Relationships of depressive behavior and sertraline treatment with walking speed and activity in older female nonhuman primates

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Abstract Depression is the most common mental health problem in aging persons and is a leading risk factor for physical disability, especially in women. Though antidepressant drugs such as serotonin reuptake inhibitors (SSRI) are commonly prescribed, epidemiological evidence reveals mixed effects of long-term antidepressant use on physical function and activity, possibly depending on depressive status. The purpose of this preclinical trial was to determine the relationships of depressive behavior and the potential for an SSRI treatment to modulate walking speed and activity patterns in older adult female cynomolgus monkeys (*Macaca fascicularis*). We evaluated the effects of depression and a commonly prescribed SSRI, sertraline HCl (20 mg/kg/day p.o.), on (a) walking speed, (b) accelerometry-derived activity (counts) and sedentariness (daytime 60-s sedentary epochs), and (c) observed locomotor and sedentary behaviors (% time) in adult female depressed and nondepressed monkeys ($n = 42$; 17.2 ± 1.8 years) during an 18 month pre-

treatment phase and an 18 month treatment phase using a longitudinal, stratified placebo–control study design. Monkeys that were depressed prior to treatment (19/42) subsequently had slower walking speeds ($F_D [1, 38] = 4.14$; $p \leq 0.05$) and tended to be more sedentary during the daytime ($F_D [1, 38] = 3.63$; $p \leq 0.06$). Sertraline did not affect depressive behaviors, walking speed, accelerometry-derived physical activity or sedentariness, or time observed in total locomotor or sedentary behavior (all $p > 0.10$). This study provides the first experimental demonstration of relationships between nonhuman primate behavioral depression and walking speed, activity, and sedentariness and provides evidence for a lack of an effect of SSRI treatment on these phenotypes.

Keywords Nonhuman primates · Depression · SSRI · Physical function · Walking speed · Sedentary

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Introduction

Advancing age is associated with declines in mobility and physical activity that increase risk of disability, chronic disease, loss of independence, and reduced quality of life (Newman et al. 2006; Paterson et al. 2007; Paterson and Warburton 2010; Studenski et al. 2011; Guralnik et al. 1995; Fusco et al. 2012). Depression is implicated in this disablement process; it is the leading cause of disability (impairment or activity limitation), the fourth leading cause of disease burden worldwide, and epidemiologic evidence indicates that

in community-dwelling persons aged 55–85 years, chronic depression is associated with a faster rate of physical decline than is observed in those with remitted depression or those who were never depressed (Penninx et al. 1998, 2000; Lever-van Milligen et al. 2017; Blazer 2003; Fiske et al. 2009). Depression is the most common mental health problem in aging populations with an estimated lifetime prevalence of 14–21% of persons aged ≥ 60 years (Blazer and Williams 1980; Steffens et al. 2000), and collectively neuropsychiatric disorders including depression account for $\sim 7\%$ of all disability in those over the age of 60 and 17.4% of years lived with disability (WorldHealthOrganization 2016). Given the marked increases in the number of older adults expected in the coming decades, assessing the effects of depression and its treatments on mobility and activity declines in middle-aged and older adults is a high biomedical research priority (Seals et al. 2015; Olshansky et al. 2009; Manton et al. 2009).

Antidepressant drugs are one of the most commonly prescribed medications in the USA (Olfson and Marcus 2009). This antidepressant use may escalate with age, with middle-aged and older adults substantially more likely to take antidepressants compared with younger adults (Fiske et al. 2009). For example, in 2005–2008, 14.5% of persons aged 60 years or older took antidepressants, compared with only 6.1% of those aged 18–39 years, despite similar or less frequent diagnosis of depression (Pratt et al. 2011). Women are more than 2.5 more likely to take antidepressants than men; 23% of women aged 40–59 years take some form of antidepressant, and an estimated 10–11% of women take antidepressants for reasons other than depression (Steffens et al. 2000; Pratt et al. 2011). Additionally, while total antidepressant use has increased from 1999 to 2010, the prevalence of long-term use of antidepressants has more than doubled, from 3 to 7% of the population taking antidepressants for ≥ 24 months, accounting for 67% of all antidepressant users (Mojtabai and Olfson 2014). Of the antidepressants prescribed, selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed and are administered for depression as well as many other mood and nonmood-related disorders, including agitation and aggression in dementia and other degenerative neurologic conditions (Henry et al. 2011), chronic pain (Pergolizzi et al. 2013), hot flashes (Shams et al. 2014), and stroke recovery (Mead et al. 2012). Given their widespread use in depressed and nondepressed persons, as well as the upsurge in

prevalence and long-term use of antidepressants among middle-aged and older women, understanding the impact of SSRI's effects on physical health beyond depressive symptom management is an important public health consideration.

Despite the prevalence of prescribed SSRIs, there are no experimental clinical trials to determine whether these antidepressants are safe or efficacious for mitigating the impact of depression on mobility and activity. Further, few long-term clinical studies have assessed outcomes related to mobility or physical activity, and those that have demonstrated mixed results, likely depending on depression status. For example, nursing home residents with untreated depression exhibited elevated risk of functional limitation and loss of activities of daily living over a 9-year follow-up compared with residents either without depression or with depression treated by antidepressants (Luo et al. 2015). Depression, as well as long-term antidepressant use (> 1 year) in a nationally representative sample of older adults, was associated with an increased risk of functional limitation (An and Lu 2016), and there did not appear to be differences by antidepressant type in this study. A recently developed comprehensive drug-based index of physical function for older adults ranked the commonly prescribed SSRI, sertraline HCl, as one of the 10 drugs identified out of a list of 600 + medications with the greatest negative impact on physical function in older adults (Hall et al. 2017). These studies underscore the hypothesis that treatment with antidepressant sertraline may not be beneficial and could exacerbate risk of physical function declines with aging.

