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Review article

The impact of treatment with selective serotonin reuptake inhibitors on primate cardiovascular disease, behavior, and neuroanatomy

Carol A. Shively (PhD)^{a,*}, Marnie Silverstein-Metzler (DVM PhD)^a, Jamie Justice (PhD)^b,
Stephanie L. Willard (PhD)^c

^a Department of Pathology, Wake Forest School of Medicine, United States

^b Department of Internal Medicine – Geriatrics, J. Paul Sticht Center on Aging, Wake Forest School of Medicine, United States

^c Center for Neurobiology and Behavior, University of Pennsylvania, United States

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ABSTRACT

Selective serotonin reuptake inhibitor (SSRI) use is ubiquitous because they are widely prescribed for a number of disorders in addition to depression. Depression increases the risk of coronary heart disease (CHD). Hence, treating depression with SSRIs could reduce CHD risk. However, the effects of long term antidepressant treatment on CHD risk, as well as other aspects of health, remain poorly understood. Thus, we undertook an investigation of multisystem effects of SSRI treatment with a physiologically relevant dose in middle-aged adult female cynomolgus monkeys, a primate species shown to be a useful model of both depression and coronary and carotid artery atherosclerosis. Sertraline had no effect on depressive behavior, reduced anxious behavior, increased affiliation, reduced aggression, changed serotonin neurotransmission and volumes of neural areas critical to mood disorders, and exacerbated coronary and carotid atherosclerosis. These data suggest that a conservative approach to prescribing SSRIs for cardiovascular or other disorders for long periods may be warranted, and that further study is critical given the widespread use of these medications.

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* Corresponding author at: Department of Pathology-Comparative Medicine, Medical Center Blvd., Winston-Salem, NC 27157-1040, United States.

E-mail address: cshively@wakehealth.edu (C.A. Shively).

1. Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality of US women, exceeding that of all cancers combined. CHD in women is understudied, and less well understood than in men (Go et al., 2014). Coronary artery atherosclerosis and its sequelae are frequent causes of CHD. The premenopausal life stage is important in determining the extent of postmenopausal coronary artery atherosclerosis and CHD risk because the extent of premenopausal coronary artery atherosclerosis sets the starting point and trajectory for coronary artery plaque progression in the postmenopause (Kaplan et al., 2002).

Depressive disorders are twice as likely and have more serious consequences in women as men (Gorman, 2006; Kim et al., 2015). The lifetime prevalence of depression in women is 20%, occurring most commonly in the reproductive years (Pratt and Brody, 2014). Depression is highly co-morbid with CHD. The relationship between depression and CHD could be one of three natures: CHD may cause depression; depression may cause CHD; or both diseases may be the product of perturbations of common underlying mechanisms. Clinical studies cannot easily discriminate among these three possibilities. However, several studies demonstrate graded relative risk of CHD with depression, suggesting that milder forms of depression in addition to major depressive disorder may be clinically relevant (Leung et al., 2012; Rugulies, 2002; Rudisch and Nemeroff, 2003; Rugulies, 2002; Rudisch and Nemeroff, 2003). Meta-analyses suggest that depression is independently associated with a significantly increased risk of CHD and MI (Gan et al., 2014; Wu and Kling, 2016). Furthermore, development of atherothrombotic CHD is generally predicated by years of coronary artery atherogenesis. These observations suggest a causal role of depression in progression of CHD, although this remains to be evaluated conclusively. When depression may exert its adverse effects during CHD pathogenesis is not well understood. For example, it could be that depression effects CHD rather late in clinical development by precipitating coronary events in the presence of complicated plaques through adverse effects on arrhythmias or platelet reactivity. Depression could also exert adverse effects very early in CHD pathogenesis by promoting atherogenesis. Since CHD is the leading cause of death of women, and women experience twice the prevalence of depression than men, understanding the cardiovascular pathobiology of depression may be particularly important to the cardiovascular health of women (Moller-Leimkuhler, 2010).

Antidepressants are among the most widely used medications in the US, and 60% of those taking antidepressants have done so for 2 years or longer. Women are 2.5 times more likely than men to take antidepressants, and 23% of women aged 40–59 years take antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants (Pratt et al., 2011). In addition to depression, SSRIs are prescribed for a number of other disorders including obsessive-compulsive disorder, bulimia and binge eating, agitation and aggression in dementia and other central nervous system degenerative diseases fibromyalgia, osteoarthritis, and diabetic neuropathy pain, hot flashes, stroke recovery and premature ejaculation (Chouinard, 2006; McElroy et al., 2012; Henry et al., 2011; Pergolizzi et al., 2013; Shams et al., 2014; Mead et al., 2012; Moreland and Makela, 2005; Shams et al., 2014; Mead et al., 2012; Moreland and Makela, 2005). Remarkably little is known about the multisystem effects of SSRIs in those treated for disorders other than mood disorders.

