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Serotonin Modulation of Cerebral Glucose Metabolism in Depressed Older Adults

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Abstract

Background—Monoamine dysfunction, particularly of the serotonin system, has been the dominant hypothesis guiding research and treatment development in affective disorders. The majority of research has been performed in mid-life depressed adults. The importance of understanding the neurobiology of depression in older adults is underscored by increased rates of mortality and completed suicide and an increased risk of Alzheimer's dementia. To evaluate the dynamic response of the serotonin system, the acute effects of citalopram infusion on cerebral glucose metabolism was measured in depressed older adults and control subjects. The hypothesis was tested that smaller decreases in metabolism would be observed in cortical and limbic regions in depressed older adults relative to controls.

Methods—Sixteen depressed older adults and thirteen controls underwent two resting Positron Emission Tomography (PET) studies with the radiotracer [18F]-2-deoxy-2-fluoro-D-glucose after placebo and citalopram infusions.

Results—In controls compared to depressed older adults, greater citalopram induced decreases in cerebral metabolism were observed in the right anterior cingulate, middle temporal (bilaterally), left precuneus, and left parahippocampal gyri. Greater decreases in the depressed older adults than controls was observed in left superior and left middle frontal gyri and increases in left inferior parietal lobule, left cuneus, left thalamus and right putamen.

Conclusion—In depressed older adults relative to controls, the cerebral metabolic response to citalopram is blunted in cortico-cortico and cortico-limbic pathways and increased in the left hemisphere (greater decrease anteriorly and increases posterior). These findings suggest both blunted and compensatory cerebral metabolic responses to citalopram in depressed older adults.

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Keywords

selective serotonin reuptake inhibitors; citalopram; serotonin; Positron Emission Tomography (PET); glucose metabolism; depression; aging

Introduction

The primary neurobiological hypothesis in major depressive disorder is that of decreased monoaminergic function (norepinephrine, dopamine, and in particular, serotonin; ^{1,2}). The monoamine hypothesis has been a major focus of post-mortem and neuroimaging research. However, these studies have been performed mainly in mid-life depressed patients. The striking decline in monoamine neurotransmission with the normal aging process may underlie the higher rates of relapse and suicidality associated with major depression in late life (^{3,4,5}). Evidence from clinical, neuropsychological, and epidemiological studies demonstrates the substantial impact of depressive symptoms in late life with respect to cognitive impairment, apathy, functional disability, and mortality (⁶⁻⁹). Thus, there is a compelling need to understand the neurobiological substrates of depressive symptoms in late life (¹⁰).

To evaluate monoaminergic dysfunction in depression, neuroimaging studies have focused primarily on the serotonin system. Prior studies have measured the cerebral metabolic response to pharmacologic alterations in serotonin, as well as serotonin synthesis rates, serotonin transporter and serotonin receptor (5-HT1A, 5-HT2A) availability. These studies have provided evidence of reduced serotonin synthesis, modest or no reductions in serotonin transporter, 5-HT1A and 5-HT2A receptor availability. Studies of the effects of antidepressant treatment on serotonin receptor availability are controversial. (as reviewed by ^{10, 11}). While not as neurochemically specific as using a serotonergic radiotracer, measures of regional cerebral blood flow (rCBF) or glucose metabolism have consistently demonstrated sensitivity in detecting the effects of illness and treatment that are correlated with severity of depressive symptoms at the time of scanning (¹²⁻¹⁵). The combination of rCBF or glucose metabolism measures with a pharmacologically selective serotonergic intervention may further enhance the information obtained from these neuroimaging measures, as shown by studies in mid-life depressed adults (¹⁶⁻¹⁸). A table summarizing representative studies is provided as supplemental data. As glucose metabolic activity represents the final common pathway of neurochemical activity in the brain, the functional neuroanatomic data would inform subsequent studies to characterize the neurochemical mechanisms underlying the glucose metabolic effect using PET and selective neuroreceptor radiotracers.