Long-term randomized clinical trials are unlikely given cost and ethical considerations; therefore, preclinical investigations are needed to assess the effects of long-term antidepressant treatment in depressed and nondepressed animals. We investigated adult female cynomolgus monkeys (*Macaca fascicularis*), an established model of spontaneous depression, social stress, and age-related physical dysfunction (Shively et al. 1986, 2008, 2012, 2015; Willard and Shively 2012). The relationships between depressive behavior and the effects of the commonly prescribed SSRI, sertraline HCl, on physical function were assessed over a 3-year study with an 18-month treatment phase using a longitudinal, stratified, placebo-controlled design. We hypothesized that depression would be associated with slower walking speed, less physical activity, and greater sedentariness and that sertraline treatment would attenuate these differences in depressed animals. The

clinically meaningful primary trial outcomes were (a) walking speed, and (b) accelerometry-determined physical activity and sedentariness; these were supported by (c) observations of locomotor and sedentary behaviors (secondary outcomes). Finally, since both depression and poorer physical function/activity may be associated with psychosocial stress and low socioeconomic status in humans (Lorant et al. 2003, 2007; Missinne and Bracke 2012; Ruiz-Perez et al. 2011; Plouvier et al. 2016; Brunner et al. 2009), we constructed regression models to explain the variance in walking speed, total activity and sedentariness based on depression, anxiety, and social status.

Materials and methods

Subjects

Forty-five adult pre-menopausal female cynomolgus monkeys were imported from Indonesia (Institute Pertanian Bogor, Bogor, Indonesia) and placed into social groups in indoor climate controlled pens ($n = 4\text{--}5/\text{pen}$; $3.05\text{ m} \times 3.05\text{ m} \times 3.05\text{ m}$; 12:12-h light/dark cycle) following a 1-month quarantine. All monkeys

were fed a Western-like diet containing 44% of calories from fat and 0.29 mg/Cal cholesterol, comparable to a human consumption of 500 mg cholesterol/2000 Cal, or 2 eggs per day as detailed in previous reporting of the trial design and primary outcomes (Shively et al. 2014, 2015; Willard et al. 2015). At arrival, the monkeys were approximately 15.7 ± 0.3 years as estimated by dentition (approximate human equivalent 48 years) and were about 18.7 years of age on average at the end of the treatment phase (approximate human equivalent 57 years). All study procedures complied with the institutional, state, and federal laws for the use of nonhuman primates in laboratory settings and were approved by the institutional animal care and use committee.

Experimental design (Fig. 1)

This 3-year stratified placebo–control study was divided into an 18-month pre-treatment phase and 18-month treatment phase. During the pre-treatment and treatment phases combined, three animals died of causes unrelated to the experiment and 42 subjects completed the study (Shively et al. 2015). Behavioral observations were conducted routinely across the pre-treatment phase and subjects exhibiting depressive behavior rates above the

Fig. 1 Experimental design. This was a stratified placebo–controlled trial in 42 middle-aged socially housed female pre-menopausal cynomolgus macaques (*Macaca fascicularis*). The monkeys consumed a Western diet and had routine behavioral observations to assess depression, anxiety, locomotion, and social status during weekly focal observation periods throughout the 3-year trial. The trial was subdivided into an 18-month pre-treatment phase and an 18-month treatment phase; during

the 18-month treatment phase, the monkeys were assigned to oral sertraline (20 mg/kg) or placebo balanced on pre-treatment depressive behavior and body weight. In the latter part of both the pre-treatment and treatment phases, the primary outcomes for this analysis were assessed: (1) walking speed, (2) accelerometry-derived 24-h total physical activity counts, and (3) accelerometry-derived daytime sedentariness (number of 60-s epochs without recorded activity)

mean rate across the pre-treatment phase were classified as depressed (19/42 monkeys depressed). Towards the end of the pre-treatment phase, primary outcomes of walking speed and remote physical activity monitoring (accelerometry) were assessed (Shively et al. 2014, 2015; Silverstein-Metzler et al. 2016). Monkeys were then trained to run into a dosing cage for daily oral administration of study drug or vehicle (in pudding) and randomized to either sertraline HCl (Zoloft®; 20 mg/kg/day; $n = 21$) or placebo ($n = 21$) using a stratified procedure balanced on pre-treatment depressive behavior, body weight, and iliac artery atherosclerotic extent (Shively et al. 2014, 2015).

Sertraline was orally administered with a gradually increasing dose over 4 weeks until the desired dose of 20 mg/kg was achieved. As previously reported (Ruiz-Perez et al. 2011), circulating concentrations of sertraline and its primary metabolite desmethylsertraline were similar to those observed in patients treated for depression (Shively et al. 2014; Reis et al. 2004) and cerebrospinal fluid concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) decreased ($p < 0.001$) in response to sertraline indicating that the drug crossed the blood–brain barrier and affected central serotonergic metabolism similarly to that observed in patients treated with sertraline (Sheline et al. 1997). Towards the end of the 18-month treatment phase, walking speed, accelerometry-derived activity, and sedentariness were remeasured.

Subject characteristics

Body weight and *trunk length* were measured at the end of the pre-treatment phase and 16 months after the treatment phase. *Body mass index* (BMI) was calculated from ratio of the weight to the square of the trunk length (Silverstein-Metzler et al. 2016). Body composition including *total body fat* and *lean mass* was determined using dual-energy X-ray absorptiometry (Hologic Discovery A Dual X-ray Bone Densitometer, Bedford, MA) on anesthetized animals; percent fat and lean mass were calculated as a percent of whole body mass (Silverstein-Metzler et al. 2016).