There has been much discussion over the last several years about whether SSRIs are safe for treating depression in CHD patients (Davidson et al., 2006; Zuidersma et al., 2013). Some have gone so far as to recommend SSRIs to inhibit atherosclerosis progression (Wozniak et al., 2011). These recommendations stem from evidence of increased cardiovascular risk factors in depression such

as arrhythmias, platelet reactivity, proinflammatory processes, cortisol concentrations, and low high-density lipoprotein cholesterol (HDLc) concentrations in women (Carney et al., 2002; Shively et al., 2009; Fantidis, 2010; Tedders et al., 2011). Of these risk factors, the available evidence suggests that SSRIs have inhibitory effects on platelet reactivity (de Abajo, 2011) and inflammatory processes (Hannestad et al., 2011; Walker, 2013) although evidence that these affects have cardiovascular significance is scarce. Conversely, SSRIs also have been observed to have adverse effects on CHD risk factors including increasing body weight (BW), body mass index (BMI), waist circumference, fasting glucose, total plasma cholesterol (TPC), low density lipoprotein cholesterol, and triglyceride concentrations (Beyazyuz et al., 2013; Wei et al., 2009; Kesim et al., 2011), all factors that may be affected by food consumption. It is notable that disorders for which SSRIs are commonly prescribed, such as depression, also may affect food consumption. Since all the SSRI-CHD risk factor studies assessed patient populations, the effects of SSRIs on these CHD risk factors are confounded by the disorder for which they were prescribed.

There are no experimental investigations of the effects of SSRIs on coronary artery atherosclerosis extent and severity, and few long term clinical studies of the effect of SSRI use on CHD morbidity and mortality. SADHART (Sertraline AntiDepressant Heart Attack Trial) demonstrated that sertraline was relatively safe and efficacious in depressed patients with ischemic heart disease but was under-powered to detect a mortality difference between sertraline and placebo. Secondary analyses of the ENRICHD (ENhancing Recovery in Coronary Heart Disease) trial suggested that SSRIs in myocardial infarction patients might reduce subsequent morbidity and mortality but the trial was not designed to detect these relationships (Taylor et al., 2005; Joynt and O'Connor, 2005). More recently, increased cardiovascular morbidity and mortality in patients using SSRIs, versus non-SSRIs or no antidepressant, was observed in a 42 month follow up study of CHD patients (Rieckmann et al., 2013). In addition, among women with symptoms of myocardial ischemia, the use of antidepressant medication was associated with subsequent cardiovascular events (e.g. nonfatal myocardial infarction, stroke, congestive heart failure, unstable angina) (Krantz et al., 2009).

Some studies also suggest that SSRI use may increase the risk of ischemic stroke, which is due to atherosclerosis in the cerebral vasculature. A recent meta-analysis of these studies suggests that the use of SSRIs is associated with an odds ratio of 1.48 (CI = 1.08, 2.02) for ischemic stroke (Shin et al., 2014). Likewise, an association between increased carotid intimal-medial thickening, a powerful predictor of myocardial infarct risk (Simon et al., 2002), and SSRI treatment in a study of twins discordant for SSRI has been reported (reported in Shah et al., 2011 American College of Cardiology Scientific Sessions).

Taken together, these observations of associations of worsened cardiovascular risk factors, increased ischemic stroke incidence and carotid intimal-medial thickening, and increased cardiovascular disease (CVD) events in patients with SSRI use suggest a need for better information concerning SSRI effects on the development and progression of atherosclerosis. As long term randomized clinical trials are unlikely due to cost and ethical considerations, we studied these relationships in adult female cynomolgus monkeys (*Macaca fascicularis*) because they are among the best models of depression and atherosclerosis.

2. Monkey model of depression (Fig. 1)

Adult female cynomolgus macaques are a well-established non-human primate (NHP) model of depression (Shively and Willard, 2012; Willard and Shively, 2012). Depressive behavior in socially

housed female cynomolgus monkeys occurs in captivity without experimental manipulation. In our laboratory, behavioral depression is operationally defined by a slumped or collapsed body posture, accompanied by a lack of responsiveness to environmental stimuli to which other monkeys are attending, and open eyes to distinguish this behavior from resting or sleeping (Shively et al., 1997; Shively et al., 2005). This definition closely matches those used other laboratories (Perera et al., 2011; Camus et al., 2014; Hennessy et al., 2014 Camus et al., 2014; Hennessy et al., 2014) and is exhibited predictably over time (Shively et al., 2005).

Behavioral depression in adult female cynomolgus macaques appears similar to human depression in physiological, neurobiological, and behavioral characteristics, and established validity as a comparative model of the clinical depression syndrome (Shively and Willard, 2012; Willard and Shively, 2012). Compared to their nondepressed counterparts, depressed monkeys have lower body weight, body mass index, and activity levels, perturbed hypothalamic-pituitary adrenal function, dyslipidemia, suppressed ovarian function, and increased heart rate (Shively and Willard, 2012; Willard and Shively, 2012; Shively et al., 2008 Shively et al., 2008). Depressed monkeys also have reduced serotonin 1a receptor binding potential in the dorsal raphe, amygdala, hippocampus and anterior cingulate gyrus compared to their nondepressed counterparts (Fig. 1) (Shively et al., 2006). The macaque hippocampus (HC) more closely parallels the cellular organization and connectivity patterns of the human hippocampus than does that of the rat (Amaral and Lavenex, 2007), and macaques have complex and differentiated cortical areas, similar to those of human beings, that are important in human depression (Carmichael et al., 1994; Machado et al., 2008). Our group has previously reported reduced anterior hippocampal volume in untreated, behaviorally depressed female cynomolgus macaques. Postmortem in vitro analysis (Willard et al., 2009) and pre-mortem in vivo MRI measures (Willard et al., 2011) demonstrated region-specific reductions in hippocampal volume in depressed versus nondepressed females. The reduced size of the anterior hippocampus in depressed monkeys appears to arise from reductions in numbers of glia and extent of neuropil, but not numbers of neurons, in the CA1 and DG (Willard et al., 2013). Behavioral depression is also accompanied by compromised postsynaptic integrity due to astrocytic and synaptic protein alterations in the CA1 (Willard et al., 2014). Socially subordinate females are more likely than dominants to display depressive behavior; however not all subordinates display depressive behavior and some socially dominant animals do (Shively and Willard, 2012; Willard and Shively, 2012).