The impetus for the present study was that the integration of cerebral glucose metabolism measures with acute, intravenous administration of a pharmacologically selective antidepressant drug would be a unique opportunity to evaluate serotonin modulation of neural circuitry in geriatric depression. Positron Emission Tomography (PET) imaging was employed to measure the acute cerebral metabolic effects of the selective serotonin reuptake inhibitors (SSRI), citalopram (celexa) in depressed older adults and in non-depressed control subjects. In the absence of a radiotracer that could be used to directly measure serotonin function, the methodology used in this study represented the most direct and non-invasive method available to measure serotonergic function *in vivo* in human subjects (^{19,20}). Prior neuroimaging studies to evaluate the effects of antidepressants in mid-life and depressed older adults, including total sleep deprivation (TSD) and pharmacologic treatments (^{12-17, 19-22}) have shown reductions in cerebral glucose metabolism in anterior cingulate, middle and inferior frontal cortices and precuneus. Increases in inferior parietal lobule, occipital cortex and basal ganglia have been observed, as well (¹⁴). As these findings may be attributable in part to an increase in serotonin concentrations, it was hypothesized that acute administration of a selective serotonergic agent,

citalopram, would be associated with a reduction in cerebral metabolism in cortical areas, including the anterior cingulate gyrus (BA 24), superior and middle prefrontal and parietal (precuneus) cortices and increases in basal ganglia (putamen) and occipital cortex. The acute decreases in metabolism were hypothesized to be greater in the control subjects compared to the depressed older adults, particularly in cortical and limbic structures (anterior cingulate gyrus, precuneus and parahippocampal gyrus), indicative of decreased functional serotonergic response in depressed older adults. Prolactin concentrations were measured to evaluate the effects of citalopram administration on the serotonin system independently of the glucose metabolism measures. The acute increase in prolactin after a pharmacologic increase in serotonin has been observed in numerous human studies and has been shown in preclinical studies to reflect an activation of post-synaptic, hypothalamic serotonin receptors (5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} subtypes; as reviewed by ²³). Thus, the decreased cerebral metabolic response to citalopram in depressed older adults relative to controls was hypothesized to be accompanied by a decreased neuroendocrine (prolactin) response.

Materials and Methods

Study Design

Depressed older adults and controls underwent two PET scans on two consecutive days to measure the effects of saline/citalopram administration on cerebral glucose metabolism, as described previously (19, 20, 24).

Subject Screening and Selection

Both depressed older adults and control subjects underwent psychiatric evaluation (including a structured clinical interview, [SCID25]), laboratory testing (including CBC and blood chemistry, glucose levels and thyroid function tests), toxicology screening and Magnetic Resonance (MR) imaging scans (GE 1.5T Magnetom Vision) prior to the PET scans. Depressed older adults were recruited from the Geriatric Psychiatry Outpatient Clinic at the Zucker Hillside Hospital and also from advertisements in the community. Control subjects were recruited from advertisements in the community.

Sixteen depressed older adults (six male/ten females, mean age of 65.3±9.1 years) who met DSM-IV criteria for current major depressive episode (non-bipolar, non-psychotic) were enrolled. Thirteen control subjects (five males/eight females, mean age of 67.4±7.4 years) were enrolled who did not meet DSM-IV criteria for current or past Axis I psychiatric disorders in themselves or in their first degree relatives. Depression and anxiety symptoms were assessed by the following scales: Hamilton Depression Rating Scale-24 item [HDRS26], Hamilton Anxiety Rating Scale [HARS27], Beck Depression Inventory [BDI28], and Geriatric Depression Scale [GDS29]). The differences in age between the two groups were not statistically significant ($F(1,27)=-0.47, p > 0.5$). The controls and depressed older adults did not differ significantly in body weight (controls: 69.1 ± 13.3, depressed older adults: 73.1 ± 17.4; $F(1,27)=-0.47, p > 0.5$). Subjects were excluded who had a history of or current neurological or other Axis I psychiatric disorders (including substance abuse) or who were not medically stable (including a current diagnosis of insulin dependent diabetes and poorly controlled hypertension) or who had used prescription (including beta blockers), over the counter medications (e.g. antihistamines, cold medications) or herbal supplements with central nervous system effects within the past two weeks. The preliminary results of six of the depressed older adults and five of the controls in the present sample were described in an earlier report (20). The demographic characteristics between these subjects and the subjects recruited subsequently did not differ significantly. Twelve depressed older adults (75%) had never been treated with psychotropic drugs. These subjects experienced the first episode of depression for which medication was prescribed. Of the four depressed older adults previously treated, three

