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Longitudinal Studies of Cerebral Glucose Metabolism in Late-Life Depression and Normal Aging

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Abstract

Objective—Late-life depression (LLD) has a substantial public health impact and is both a risk factor for and prodrome of dementia. Positron Emission Tomography (PET) studies of cerebral glucose metabolism have demonstrated sensitivity in evaluating neural circuitry involved in depression, aging, incipient cognitive decline and dementia. The present study evaluated the long term effects of a course of antidepressant treatment on glucose metabolism in LLD patients.

Methods—Nine LLD patients and 7 non-depressed control subjects underwent clinical and cognitive evaluations as well as brain magnetic resonance imaging and PET studies of cerebral glucose metabolism at baseline, after 8 weeks of treatment with citalopram for a major depressive episode (patients only), and at an approximately 2 year follow-up.

Results—The majority of LLD patients were remitted at follow-up (7/9). Neither patients nor controls showed significant cognitive decline. The patients showed greater increases in glucose metabolism than the controls in regions associated with mood symptoms (anterior cingulate and insula). Both groups showed decreases in metabolism in posterior association cortices implicated in dementia.

Conclusions—Longitudinal changes in cerebral glucose metabolism are observed in controls and LLD patients without significant cognitive decline that are more extensive than the decreases in brain volume. Longer duration follow-up studies and the integration of other molecular imaging methods will have implications for understanding the clinical and neurobiological significance of these metabolic changes.

Keywords

late-life depression; cerebral glucose metabolism; PET; citalopram; aging

Introduction

Late-life depression (LLD) has substantial public health impact given its association with serious disability, completed suicide, and mortality in medically ill elderly (Alexopoulos et

al. 1996, Henriksson et al. 1995, Conwell et al. 1996). Despite effective antidepressant agents, developed for younger people, more than half of patients with LLD are partial responders or treatment refractory (Dew et al. 1997). Cognitive impairment is also a frequent feature of LLD and often persists after improvement in mood symptoms (Alexopoulos et al. 1993, Alexopoulos, Young & Meyers 1993, Bhalla et al. 2006). Furthermore, substantial evidence suggests LLD is both a risk factor for and a prodrome of dementia, approximately doubling the risk of subsequent Alzheimer's dementia (AD; Jorm 2001, Ownby et al. 2006).

Functional neuroimaging studies, particularly positron emission tomography (PET) studies of cerebral glucose metabolism, are sensitive to detecting changes in neural circuitry associated with mid-life depression and antidepressant response, as well as with normal aging, cognitive impairment and dementia vulnerability (Smith et al. 2009b, Smith et al. 2009a, Diaconescu et al. 2011, Mayberg et al. 2000, Reiman et al. 1996). Thus, such studies are a logical focus for understanding changes in neural circuitry underlying affective symptom response and cognitive decline in LLD (Smith et al. 2009b, Smith et al. 2009a, Diaconescu et al. 2011). In unmedicated LLD patients, relative to age matched controls, cerebral glucose metabolism was increased in anterior (right and left superior frontal gyrus) and posterior (precuneus, inferior parietal lobule) cortical regions (Smith et al. 2009b). These metabolic increases correlated with greater depression and anxiety symptoms and were observed in regions demonstrating cerebral atrophy.

With respect to the effects of antidepressant treatment on cerebral metabolism, studies in LLD observed decreased anterior cortical and limbic and increased posterior cortical metabolism with antidepressant interventions, including selective serotonin reuptake inhibitors (SSRIs) and total sleep deprivation (Smith et al. 2009a, Diaconescu et al. 2011, Smith et al. 2002a, Smith et al. 2002b). With respect to neural networks associated with improvement of affective and cognitive symptoms in LLD, a subcortical-limbic-frontal network was associated with improvement in affect (mood and anxiety), while a medial temporal-parietal-frontal network was associated with improvement in cognition (immediate verbal learning/memory and verbal fluency; Diaconescu et al. 2011).

