

2014

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## Recommended Citation

Marano C, Workman C, Lyman C, Kramer E, Hermann C, Ma Y, Dhawan V, Chaly T, Eidelberg D, Smith G. The relationship between fasting serum glucose and cerebral glucose metabolism in late-life depression and normal aging. . 2014 Jan 01; 222(1-2):Article 1073 [p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/1073>. Free full text article.

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Published in final edited form as:

*Psychiatry Res.* 2014 April 30; 222(0): 84–90. doi:10.1016/j.psychres.2014.01.009.

## The relationship between fasting serum glucose and cerebral glucose metabolism in late-life depression and normal aging

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### Abstract

Evidence exists for late-life depression (LLD) as both a prodrome of and risk factor for Alzheimer's disease (AD). The underlying neurobiological mechanisms are poorly understood. Impaired peripheral glucose metabolism may explain the association between depression and AD given the connection between type 2 diabetes mellitus with both depression and AD. Positron emission tomography (PET) measures of cerebral glucose metabolism are sensitive to detecting changes in neural circuitry in LLD and AD. Fasting serum glucose (FSG) in non-diabetic young (YC; n=20) and elderly controls (EC; n=12) and LLD patients (n=16) was correlated with PET scans of cerebral glucose metabolism on a voxel-wise basis. The negative correlations were more extensive in EC versus YC and in LLD patients versus EC. Increased FSG correlated with decreased cerebral glucose metabolism in LLD patients to a greater extent than in EC in heteromodal association cortices involved in mood symptoms and cognitive deficits observed in LLD and dementia. Negative correlations in YC were observed in sensory and motor regions. Understanding the neurobiological consequences of diabetes and associated conditions will have substantial public health significance given that this is a modifiable risk factor for which prevention strategies could have an important impact on lowering dementia risk.

### Keywords

late-life depression; fasting blood glucose; FDG PET; normal aging; insulin resistance

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## 1. Introduction

Late-life depression (LLD) has a substantial public health impact given its association with serious disability, completed suicide, and mortality in the medically ill elderly (Henriksson et al., 1995; Alexopoulos et al., 1996; Conwell et al., 1996). Cognitive impairment is a common feature of LLD and often persists after mood symptom remission (Alexopoulos et al., 1993; Alexopoulos et al., 1993; Bhalla et al., 2006). Furthermore, substantial evidence suggests LLD is both a risk factor for and a prodrome of dementia. A meta-analysis estimated that depression doubles the risk of subsequent Alzheimer's disease (AD) (Ownby et al., 2006). However, the mechanisms linking LLD to cognitive impairment and dementia are poorly understood. Ultimately, understanding these mechanisms will allow for the identification of individuals with LLD at increased risk for subsequent cognitive decline and identification of treatment targets to prevent or delay transition to dementia.

Abnormal glucose metabolism may represent a mechanistic link between LLD and dementia (Rasgon and Jarvik, 2004). Individuals with type 2 diabetes mellitus (DM) have elevated rates of AD and vascular dementia (Schmidt et al., 1992; Pasquier et al., 2006). Depression approximately doubles the risk for future development of type 2 DM (Eaton et al., 1996). Though hyperglycemia defines DM, hyperglycemia is not an immediate feature of insulin resistance, which is the underlying pathophysiologic abnormality of type 2 DM. When an individual develops insulin resistance, the pancreas initially increases insulin production to maintain euglycemia. Ultimately, insulin resistance overwhelms the compensatory insulin response and hyperglycemia develops. Insulin resistance is a continuous process. However, diabetes and "pre-diabetes" (impaired glucose tolerance and impaired fasting glucose) are diagnosed only by measured hyperglycemia (American Diabetes Association, 2013). Of note, some depressed individuals manifest insulin resistance (Nathan et al., 1981; Menna-Perper et al., 1984; Winokur et al., 1988; Okamura et al., 2000; Hennings et al., 2010) which improves with depression treatment (Nathan et al., 1981; Okamura et al., 2000; Hennings et al., 2010; Mueller et al., 1969; Weber-Hamann et al., 2008).