Heart rate was determined via telemetry as described previously. Briefly, monkeys were jacketed with a portable electrocardiogram telemetry unit; heart rate was recorded for 24 h and an average was calculated for analysis (Shively et al. 2009, 2015). *Atherosclerosis extent* was measured as the area between the internal

elastic lamina and the lumen of the biopsied left common iliac artery reported in detail elsewhere (Shively et al. 2015).

Walking speed

Usual walking speed was quantified via stopwatch as the time it took the monkey to traverse a minimum of 3 ft at a normal pace without provocation (i.e., not fleeing or instigating an attack) (Shively et al. 2012). Assessments of usual walking speed were conducted during the day (0900–1600 h) over the course of a month towards the end of the pre-treatment and treatment phases, as previously reported (Shively et al. 2012). A minimum of five valid instances were used to calculate the mean speed as time per distance traversed.

Accelerometry-derived physical activity and sedentariness

Physical activity was assessed by recording activity counts during 24 h monitoring using Actigraph accelerometry units (Actigraph 7164 uniaxial activity monitor, analyzed with ACTILIFE-Desktop Software, Pensacola, FL) (Silverstein-Metzler et al. 2016). Each monkey was sedated and fitted with a nylon mesh protective jacket over a portable actigraphy unit. After a 24-hr sedation recovery period, activity counts were recorded for the following 24-hr. Counts were summed over each hour and over the 24-h recording period.

Sedentariness was determined as the number of 60-s epochs with no activity counts and summed for each hour. Daytime sedentariness was determined as the total number of sedentary epochs during daytime hours only (600–1900 h).

Behavioral observations

Behavior observations were recorded during 10-min focal animal observations, six to eight times per month, counterbalanced for time of day, for 12 months during the pre-treatment phase and 12 months during the treatment phase (total 33.3 focal hours per monkey), using previously described and validated focal techniques (Shively et al. 2008, 2014). Primary behavior outcomes included (1) depressive behavior, (2) anxious behavior, (3) social status, (4) locomotion, and (5) sedentary behaviors.

Depressive behaviors in female cynomolgus macaques have been previously defined and well documented (Shively et al. 2008; Willard and Shively 2012). The operational definition of depressive behavior includes three components: (a) sitting in a slumped or collapsed body posture, (b) a relative lack of responsiveness to environmental stimuli, and (c) eyes open (to distinguish from sleep). The average frequency/hour of observed depressive focal behavior was calculated. Twenty-three monkeys (55%) displayed little to no depressive behaviors (0–4 observed depressive instances) during the pre-treatment phase and were considered nondepressed in the present analysis.

Behavioral indices of anxiety were recorded as the frequency/hour of observed self-directed behaviors including scratching (> 1 s repeated skin scratching with fingertips) and self-grooming (combing of skin, hair, teeth, or nails with hands) based on previous studies (Shively et al. 2015, 2017; Willard et al. 2015).

Social status was determined monthly based on the direction of the outcome of agonistic interactions, as previously reported (Shively et al. 1986). Social status was averaged during the pre-treatment and treatment phases for analysis (Shively et al. 2014). Social status hierarchies were linear and stable over the course of the experiment.

Locomotion was recorded as traversing space at any speed with a minimum of three continuous steps. Locomotion was quantified as the percentage of time spent in observed behaviors per hour.

Sedentary behavior was defined as behavior or activity performed without locomotion and included lying down and seated behaviors (resting, alert active watching, or being groomed), and further classified as sedentary behavior observed while in a depressive posture or nondepressed sedentary behavior (alert, scanning, or resting). Sedentary behaviors were quantified as the percentage of time spent in observed sedentary activities per hour.

Statistics

Data are presented as mean $\pm$ SEM (figures) or mean $\pm$ SD (tables and text). Statistical analysis was performed with the SPSS software (v21, IBM). Prior to primary analysis, normality of each variable was assessed with the Kolmogorov–Smirnov test. A basement effect was noted for percent time spent in observed locomotor and depressive behaviors; square root transformation was

used to reduce skewness in these data. No outliers (> 3 SD) were identified for walking speed or sedentary activity; one outlier was identified with 24-h activity counts (nondepressed, sertraline treated at the end of 18 month treatment phase), but removal did not alter primary findings or interpretation. Homogeneity of variance was assessed by Levene's test ($p > 0.05$). Subject characteristics compared at pre-treatment by 2 (depression: depressed, nondepressed) $\times$ 2 (treatment: sertraline, placebo) ANOVA. The remaining dependent variables were analyzed by a 2 (time, within factor) $\times$ 2 (pre-treatment depression, between factor) $\times$ 2 (treatment, between factor) mixed model ANOVA. All tests were two-sided; the α -level for significance was 0.05; effect sizes (Cohen's d) and trends (α -level of $p < 0.1$) are reported.

The associations between dependent variables were determined by Pearson correlation coefficients (r). The relations between depressive behavior at pre-treatment and changes in walking speed, activity, and sedentariness over the 18-month treatment phase were examined with independent linear regression models (coefficient of determination; R^2), and the contribution of age, anxiety behavior, social status, and sertraline treatment to these relations was assessed by the hierarchical linear regression model. An absence of multicollinearity for the explanatory variables was verified by variance inflation factor (VIF) and tolerance.

Results

Pre-treatment subject characteristics

Means, SDs, and statistics for animal characteristics at pre-treatment phase are depicted in Table 1. As previously observed, depressed animals had a greater frequency of observed depressive behavior and were of lower social rank. Depressed animals also had significantly lower body mass, BMI, body fat, and lean mass and higher 24-h heart rates than nondepressed animals, though no differences were observed in anxiety behaviors (Shively et al. 2008, 2015; Willard and Shively 2012; Silverstein-Metzler et al. 2016). Pre-treatment of the sertraline- and placebo-treated groups did not differ in depressive behavior, body mass, atherosclerotic extent, anxiety behaviors, social rank, body composition, or heart rate between the treatment groups (all $p > 0.10$).