depressed older adults were treated with Zoloft prior to study entry (treatment ended from six months to two years prior to study enrollment) and a fourth depressed older adults had been treated with nortriptyline until two weeks prior to the PET scan (at which time the plasma nortriptyline concentrations were undetectable). The clinical, neuroendocrine and neuroimaging data for this patient did not differ significantly from that of the rest of the patient group, despite the relatively recent exposure to nortriptyline. After a complete description of the study to the subjects, 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.

Acute Citalopram Intervention

The subjects were scanned on two consecutive days after an infusion of either placebo (250ml of saline) or citalopram (40mg of the drug diluted in 250ml saline) over 60 minutes. The radiotracer was injected approximately 30 minutes after the end of the infusion, the time when the maximal effects on cerebral metabolism and neuroendocrine function have been observed (19). The study was single blind in that the subjects were told that they would receive either citalopram or placebo (saline) prior to each study, but the investigator knew the identity of the infusion. The order of placebo-drug administration was not randomized because if the drug were administered first, there may be carry over effects to the second scan. As pointed out by Kapitan et al. (30), a time interval of at least three weeks would be necessary between placebo and drug conditions due to the known carry-over effects of serotonergic drugs. It would not be possible for ethical reasons to maintain the depressed older adults unmedicated during such a long time interval.

On the days of the infusion studies, serum and plasma samples were obtained at pre-determined intervals (baseline, end of infusion, 15, 30, 60 90, 120 minutes post-infusion) to measure concentrations of citalopram and prolactin, respectively. The plasma samples were analyzed in the Geriatric Psychopharmacology Laboratory, Department of Psychiatry, University of Pittsburgh School of Medicine as described previously (19,20). The drug levels and neuroendocrine data were analyzed using repeated measures analysis of variance with diagnosis (comparison subject/ depressed older adult) as a between subject factor and condition (2 levels: placebo/citalopram) and time (7 levels: pre, end of infusion, 15, 30, 60, 90 and 120 minutes post-infusion) as within subject factors.

PET Imaging Procedures

The PET scans were performed using a GE Advance Tomograph in the Center for Neurosciences, Feinstein Institute for Medical Research, as described previously (19,20). All PET studies began at the same time of day (10 AM). Upon arrival at the PET Facility, one catheter was placed in a vein in the left arm for radiotracer and placebo/citalopram infusion and a second catheter was placed in a vein in the right arm for sampling of citalopram and neuroendocrine levels. Fifteen to thirty minutes after the end of the infusion of placebo/ citalopram, 5 mCi of [¹⁸F]-2-deoxy-2-fluoro-D-glucose ([¹⁸F]-FDG) was injected as an intravenous bolus. During the uptake interval, the subjects sat in a darkened quiet room with eyes open and ears unoccluded. Twenty-five minutes after radiotracer injection, subjects were positioned in the GE Advance Tomograph. A ten-minute transmission scan and a five-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, the subjects were removed from the PET scanner and the intravenous lines were removed after completion of the blood sampling. The subjects were debriefed as to her/his perception of the study.