Positron emission tomography (PET) studies of cerebral glucose metabolism demonstrate sensitivity to detecting changes in neural circuitry associated with depression and dementia, as well as in individuals at genetic risk for AD (Reiman et al., 1996; Mayberg et al., 2000; Smith et al., 2009a; Smith et al., 2009b; Diaconescu et al., 2011). In cognitively normal adults with "pre-diabetes" or early type 2 DM, Baker et al. showed that greater insulin resistance was associated with an AD-like pattern of reduced cerebral glucose metabolism (Baker et al., 2011). In healthy subjects (age range 47-68 years), Burns et al. reported a correlation between higher fasting serum glucose (FSG) and lower cerebral glucose metabolism in regions affected in AD. This correlation was stronger in individuals carrying the APOE 4 allele, an AD risk factor (Burns et al., 2013). Thus, even in cognitively normal subjects, higher FSG may be associated with vulnerability to AD-like changes in cerebral glucose metabolism.

The present analyses correlated FSG with cerebral glucose metabolism in non-diabetic young controls (YC) and elderly controls (EC) as well as non-diabetic LLD patients. The hypotheses tested were: 1) Increased FSG will correlate with decreased cerebral glucose

metabolism in LLD patients. The negative correlations will be observed in frontal and parietal heteromodal association cortices which are associated with mood and cognitive symptoms in LLD, and also demonstrate decreased cerebral glucose metabolism and neuropathology in AD (neurofibrillary tangles and amyloid plaques). These areas include the anterior cingulate, middle frontal, posterior cingulate, precuneus, and fusiform gyri (Smith et al., 2009b; Diaconescu et al., 2011; Arnold et al., 1991; Langbaum et al., 2009). 2) The negative correlations will be greater in the LLD patients than the EC in frontal and parietal association cortices. 3) The negative correlations will be greater in the EC compared to the YC in frontal and parietal association cortices.

## 2. Methods

### 2.1 Subject screening and selection

LLD patients, EC and YC subjects underwent psychiatric evaluation including a structured clinical interview (First et al., 1995), laboratory testing (including complete blood count, blood chemistry including screening glucose level, thyroid function tests, and toxicology screening), and brain magnetic resonance (MR) imaging scan (GE 1.5T Magnetom Vision) prior to the PET scans. The subjects were enrolled in a study to evaluate the acute effects of the antidepressant citalopram on cerebral glucose metabolism. The data for the baseline (placebo) PET scans in the LLD patients and controls have been published previously (Smith et al., 2009a; Smith et al., 2009b; Goldberg et al., 2004).

The sample included 16 older adults who met DSM-IV criteria for current major depressive episode as well as 20 YC and 12 EC subjects who did not meet DSM-IV criteria for current or past Axis I psychiatric disorders (as shown in Table 1). None of the participants had a prior diagnosis of diabetes mellitus or screening laboratory values consistent with diabetes mellitus (i.e. random blood glucose  $\geq 200$  mg/dl, fasting blood glucose  $\geq 126$  mg/dl). Exclusion criteria were: past or current neurological disorder, other Axis I psychiatric disorder (including substance abuse), lack of medical stability (including uncontrolled hypertension), and use of a centrally acting medication or supplement within the past 2 weeks (including beta blockers, benzodiazepines, antihistamines, and cold medications). All subjects were scanned on two consecutive days after an infusion of either placebo (250ml of saline; scan 1) or citalopram (40mg of the drug diluted in 250ml saline; scan 2) over 60 minutes (Smith et al., 2009a). For the present study, only the PET scans following placebo infusions were included in the analysis, before the citalopram was administered.

Thirteen of the LLD patients had never been treated with psychotropic medications (including antidepressants and antipsychotics). Of the remaining three patients, two took sertraline prior to study entry (stopped 6 months to 2 years prior to enrollment). The third patient took nortriptyline for 2 years up until 2 weeks prior to the PET scan (at which time the plasma nortriptyline concentrations were undetectable). None of the patients took citalopram previously. After a complete study description to potential participants, written informed consent was obtained according to procedures established by the Institutional Review Board and the Radiation Safety Committee of the North Shore-Long Island Jewish Health System.