3. Comorbidity of depression and coronary artery atherosclerosis (Fig. 2)

Cynomolgus monkeys are a useful model of atherosclerosis. In response to the consumption of a Western-like diet, these animals develop arterial plaques that are similar in location and composition to those of human beings (Clarkson and Klumpp, 1990). Depressed monkeys have characteristics that increase cardiovascular risk including high circulating cortisol levels which affect endothelial function, autonomic dysfunction resulting in high heart rate, decreased activity levels, dyslipidemia characterized by high circulating total cholesterol, low high-density lipoprotein cholesterol, a high ratio of Ω6:Ω3 fatty acid concentrations, and low concentrations of ovarian steroids (Shively and Willard, 2012; Willard and Shively, 2012) (Fig. 2). All of these are cardiovascular risk factors in women. For this reason we examined coronary artery atherosclerosis extent in monkeys that had, or had not exhibited depressive behavior in the previous 4 years. We found that depressed monkeys had four times the atherosclerosis in their coro-

nary arteries as their nondepressed counterparts (Shively et al., 2009; Shively et al., 2008; Chilton et al., 2011).

Wild monkeys have little or no atherosclerosis; atherogenesis is driven by the consumption of a Western-type diet containing cholesterol and saturated fat (Clarkson and Klumpp, 1990), allowing the examination of the relationship between depressive behavior and early atherogenesis in this study. These observations suggest that depressive behavior predicts early coronary artery atherosclerosis in female primates. Clinical observations suggest that depression predicts CHD up to perhaps a decade before a clinical event. Atherogenesis has been underway for several decades by that time, and atherosclerosis is well advanced. The observations reported here push back the temporal relationship between depression and atherosclerosis to the earliest stages of atherogenesis.

4. SSRI effects on coronary and carotid atherosclerosis

Given the exacerbated coronary artery atherosclerosis in depressed monkeys, and the comorbidity of depression and CHD in human beings, we tested the hypothesis that treating depression would slow coronary artery atherosclerosis, attenuating the exacerbated atherosclerosis we had previously observed in depressed monkeys (Shively et al., 2015). The overall objective of this study was to determine the effects of long-term SSRI treatment on cardiovascular disease, and associated behavior, and neuroanatomy.

4.1. Methods

The study design was a controlled, prospective, randomized, preclinical trial. Forty-two middle-aged socially housed adult female cynomolgus macaques consumed a Western diet and were characterized during an 18-month pretreatment phase and assigned to SSRI (sertraline hydrochloride 20 mg/kg, once a day) or placebo balanced on pretreatment depression, body weight (BW), and iliac artery atherosclerosis extent measured via biopsy. We chose a commonly prescribed SSRI, sertraline HCl (Zoloft®) as the intervention. Monkeys were trained for oral administration of placebo or 20 mg/kg sertraline HCl daily for 18 months, a time period approximately equivalent to 5 human years. Circulating concentrations of sertraline/desmethylsertraline and CSF levels of 5-hydroxyindole acetic acid were similar to those observed in patients. Depressive, anxious and social behaviors were recorded during both the pretreatment and treatment phases. Cardiovascular risk factors were measured prior to and after an 18-month treatment phases. After 18 months of treatment, neuroanatomy was assessed in vivo with magnetic resonance imaging (MRI) and coronary and carotid artery atherosclerosis extent was measured ex vivo using histomorphometry.

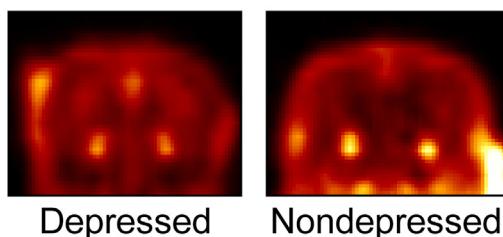
4.2. Effects of SSRI treatment on coronary artery atherosclerosis and cardiovascular risk factors

There were no pretreatment differences between the sertraline and placebo groups in any of the risk factors measured. Before and during treatment, depressed monkeys had lower BW, body mass index, and plasma high-density lipoprotein cholesterol, and higher heart rates during the pretreatment phase. Sertraline reduced anxious behavior but had no effect on BW, body mass index, heart rate, plasma lipids, or depression. Coronary artery atherosclerosis, analyzed by a 2 (depressed, nondepressed) × 2 (placebo, sertraline) × 3 (coronary arteries) analysis of covariance (ANCOVA) adjusted for pretreatment iliac atherosclerosis, was greater in depressed than in nondepressed monkeys ($p=0.036$), and in sertraline than in placebo-treated monkeys ($p=0.040$) (Fig. 3). The