Data and Image Analysis

Glucose metabolic rates were calculated (in ml/100g/min) on a pixel by pixel basis according to validated methods (31). PET data processing was performed on the quantitative glucose metabolism images using the statistical parametric mapping program (SPM5, Institute of Neurology, London; 32). 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 (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 groups and conditions ($p > 0.05$). 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. 33). For the PET data, two different analyses were performed using the flexible factorial option in SPM5. First, a within subject comparison for placebo and citalopram conditions was performed for the control and depressed older adult groups, separately. Secondly, a between group comparison (control subjects versus depressed older adults) of the differences in response (placebo/citalopram) was performed to evaluate whether the acute cerebral metabolic response to citalopram differed between depressed older adults and control subjects. To control for multiple comparisons, a more stringent probability level ($p < 0.001$) and cluster size (greater than 50 voxels) is used to limit the significant regional differences reported. The comparisons were considered significant at a t threshold greater than 3.51 ($z > 2.98$, $p < 0.001$; uncorrected for multiple independent comparisons).

Results

The clinical characteristics of the groups, including the means and standard deviations for depressive and anxiety symptoms and global cognitive function for the controls and depressed older adults are shown in Table 1. The means and standard deviations for the citalopram and prolactin concentrations and the percentage change between placebo and citalopram infusions for the prolactin concentrations are shown in Table 2. For the citalopram concentrations, there was a significant effect of time ($F=12.41$, $df=2,19$, $p < 0.001$), but the effect of group ($F=0.17$, $df=2,19$, $p > 0.1$) and the group by time ($F=0.43$, $df=2,19$, $p > 0.1$) interaction was not-significant. This indicates that the citalopram concentrations and time course did not differ significantly between depressed older adults and controls. The citalopram concentration at the end of infusion was non-significantly higher in the controls than the depressed older adults. However, during the time of the [18F]-FDG radiotracer uptake (30-60 minutes post-end of infusion), the citalopram concentrations were similar between the two groups.

For the prolactin concentrations, there was a significant effect of condition ($F=13.8$, $df=1$, $p < 0.001$) and time ($F=3.9$, $df=6$, $p < 0.05$), but the main effect of group ($F=2.57$, $df=1,24$, $p > 0.05$), group by condition ($F=0.8$, $df=1,24$; $p > 0.1$), group by time ($F=0.573$, $df=6,144$; $p > 0.1$) and group by condition by time ($F=0.6$, $df=6,144$; $p > 0.1$) interactions were not-significant. Thus, significantly higher prolactin concentrations were associated with citalopram administration. The magnitude of this effect did not differ significantly between depressed older adults and controls. The percentage differences in prolactin concentrations indicate that at most of the time points (except 120 minutes post-infusion), the magnitude change was non-significantly greater for controls than depressed older adults. The between group differences in citalopram or prolactin concentrations were not significantly different when the subjects' weight was included as a covariate in the analysis. The results of the SPM analysis of the cerebral metabolic data are shown in Tables 3A, B, and C. The results of the within group comparisons (citalopram versus placebo) are shown in Table 3A (controls) and 3B (depressed older adults). Table 3C shows the comparison of the citalopram response (citalopram versus placebo conditions) in control subjects relative to depressed older adults

Cerebral Metabolic Response to Acute Citalopram in Control Subjects (Table 3A)

Decreases in metabolism were observed in right and left cingulate gyrus, left superior, middle and inferior frontal gyrus, left middle temporal gyrus, right and left thalamus and left parahippocampal gyrus. Increases in metabolism were observed in the right superior, middle and inferior frontal gyri, left precuneus, left superior occipital gyri and cerebellum (bilaterally).

Cerebral Metabolic Response to Acute Citalopram in Depressed Older Adults (Table 3B)

Decreases in metabolism were observed in the right cingulate gyrus, superior and middle frontal gyrus (bilaterally), right superior temporal gyrus and parahippocampal gyrus (bilaterally). Increases in metabolism were observed in the left superior and left inferior parietal lobule, right inferior occipital gyrus, left brainstem and cerebellum (bilaterally).

Comparison of Cerebral Metabolic Response to Acute Citalopram in Control Subjects versus Depressed Older Adults [Citalopram versus Placebo Conditions] (Table 3C)

Greater decreases in the control subjects relative to the depressed older adults were observed in the right cingulate gyrus, left pre and post-central, left middle temporal, left parahippocampal, left supramarginal gyri and left precuneus. Greater increases in the control subjects than depressed older adults were observed in right superior and right middle frontal gyri. Greater decreases in depressed older adults than control subjects were noted in the left superior and left middle frontal gyri. Greater increases in the depressed older adults relative to control subjects were observed in the left cuneus, left inferior parietal lobule and left thalamus, as well as the right putamen.