## 2.2 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., 2009a; Smith et al., 2009b; Diaconescu et al., 2011). All PET studies began at the same time of day (10 AM). Subjects were instructed not to eat after midnight the evening before the scans. Upon arrival at the PET facility, subjects received one intravenous catheter in the left arm for radiotracer infusion and a second catheter in the right arm for sampling of glucose and citalopram levels. Five mCi of [18F]-2-deoxy-2-fluoro-D-glucose ([18F]-FDG) was injected as an intravenous bolus. The FSG determined at this time was used for the correlation analyses. During the [18F]-FDG uptake interval, the subjects sat in a darkened, quiet room with eyes open and ears unoccluded. At 25 minutes after radiotracer injection, subjects were positioned in the GE Advance Tomograph. 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 40 minutes after radiotracer injection and lasted for 10 minutes. At the end of the scan, subjects were debriefed as to their perceptions of the study.

## 2.3 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. In summary, for each subject, all PET scans were realigned using a generated mean image (the placebo scan 1 was used for the analyses in this article). The PET scans were normalized to the SPM5 PET template in Montreal Neurological Institute (MNI) space and then smoothed with an isotropic Gaussian kernel (full width at half maximum 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)). Voxel-wise correlations between FSG and cerebral glucose metabolism were performed for the EC, EC and LLD patients separately using the one sample t-tests option with FSG as a covariate in SPM5. Then, the correlations were compared between groups with the two-sample t-test option with FSG as a covariate. Representative design matrices for the two analysis methods are provided as supplemental material. The two comparisons performed were the YC versus the EC and the EC versus LLD. To control for multiple comparisons, both probability level and cluster size thresholds were used. The comparisons were considered significant at a  $t$  threshold greater than 2.98 ( $z > 2.58$ ,  $p < 0.005$ ; uncorrected for multiple independent comparisons) and at a predetermined cluster size greater than 100 voxels.

The comparisons that were also significant at the at the uncorrected cluster level are indicated ( $p < 0.05$ ). The results were not significant when corrected for multiple

comparisons. The significance level reported was similar to recent studies that showed an association between FSG and glucose metabolism (Burns et al., 2013).

### 3. Results

#### 3.1 Subject characteristics

The demographic characteristics and FSG at the time of PET scanning for YC, EC and LLD patients appear in Table 1. The YC were significantly younger than the EC and LLD patients ( $p < 0.01$ ), but the EC and LLD patients did not differ significantly in age ( $p > 0.1$ ). The three groups did not differ significantly in years of education, FSG or body mass index (BMI) ( $p > 0.1$ ). The EC and LLD patients did not differ significantly in global cognitive function ( $p > 0.1$ ) as measured by the Mini-Mental Status Examination (MMSE) and the Dementia Rating Scale (DRS) (Folstein et al., 1975; Mattis, 1976).

Correlations of FSG with age, BMI, depressive symptoms, cognition (California Verbal Learning Test [CVLT], verbal fluency) were not significant within groups. Thus, these variables were not used in the statistical analyses. Gender was correlated with BMI in the LLD patients and with FSG in the EC only. Because a systematic relationship of gender with BMI and FSG was not observed across groups, gender was not included as a covariate.

#### 3.2 YC (Table 2a)

Positive correlations between FSG and cerebral glucose metabolism were observed in the right lingual gyrus (Brodmann area (BA) 18). Negative correlations were observed in the medial frontal gyrus (BA 6 bilaterally, left BA 10), left precentral gyrus (BA 6), right superior temporal gyrus (BA 22) and left putamen.

#### 3.3 EC (Table 2b)

Positive correlations were observed in the left middle frontal gyrus (BA 8), left medial frontal gyrus (BA 6) and left inferior parietal lobule (BA 40). Negative correlations were observed in the left anterior cingulate gyrus (BA 32), right middle frontal gyrus (BA 6), right precentral gyrus (BA 4), left superior temporal gyrus (BA 42), right posterior cingulate gyrus (BA 31) and right precuneus (BA 7).

