	5.59 ± 1.56	4.32 ± 1.51
L. Lt. temporal	3.28 ± 0.49*	5.27 ± 1.35	3.83 ± 1.33*
R. M. temporal	3.78 ± 0.77†	6.10 ± 1.98	5.36 ± 1.99
L. M. temporal	3.58 ± 0.71†	5.70 ± 1.78	4.99 ± 1.76
R. parietal	3.43 ± 0.67*	5.10 ± 1.10	3.76 ± 1.13*
L. parietal	3.31 ± 0.51*	4.79 ± 0.83	3.45 ± 1.08*
R. sen. motor	3.41 ± 0.69†	4.84 ± 1.04	4.03 ± 0.99
L. sen. motor	3.54 ± 0.75*	5.06 ± 0.82	3.84 ± 1.00*
R. calcarine	3.80 ± 0.41	6.24 ± 2.11	5.03 ± 2.14
L. calcarine	3.78 ± 0.54	6.16 ± 2.16	4.47 ± 2.02
Paralimbic			
R. ant. cingl.	3.26 ± 0.56*	5.01 ± 1.31	3.91 ± 0.81*
L. ant. cingl.	3.18 ± 0.62*	5.00 ± 1.32	3.78 ± 0.85*
R. post. cingl.	4.38 ± 0.57†	6.48 ± 1.45	5.40 ± 1.55
L. post. cingl.	4.49 ± 0.66†	6.64 ± 1.53	5.26 ± 1.64
R. orb. frontal	2.80 ± 0.86*	5.70 ± 2.05	4.06 ± 1.51
L. orb. frontal	3.04 ± 0.76*	5.48 ± 1.82	3.78 ± 1.29*
Subcortical			
R. caudate	4.16 ± 0.88†	6.15 ± 1.63	5.00 ± 0.94
L. caudate	3.96 ± 0.58*	6.03 ± 1.64	4.50 ± 1.04*
R. lentic. nucl.	4.09 ± 0.83†	5.91 ± 1.47	5.36 ± 1.29
L. lentic. nucl.	3.72 ± 0.60†	5.51 ± 1.35	4.83 ± 1.10†
R. thalamus	4.63 ± 0.96	6.26 ± 1.44	5.39 ± 1.29
L. thalamus	4.41 ± 0.88	5.91 ± 1.40	4.99 ± 1.05
R. cerebellum	3.82 ± 0.52†	6.68 ± 2.48	4.43 ± 0.47
L. cerebellum	3.45 ± 0.59	5.86 ± 2.13	5.13 ± 2.67

Age (mean ± SD): depressed, 71.2 ± 5.6 years; control, 66.5 ± 5.2 years; DAT, 67.2 ± 9.3 years. Ant., anterior; post., posterior; cingl., cingulate; sen., sensory; orb., orbital; Lt. temporal, lateral temporal; M. temporal, mesial temporal; R., right; L., left; nucl., nucleus.
*Significantly different from controls ($P < 0.01$).
†Significantly different from controls ($P < 0.05$).

compared to control values. The rCMRglc in the depressed group, for all major regions examined, was only marginally lower than that in the DAT group. The differences between the depressed and DAT groups, however, were not statistically significant (Fig. 1).

DISCUSSION

Our preliminary data suggest that subjects with late-life depression present with marked statistically significant reductions in rCMRglc when compared to healthy age-matched controls. The decrements in rCMRglc were widespread and occurred in all major neocortical and paralimbic regions of the brain and the caudate and lenticular nuclei. This pattern of widespread decline in CMRglc observed in the depressed group was similar to that seen in our DAT group. However, although the magnitude of decline in rCMRglc across all regions in these two groups was comparable, the subjects with late-life depression demonstrated a more homogenous pattern of hypometabolism with no preferential involvement of any region (Fig. 2).

Earlier studies examining cerebral blood flow in younger depressives have been conflicting, with studies showing either a decrease or no change in blood flow in the depressed group when compared to age-matched controls (35, 36). One study suggested that while resting flow in the depressed group did not differ from controls, activation studies established differential responses between the groups (37). ^{18}FDG PET studies in younger subjects with major depressive

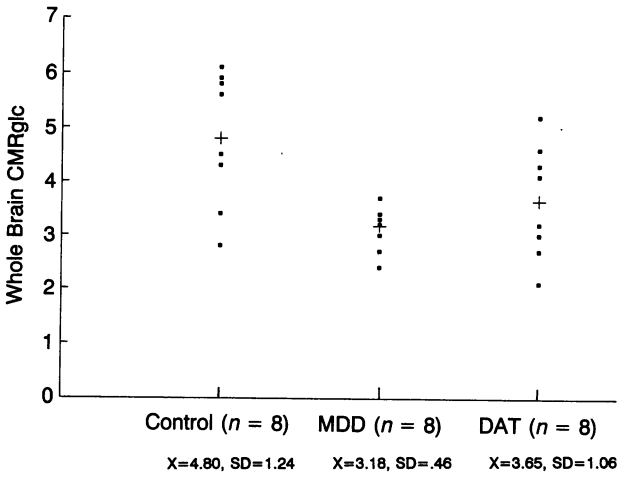

FIG. 1. Scatter plot of the whole-brain CMRglc (mg per 100 g per min) in the depressed (MDD), DAT, and control groups. Note the differences in means between the depressed and control groups and the comparable magnitude of decline in CMRglc between the depressed and DAT groups.