The prior work has measured changes in glucose metabolism in response to a relatively short antidepressant course (e.g. 2-3 months). In the present study, clinical and neuropsychological assessments, PET scans of cerebral glucose metabolism, and magnetic resonance (MR) imaging studies of brain volumetric alterations were obtained in LLD patients and controls prior to treatment and repeated about 1.5 to 2.5 years after initial treatment. The primary questions addressed by this study were: 1) to what extent are longitudinal changes in cerebral glucose metabolism similar in LLD compared to normal aging; and 2) does antidepressant treatment/depressive symptom remission affect longitudinal changes in cerebral glucose metabolism in LLD compared to normal aging?

Methods

Subject Screening and Selection

Both LLD patients and healthy, non-depressed control subjects underwent psychiatric evaluation including a structured clinical interview (First et al. 1995), laboratory testing (including complete blood count, chemistry, glucose level, thyroid function tests, and toxicology screening), and a brain MR scan (GE 1.5T Magnetom Vision) prior to the PET scans. A single spoiled gradient-recalled echo (SPGR) MR pulse sequence was used for the volumetric analyses (TE=5, TR=24, flip angle=20 degrees, NEX=1, 1.5mm slice thickness; Johnson et al. 1993, Smith et al., 2009b).

In the original study, 16 adults age 60 and older who met DSM-IV criteria for current major depressive episode were enrolled (Diaconescu et al. 2011). Thirteen control subjects not meeting DSM-IV criteria for current or past Axis I psychiatric disorders were also enrolled. Exclusion criteria were: past or current neurological disorder, other Axis I psychiatric disorder (including substance abuse), lack of medical stability (including diabetes requiring insulin and uncontrolled hypertension), and use of a centrally acting medication or supplement within the past 2 weeks (including beta blockers, benzodiazepines, antihistamines, and cold medications). Six of the LLD patients had never been treated with any psychotropic medications. Of the remaining 3 patients, two received sertraline prior to study entry (treatment ended from 6 months to 2 years prior to study enrollment). The third patient received nortriptyline for 2 years up until 2 weeks prior to the PET scan (with undetectable plasma nortriptyline concentration at that time). None of the patients previously received citalopram.

Subjects underwent PET scans of cerebral glucose metabolism on 2 consecutive days after infusion of either placebo (250ml of saline) or citalopram (40mg of the drug diluted in 250ml saline) over 60 minutes (Smith et al. 2009a). Patients then began a 12 week treatment trial with flexibly dosed oral citalopram. After 8-10 weeks of treatment, patients underwent repeat cognitive testing and a PET scan of cerebral glucose metabolism. About 1.5 to 2.5 years after completion of the initial study, depressed patients and controls were re-contacted for follow-up clinical, neuropsychological, and neuroimaging evaluations. After complete description of the study to potential subjects, written informed consent was obtained according to procedures established by the Institutional Review Board and Radiation Safety Committee of the North Shore-Long Island Jewish Health System.

Neuropsychological Assessment

The neuropsychological battery included tests sensitive to detecting differences between depressed patients and non-depressed controls, as well as tests sensitive to mild cognitive impairment or dementia (Kramer-Ginsberg et al., 1999; Lockwood et al., 2000). The battery was designed to assess specific cognitive domains (psychomotor speed, executive function, verbal and spatial memory, verbal fluency). Data are shown for global cognitive measures (Mini Mental State Examination [MMSE; Folstein, Folstein & McHugh 1975], Dementia Rating Scale [DRS; Mattis 1976]) and representative measures most sensitive to change in prior studies (e.g. Diaconescu et al. 2011) including California Verbal Learning Test (CVLT; Delis et al. 1988) and Controlled Oral Word Association Test (COWAT; Benton and Hamsher 1978).

PET Imaging Procedures

PET scans were performed using a GE Advance Tomograph in the Center for Neurosciences, Feinstein Institute for Medical Research, as described previously (Smith et al. 2009b, Smith et al. 2009a, Diaconescu et al. 2011). Five mCi of [18F]-2-deoxy-2-fluoro-D-glucose ([18F]-FDG) was injected as an intravenous bolus. During the uptake interval, subjects sat in a darkened, quiet room with eyes open and ears unoccluded. Twenty-five minutes after radiotracer injection, subjects were positioned in the scanner. A 10 minute transmission scan and a 5 minute two-dimensional emission scan were acquired first to perform photon attenuation correction. A three-dimensional emission scan began at 40 minutes after radiotracer injection and lasted for 10 minutes. At the end of the PET scan, subjects were removed from the scanner and the intravenous lines were removed. Subjects were then debriefed as to their perceptions of the study.