Table 1 Subject characteristics at the end of pre-treatment phase before sertraline administration was initiated

	Nondepressed		Depressed		Effects			
	Sertraline	Placebo	Sertraline	Placebo	Depression		Treatment	
	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	F_D	p	F_{Tx}	p
<i>n</i> (female)	11	12	10	9				
Age (years)	17.9 $\pm$ 2.0	17.3 $\pm$ 1.4	17.5 $\pm$ 2.2	16.2 $\pm$ 1.8	1.71	0.19	2.54	0.11
Depressive behavior	0.01 $\pm$ 0.02	0.01 $\pm$ 0.02	1.37 $\pm$ 1.52	2.10 $\pm$ 3.30	10.8	< 0.01	0.50	0.41
Anxiety behavior	44.1 $\pm$ 14.6	42.9 $\pm$ 22.6	42.2 $\pm$ 22.2	42.0 $\pm$ 11.0	0.06	0.92	0.02	0.99
Social status	0.73 $\pm$ 0.47	0.67 $\pm$ 0.49	0.40 $\pm$ 0.52	0.38 $\pm$ 0.52	3.90	0.05	0.01	0.79
Body mass (kg)	4.0 $\pm$ 0.9	3.9 $\pm$ 1.0	3.1 $\pm$ 0.2	2.8 $\pm$ 0.4	21.1	< 0.01	0.89	0.37
BMI (kg/m ²)	44.8 $\pm$ 8.0	51.7 $\pm$ 9.2	39.7 $\pm$ 3.9	39.5 $\pm$ 4.2	15.9	< 0.01	2.45	0.11
Body fat (%)	19.8 $\pm$ 6.6	23.1 $\pm$ 10.9	14.9 $\pm$ 2.8	17.6 $\pm$ 4.7	5.34	0.03	1.84	0.20
Lean mass (%)	76.4 $\pm$ 6.3	73.3 $\pm$ 10.5	81.1 $\pm$ 2.7	78.4 $\pm$ 4.4	5.2	0.03	1.8	0.18
Heart rate (bpm)	131 $\pm$ 17	139 $\pm$ 10.8	149 $\pm$ 15	148 $\pm$ 22	7.29	0.02	0.40	0.63
Iliac artery atherosclerosis (mm ²)	0.03 $\pm$ 0.06	0.16 $\pm$ 0.19	0.10 $\pm$ 0.19	0.06 $\pm$ 0.09	0.08	0.82	0.81	0.36
Walking speed (cm/s)	62.7 $\pm$ 14.0	68.0 $\pm$ 10.8	69.9 $\pm$ 13.3	70.1 $\pm$ 9.7	1.52	0.23	0.51	0.48
24-h activity (count)	32.9 $\pm$ 27.7	24.9 $\pm$ 10.3	21.4 $\pm$ 11.6	21.7 $\pm$ 12.5	1.91	0.18	0.53	0.47
Sedentariness (epochs in 24-h)	20.9 $\pm$ 11.0	20.0 $\pm$ 11.3	18.4 $\pm$ 7.5	24.2 $\pm$ 9.8	0.08	0.79	0.61	0.44

Values presented as mean $\pm$ SD. Effects determined using 2 (F_D = depressed, nondepressed) $\times$ 2 (F_{Tx} = placebo, sertraline) analysis of variance. Italics: $p \leq 0.10$. Nondepressed: monkeys exhibiting little to no depressive behavior; depressed: monkeys exhibiting depressive behavior greater than the mean rate during the pre-treatment phase. Sert: sertraline-treated; Pl: placebo-treated. Depressive and anxiety behaviors are rates of observed behavior during focal window (frequency/hour). Social status as relative social rank on a scale of 0–1 for pens of 4–5 animals: 1 = dominant, 0 = subordinate. Body fat (%) and lean mass (kg) were determined from the DEXA scan. Heart rate is mean 24 h heart rate in beats/min. Iliac artery atherosclerosis (mm²) was determined from a biopsy of the left common iliac artery; groups were balanced according to depression, body mass, and atherosclerotic extent. Total physical activity was assessed by 24-h accelerometry counts; daytime sedentariness was determined by number of 60-s epochs without an accelerometer-detected activity count during daylight hours

Behavioral effects of depression and sertraline

As seen in Table 2 and as reported previously (Shively et al. 2014), depressive behavior increased but anxiety behaviors were mitigated with sertraline over the 18-month treatment phase. Depressed animals had a significantly greater increase in the rate of observed depressive behaviors compared to their nondepressed counterparts as evidenced by significant depression $\times$ time interaction ($p < 0.001$), with no significant effect of sertraline treatment on depressive behavior ($p = 0.38$) or depression $\times$ treatment $\times$ time interaction ($F_{D \times Tx}$ [1, 38] = 2.03; $p = 0.16$; Cohen's $d = 0.464$). In contrast, behavioral indicators of anxiety were significantly reduced in animals following the 18-month sertraline treatment ($p = 0.04$), with no difference between depressed and nondepressed animals ($p = 0.78$) or

depression $\times$ treatment $\times$ time interaction ($F_{D \times Tx}$ [1, 38] = 0.302; $p = 0.59$; Cohen's $d = 0.180$). Social status was stable across time, with no significant interaction effects of depression $\times$ time ($p = 0.78$) or sertraline treatment $\times$ time ($p = 0.24$), or depression $\times$ treatment $\times$ time ($F_{D \times Tx}$ [1, 38] = 0.07; $p = 0.80$; Cohen's $d = 0.090$).