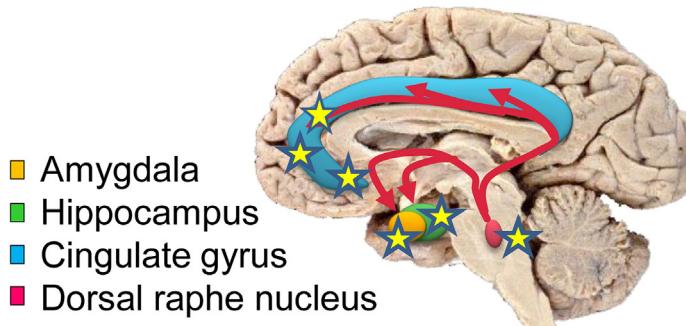
The Neurobiology of Depressed Monkeys



Reduced serotonin-1a receptor binding



Perturbed anterior hippocampal CA1



- Reduced glial & neuropil
- Compromised postsynaptic integrity
- Increased GFAP
- Astrocyte-mediated impaired synaptic plasticity

Fig. 1. The neurobiology of depressed monkeys. Behavioral depression in adult female cynomolgus macaques is associated with altered serotonin-1a receptor binding potential in mood related brain regions, as well as perturbed cellular and molecular characteristics of the hippocampus. CA1, cornu ammonis 1; GFAP, glial fibrillary acidic protein.

observed coronary artery atherosclerosis extent in depressed monkeys treated with sertraline was 4.9 times higher than that in untreated depressed monkeys, and 6.5 times higher than that in nondepressed monkeys, on average. Thus, we replicated our previous observation that depressed animals developed more coronary artery atherosclerosis, and long-term treatment with sertraline resulted in more extensive coronary artery atherosclerosis resulting in the most extensive coronary artery atherosclerosis in depressed monkeys (Shively et al., 2015). No established CHD risk factors were worsened by SSRI treatment leaving open the question of the mechanism of this effect.

4.3. SSRI effects on carotid artery atherosclerosis (Fig. 4)

The effect of depression on carotid artery atherosclerosis has not been previously examined in the nonhuman primate. Clinical observations suggest that depressed women are at an increased risk for carotid artery plaque formation (Jones et al., 2003) and

ischemic stroke (Wassertheil-Smoller et al., 1996; Pan et al., 2011), a sequela of carotid artery atherosclerosis. Given that SSRIs are associated with an increased risk of ischemic stroke and coronary artery atherosclerosis was most extensive in sertraline-treated depressed monkeys, we evaluated the effects of SSRI and depression on carotid artery atherosclerosis in these same monkeys (). After the 18-month treatment phase, carotid artery atherosclerosis extent was measured in the right and left extracranial carotid arteries (common carotids arteries and carotid artery bifurcations) using histomorphometry. Sertraline and depression effects were analyzed using 2 (placebo, sertraline) \times 2 (nondepressed, depressed) \times 2 (carotid arteries) ANCOVAs adjusted for pretreatment circulating lipids (TPC/HDLc) to determine the effects of sertraline and depression on the individual arteries.

Depressed monkeys tended to have greater carotid artery atherosclerosis than nondepressed monkeys, although this effect did not reach significance. The interaction between sertraline treatment and depression significantly affected atherosclerosis extent in

Coronary Artery Atherosclerosis and Depression in Female Monkeys

Characteristics of Depressed Female Monkeys

- Altered neurobiology
- Low BW, BMI
- Perturbed HPA axis
- High 24 hr heart rates
- Dyslipidemia
 - High total
 - Low HDL-C
 - High ω-6:ω-3 fatty acids
- Decreased activity
- Ovarian dysfunction with preserved menses
- More coronary artery atherosclerosis

Nondepressed Depressed

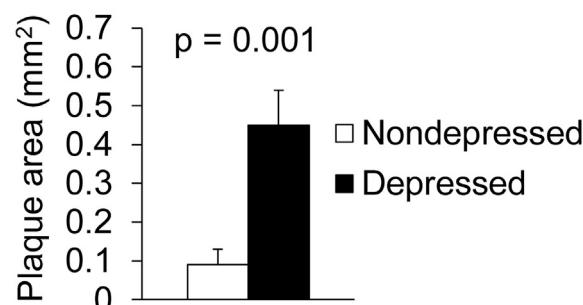
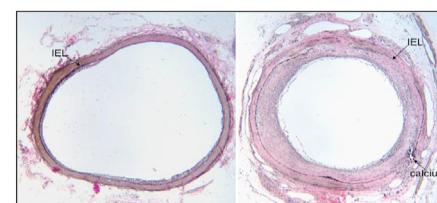


Fig. 2. Coronary artery atherosclerosis and depression in female monkeys. Behaviorally depressed adult female cynomolgus macaques appear similar to depressed patients in physiological, neurobiological, and behavioral characteristics. Several of these characteristics are cardiovascular risk factors in women. Indeed, depressed female monkeys have 4 times the atherosclerotic plaque of their nondepressed counterparts. BW, body weight; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; HPA, hypothalamic-pituitary-adrenal.

the right extracranial carotid artery ($p=0.03$) such that atherosclerosis extent was 45–70% greater in sertraline-treated depressed monkeys compared to all other groups. No other carotid artery locations were significantly affected by sertraline, depression, or their interaction. Because none of the traditional cardiovascular risk factors examined were worsened by sertraline, we identified predictors of carotid artery atherosclerosis and then examined whether these relationships were mediated by SSRI treatment. Linear regression analysis revealed that sertraline and depression effects on atherosclerosis extent were not mediated via effects on behavioral and physiological risk factors. Although a mechanism remains to be elucidated, these observations suggest that long-term SSRI treatment may promote carotid artery atherosclerosis which may increase ischemic stroke risk, particularly in depressed women ().