Data and Image Analysis

Glucose metabolic rates were calculated (in ml/100g/min) on a voxel-wise basis according to validated methods (Takikawa et al. 1993). PET data processing was performed on the quantitative glucose metabolism images using the statistical parametric mapping program (SPM5, Institute of Neurology, London). This is a data-driven analytic approach that performs statistical tests on each voxel in the image. The images were smoothed with an isotropic Gaussian kernel (full width at half maximum [FWHM] 8mm for all directions). The glucose metabolic rates were normalized by scaling to a common mean value (50) across all scans, after establishing that the global means did not differ significantly between and within groups at each time point ($p > 0.05$). The data were normalized to a global mean because of the greater test-retest variability for absolute compared to relative glucose metabolism observed in numerous studies (e.g. Bartlett et al. 1988). For the PET data, two different analyses were performed using the flexible factorial option in SPM5. First, a within subject comparison for baseline and follow-up conditions (baseline/follow-up, and post-treatment/follow-up for the patients) was performed for the control and depressed groups, separately. Second, a between group comparison (control subjects versus depressed) of the longitudinal change (baseline/follow-up and post-treatment/follow-up for the patients compared to baseline/follow-up for the controls) was performed to evaluate whether the change in cerebral glucose metabolism differed over time in the patients (in the baseline untreated and treated states) compared to the controls. To control for multiple comparisons, both a probability level and cluster size were used to limit the significant regional differences reported. Comparisons were considered significant at t threshold greater than 3.51 ($z > 2.98$, $p < 0.00288$; uncorrected for multiple independent comparisons) and a cluster size greater than 50 voxels (uncorrected for multiple independent comparisons). The MR data were analyzed using voxel based morphometry (VBM) as described previously (Smith et al. 2009b). The results for cerebrospinal fluid (CSF) and grey matter are reported given that increased CSF between groups is most likely to contribute to differences in the PET data due to partial volume effects.

Results

Clinical and Neuropsychological Data (Table 1)

Of the original subjects enrolled, 9 patients and 7 controls participated in the longitudinal follow-up. There were no statistically significant differences ($p > 0.05$) in demographic characteristics between the subjects who participated in the longitudinal follow-up study compared to those who did not including: age, MMSE score, and Hamilton Depression Rating Scale (HDRS; Hamilton 1960). Table 1 shows characteristics of patients and control subjects who participated in the longitudinal follow-up study. The patients and controls did not differ significantly in age as well as MMSE and DRS scores when comparing the scores at baseline or follow-up or the change over time between groups ($p > 0.05$). Other cognitive measures did not show a significant difference over time in either group between baseline and post-8 week treatment and long term follow-up ($p > 0.05$). The data for the MMSE, DRS, CVLT and COWAT are shown in Table 1. Controls did not differ significantly over time in HDRS, whereas patients showed a significant decrease in HDRS between baseline compared to both post-8 week treatment and follow-up, but not between post-8 week treatment and follow-up. After 8 weeks of citalopram treatment, 8 of 9 patients met criteria for response (showed greater than a 50% reduction in HDRS) and 7 of 9 patients met criteria for response at 2 year follow-up. Six patients continued citalopram treatment throughout the follow-up period (including the 2 patients meeting depression criteria). Except for the 6 patients still taking citalopram, both patients and controls were psychotropic medication free at follow-up (including antidepressants and benzodiazepines) as confirmed by toxicology

testing. Mean serum citalopram concentration in the six patients who continued treatment to 2 year follow-up was 146.5 ± 71.5 ng/ml (35.5 - 243.6), indicating adherence to treatment.

Neuroimaging data—Results of the comparison of baseline to follow-up in the controls, baseline and post-8 week treatment to follow-up in patients, and comparisons of change between the controls and patients from baseline and post-8 week treatment to follow-up in patients and baseline to follow-up in controls are shown in Tables S1 through S5 (Supplemental data).