#### 3.4 LLD Patients (Table 2c and Fig. 1)

There were no positive correlations observed in the LLD patients. Negative correlations were observed in the right medial frontal gyrus (BA 10), right inferior frontal gyrus (BA 47), left precentral gyrus (BA 6), left superior temporal gyrus (BA 42), right inferior parietal lobule (BA 40) and bilateral fusiform gyrus (BA 37).

#### 3.5 Comparison of EC versus YC (Table 3a)

Greater positive correlations in the EC than YC were observed in the right insula (BA 13), bilateral middle frontal gyrus (BA 8/6), left putamen and left inferior parietal lobule (BA 40). Greater negative correlations in the EC than YC were observed in the right inferior frontal gyrus (BA 9), right precentral gyrus (BA 4), right precuneus (BA 7) and right fusiform gyrus (BA 37).

### 3.6 Comparison of LLD Patients versus EC (Table 3b)

Greater positive correlations in the LLD patients than the EC were observed in the right postcentral gyrus (BA 3). Greater negative correlations in the LLD patients than the EC were observed in the bilateral middle frontal gyrus (BA 8), left putamen, right insula (BA 13) and left fusiform gyrus (BA 37).

## 4. Discussion

In the present study, in the YC, negative correlations between cerebral glucose metabolism and FSG were observed mainly in primary sensory (auditory cortex) and motor (pre-central gyrus and putamen) areas. A positive correlation was observed for visual association cortex and a negative correlation for middle frontal gyrus. In the EC, positive correlations were observed in medial frontal gyrus and inferior parietal lobule. Negative correlations were observed in both primary sensory (auditory) and motor cortex as well as frontal and parietal association cortices (anterior cingulate, middle frontal, posterior cingulate, and precuneus). In the LLD patients, similar to the EC subjects, negative correlations were observed in both primary sensory (auditory) and motor cortices as well as frontal and parietal association cortices (middle and inferior frontal, inferior parietal lobule and precuneus).

The results are consistent with the primary study hypotheses of greater negative correlations in frontal and parietal association cortices in EC compared to YC and LLD compared to EC. While the correlations in the YC were mainly observed in sensory and motor regions, the correlations in EC and LLD patients were observed mainly in heteromodal association cortices involved in depressive symptoms and cognitive functions (attention, memory, visuo-spatial processing) affected in LLD and AD as shown by PET studies of glucose metabolism in LLD and AD and in neuropathological studies in AD (Smith et al., 2009b; Diaconescu et al., 2011; Arnold et al., 1991). Several results were unexpected. In all groups, negative correlations in both primary sensory (auditory cortex) and motor cortex were observed. Secondly, positive correlations were observed, to a greater extent in EC than YC, in areas involved in attention and affective processing that may indicate a compensatory response. Interestingly, these positive correlations are not observed in the untreated LLD patients.

The results in EC are consistent with the findings of Burns et al (Burns et al., 2013). The investigators reported correlations between higher FSG levels and lower cerebral glucose metabolism in temporal and parietal cortical regions that show reductions in cerebral glucose metabolism in AD. In their study, the correlations were greater in APOE4 carriers than controls without an APOE4 allele. The results of the present study replicate these findings and extend these observations to YC and EC and to LLD, a condition also associated with increased risk of cognitive decline.

Importantly, study participants were not diabetic. Therefore, cerebral glucose metabolism data could be interpreted without the potential confound of significant fluctuation in FSG during the PET scan. It is noteworthy that significant associations between cerebral metabolism and FSG were obtained within this restricted range of values (highest value 113 mg/dL). Also of note, the EC and LLD patients did not meet criteria for mild cognitive

impairment or AD and performed within the normal range in dementia scales, as well as specific cognitive tests of verbal and visuo-spatial memory, attention and executive function (data not shown). Further, the cognitive tests were not correlated with FSG (data not shown).