Effects of depression on walking speed, physical activity, and sedentariness over time

As seen in Fig. 2 and Table 1, there were no significant differences between nondepressed and depressed animals during the pre-treatment phase in walking speed, 24-h physical activity, or daytime sedentary epochs (2 $\times$ 2 ANOVA; all $p > 0.10$). A depression $\times$ time interaction was observed for walking speed revealing

Table 2 Change in observed rate of depressive and anxiety behaviors and social status in nondepressed and depressed animals treated with sertraline or placebo

	Nondepressed		Depressed		Effects					
	Sertraline	Placebo	Sertraline	Placebo	Depression $\times$ time			Treatment $\times$ time		
	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	F_D	p	d	F_{Tx}	p	d
Depressive behavior	0.01 $\pm$ 0.02	0.01 $\pm$ 0.02	1.37 $\pm$ 1.52	2.10 $\pm$ 3.30	13.8	≤ 0.01	1.2	0.78	0.38	0.29
Anxiety behavior	− 7.4 $\pm$ 7.7	− 2.1 $\pm$ 16	− 8.3 $\pm$ 9.0	+ 0.72 $\pm$ 6.8	0.08	0.78	0.09	4.45	0.04	0.69
Social status	− 0.02 $\pm$ 0.14	+ 0.03 $\pm$ 0.12	− 0.02 $\pm$ 0.08	+ 0.01 $\pm$ 0.10	0.08	0.78	0.09	1.46	0.24	0.39

Results are reported previously in (Willard et al. 2015). Effects determined using 2 (time: pre-treatment, treatment phase) $\times$ 2 (F_D = depressed, nondepressed) $\times$ 2 (F_{Tx} = sertraline, placebo) analysis of variance. For simplicity, values are presented in table as mean change: (treatment–pre-treatment) $\pm$ SD. Italics: $p \leq 0.10$, d = Cohen's d estimate of effect size. Nondepressed: monkeys exhibiting little to no depressive behavior; depressed: monkeys exhibiting depressive behavior greater than the mean rate during the pre-treatment phase. Depressive and anxiety behaviors are rates of observed behavior during focal window (frequency/hour). Social status as relative social rank on a scale of 0–1 for pens of 4–5 animals: 1 = dominant, 0 = subordinate

differential change in walk speed over time for depressed and nondepressed animals (Fig. 2A; F_D [1, 38] = 4.14; p = 0.048; Cohen's d = 0.659); posthoc analysis revealed marginal decline in walking speed over the 18-month treatment phase in the depressed animals (− 2.74 $\pm$ 12.6 cm/s; p = 0.50) and an increase in walking speed in the nondepressed animals (+ 5.60 $\pm$ 14.0 cm/s; p = 0.01). Total physical activity declined over the 18-month treatment phase similarly for nondepressed and depressed monkeys (Fig. 2B; time main effect: F_{Time} (An and Lu 2016; Reis et al. 2004) = 7.83; p = 0.01; Cohen's d = 0.934; depression $\times$ time; F_D (An and Lu 2016; Reis et al. 2004) = 0.13; p = 0.76; Cohen's d = 0.110). The number of daytime sedentary epochs may increase over time in depressed animals only, as evidenced by a nonstatistically significant trend (Fig. 2C; depression $\times$ time; F_D (An and Lu 2016; Reis et al. 2004) = 3.633; p = 0.060; Cohen's d = 0.617).

Sertraline effects on walking speed, total activity, and sedentariness

There were no significant differences between sertraline- and placebo-treated animals in the primary outcome measures (Fig. 3). During the pre-treatment phase, walking speed, 24-h total physical activity, and daytime sedentary epochs were similar between treatment groups (Table 1; 2 $\times$ 2 ANOVA; all p > 0.10). No

significant effects were observed in primary outcomes over time in sertraline- versus placebo-treated animals: walking speed (treatment $\times$ time, F_{Tx} [1, 38] = 1.027; p = 0.32; Cohen's d = 0.327), total physical activity (treatment $\times$ time, F_{Tx} (An and Lu 2016; Reis et al. 2004) = 0.128; p = 0.72; Cohen's d = 0.127), and daytime sedentary epochs (treatment $\times$ time, F_{Tx} (An and Lu 2016; Reis et al. 2004) = 0.154; p = 0.70; Cohen's d = 0.127). Moreover, no significant depression $\times$ treatment $\times$ time interactions were observed for walking speed ($F_D \times Tx$ (An and Lu 2016; Ruiz-Perez et al. 2011) = 0.106; p = 0.75; Cohen's d = 0.110), total physical activity ($F_D \times Tx$ (An and Lu 2016; Reis et al. 2004) = 0.201; p = 0.56; Cohen's d = 0.356), or daytime sedentary epochs ($F_D \times Tx$ (An and Lu 2016; Ruiz-Perez et al. 2011) = 0.159; p = 0.22; Cohen's d = 0.408).