Changes in brain volumes in LLD and controls—The VBM analysis (data not shown) revealed baseline increased CSF and decreased grey matter in the left precuneus in controls compared to LLD patients. For the longitudinal comparisons, increased CSF and decreased grey matter were observed in controls in the left anterior cingulate gyrus (BA 32), left middle frontal gyrus and right insula. In LLD patients, increased CSF and decreased grey matter were observed in the right inferior frontal gyrus and right cerebellum.

Cerebral glucose metabolism at follow-up relative to baseline in controls

(Table S1)—Increases in metabolism were observed in the thalamus (bilateral) and cerebellum (tonsil and culmen, bilateral and left, respectively). Decreases in metabolism were observed in mainly right cortical regions (except the left anterior cingulate [BA 23]), including frontal (superior, middle and inferior frontal gyri), temporal (superior and middle temporal gyri), parietal (posterior cingulate gyrus and inferior parietal lobule) and occipital (cuneus and inferior occipital gyri [bilateral]) and caudate (bilateral).

Cerebral glucose metabolism at follow-up relative to pre-treatment baseline in LLD patients (Table S2)

—Increases in metabolism were observed in the left medial frontal gyrus, left superior temporal gyrus, parietal (bilateral superior parietal lobule, left postcentral gyrus) and occipital cortical regions (left superior and bilateral middle occipital gyri and left cuneus) and cerebellum (bilateral declive). Decreases in metabolism were observed in the following cortical regions bilaterally: superior frontal gyri, precentral gyri, insula, middle and inferior temporal gyri, posterior cingulate gyri and supramarginal gyri as well as the right putamen and left thalamus.

Cerebral glucose metabolism at follow-up relative to post-8 week citalopram treatment in LLD patients (Table S3)

—Increases in metabolism were observed in the right anterior cingulate gyrus (BA 24), left precentral gyrus, bilateral insula, bilateral superior temporal gyrus, left postcentral gyrus, left inferior parietal lobule, left cuneus and left cerebellum (tonsil and culmen). Decreases in metabolism were observed in the frontal cortex (bilateral superior frontal gyri, right medial frontal gyrus, and bilateral inferior frontal gyri), bilateral temporal cortex (middle and inferior temporal gyri), right parietal cortex (precuneus, posterior cingulate gyrus), left occipital cortex (superior and inferior occipital gyri) and bilateral putamen and thalamus.

Differences between LLD patients relative to controls in the follow-up cerebral metabolism compared to baseline (pre-treatment; Table S4)

—Greater decreases in controls than patients were observed in the bilateral middle frontal gyri, left precentral gyrus, bilateral inferior parietal lobule, right middle temporal gyrus, right postcentral gyrus, and right cuneus.

Greater increases in patients than controls were observed in the bilateral anterior cingulate gyrus (BA 24), bilateral medial frontal gyrus, left superior temporal gyrus, left angular gyrus, left postcentral gyrus, right superior parietal lobule, left cuneus, left middle occipital

gyrus, left cerebellum (declive) and left thalamus. Greater **decreases** in patients than controls were observed in the bilateral inferior temporal gyri, left posterior cingulate gyrus, left supramarginal gyrus, and right thalamus.

Differences between LLD patients relative to controls in the follow-up cerebral metabolism compared to baseline (post-8 week treatment; Table S5)—Greater **increases** in controls relative to patients were observed in left superior and inferior parietal lobule and left cerebellum (culmen). Greater **decreases** in controls than patients were observed in the right superior frontal gyrus, left middle frontal gyrus, bilateral superior temporal gyri, right precuneus, right supramarginal gyrus, right cuneus and left cerebellum (declive).

Greater **increases** in patients than controls were observed in the left anterior cingulate gyrus (BA 23), left insula, bilateral angular gyrus, left cerebellum (tonsil). Greater **decreases** in the patients than controls were observed in the bilateral middle temporal gyri, right inferior temporal gyrus, left middle occipital gyrus, left caudate, bilateral putamen and right thalamus.

Discussion

As a group, the LLD patients and controls studied did not show significant cognitive decline or change in depressed mood approximately 2 years after the initial study. In contrast, changes in metabolism were observed in patients and controls. The changes in metabolism were more extensive than the changes in brain structure. In elderly controls, the primary findings are lateralized cortical decreases in glucose metabolism in the right hemisphere including frontal, anterior and posterior cingulate regions and increases in occipital cortex, thalamus and cerebellum. The areas of decrease include both primary sensory areas, as well as association areas. These findings are consistent with some studies reporting decreases in cerebral metabolism in the normal aging process, though other studies have reported no change (Ibanez et al. 2004). The areas of decreased metabolism overlap with frontal areas affected in normal aging, as well as temporal and parietal (including posterior cingulate) areas affected in mild cognitive impairment (MCI) and AD.