Discussion

The present study demonstrated differences in the acute cerebral metabolic response to citalopram between depressed older adults and control subjects. Greater metabolic decreases in the depressed older adults relative to the control subjects were observed in left frontal cortex, whereas the control subjects demonstrated greater right anterior cingulate and left posterior metabolic decreases than the depressed older adults. Control subjects showed greater metabolic increases than depressed older adults in right superior and middle frontal gyrus. The findings of greater metabolic increases in frontal cortex of control subjects relative to depressed older adults is consistent with the findings of Anderson et al.(17) who made a similar observation with respect to the acute cerebral metabolic effects of the serotonin releasing agent and reuptake inhibitor, fenfluramine, in younger depressed adults and control subjects. The magnitude of the neuroendocrine response (prolactin) to citalopram was also decreased in depressed older adults relative to controls, although the differences were not statistically significant.

In interpreting the results of the present study it is important to note that after completion of the acute citalopram study, the depressed older adults underwent a twelve week treatment trial with oral citalopram. 75% met criteria for treatment response (greater than 50% reduction in HDRS score and HDRS score less than ten after twelve weeks of treatment). Thus, the results observed in the present study largely reflect changes in the functional serotonergic response in treatment responders. This issue is raised because the cerebral metabolic response to citalopram in treatment resistant patients may be different. Neurobiological predictors associated with treatment response in geriatric depression involve similar neural pathways as affected by acute citalopram in the present study including observations of altered white matter functional connectivity and anterior cingulate activation during conflict processing (34³⁵).

The regional cerebral metabolic effects observed comprise several networks implicated in affective and cognitive function. Decreases in a fronto-temporal-parietal network (including the anterior cingulate gyrus, superior temporal gyrus and precuneus) are observed. This

network is activated in tasks involving visuo-spatial imagery, episodic memory retrieval and self processing (as reviewed by ³⁶), aspects of cognition that are affected in depression (³⁷, ³⁸). This network also includes the regions that comprise the ‘default network’, regions that are more active during the “resting” state than under conditions of cognitive activation (³⁹, ⁴⁰⁻⁴¹). The metabolic decreases in limbic structures that have a high concentration of serotonin and connectivity to neocortical regions (parahippocampal gyrus and amygdala) are observed uniquely in the present study compared to previous cerebral metabolism studies in geriatric depression (¹⁴, ¹⁵, ²⁰). Afferent projections from the parahippocampal gyrus to the anterior cortical regions (anterior medial frontal, anterior cingulate cortices, insular cortex) have been characterized (⁴²), as well as reciprocal projections between the amygdala (lateral, basal and accessory nuclei) and cortical regions including the medial prefrontal and anterior cingulate gyrus, superior temporal and insula (⁴³). In contrast to the decreases in metabolism observed in these regions, the inferior parietal lobule, which integrates sensory and motor inputs, in addition to sensory (cuneus) and motor (putamen, cerebellum) show increased metabolism with treatment. These structures comprise a network that is activated during the visual information processing (e.g. visually guided reaching and voluntary saccadic eye movements ^{44,45}).

Decreased cortical responsiveness measured with functional magnetic resonance imaging (fMRI) in several cognitive activation paradigms has been observed in depressed older adults relative to controls. In an executive function task, decreased right middle frontal, cingulate and inferior parietal hypoactivation was observed in symptomatic depressed older adults and cingulate and inferior parietal hypoactivation in remitted depressed older adults (⁴⁶). Bilateral hypoactivation of dorsal anterior cingulate and hippocampus was observed during a verbal fluency task (⁴⁷) and decreased prefrontal and increased caudate activation to an explicit sequence learning task has also been observed (⁴⁸). Older depressed adults demonstrated a decreased response to negatively valenced stimuli in ventromedial prefrontal cortex (orbitofrontal cortex, rostral cingulate cortex and ventral medial frontal gyrus) which was correlated with depression severity and normalized with antidepressant treatment (⁴⁹). With respect to episodic memory, older depressed adults demonstrated decreased activation of temporo-limbic structures relative to control subjects (⁵⁰). These data suggest that the emotional circuitry that is overactive in younger depressed adults is underactive in older depressed adults. The circuitry associated with cognitive processing, especially executive function, is also underactive.