The association between higher FSG and lower glucose metabolism in heteromodal association vulnerable areas affected in AD is consistent with the observations that diabetes and associated risk factors (e.g. hyperglycemia, hyperinsulinemia, insulin resistance) are associated with increased risk of AD (Haan, 2006). The biological mechanisms that underlie how diabetes increases the risk and accelerates the progression of AD are an active area of investigation. There are numerous potential mechanisms associated with diabetes and related conditions that could be associated with increased dementia risk (and decreased glucose metabolism). For instance, insulin resistance is directly implicated in AD pathology via both increased amyloid-beta and tau hyperphosphorylation (Craft and Watson, 2004). Furthermore, intranasal insulin is a promising potential treatment for AD as evidenced by recent clinical trials (Reger et al., 2006; Dhamoon et al., 2009; Craft et al., 2012). Other potential mechanisms include activation of mitogen activated protein kinase (MAPK) and Akt signaling pathways, inflammation and increased oxidative stress combined with increased intracellular calcium that could result in mitochondrial damage and neuronal death (for review, see (Sims-Robinson et al., 2010)).

The same two mechanisms that might explain insulin resistance-induced cognitive impairment are also the same pathophysiologies that may explain cognitive impairment in LLD, i.e. Alzheimer's and vascular pathologies. First, LLD may represent, in some cases, an AD prodrome as the first non-cognitive manifestation of Alzheimer's pathology. Second, as articulated in the vascular depression hypothesis, brain vascular disease underlies the pathophysiology of LLD including associated cognitive impairment (Alexopoulos et al., 1997; Krishnan et al., 1997). Furthermore, executive dysfunction is a frequent domain of cognitive impairment in both LLD and insulin resistance, and is associated with vascular pathology in LLD, particularly damage to frontostriatal circuits (Alexopoulos, 2001; Abbatecola et al., 2004). Thus, insulin resistance, through both vascular and Alzheimer's pathologies, may represent a modifiable mechanism underlying the increased risk of cognitive decline in LLD.

It is important to note that insulin resistance does not necessarily result in hyperglycemia, at least in its early stages. In the present study, we did not measure insulin resistance, which is a study limitation. However, significant associations between cerebral metabolism and FSG were obtained within a restricted range of FSG. Though we do not know if subjects in the study manifest insulin resistance, our findings suggest that individuals who demonstrate elevated FSG may be vulnerable to lower cerebral glucose metabolism in regions implicated in AD and cognitive status should be followed more closely.

Given that the participants in the study were not diabetic, outside of undetected insulin resistance, another possible explanation for the negative correlation between cerebral glucose metabolism and FSG in selected brain regions is that these regions may be particularly vulnerable to variations in peripheral glucose concentrations. This differential

sensitivity could have implications for areas first affected by insulin resistance mediated AD pathology, though further study is needed.

Study limitations include: the lack of APOE genotyping and the lack of additional measures of peripheral glucose metabolism (such as fasting insulin levels). Fasting insulin levels would have allowed us to estimate insulin resistance and, thus, correlate insulin resistance and cerebral glucose metabolism. APOE genotype appears to affect insulin metabolism in AD patients (Craft et al., 1999), as well as cognitive response to intranasal insulin (Reger et al., 2006). While we did not observe correlations of FSG with age, BMI, depressive symptoms or cognition (California Verbal Learning Test [CVLT], verbal fluency) within groups, the possibility still exists that the association between fasting glucose and regional metabolism is mediated by one of these variables.

Future studies will use multi-modality imaging methods with more direct measures of Alzheimer pathology (such as brain amyloid) and vascular pathology (such as MR white matter hyperintensities) as well as more sensitive measures of peripheral glucose metabolism and insulin resistance (such as the oral glucose tolerance test) to better characterize the relationship between impaired glucose metabolism, depression, and dementia. Understanding the neurobiological consequences of diabetes and associated conditions will have substantial public health significance given that this is a modifiable risk factor for which prevention strategies could have an important impact on lowering dementia risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgement

The present study was supported in part by National Institute of Health: MH 01621 (GSS), MH 49936 (GSS), MH 57078 (GSS), MH 64823 (GSS), MH M01 RR 018535 (Chiorazzi).