disorder revealed that in bipolar depressives, there was a global decline in CMRglc, whereas subjects with unipolar depression showed a relative decline in rCMRglc in the caudate nucleus (38). The same group of investigators additionally reported that a decrease in normalized rCMRglc in the anterolateral prefrontal cortex was found in three distinct types of depressive illness, thereby suggesting that there may be a common biologic pathway that mediates depressive illness across heterogenous clinical states (39). In this particular study, however, rCMRglc in other brain regions was not examined thereby making it difficult to comment on the role of other brain regions in the pathophysiology of depression (39). Another report (40) on PET FDG in depressed subjects claimed that normalized glucose metabolism in the right temporal lobe was lower in the depressed group when compared to control subjects.

The aforementioned studies were all performed on younger subjects with major depression, leaving open the question of what physiological changes (i.e., changes in cerebral glucose metabolism and blood flow) occur in subjects with late-life depression. In a study using the xenon-133 inhalation technique to examine cortical blood flow in a sample composed of elderly and young subjects with major depressive disorder, Sackheim *et al.* (10) demonstrated that in their depressed group reductions in blood flow were observed in the frontal, temporal, parietal, and occipital lobes. In addition, they commented that the magnitude of reductions in blood flow in depressed subjects was comparable to that observed (41) in subjects with DAT and cerebrovascular disease. In a recent study examining regional cerebral blood flow using PET (42) in another sample consisting of both elderly and younger depressed subjects, the investigators suggested that blood flow in the anterior cingulate and dorsolateral prefrontal cortex was significantly lower in the depressed group when compared to the control group. Gonzalez *et al.* (43) in a resting FDG PET study of five subjects with late-onset depression reported that absolute rCMRglc was increased in the right orbitofrontal and temporal lobes in their depressed subjects when compared to healthy controls. The lower mean age of the depressed subjects (57 ± 5.4 vs. 71.2 ± 5.6 years) and the late age of onset of the illness in that study make a direct comparison between their study and ours less relevant. The possibility, however, remains that there are several metabolic profiles in subjects with major depressive disorder, with the subject's age and age of onset of illness serving as important discriminating features between subgroups. Both

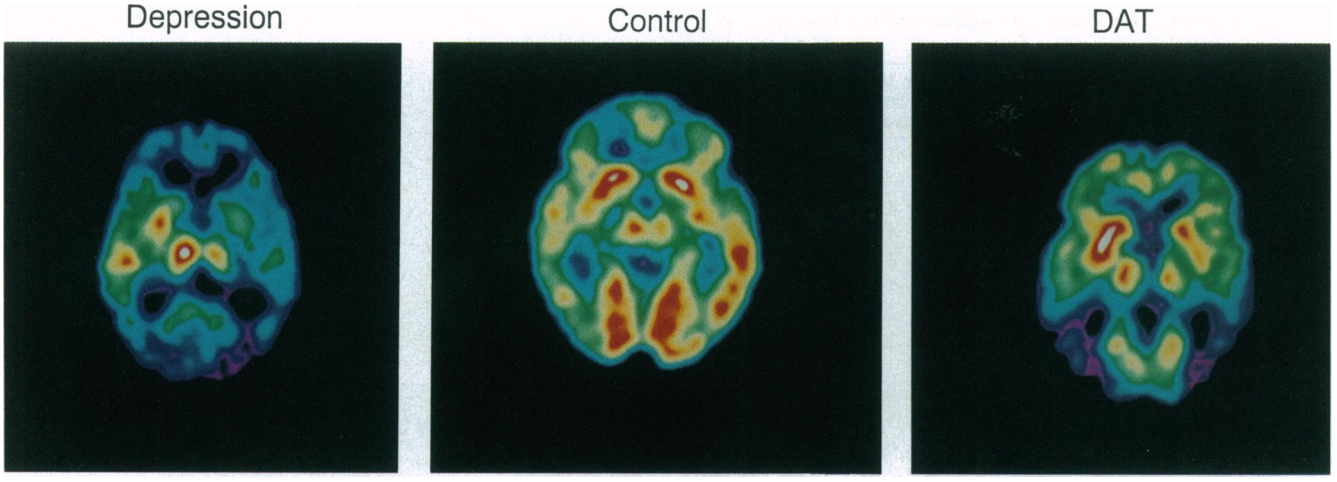

FIG. 2. 18 FDG uptake in the cortical and subcortical regions at the level of the basal ganglia in late-life depression, DAT, and an age-matched control. Orange and red show areas of high FDG uptake; green and blue represent regions with low FDG uptake. The right side of the image represents the left side of the brain and vice versa. Note the widespread decline in FDG uptake that occurs in late-life depression and DAT relative to the control.

the xenon-133 inhalation technique and SPECT studies using Tc-HMPAO have technical limitations that limit the scope of these studies. The xenon-133 technique examines only cortical flow and leaves unanswered the role of subcortical and mesial structures in the pathophysiology of depression. Tc-HMPAO SPECT, as currently used, examines normalized (region/whole brain) uptake of the radiotracer in various brain regions. In clinical states where the physiologic dysfunction may be global, examining such normalized relative measures of tracer uptake may fail to show differences between groups. This limitation could result in erroneous biological conclusions being drawn about the disease state that is examined.