The acute metabolic alterations observed in the cortical and limbic regions are likely to be involve a serotonergic effect. Studies in animals and humans have shown 80% serotonin transporter occupancy, as well as increases in endogenous serotonin concentrations after acute citalopram administration (⁵¹⁻⁵³). As has been reviewed previously, given that the regional pattern of metabolic alterations extends beyond the primary serotonergic projections, the metabolic alterations are likely to reflect secondary changes in other neurochemical systems known to be modulated by serotonin and located within the cortical and limbic regions affected (including glutamate, dopamine and acetylcholine ¹⁹, ⁵⁴⁻⁵⁶). For example, the same dose, route and time course of administration of citalopram has been shown to produce an increase in endogenous dopamine in healthy control subjects (as shown by an decrease in dopamine D2 receptor availability measured with PET and [¹¹C]-raclopride) as the metabolic alterations reported in the present study (⁵⁷).

In summary, differences in serotonin modulation of cerebral glucose metabolism were observed in controls relative to older depressed adults. Future studies to compare younger to younger depressed adults are important to understand the neurobiological mechanism underlying the greater impact of depression in late life with respect to disease course and cognitive impairment. While the majority of depressed older adults enrolled in the present

study had not been treated previously with antidepressant medication and demonstrated significant clinical improvement with citalopram, a critical next step for this research is the investigation of depressed older adults who fail to respond despite an adequate course of antidepressant treatment. Early biomarkers of treatment response in geriatric depression, as we have shown previously with TSD (15), would be useful to identify patients who might have a greater clinical benefit from a different class of antidepressants (e.g. selective noradrenergic reuptake inhibitors) or require more intensive treatment. The functional neuroanatomic differences observed between depressed older adults and controls inform the design of future mechanistic studies to understand the neurochemical and cognitive mechanisms underlying the metabolic effects. Such information would provide a more comprehensive understanding of the neurobiology of geriatric depression, which may have implications for the development of more effective prevention and intervention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The Effects of Acute Citalopram Treatment on Cerebral Glucose Metabolism in Geriatric Depression. Regions of metabolic decrease (green) and increase (red) are superimposed on an MR rendering from a representative subject.

Table 1

Mood and Anxiety Ratings

	Mean ± Standard Deviation				
	Hamilton Depression Rating Scale	Geriatric Depression Scale	Beck Depression Inventory	Hamilton Anxiety Rating Scale	MMSE
Controls	0.6 ± 0.9	1.5 ± 1.6	0.55 ± 0.93	1.8 ± 2.1	28.8 ± 1
Older Depressed Adults	26.0 ± 3.5	20.1 ± 5.2	11.8 ± 3.0	13.1 ± 5.4	28.6 ± 1

