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Behavioral depression is associated with increased vagally mediated heart rate variability in adult female cynomolgus monkeys (*Macaca fascicularis*)

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Abstract

Introduction: Depressive symptoms (DS) in humans are associated with decreased resting state vagal activity, but sex seems to moderate this association. Recently, in human females DS have been associated with greater or similar cardiac vagal activity compared to men in both, clinical and non-clinical samples. A previously validated animal model of behavioral depression was used in the present study to investigate the association of DS and cardiac vagal activity in non-human primates.

Methods: The root mean square of successive differences between adjacent heart beats (RMSSD) was used as an indicator of vagally-mediated heart rate variability in 24 hour heart rate recordings collected via telemetry in 42 adult female cynomolgus monkeys (*Macaca fascicularis*). Hierarchical regression models were used to estimate differences in RMSSD comparing monkeys with and without DS. To capture circadian variation patterns of RMSSD, additional quadratic, cubic and quartic terms of hour were added.

Results: Monkeys showing behavioral DS had higher overall 24-h RMSSD. The interaction term of daytime with DS and polynomials of hour contributed significantly to the variance across models.

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Disclosure Statement

The other authors of this study report no relevant conflict of interest with the subject matter or materials discussed in the manuscript

Conclusions: This is the first study investigating the association of DS and 24h cardiac vagal control in female non-human primates. Results replicate existing human studies showing higher cardiac vagal control in behavioral depressed vs. non-depressed female monkeys.

Keywords

Depression; Heart rate variability; sex difference; depressive symptoms; animal model; non-human primate

1. Introduction

Reduced resting state as well as overall cardiac vagal activity are associated with future morbidity and mortality from a host of disorders and conditions including cardiovascular disease and inflammatory dysregulation (Jarczok et al., 2014; Thayer et al., 2010; Thayer and Lane, 2007; Tracey, 2010). A non-invasive and widely applied measure of vagal activity is based on the variability of the heart rate (HR) time series. Rapid changes in HR (i.e. high variability) are attributed to changes in vagus nerve activity at the sinoatrial node of the heart. In healthy human subjects, substantial sex differences in cardiac vagal control have been reported with women showing greater power in the high-frequency band, indicating that despite increased mean HR, women show increased vagal activity (Koenig and Thayer, 2016). Of particular relevance, substantial sex differences have also been reported in the association of vagal activity with depressive symptoms (DS) such that resting state vagal activity is decreased in depressed men (compared to non-depressed controls) but increased or unchanged in depressed women (compared to controls) (Garcia et al., 2012; Kemp et al., 2010; Koenig et al., 2016; Thayer et al., 1998). A cross-lagged analysis (within subject level) over a 10-year period using the Whitehall II study data reported higher baseline cardiac vagal activity to be associated with a lower likelihood of incident DS at follow-up in men but not in women (Jandackova et al., 2016). In other studies, depressed women showed greater cardiac vagal activity compared to depressed men (Chambers and Allen, 2007; Verkuil et al., 2015). In particular, a momentary assessment study analyzed the association between sadness (a core symptom in depression) and 24h cardiac vagal activity using multilevel analysis in a sample of n = 60 apparently healthy employees in the US (Verkuil et al., 2015). The authors reported a significant moderation by sex such that women with higher levels of self-reported sadness showed overall higher levels of cardiac vagal activity compared to men.

Changes in cardiac vagal activity in depressed humans can occur from multiple factors such as medication intake and medication history (Kemp et al., 2016) day/night light cycles, diet, smoking, alcohol consumption, drug use, activity levels and age and should be accounted for. However, most of those factors can be controlled in animal models. Thus, animal models of depression can contribute significantly to the understanding of mechanism(s) underlying disease. However, the primary depression model is in rodents, but most rodent models are limited to males only (Willard and Shively, 2012). The prevalence of diagnosed depression in women is twice as high for both lifetime (women 15.4 %; men 7.8 %), and 12-months (women: 8.1 %; men: 3.8 %) compared to men in Germany (Busch et al., 2013). This 2:1 ratio is similar in other countries (Albert, 2015; Kendler and Gardner, 2014; Kessler, 2003;

Shively et al., 2005), although the overall prevalence differs between countries (Kessler and Bromet, 2013).