Effects of depression and sertraline on observed locomotor and sedentary behaviors

Pearson correlation analyses at pre-treatment and treatment (Supplemental Table 1) revealed significant correlations between measures of sedentariness, activity, and walking speed. Negative correlations were observed between accelerometry-derived measures of total physical activity and daytime sedentariness such that higher total activity was associated with fewer recorded sedentary epochs (both p < 0.001). Walking speed was significantly correlated with percent time observed in

Fig. 2 Walking speed decreased and sedentariness increased over time in depressed animals, whereas total activity declined similarly in depressed and nondepressed monkeys. Walking speed and accelerometry-assessed physical activity and sedentariness in nondepressed (green) and depressed (blue) monkeys during pre-treatment and 18-month treatment phase. Bars are mean $\pm$ SEM; circles represent individual monkeys. Walking speed changed differently over time for depressed and nondepressed animals ($p = 0.048$; Cohen's $d = 0.659$); posthoc analysis revealed a marginal change in walking speed over the 18-month treatment phase in the depressed animals ($p = 0.50$) and an increase in

walking speed in the nondepressed animals ($p = 0.01$) (a, b). Total physical activity as assessed by 24-h accelerometry counts, declined over the 18-month treatment phase similarly for nondepressed and depressed monkeys (time main effect: $p = 0.01$; depression $\times$ time: $p = 0.76$; c, d). Daytime sedentariness, determined by number of 60-s epochs without an accelerometer-detected activity count during daylight hours (0600–1900 h), increased over the 18-month treatment phase for all animals, but depressed animals tended to exhibit an exaggerated increase in the number of 60-s sedentary epochs (depression $\times$ time: $p = 0.060$; e, f). * $p < 0.05$ main effect for time

sedentary depressed behaviors such that faster walk speed was related to less time spent in sedentary depressed postures at pre-treatment ($p = 0.030$).

Effects of depression Supporting analyses of observed locomotor and sedentary behaviors revealed significant differences between nondepressed and depressed animals (Fig. 4). Nondepressed animals spent more time locomoting (depression main effect; F_D (An and Lu 2016; Ruiz-Perez et al. 2011) = 5.08; $p = 0.03$; Cohen's $d = 0.73$), and over the 18-month treatment phase, nondepressed animals increased the percent time spent

locomoting (depression $\times$ time; F_D (An and Lu 2016; Ruiz-Perez et al. 2011) = 4.56; $p = 0.039$; Cohen's $d = 0.69$) (Fig. 4A). Similarly, time engaged in sedentary behavior (Fig. 4B) was lower in nondepressed animals (depression main effect; F_D [1, 38] = 11.2; $p = 0.002$; Cohen's $d = 1.084$), and this did not change across the 18-month treatment phase (depression $\times$ time; F_D (An and Lu 2016; Ruiz-Perez et al. 2011) = 2.04; $p = 0.16$; Cohen's $d = 0.46$). To gain resolution regarding the types of sedentary behaviors that may be changing over time, sedentary nondepressed behaviors and sedentary depressed behavior were examined independently. No

Fig. 3 SSRI treatment did not alter walking speed, total activity, or sedentariness over time compared with placebo treatment in female monkeys. SSRI treatment effects on walking speed and accelerometry-derived physical activity and sedentariness in sertraline (20 mg/kg, black) or placebo (white) monkeys at pre-treatment or with 18-month treatment. Bars are mean $\pm$ SEM; circles represent individual monkeys at pre-treatment and the

following 18 months. No significant effects of treatment were observed in walking speed (**a**; Cohen's $d = 0.327$; $p = 0.32$), total physical activity as assessed by 24-h accelerometry counts (**b**; Cohen's $d = 0.127$; $p = 0.72$), or daytime sedentariness determined by number of 60-s epochs without an accelerometer-detected activity count during daylight hours (**c**; Cohen's $d = 0.127$; $p = 0.70$). * $p < 0.05$ main effect for time

change in percent time spent engaged in alert, scanning, or resting sedentary behavior was observed (all $p < 0.10$) (Fig. 4d), but a depression $\times$ time interaction was observed for percent time spent in depressive sedentary behavior (F_D (An and Lu 2016; Ruiz-Perez et al. 2011) = 18.2; $p < 0.001$; Cohen's $d = 1.38$), and posthoc analysis revealed an increase in depressed animals only ($p < 0.001$) (Fig. 4C).

Effects of sertraline treatment Supporting analyses of observed locomotor and sedentary behaviors revealed no significant differences between treatment groups (Fig. 5). At pre-treatment, there were no significant differences between sertraline compared with placebo-treated animals in observed locomotor or sedentary

behaviors (2×2 ANOVA; all $p > 0.10$). Sertraline treatment had no significant effect on observed locomotor behaviors (treatment $\times$ time, F_{Tx} [1, 38] = 0.85; $p = 0.36$; Cohen's $d = 0.30$; Fig. 5A) or sedentary behaviors (treatment $\times$ time, F_{Tx} [1, 38] = 1.86; $p = 0.15$; Cohen's $d = 0.44$; Fig. 5B). Likewise, neither alert/scanning/resting or depressive sedentary behavior changed differently with sertraline treatment compared with placebo ($p > 0.10$; Fig. 5D), though time spent in depressive posture did increase over the 18-month treatment phase for both groups (time main effect: F_{Time} [1, 38] = 37.5; $p < 0.001$; Cohen's $d = 0.138$), and a trend was observed for greater increase in sedentary depressed behavior in the sertraline-treated animals (depression $\times$ treatment $\times$ time, F [1, 38] = 3.176; $p = 0.08$; Cohen's $d = 0.58$) (Fig. 5C).