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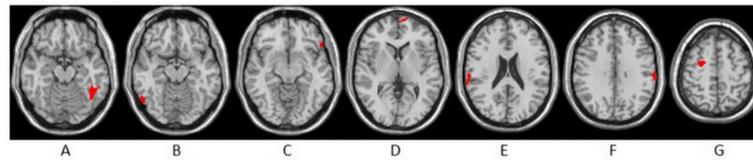
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**Figure 1.**

Negative correlation between FSG and Cerebral Glucose Metabolism in LLD Patients

A and B: Bi-lateral Fusiform Gyrus (BA 37); C: Right Inferior Frontal Gyrus (BA 47); D: Right Medial Frontal Gyrus (BA 10); E: Left Superior Temporal Gyrus (BA 42); F: Right Inferior Parietal Lobule (BA 40); G: Left Precentral Gyrus (BA 6)

**Table 1**  
**Characteristics of Young Controls, Elderly Controls, and LLD Patients (mean ± standard deviations [range])**

	Young Controls (n = 20)	Elderly Controls (n = 12)	LLD Patients (n = 16)
Age	27.9 ± 7.9	66.9 ± 7.5	65.3 ± 9.1
Sex (M/F)	9 / 11	5 / 7	6 / 10
Years of Education	16.9 ± 1.7	14.2 ± 2.9	13.8 ± 2.7
MMSE		28.8 ± 1.0	28.6 ± 1.0
HDRS		0.6 ± 0.9	26.0 ± 3.5
Fasting Serum Glucose(mg/dL)	91.6 ± 8.1 (77 – 113)	91.6 ± 7.4 (82 – 106)	91.1 ± 8.4 (76 – 110)
Number of subjects who meet ADA criteria for pre-diabetes (FSG range 100-120)	3	2	2
Body Mass Index	25.7 ± 4 (19.8 – 35.4)	25.2 ± 4 (19.5 – 29.1)	25.4 ± 5 (20.3 – 35.9)

All between group comparisons are not significant ( p > 0.1) except for the comparison of age in the young controls compared to the elderly controls and LLD patients ( p < 0.01).

**Table 2a**  
**Correlations between FSG and Cerebral Glucose Metabolism in Young Controls**

LEFT			Brain Region (BA L/R)		RIGHT			
X	Y	Z	Z-Score		X	Y	Z	Z-Score
<b>Positive Correlations</b>								
				Lingual Gyrus (BA 18)	7	-88	-15	2.95*
<b>Negative Correlations</b>								
-7	-11	66	2.91*	Medial Frontal Gyrus (BA 6)	20	7	49	3.19 <sup>†</sup> **
-3	55	7	3.02 <sup>†</sup> **	Medial Frontal Gyrus (BA 10)				
-48	-3	20	2.73	Precentral Gyrus (BA 6)				
				Superior Temporal Gyrus (BA 22)	63	-8	0	2.67
-19	7	5	2.88*	Putamen				

All comparisons reported are significant at  $p < 0.005$ ;

<sup>†</sup>  $p < 0.001$

\* significant at the cluster level (uncorrected)  $p < 0.05$

\*\* significant at the cluster level (uncorrected)  $p < 0.01$

**Table 2b**  
**Correlations between FSG and Cerebral Glucose Metabolism in Elderly Controls**

LEFT			Brain Region (BA L/R)		RIGHT			
X	Y	Z	Z-Score		X	Y	Z	Z-Score
<b>Positive Correlations</b>								
-33	25	39	2.8	Middle Frontal Gyrus (BA 8)				
-12	4	59	4.66 <sup>‡</sup>	Medial Frontal Gyrus (BA 6)				
-62	-33	36	2.93 <sup>**</sup>	Inferior Parietal lobule (BA 40)				
<b>Negative Correlations</b>								
-2	13	25	2.65	Anterior Cingulate Gyrus (BA 32)				
				Middle Frontal Gyrus (BA 6)	53	5	43	2.6
				Precentral Gyrus (BA 4)	23	-25	55	2.77
-63	-22	14	2.67	Superior Temporal Gyrus (BA 42)				
				Posterior Cingulate Gyrus (BA 31)	3	-30	30	3.80 <sup>‡*</sup>
-32	-62	45	2.57	Precuneus (BA 7)	34	-72	43	3.07 <sup>‡</sup>