Table 2

Plasma Concentrations of Citalopram and Prolactin

Citalopram Concentrations (ng/mL) Mean $\pm$ Standard Deviation		Depressed Older Adults	
Controls			
End of Infusion (EOI)	87.8 $\pm$ 51.9	76.2 $\pm$ 33.5	
15 minutes Post-EOI	56.4 $\pm$ 12.0	52.5 $\pm$ 14.2	
30 minutes Post-EOI	52.2 $\pm$ 15.8	51.1 $\pm$ 13.3	
60 minutes Post-EOI	48.3 $\pm$ 10.9	46.2 $\pm$ 13.5	
90 minutes Post-EOI	46.3 $\pm$ 8.4	42.5 $\pm$ 10.5	
120 minutes Post-EOI	43.9 $\pm$ 11.4	44.1 $\pm$ 13.1	
Prolactin Concentrations (ng/mL) Mean $\pm$ Standard Deviation		Depressed Older Adults	
Controls			
Pre-Infusion	Placebo	Placebo	% Δ
	8.1 $\pm$ 3.2	7.1 $\pm$ 2.4	13.1 $\pm$ 50.1
End of Infusion (EOI)	9.5 $\pm$ 4.6	7.4 $\pm$ 4.2	47.3 $\pm$ 68.8
15 minutes Post-EOI	9.1 $\pm$ 3.8	7.3 $\pm$ 3.7	25.3 $\pm$ 52.9
30 minutes Post-EOI	9.3 $\pm$ 3.9	6.9 $\pm$ 2.8	39.8 $\pm$ 75.3
60 minutes Post-EOI	8.7 $\pm$ 3.7	6.2 $\pm$ 2.1	52.5 $\pm$ 77.2
90 minutes Post-EOI	9.5 $\pm$ 4.4	6.6 $\pm$ 2.8	50.6 $\pm$ 62.8
120 minutes Post-EOI	10.5 $\pm$ 4.7	7.0 $\pm$ 2.6	43.9 $\pm$ 47.9
	Citalopram	Citalopram	
	9.0 $\pm$ 4.6	7.8 $\pm$ 3.0	
	16.3 $\pm$ 14.9	12.4 $\pm$ 7.6	
	14.8 $\pm$ 13.7	11.5 $\pm$ 7.8	
	15.6 $\pm$ 10.6	11.1 $\pm$ 6.1	
	14.8 $\pm$ 8.5	10.5 $\pm$ 5.2	
	14.1 $\pm$ 6.9	10.3 $\pm$ 4.6	
	13.3 $\pm$ 6.3	11.3 $\pm$ 6.8	
			% Δ
			6.0 $\pm$ 25.5
			69.5 $\pm$ 142.0
			59.8 $\pm$ 116.8
			81.5 $\pm$ 125.3
			81.5 $\pm$ 105.0
			58.6 $\pm$ 64.0
			31.5 $\pm$ 37.4

Table 3

Table 3A: Cerebral Metabolic Response to Acute Citalopram in Controls [Citalopram – Placebo Conditions]										
DECREASE	Left Hemisphere				Cluster size	Structure	x (mm)	y (mm)	Right Hemisphere	
x (mm)	y (mm)	z (mm)	Z score						z (mm)	Cluster size
-1	-16	42	2.8	1935	Anterior Cingulate Gyrus	8	-32		35	2.88
-2	57	-1	3.41	889	Superior Frontal Gyrus					
-37	12	52	3.15	2278	Middle Frontal Gyrus (BA 6)					
-55	4	29	2.98	1666	Inferior Frontal Gyrus					
-51	-1	-16	3.39	3045	Middle Temporal Gyrus					
-25	-9	-29	3.8	625	Parahippocampal gyrus					
-15	-30	9	3.02	576	Thalamus (Pulvinar)	21	-32		3	3.13
INCREASE	Left Hemisphere								Right Hemisphere	
x (mm)	y (mm)	z (mm)	Z score	Cluster size		x (mm)	y (mm)		z (mm)	Cluster size
					Structure	30	51		24	3.06
					Superior Frontal Gyrus					5794
					Middle Frontal Gyrus (BA 6)	37	11		55	3.48
					Inferior Frontal Gyrus	54	26		8	3.03
-15	-67	42	3	2661	Precuneus					
-39	-85	23	3.1	143	Superior Occipital Gyrus (BA 19)					
-29	-33	-26	3.02	324	Cerebellum	10	-41		-17	3.07
Table 3B: Cerebral Metabolic Response to Acute Citalopram in Depressed Older Adults [Citalopram – Placebo Conditions]										
DECREASE	Left Hemisphere				Cluster size	Structure	x (mm)	y (mm)	Right Hemisphere	
x (mm)	y (mm)	z (mm)	Z score						z (mm)	Cluster size
					Cingulate Gyrus	5	-39		29	3.13
-15	24	48	4.21	1817	Superior Frontal Gyrus	15	52		18	3.10
-26	49	7	2.98	672	Middle Frontal Gyrus	46	27		30	3.17
					Superior Temporal Gyrus	50	-26		3	3.67
-31	-19	-19	3.14	438	Parahippocampal Gyrus	31	-14		-15	3.05
INCREASE	Left Hemisphere								Right Hemisphere	
x (mm)	y (mm)	z (mm)	Z score	Cluster size		x (mm)	y (mm)		z (mm)	Cluster size
-22	-55	61	3.16	694	Superior Parietal Lobule					