For LLD patients, two analyses were performed. In the first analysis, the pretreatment depressed state was compared to the 2 year follow-up (at which time most patients were in the remitted state and on medication). The second analysis compared cerebral metabolism after 8-10 weeks of citalopram treatment to the effects of long term treatment/remission. This analysis addresses the changes in brain function that occurred in a group of patients, the majority of whom were remitted for 2 years. In the patients, comparing metabolism at follow-up to metabolism in the baseline depressed state both increases and decreases in metabolism were observed. Increases in metabolism were observed in medial frontal, superior temporal, postcentral and superior and middle occipital gyri. Decreases were observed in regions including the superior frontal, middle and inferior temporal, posterior cingulate, precentral and supramarginal gyri, insula, putamen and thalamus. It is important to note that many of the regions that showed decreases in metabolism are regions that are hypermetabolic before the start of antidepressant treatment and that decreases in metabolism in these regions are associated with improvement of depressive symptoms. As most of the patients were remitted at the time of scanning, the decreases in metabolism relative to the untreated baseline probably reflect persistent remission of depressive symptoms at two year follow-up.

Comparing metabolism at follow-up to metabolism after 8 weeks of citalopram treatment, a similar pattern of increases and decreases was observed with some exceptions. The baseline

condition in this comparison is cerebral metabolism after citalopram treatment in which metabolism is reduced relative to pre-treatment metabolism. The right anterior cingulate (BA 24) and bilateral insula (areas affected by antidepressant treatment) show an increase, despite the fact that the majority of patients were still remitted at the time of follow-up scanning. To address the possibility that the persistent increases in metabolism were due to the 2 LLD patients who had increased HDRS scores at follow-up, a correlation between changes in metabolism and HDRS scores from both baseline and post-8 week treatment to 2 year follow-up was performed. These analyses showed that the increase in the insula, not the anterior cingulate, was correlated with less improvement in HDRS score (data not shown).

Both patients and controls demonstrated longitudinal decreases in metabolism in frontal, temporal and parietal cortical areas. The patients showed relatively greater decreases in temporal and parietal cortices and subcortical regions. The patients also showed greater increases in cortical regions associated with mood symptoms (anterior cingulate and insula) than the controls. The controls showed relatively greater decreases in frontal regions associated with normal aging, as well as parietal cortical regions. As noted previously, both the controls and LLD patients did not show evidence of significant decline in cognition during the follow-up interval. To evaluate whether the changes in these regions are associated with subsequent cognitive decline, further longitudinal follow-up is needed.

The longitudinal functional neuroimaging studies in LLD are limited. A single photon emission computed tomography (SPECT) study of 10 treated LLD patients showed decreased depressive symptoms (HDRS), stable global cognition (MMSE), and increases in perfusion in the right cingulate gyrus, similar to the present study (Halloran et al. 1999). Another SPECT study showed normalization of frontal hypoperfusion relative to controls at 12 month remission in LLD patients who received antidepressant medications or electroconvulsive therapy (Navarro et al. 2002, 2004). In the current study, frontal metabolism in patients is normalized relative to controls, but is decreased rather than increased, because the patients showed increased baseline metabolism.

Several limitations of the study should be acknowledged. Because of the limited sample size and high remission rate among the patients studied, it was not possible to compare changes in cerebral metabolism between patients who had remitted to the 2 patients who had relapsed or to compare patients who were treated versus those who were not treated. Some variables that are associated with cognitive decline, such as ApoE genotype, were not evaluated. The unique aspects of the study include the fact that the patients were treated with either citalopram or were not treated with psychotropic drugs as opposed to a variety of medications and that clinical, cognitive and multi-modality neuroimaging methods were performed longitudinally.