5. SSRI effects on body composition and carbohydrate metabolism (Table 1)

While weight gain is one of the most commonly reported side-effects of SSRI treatment (Cascade et al., 2009), little is known regarding the effects of SSRIs on cardiometabolic risk factors such as body composition and carbohydrate metabolism. Additionally,

changes in weight, either gain or loss, are recognized diagnostic criteria for depressive disorders DSM-V (American Psychiatric Association, 2016; Polivy and Herman, 1976). This makes it difficult to separate out the effects of SSRI-treatment from those of the underlying depressive disorder. In this same experiment, we evaluated SSRI effects on body weight and composition, fat distribution, carbohydrate metabolism, and activity using measures taken prior to and after the 18 months of sertraline treatment (Silverstein-Metzler et al., 2016). In order to determine the best estimate of the magnitude of the treatment effect, treatment values were adjusted for pretreatment values using 2 (depressed, nondepressed) \times 2 (placebo, sertraline) ANCOVAs.

Over the 18 month treatment period, the placebo group experienced increases in body weight, body fat (visceral and subcutaneous), fasting insulin concentrations, and homeostasis model assessment of insulin resistance scores (HOMA-IR). Sertraline treatment prevented increases in body weight, fat, insulin, and HOMA-IR (all $p < 0.05$), without significantly altering activity levels (Table 1). Interestingly, sertraline treatment reduced circulating adiponectin in depressed monkeys without affecting fat mass or body weight. Deleterious effects on adiponectin, a potentially insulin-sensitizing and atheroprotective protein, may explain adverse effects on

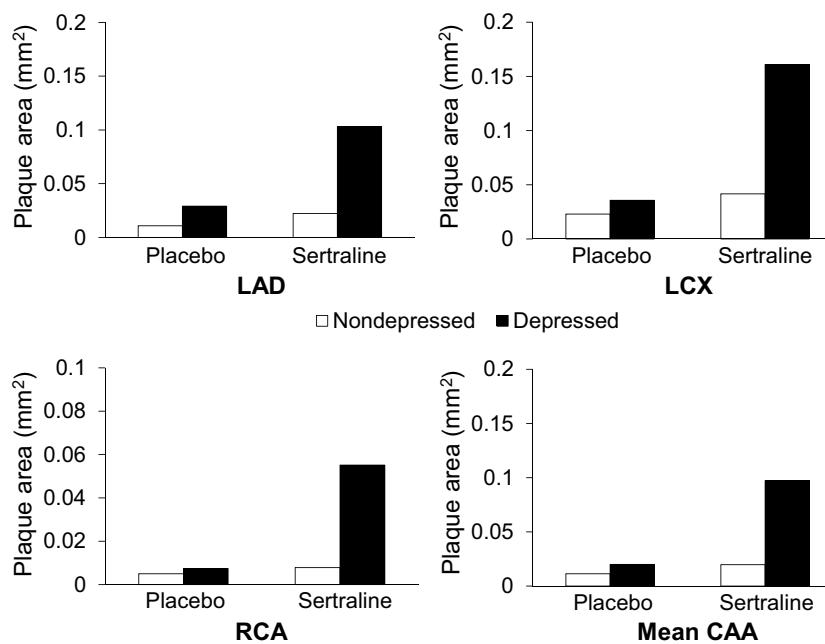


Fig. 3. Sertraline exacerbates coronary artery atherosclerosis in depressed female monkeys. Coronary artery atherosclerosis (CAA) was greater in depressed than in nondepressed monkeys ($p < 0.036$), and in sertraline-treated compared with placebo-treated monkeys ($p = 0.040$). LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

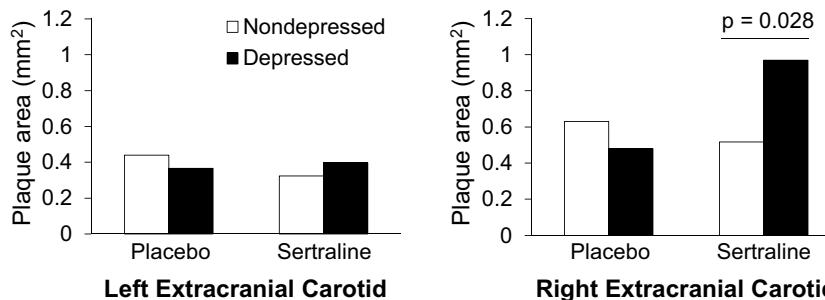


Fig. 4. SSRI effects on carotid artery atherosclerosis. Sertraline treatment increased atherosclerosis in the right extracranial carotid arteries (common carotid and carotid artery bifurcation) of depressed monkeys ($p = 0.03$).

Table 1

SSRI effects on body composition and carbohydrate metabolism.