Fig. 4 Time observed in locomotor behavior was lower and time in sedentary behaviors was greater in depressed versus nondepressed female monkeys. Percent time spent observed in locomotor and sedentary behaviors in nondepressed (green) and depressed (blue) monkeys at pre-treatment and 18-month treatment phase. Bars are mean $\pm$ SEM. Percent time observed in locomotor activity (time spent traversing space with ≥ 3 continuous steps) was greater in nondepressed animals ($p = 0.03$) and increased during the treatment phase compared with depressed animals (**a**; Cohen's $d = 0.69$; $p = 0.039$). Time engaged in sedentary behavior (**b**)

was lower in nondepressed animals (Cohen's $d = 1.084$; $p = 0.002$), but this did not change across the 18-month treatment phase (depression $\times$ time; $p = 0.16$; Cohen's $d = 0.463$). Sedentary nondepressed behaviors (**c**; percent time alert, resting, or being groomed either seated or lying down) and sedentary depressed behavior (**d**) were examined independently. No change in percent time spent engaged in nondepressed sedentary behavior was observed (**d**; $p > 0.10$), but percent time spent in depressed sedentary behavior increased in depressed animals (**c**; Cohen's $d = 1.38$; $p < 0.001$). †depression main effect $p \leq 0.05$

Regression analyses of associations between depression and walking speed, physical activity, sedentariness

Multiple independent regression models were developed to explore the associations between depression and changes in the primary outcomes of walking speed, total activity, and sedentary epochs over time (Table 3). The rate of depressive behaviors during pre-treatment phase (used to distinguish nondepressed and depressed monkeys) explained 9% of the variance in the change in walking speed ($p = 0.050$) and daytime sedentary epochs ($p = 0.058$) over the 18-month treatment phase but only 1% of the variance in the change in total

physical activity ($p = 0.57$). To examine the contribution of potential covariates on these relations, age, rate of anxiety behaviors, social status, and sertraline treatment were entered into hierarchical regression models. The regression model with covariates included still explained 9% of the variance in change in walking speed and 4% of the variance in change in total physical activity, without significant contribution from anxiety, social rank, or treatment group. Though still nonsignificant, when covariates were considered in the model for sedentary epochs, 16% of the variance was explained, with trends emerging for associations of both depression and anxiety behaviors (both $p < 0.10$).

Fig. 5 Time observed in locomotor behavior was lower and time in sedentary behaviors was greater in depressed compared with nondepressed female monkeys. SSRI treatment effects on percent time spent observed in locomotor and sedentary behaviors in sertraline (20 mg/kg; black) or placebo (white) monkeys at pre-treatment or with 18-month treatment. Bars are mean $\pm$ SEM. Percent time observed in locomotor activity (time spent traversing space with ≥ 3 continuous steps) increased over time in both sertraline- and placebo-treated animals (**a**; time $\times$ treatment: $p = 0.36$; Cohen's $d = 0.307$). Time engaged in sedentary behavior (**b**) was similar for sertraline- and placebo-treated animals at pre-

treatment and treatment phases (**b**; $p = 0.15$; Cohen's $d = 0.300$). Sedentary nondepressed behaviors (**c**; percent time alert, resting, or being groomed either seated or lying down) and sedentary depressed behavior (**d**) were examined independently. No change in percent time spent engaged in nondepressed sedentary behavior was observed (**d**; Cohen's $d = 0.483$; $p > 0.10$), but percent observation time spent in depressed sedentary behavior increased over time in sertraline- and placebo-treated animals (**c**; depression $\times$ treatment $\times$ time: $p = 0.08$, Cohen's $d = 0.58$; time main effect: $p < 0.001$, Cohen's $d = 1.98$). * $p < 0.05$ main effect for time

Discussion

This is the first published study examining the effects of depression and long-term SSRI treatment on walking speed and sedentariness in a placebo-controlled randomized preclinical trial. The key finding is that depression and/or its determinant may exacerbate age-related differences in walking speed and increase sedentariness, but there was no effect of sertraline treatment in female cynomolgus monkeys. This finding is consistent with the clinical observations of (Luo et al. 2015) of increased risk of developing functional impairment and

physical disability in older persons with depression. In contrast to clinical literature, sertraline treatment did not attenuate the age- or depression-related changes in walking speed, activity, or sedentariness in either depressed or nondepressed monkeys (An and Lu 2016; Hall et al. 2017). These data suggest that deleterious effects of antidepressants on functional decline observed in clinical studies may not be a drug effect per se, but may stem from other uncontrolled characteristics of clinical study participants.

These results are compelling, because to our knowledge, this is the first study to report an effect of

Table 3 Regression models of associations between depression and walking speed and accelerometer-derived physical activity and sedentariness following the 18-month treatment phase, and

effect of age, anxiety, relative social rank, and treatment group on these associations

	Beta	Standard error	Partial correlation	<i>p</i> value
Walking speed				
$R^2 = 0.09$				
Depression	− 8.34	4.26	− 0.30	0.05
$R^2 = 0.13, p = 0.37$				
Depression	− 9.45	4.52	− 0.33	0.04
Age	0.51	1.31	− 0.06	0.70
Anxiety	− 0.05	0.12	0.06	0.72
Social status	− 5.57	6.94	− 0.13	0.43
Treatment group	3.76	4.41	0.14	0.40
Physical activity				
$R^2 = 0.01$				
Depression	− 22.8	40.4	− 0.09	0.58
$R^2 = 0.04, p = 0.92$				
Depression	17.4	44.4	0.06	0.70
Age	0.29	12.7	0.04	0.82
Anxiety	− 0.09	0.01	− 0.12	0.48
Social status	− 36.3	67.2	− 0.09	0.59
Treatment group	− 22.3	43.4	− 0.09	0.61
Sedentariness				
$R^2 = 0.09$				
Depression	5.32	2.74	0.29	0.06
$R^2 = 0.16, p = 0.24$				
Depression	5.25	2.93	0.29	0.08
Age	0.28	0.85	0.05	0.75
Anxiety	0.14	0.08	0.29	0.08
Social status	− 2.04	4.49	− 0.08	0.65
Treatment group	0.41	2.86	0.02	0.89