All comparisons reported are significant at  $p < 0.005$ ;

<sup>‡</sup>  $p < 0.001$

\* significant at the cluster level (uncorrected)  $p < 0.05$

\*\* significant at the cluster level (uncorrected)  $p < 0.01$

**Table 2c**  
**Correlations between FSG and Cerebral Glucose Metabolism in LLD Patients**

LEFT				Brain Region (BA L/R)		RIGHT			
X	Y	Z	Z-Score			X	Y	Z	Z-Score
Negative Correlations									
-3	42	29	2.55	Medial Frontal Gyrus (BA 9/10)	7	62	13	3.19 <sup>‡</sup>	
				Inferior Frontal Gyrus (BA 47)	50	25	-2	2.81	
-27	-11	53	3.08 <sup>‡</sup>	Precentral Gyrus (BA 6)					
-64	-34	22	2.59	Superior Temporal Gyrus (BA 42)					
				Inferior Parietal Lobule (BA 40)	64	-25	32	3.72 <sup>‡</sup>	
-54	-59	-12	3.22 <sup>‡</sup>	Fusiform Gyrus (BA 37)	41	-42	-13	2.99 <sup>‡</sup>	

All comparisons reported are significant at  $p < 0.005$ ;

<sup>‡</sup>  $p < 0.001$

\* significant at the cluster level (uncorrected)  $p < 0.05$

\*\* significant at the cluster level (uncorrected)  $p < 0.01$

**Table 3a**  
**Comparison of Correlations between FSG and Cerebral Glucose Metabolism in Elderly versus Young Controls**

LEFT			Brain Region (BA L/R)		RIGHT			
X	Y	Z	Z-Score		X	Y	Z	Z-Score
<b>Greater Positive Correlations in the Elderly than Young Controls</b>								
				Insula (BA 13)	39	1	18	2.75*
-35	24	39	2.86	Middle Frontal Gyrus (BA 8/6)	28	-1	47	2.78
-24	10	7	2.78*	Putamen				
-63	-34	35	2.89	Inferior Parietal lobule (BA 40)				
<b>Greater Negative Correlations in the Elderly than Young Controls</b>								
				Inferior Frontal Gyrus (BA 9)	50	14	26	3.00 <sup>†</sup>
				Precentral Gyrus (BA 4)	56	-15	42	3.43 <sup>†</sup>
				Precuneus (BA 7)	37	-72	44	2.69
				Fusiform Gyrus (BA 37)	52	-66	0	2.91

All comparisons reported are significant at  $p < 0.005$ ;

<sup>†</sup>  $p < 0.001$

\* significant at the cluster level (uncorrected)  $p < 0.05$

\*\* significant at the cluster level (uncorrected)  $p < 0.01$

**Table 3b**  
**Comparison of Correlations between FSG and Cerebral Glucose Metabolism in Elderly Controls versus LLD Patients**

LEFT			Brain Region		RIGHT			
X	Y	Z	Z-Score	(BA L/R)	X	Y	Z	Z-Score
<b>Greater Positive Correlations in the LLD patients than Elderly Controls</b>								
				Postcentral Gyrus (BA 3)	55	-19	41	3.40 <sup>†***</sup>
<b>Greater Negative Correlations in the LLD patients than the Elderly Controls</b>								
-36	25	40	3.33 <sup>†</sup>	Middle Frontal Gyrus (BA 8)	42	31	39	2.82
-29	-20	9	3.31 <sup>†***</sup>	Putamen				
				Insula (BA 13)	36	-1	16	2.92 <sup>***</sup>
-54	-59	-12	2.78	Fusiform Gyrus (BA 37)				

All comparisons reported are significant at  $p < 0.005$ ;

<sup>†</sup>  $p < 0.001$

\* significant at the cluster level (uncorrected)  $p < 0.05$

\*\* significant at the cluster level (uncorrected)  $p < 0.01$