Variables	Placebo		Sertraline		% Difference ^c
	Nondep ^a n = 12	Dep ^b n = 9	Nondep n = 11	Dep n = 10	
Body Weight, kg	3.78 (0.08)	3.65 (0.09)	3.42 (0.08)	3.47 (0.08)	-7.23
Body Mass Index, kg/m ²	46.4 (1.3)	44.7 (1.4)	44.9 (1.2)	44.5 (1.3)	-1.84
Lean Mass, kg	2.73 (0.05)	2.80 (0.07)	2.66 (0.06)	2.70 (0.05)	-2.97
Fat Mass, kg	0.97 (0.06)	0.79 (0.07)	0.71 (0.06)	0.75 (0.07)	-17.6
Abdominal Fat Volume, cm ³	33.7 (3.0)	26.1 (3.3)	17.3 (2.9)	18.4 (3.2)	-40.3
Visceral Abdominal Fat Volume, cm ³	15.9 (1.9)	12.7 (2.1)	9.81 (1.9)	7.64 (2.0)	-38.9
Subcutaneous Abdominal Fat Volume, cm ³	14.6 (1.5)	12.4 (1.6)	8.45 (1.4)	10.6 (1.7)	-29.3
Visceral: Subcutaneous Abdominal Fat	1.17 (0.15)	1.55 (0.17)	1.22 (0.16)	1.14 (0.18)	-13.3
Leptin, ng/ml	3.67 (0.51)	1.94 (0.58)	2.17 (0.51)	1.33 (0.54)	-37.5
Adiponectin, ng/ml	61.3 (8.7)	74.5 (10)	70.2 (9.3)	56.1 (10)	-7.01
Triglycerides, ng/dl	59.0 (46)	119 (53)	146 (49)	56.7 (50)	14.0
Glucose, mg/dl	81.3 (6.1)	79.7 (7.2)	76.3 (6.4)	72.8 (6.8)	-7.40
Insulin, mIU/l	43.3 (11)	52.8 (12)	10.9 (11)	19.4 (12)	-68.6
HOMA-IR	9.34 (2.9)	12.4 (3.4)	1.93 (3.1)	3.76 (3.2)	-73.8
24 h Activity counts	202,632(33,845)	229,537(39,206)	206,816(36,258)	191,169(37,346)	-7.91

Adapted from Silverstein-Metzler et al. (2016).

Values are presented as mean (SEM). Adjusted means analyzed by 2 (depressed, nondepressed) \times 2 (placebo, sertraline) analyses of covariance (pretreatment values as covariate). Boldface indicates a significant main effect of treatment ($p < 0.05$).

^a Nondep = monkeys exhibiting little or no depressive behavior.

^b Dep = monkeys exhibiting depressive behavior.

^c % Difference calculated from adjusted sertraline- and placebo-group means. HOMA-IR, homeostasis model assessment of insulin resistance scores.

atherosclerosis despite otherwise beneficial effects on body composition and carbohydrate metabolism.

6. SSRI effects on behavior

As mentioned above, over an 18 month treatment period, sertraline had no effect on depressive behavior (2 [pretreatment, treatment] \times 2 [placebo, sertraline] mixed-models analysis of variance [ANOVA], $p = 0.43$) ([Shively et al., 2015](#)). Similarly in patients, SSRI effects on depressive symptoms are inconsistent (nearly 50% of patients fail to respond to first-line SSRI treatment) and specific drug effects only mildly improve upon placebo-expectancy effects ([Arroll et al., 2005](#)). Thus, this model recapitulates the frequent treatment-resistant depression observed in patients. Sertraline has been shown to be efficacious for anxiety in patients, ([Brawman-Mintzer et al., 2006](#); [Mokhber et al., 2010](#)) and also reduced anxious behavior (2 [pretreatment, treatment] \times 2 [placebo, sertraline] mixed-models ANOVA, $p = 0.04$) in the monkeys.

We also analyzed shorter term effects of sertraline on agonistic and affiliative behavior in these monkeys ([Shively et al., 2014](#)). After being trained to participate in oral dosing, the sertraline treatment group began a 5-week cumulative dose-response study. Serial doses of 0, 5, 10, 15, and 20 mg/kg of sertraline were administered orally for 1 week each. The final dose of 20 mg/kg/day was chosen based off a previous study in which macaques were administered sertraline (20 mg/kg/day p.o.) for 7 wks, and the resulting plasma sertraline levels were within the therapeutic range for human patients ([Higley et al., 1998](#)). Behavior was recorded daily during 10-min observations before and 4 h after dosing. On the seventh day of dosing, circulating sertraline/desmethylsertraline and CSF monoamines/metabolites were determined 4 h after the last dose. At 20 mg/kg, circulating sertraline/desmethylsertraline was in the therapeutic range, and CSF 5-hydroxyindole acetic acid had decreased by 33% (one-way repeated measures ANOVA, $p < 0.05$). Overall aggression, submission, locomotion, and time alone decreased, whereas the affiliative behaviors, time spent in body contact and grooming, increased (2 [dominant, subordinate] \times 2 [pre-, post-dosing] \times [doses] nested repeated measures ANOVAs, all p values < 0.05). Interestingly, the effects of sertraline on aggression and submission were social status-dependent, reducing rates of aggression in dominants, and rates of submission in subordinates. Thus, a clinically relevant oral dose of sertraline altered the socioemotional behavior of female monkeys. The robust effects of sertraline on aggression and affiliation may explain the efficacy of SSRIs on a range of human behavioral pathologies that share the characteristics of increased aggression and decreased sociality ([Shively et al., 2014](#)).

7. SSRI effects on brain areas involved in depression neuroanatomy (Fig. 5)

Volumetric reductions in neural structures, measured with MRI, in depressed compared to nondepressed individuals have been observed in hippocampus (HC), amygdala, and cingulate cortex ([Arnone et al., 2013](#); [Grieve et al., 2013](#)).