depression on multiple independent physical function and activity-related outcomes in monkeys. First, this study employed observed measures of walking speed that translate to measures that are strongly predictive of mortality in humans (Studenski et al. 2011; Shively et al. 2012; Justice et al. 2015). Though an age-related decline in walking speed was not observed over time in this study, the change in walking speed over time diverged between depressed and nondepressed monkeys such that depressed animals walked slower than nondepressed. Secondly, the use of remotely monitored accelerometry to determine 24-h activity counts and sedentariness is an important strength. Though the effects of sertraline treatment on total physical activity

measured by an accelerometer in monkeys have been published previously (Silverstein-Metzler et al. 2016), to our knowledge, this is the first study to report daytime sedentariness. This distinction is clinically important, as emerging clinical evidence suggests that sedentary time may be as, or more, predictive of functional decline, disability, and death in older persons and represents a novel strategy for interventions (Katzmarzyk 2010; Biddle et al. 2016; Owen et al. 2010). In support, our findings show a clear increase in sedentariness over time that is related to physical activity but sensitive to exacerbation by depression. Moreover, the majority of clinical investigations report that sedentary behavior is a risk factor for developing depression (Teychenne et al.

2010). Our results suggest that this relation may not be unidirectional; depression and/or its determinants may also increase sedentary behavior over time, or alternatively, there could be some common factor underlying both sedentariness and depression. These measures were supported by rigorous weekly observations and recordings of a rich assortment of behaviors, categorized as locomotor and sedentary behaviors in the present study. We demonstrate that observed locomotor and sedentary behaviors are independent of the accelerometry-derived activity metrics and further support the deleterious effect of depression on locomotor behavior and sedentariness over time.

As previously reported, plasma concentrations of sertraline and desmethylsertraline demonstrated that the drug was successfully delivered via oral dosing and resulted in blood levels similar to those in patients (Reis et al. 2004) but did not improve behavioral indices of depression (Shively et al. 2014, 2017). We did not demonstrate an effect of sertraline on walking speed or sedentariness in depressed or nondepressed animals, which suggests that other uncontrolled factors may be implicated in the clinically observed risk of sertraline use on function. A number of other characteristics of the study that might affect functional declines and increase sedentary behavior were tightly controlled in the present design including sex, diet, other drug exposures, light/dark cycles, housing, and treatment compliance. Sertraline use in humans has known side effects that could be related to functional and activity-related outcomes including fatigue, tiredness, and gastrointestinal effects (Meijer et al. 2002; Ferguson 2001). However, the lack of sertraline effect on walking speed, accelerometry-derived physical activity or sedentariness, or time observed in total locomotor or sedentary behavior (all $p > 0.10$) does not indicate any appreciable off-target fatigue/tiredness effects leading to declines in activity and mobility, and the observed similarity in body weights and BMI between treatment groups suggests no difference in appetite or gastrointestinal distress with chronic sertraline administration. While other unknown variables may be implicated clinically, we show that the observed relations with depression were independent of social status and anxiety in female monkeys.

This study benefited from key design strengths. First, this study used a well-established nonhuman primate model of depression (Willard and Shively 2012; Shively et al. 2017). Depressed cynomolgus macaques share many physiological, neurobiological, and

behavioral characteristics of human depression, including reduced body mass, hypothalamic–pituitary–adrenal axis perturbations, autonomic dysfunction, increased cardiovascular disease risk, reduced hippocampal volume, altered serotonergic function, decreased activity levels, low ovarian steroid levels, and increased mortality (Shively et al. 2008, 2017; Willard and Shively 2012; Willard et al. 2015; Silverstein-Metzler et al. 2017; Shively and Willard 2012). In this investigation, we also confirm the susceptibility of depressed monkeys to exhibit functional declines and increased sedentariness as observed clinically at mid to late life (Bromberger and di Scalea 2009; Lenze et al. 2005; Cronin-Stubbs et al. 2000). Second, the study benefited from measurement of multiple conceptually related but independent outcomes related to function, activity, and sedentariness. Although functional assessments of walking speed and activity measures are common in studies of human health, analogous assessments in animal models and preclinical trials are rare (Justice et al. 2015). This is especially true for serial assessments conducted before and with treatment; the ability to estimate individual differences in walking speed, physical activity, and sedentariness assures that observed depression and treatment effects were likely not to be confounded by pre-treatment differences in the groups. Another strength is the use of stratified randomization to balance treatment groups controlling for pre-treatment differences in rates of depressive behavior. This design provided the opportunity for independent analysis of depression and sertraline treatment effects, eliminating an important confound characteristic of clinical studies. Finally, the lack of effects of sertraline on walking speed, activity, and sedentariness in nondepressed monkeys is as important as the null finding in depressed animals, especially considering that sertraline and other SSRIs are widely prescribed for health conditions other than depression in older women.

Taken together, the data presented here suggest that depression, but not chronic sertraline treatment, was accompanied by relatively slower walking speed, increased sedentariness, and less locomotor behavior during the late pre-menopausal years in which there is a greater vulnerability to functional declines and depression and high rate of SSRI used by women. Clinically, slower walking speeds and sedentary behavior set the stage for loss of independence and mortality, and our report supports observed relations between depression and risk of functional declines and physical disability. Sertraline did not attenuate depression-related changes

in walking speed or sedentariness and it did not exacerbate risk. Although the results of this nonhuman primate study are compelling, replication and the elucidation of mechanisms of action are needed to understand risk levels in patients, and the generalizability of the findings across sex and age needs to be assessed. Finally, there is need for long-term clinical trials to assess the benefits and potential risks of sertraline treatment in depressed and nondepressed persons who may be vulnerable to declines in function.

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Compliance with ethical standards All study procedures complied with the institutional, state, and federal laws for the use of nonhuman primates in laboratory settings and were approved by the institutional animal care and use committee.

Conflicts of interest The authors declare that they have no conflicts of interest.

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