Conclusions

In summary, both LLD patients (most of whom were treated and remitted at longitudinal follow-up) and controls showed decreases in glucose metabolism in posterior association cortices implicated in dementia. More extensive increases in metabolism were observed in LLD patients than controls in anterior cortical regions (anterior cingulate and insula). Irrespective of whether patients were in a treated or untreated state at follow-up, the pattern of changes remained similar. Thus, despite the increase in serotonin concentrations produced by the SSRI (which may not be sustained over two years), metabolism increased in anterior regions. Another neurobiological mechanism may explain this finding (e.g. beta-amyloid deposition, brain inflammation and glutamate [Smith et al. 2007]). The change in cerebral glucose metabolism in both groups was observed without significant cognitive decline based

on the global and domain specific cognitive assessments performed in the study and are also more extensive than the changes in cerebral atrophy observed.

Future directions include performing a longer term follow-up using multi-modality neuroimaging methods to determine changes in brain structure and function that accompany cognitive decline in LLD. The present findings support future molecular imaging studies of specific mechanisms of pathophysiology implicated in both mood disorders and dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Despite a lack of significant cognitive decline, longitudinal changes in cerebral glucose metabolism are observed in non-depressed controls and LLD patients that are more extensive than the decreases in brain volume.
- LLD patients showed greater longitudinal increases in glucose metabolism than the controls in regions associated with mood symptoms (anterior cingulate and insula).
- Both LLD patients (most of whom were treated and remitted at longitudinal follow-up) and controls showed decreases in glucose metabolism in posterior association cortices implicated in dementia.
- Longer duration follow-up studies and the integration of other molecular imaging methods will have implications for understanding the clinical and neurobiological significance of these metabolic changes.

Table 1
Subject Characteristics (mean $\pm$ standard deviation)

	Baseline Age (yrs)	Follow-Up Interval (yrs)*	HDRS Baseline	HDRS Post-8 Week Treatment	HDRS 2 Year Follow-Up
Controls Range	72 $\pm$ 6	2.5 $\pm$ 0.2 (2.3 - 2.9)	0.4 $\pm$ 0.8 (0 - 2)		0.7 $\pm$ 0.9 (0 - 2)
Patients range	68 $\pm$ 8	1.9 $\pm$ 0.3 (1.5 - 2.5)	25.1 $\pm$ 2.7 (21 - 30)	5.9 $\pm$ 4.7 (0-12)	7.4 $\pm$ 7.9 (1 - 23)

	Response / Non-Response Post-8 Week Treatment	Sustained Response / Relapse at 2 Year Follow-Up	Treated / Untreated at 2 Year Follow-Up
Patients	8 / 1	7 / 2	6 / 3

	MMSE Baseline	MMSE Post-8 Week Treatment	MMSE 2 Year Follow-Up	DRS Baseline	DRS Post-8 Week Treatment	DRS 2 Year Follow-Up
Controls	28.9 $\pm$ 0.9	28.8 $\pm$ 1.0	28.8 $\pm$ 1.0	137.6 $\pm$ 3.9	138.8 $\pm$ 3.4	141.7 $\pm$ 1.6
Patients	28.8 $\pm$ 1.0	29.2 $\pm$ 1.3	29.4 $\pm$ 0.9	141.7 $\pm$ 2.9	141.9 $\pm$ 1.7	141.3 $\pm$ 3.3

	CVLT Trials 1 – 5 Baseline	CVLT Trials 1 – 5 Post-8 Week Treatment	CVLT Trials 1 – 5 2 Year Follow-Up	COWAT Baseline	COWAT Post-8 Week Treatment	COWAT 2 Year Follow-Up
Controls	42.9 $\pm$ 9.8	47.3 $\pm$ 13.8	50.7 $\pm$ 13.3	37.7 $\pm$ 12.1	44.3 $\pm$ 14.6	38.4 $\pm$ 15.1
Patients	46.6 $\pm$ 7.3	52.2 $\pm$ 7.2	50.6 $\pm$ 8.1	39.1 $\pm$ 7.8	40.7 $\pm$ 7.9	46.8 $\pm$ 11.9

* Difference significant $p < 0.05$

HRDS: Hamilton Depression Rating Scale, MMSE: Mini-Mental State Examination, DRS: Dementia Rating Scale, CVLT: California Verbal Learning Test, COWAT: Controlled Oral Word Association Test