One potential mechanism through which antidepressant therapies may promote remission is by increasing neurogenesis ([Mahar et al., 2014](#)) and a few studies suggest that antidepressant treatment may increase hippocampal volume ([Frodl et al., 2008](#); [Malykhin et al., 2010](#)). Additionally, volumetric abnormalities in brain regions associated with emotional and autonomic processing overlap, and may affect both depression and CVD progression, and recent evidence indicates that brain volume in these regulatory areas may be at the nexus of comorbid depression and vascular diseases ([Harrison et al., 2013](#); [Gianaros et al., 2008](#); [Beauchet et al., 2013](#); [Meurs et al., 2013](#)).

However, the effect of SSRI's on brain volume and this relation to depression and CHD remains unexplored. Therefore to better understand the effects of SSRIs on the depression-CHD relationship, we evaluated SSRI effects on the volumes of brain areas implicated in depression in these same monkeys in which SSRI effects on coronary artery atherosclerosis were assessed ([Willard et al., 2015](#)).

Volumes of neural regions of interest in depression were measured in magnetic resonance images after 18 months of treatment and analyzed by 2 (depressed, nondepressed) \times 2 (placebo, sertraline) ANOVA. The volumes of 8 ROIs representing key components of depression neurocircuitry (Fig. 5) were measured bilaterally (16 ROIs per monkey) in 41 monkeys for a total of 656 ROIs overall. Regions of interest included whole HC, anterior and posterior HC, whole ACC, subgenual ventral ACC (BA25), dorsal ACC (BA24), rostral ACC (BA32), and amygdala.

As mentioned above, sertraline reduced anxiety ($p = 0.04$) but not depressive behavior ($p = 0.43$). Left Brodmann's Area (BA) 32 was smaller in depressed than nondepressed monkeys (main effect of depression: $p < 0.05$). Sertraline and depression status interacted to affect volumes of left anterior cingulate cortex (ACC), left BA24, right hippocampus (HC), and right anterior HC (sertraline \times depression interactions: all p 's < 0.05). In the Placebo group, depressed monkeys had smaller right anterior HC and left ACC than nondepressed monkeys. In nondepressed monkeys, sertraline reduced right HC volume, especially right anterior HC volume. In depressed monkeys sertraline increased left ACC volume. In nondepressed monkeys, sertraline reduced left BA24 volumes resulting in smaller BA24 volumes in nondepressed than sertraline-treated depressed monkeys. These observations suggest that SSRIs may differentially affect neural structures in depressed and nondepressed individuals.

8. Relationships between brain area volumes and coronary artery atherosclerosis (Table 2)

To further elucidate relationships between depression and coronary artery atherosclerosis, we examined correlations between coronary artery atherosclerosis extent and volumes of neural regions of interest discussed above ([Shively et al., 2015](#); [Willard et al., 2015](#)). Interestingly, relationships between regional brain volumes and coronary artery atherosclerosis were divergent in depressed versus non-depressed monkeys (Table 2). Importantly, atherosclerosis was positively associated with anterior hippocampal volume in non-depressed animals, but in depressed animals, atherosclerosis was negatively associated with right amygdala and posterior hippocampus. The relationships between coronary atherosclerotic extent and hippocampal volumes were robust and remained significant after adjusting for sertraline treatment. There are functional differences along the anterior-posterior axis of the hippocampus, with the anterior primarily processing information about emotion, and the posterior involved in cognitive processes ([Nadel et al., 2013](#); [Fanselow and Dong, 2010](#)). Taken together, these observations suggest that the relationship between coronary artery atherosclerosis and neural regions involved in emotion processing may differ in depressed and non-depressed individuals.

9. Conclusions

The results of a series of papers have described an extensive list of consequences of sertraline treatment with physiologically relevant doses in an established NHP model during the late premenopausal years in which there is a high rate of SSRI use by women. Sertraline had no effect on depressive behavior, but it reduced anxious behavior, increased affiliation, and reduced aggression. Sertraline exacerbated atherosclerosis in the coronary

Differential Effects of SSRI on Neuroanatomy in Depressed and Nondepressed Monkeys