Subjects with stroke and neurodegenerative conditions such as Parkinson disease and Huntington disease often develop a superimposed major depressive disorder (14, 15, 44). It has been demonstrated using ^{18}FDG PET that subjects with Parkinson disease and depression show significant decrements in normalized glucose metabolic rates in the orbitofrontal region and caudate nucleus when compared to controls and Parkinson subjects without depression (14). Subjects with Huntington disease and depression also demonstrated an additional decline in normalized glucose metabolism in the orbitofrontal/prefrontal regions when compared to subjects without depression (15). Our finding of hypometabolism in the basal ganglia and the orbital and prefrontal regions suggests that the basal ganglia-paralimbic frontal cortex pathway (45) may be one of the pathways that is dysfunctional in late-life depression (15). However, while a "focal" dysfunction may mediate depressive symptoms in neurodegenerative conditions such as Parkinson disease and Huntington disease, the pathophysiology of depression in these specific "organic mood states" (14, 15, 24, 44) is likely to be more focal and less widespread than those responsible for major depressive disorder unassociated with any specific organic condition.

The early imaging studies in DAT reported relatively focal abnormalities in glucose metabolism and blood flow in DAT when compared to healthy controls (16, 17, 46). The more recent PET studies using high-resolution scanners demonstrate widespread metabolic dysfunction, even in the relatively early stages of the disease (13). However, the metabolic dysfunction in DAT is heterogenous, with the temporal and parietal lobes showing much greater metabolic decrements than the primary sensory and occipital areas (13). While the magnitude of the metabolic decline, in our sample of depressed subjects, is comparable to the DAT group, this pattern of widespread hypometabolism in major neocortical and subcortical regions with no preferential involvement of any particular region is similar to the glucose metabolic pattern recently reported in Parkinson disease (47).

Major depressive disorder, especially in the elderly, often presents with diverse clinical features that include somatic symptoms and cognitive disturbances in addition to the more classical neurovegetative signs and symptoms of the disorder (1, 2, 48). While no specific neuropathological correlates of late-life depression have been reported, neurochemical aberrations are widely believed to mediate the clinical and biologic changes described in depressive illness (49, 50). In addition, the neurochemical underpinnings of depressive illness are believed to involve alterations in multiple neurotransmitter systems such as the noradrenergic, serotonergic, dopaminergic, and neuropeptide systems. These neurochemical systems have widespread distribution in the neocortical, subcortical, and paralimbic regions of the brain (49, 50). Further, it has been suggested that specific neural networks, rather than discrete anatomical regions, may be responsible for mediating complex psychological functions in animals and humans (10, 51). It is therefore likely that in a disease state such as major depression, characterized by diverse psychological and neurochemical aberrations, multiple neural networks are dysfunctional and responsible for the eventual clinical picture. Our finding of widespread neocortical, paralimbic, and subcortical involvement in late-life depression is consistent with the observations that suggest aberrations in multiple neural circuits and neurochemical systems in the brain in depressive illness.

There are a few limitations of our study that need to be clarified. Our patient sample is relatively small, and while our findings are robust enough to be statistically significant even with our small sample, there is clearly need to replicate our findings using a much larger sample. Three of our depressed subjects had well-controlled hypertension at the time of the scan. Although essential hypertension has been shown to reduce glucose metabolism globally in the brain (52), two of our control subjects also had well-controlled hypertension, thereby reducing the possibility that the differences in rCMRglc between groups is the result of hypertension. Five of the eight depressed subjects were free of psychotropic medication for at least 1 week prior to the scan and the other three did not receive any psychotropic medication 72 h preceding the study. Although the delayed effects of medication on rCMRglc cannot be ruled out, we consider it extremely unlikely, given our wash-out period and the relatively short half-life of the benzodiazepine used, that medication effects

are primarily responsible for the decline in rCMRglc observed in our depressed sample.

In conclusion, these data demonstrate widespread metabolic dysfunction in our sample of subjects with late-life depression comparable to the decline in rCMRglc observed in subjects with mild-moderate DAT. The next step would be to extend this study to a larger sample of subjects to identify subgroups with distinct patterns of glucose metabolism. In addition, studies using larger samples will help us examine the relationship between glucose metabolic decline and important measures such as specific cognitive indices and age of onset of illness. Such studies will help elucidate the physiology–behavior relationship that underlies major depression in the elderly.

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