Table 3A: Cerebral Metabolic Response to Acute Citalopram in Controls [Citalopram – Placebo Conditions]

DECREASE	Left Hemisphere		Right Hemisphere		Cluster size		Z score		x (mm)		y (mm)		z (mm)		Cluster size	
x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)
-63	-40	27				808	3.59					5	-39	29		3.13
												34	-91	-3		3.25
-6	-14	-10				553	3.21									
-24	-38	-29				1641	3.19					8	-67	-20		3.73

Table 3C: Comparison of Cerebral Metabolic Response to Acute Citalopram in Controls versus Depressed Older Adults [Citalopram – Placebo]

Greater Decreases in Controls than Depressed Older Adults																
		Left Hemisphere									Right Hemisphere					
x (mm)	y (mm)	z (mm)	Cluster size	Z score	Structure	x (mm)	y (mm)	z (mm)	Cluster size	Z score	Structure	x (mm)	y (mm)	z (mm)	Cluster size	
					Cingulate Gyrus	10	-29	37							447	
-43	-5	54	3432	3.53	Pre-Central Gyrus (BA6)											
-54	-43	6	1714	3.03	Middle Temporal Gyrus	62	-6	-9		3.42					308	
-25	-11	-27	295	3.2	Parahippocampal Gyrus (BA 28)											
-54	-25	47	3884	3.43	Post-central Gyrus (BA2)											
-41	-47	32	1520	3.08	Supramarginal Gyrus											
-5	-55	48	467	3.32	Precuneus (BA7)											

Table 3D: Comparison of Cerebral Metabolic Response to Acute Citalopram in Controls versus Depressed Older Adults [Citalopram – Placebo]

Greater Increases in Controls than Depressed Older Adults																	
		Left Hemisphere		Right Hemisphere		Cluster size		Z score		x (mm)		y (mm)		z (mm)		Cluster size	
x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	

Table 3E: Comparison of Cerebral Metabolic Response to Acute Citalopram in Controls versus Depressed Older Adults [Citalopram – Placebo]

Greater Decreases in Depressed Older Adults than Controls																			
		Left Hemisphere			Right Hemisphere			Cluster size		Z score		x (mm)		y (mm)		z (mm)		Cluster size	
x (mm)	y (mm)	z (mm)																	
-24	52	24					707	3.30											
-37	12	53					2863	3.49											

Table 3F: Comparison of Cerebral Metabolic Response to Acute Citalopram in Controls versus Depressed Older Adults [Citalopram – Placebo]

Greater Increases in Depressed Older Adults than Controls																
		Left Hemisphere												Right Hemisphere		
x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)

Table 3A: Cerebral Metabolic Response to Acute Citalopram in Controls [Citalopram – Placebo Conditions]

Table 3A: Cerebral Metabolic Response to Acute Citalopram in Controls [Citalopram – Placebo Conditions]											
DECREASE		Left Hemisphere		Z score	Cluster size	Structure	x (mm)	y (mm)	Right Hemisphere		
x (mm)	y (mm)	z (mm)				Structure	x (mm)	y (mm)	z (mm)	Z score	Cluster size
x (mm)	y (mm)	z (mm)			Cluster size	Structure	x (mm)	y (mm)	z (mm)	Z score	Cluster size
-21	-85	46	3.76	491	Cuneus						
-63	-41	30	3.69	3884	Inferior Parietal Lobule						
-16	-30	9	2.79	254	Thalamus						
					Putamen		28	-17	4	2.61	185