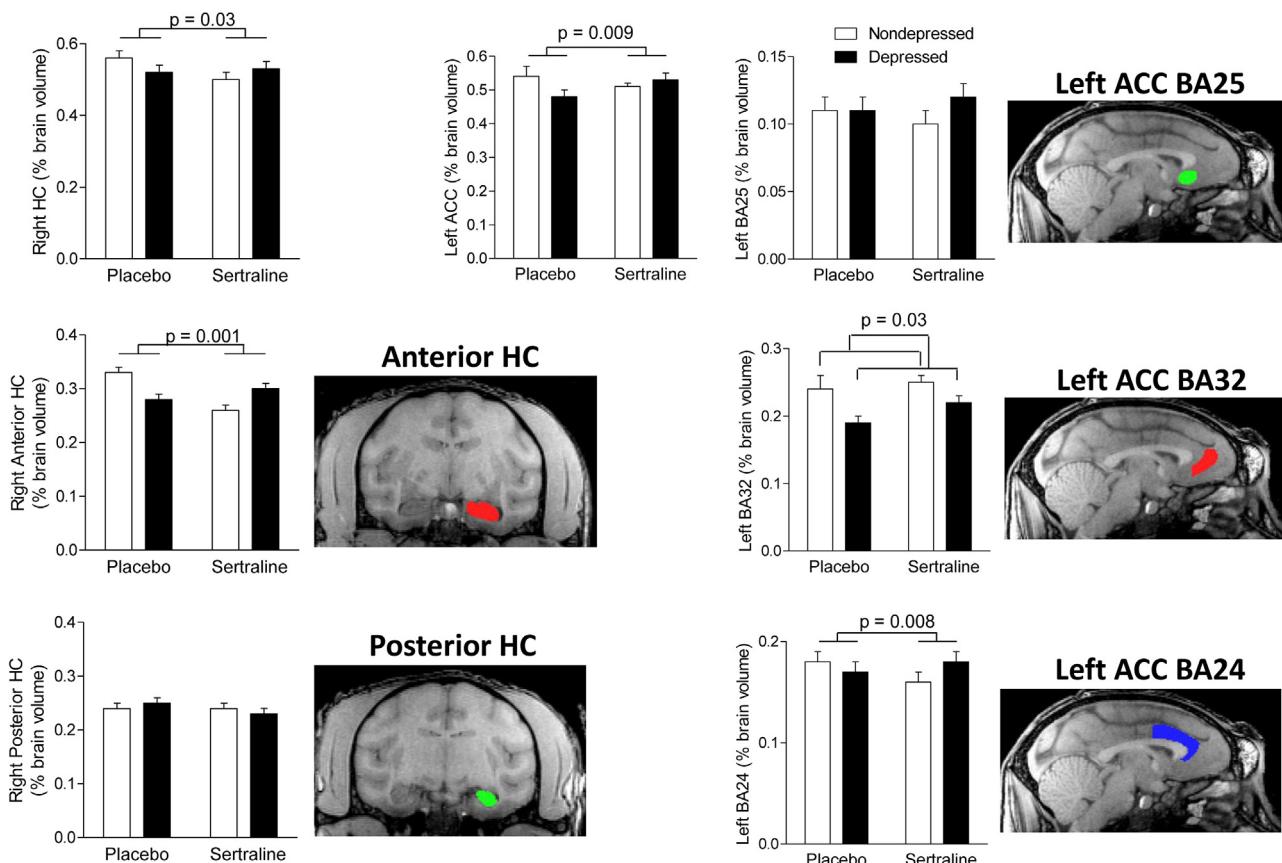


Fig. 5. Differential effects of SSRI on neuroanatomy in depressed and nondepressed monkeys. The volume of the right hippocampus (HC) was lower in placebo-treated depressed monkeys compared to nondepressed monkeys, an effect that was reversed with sertraline treatment, and limited to the right anterior HC. Left Brodmann's area (BA)32 was smaller in depressed compared to nondepressed monkeys (main effect of depression). While placebo-treated depressed monkeys had smaller left anterior cingulate cortex (ACC) volume, sertraline treatment increased this. In nondepressed monkeys, sertraline reduced left BA24 volume. SSRI, selective-serotonin reuptake inhibitor.

Table 2

Correlations between coronary artery atherosclerosis extent and volume of brain regions of interest.

	Right Amyg	Left Amyg	ACC 25	ACC 32	Ant HC	Post HC
DEPRESSED (n = 19)						
LAD	-0.48	-0.12	0.55*	-0.28	0.10	-0.42
LCX	-0.45	-0.15	0.40	-0.21	0.11	-0.57*
RCA	-0.32	-0.10	0.28	-0.18	-0.05	-0.49*
Mean CAA	-0.44	-0.13	0.43	-0.23	0.05	-0.52*
NONDEPRESSED (n = 22)						
LAD	0.21	0.29	-0.08	0.39	0.26	0.16
LCX	0.33	0.33	0.02	0.09	0.47*	0.16
RCA	0.33	0.35	0.02	0.28	0.43*	0.11
Mean CAA	0.34	0.38	-0.01	0.29	0.45*	0.16

Pearson correlations (r) between log transformed variables; correlations in bold were significant; LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery, mean CAA = mean of LAD, LCX, and RCA artery atherosclerosis extent. Amyg = amygdala; ACC 25 = anterior cingulate cortex area 25, ACC 32 = anterior cingulate cortex area 32; Ant HC = left anterior hippocampus; Post HC = left posterior hippocampus. All brain regions are expressed as percent brain volume.

* Denotes correlations that remained significant after adjusting for sertraline treatment (all p 's ≤ 0.05).

arteries and to a lesser extent the carotid arteries. This is an important observation because atherosclerosis extent at this age sets the stage for postmenopausal CHD and stroke risk, and SSRIs have recently been approved to treat hot flashes which may increase use in this age group. In contrast, sertraline protected against weight gain and pre-diabetic changes in carbohydrate metabolism. Sertraline treatment resulted in changes in serotonin neurotransmission, and volumetric changes in neural areas critical to mood

disorders. The neural effects of SSRIs appeared to be different in depressed versus nondepressed subjects, as are the relations between atherosclerosis and hippocampal volumes, which may have implications for individuals prescribed these medications for disorders other than depression. Given the number of different disorders for which SSRIs are prescribed, these observations may have important implications for human health. Taken together, these data suggest that a conservative approach to prescribing SSRIs for

a broad range of disorders or for long periods may be warranted, and that further study is critical given the widespread use of these medications.

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