More in-depth investigations of mechanisms underlying the complex pathophysiology of depression would benefit substantially from the analysis of sex-specific animal models that closely resemble human physiology, neurobiology, and behavior. As such, modeling depression in adult female cynomolgus monkeys has been successfully implemented (Willard and Shively, 2012). Briefly, depressive behavior in socially housed female cynomolgus monkeys occurs in captivity without experimental manipulation. Socially subordinate females are more likely to display depressive behavior compared to their dominant counterparts; however not all subordinates display depressive behavior and some socially dominant animals do (Carol A Shively and Willard, 2012; Willard and Shively, 2012). Behavioral depression in adult female cynomolgus macaques is comparable to human depression in its physiological, neurobiological, and behavioral characteristics, including reduced body mass, hypothalamic-pituitary-adrenal axis perturbations, autonomic dysfunction, increased cardiovascular disease risk, reduced hippocampal volume, altered serotonergic function, decreased activity levels, and increased mortality (Carol A Shively and Willard, 2012; Willard and Shively, 2012). The menstrual cycles of female cynomolgus macaques are similar to those of female humans in terms of length and hormonal fluctuations. Behaviorally depressed female monkeys show low concentrations of ovarian steroids, with preserved menses (Carol A Shively and Willard, 2012; Willard and Shively, 2012). The macaque hippocampus parallels the cellular organization and connectivity patterns of the human hippocampus more closely compared to rats (Amaral and Lavenex, 2007), and macaques have complex and differentiated cortical areas, similar to those of human individuals, that are considered to play a key-role in human depression (Barbas et al., 2003; Carmichael and Price, 1994; Machado et al., 2008). Previously, we have observed reduced anterior hippocampal volume in untreated, behaviorally depressed female cynomolgus macaques. Postmortem in vitro analysis (Willard et al., 2009) and pre-mortem in vivo MR imaging (Willard et al., 2011) demonstrated region specific reductions in hippocampal volume in depressed versus nondepressed females. Differences in volumes of areas within the anterior cingulate cortex have also been reported (Willard et al., 2015).

Given the advantages of the cynomolgus macaque model to study pathomechanisms of depression, the objective of the present study was to replicate human findings on altered vagal activity using a validated animal model of behavioral depression. It was hypothesized that, similar to human females, behavioral depressed female cynomolgus monkeys show greater cardiac vagal activity, indexed by 24h HR variability compared to non-depressed controls.

2. Methods

2.1. Sample

Forty-two adult, reproductive-aged female cynomolgus monkeys were imported from Indonesia (Institut Pertanian Bogor, Bogor, Indonesia) and single cage quarantined for 1 month. After quarantine, the monkeys were randomly assigned to social groups of n = 4–5, in indoor pens (3.05 m × 3.05 m × 3.05 m), in a climate-controlled building, with 12:12-hour

light/dark, and water ad libitum. 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 (Groban et al., 2014). All procedures involving primates were conducted in accordance with institutional, state, and federal laws for the use of nonhuman primates in laboratory settings and approved by the institutional animal care and use committee.

2.2. Measures

2.2.1. Behavioral Depression—Depressive behavior in socially housed female cynomolgus monkeys occurs in captivity without experimental manipulation. 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 also (Carol A Shively and Willard, 2012; Willard and Shively, 2012). The definition of DS included three components: 1) exhibition of a slumped or collapsed body posture; 2) a relative lack of responsiveness to environmental stimuli to which other monkeys were attending; and 3) open eyes to distinguish this behavior from resting (Shively et al., 1997). This definition has been widely used by our laboratory and others (Camus et al., 2013; Chu et al., 2014; Hennessy et al., 2017; Qin et al., 2015; Willard et al., 2015; Willard and Shively, 2012), and demonstrated associations with numerous perturbations reminiscent of human depressive disorders (Williard and Shively 2012; Willard et al., 2015).

The frequency by which the monkeys were observed in the depressed posture was recorded for 10 minutes, twice/week, counterbalanced for time of day, for 12 months (an average of 17.1 h/monkey), using a focal animal technique that has been described in detail previously (Shively et al., 2008). Depressive behavior is easily recognizable; and inter-rater reliability, determined biannually, was ≥ 0.92. The average monthly frequency/hour that the monkeys exhibited this behavior was calculated from these observations. Similar to previous studies, 23 monkeys (55%) displayed little or no depressive behavior (four instances or less observed during the data collection phase, and were considered nondepressed in the analysis).

2.2.2. Vagal activity measures—Monkeys were captured, sedated with ketamine hydrochloride (10 mg/kg), and outfitted with a nylon mesh protective jacket over a portable electrocardiogram telemetry unit (Life Sensing Instrument Co, Tullahoma, TN, US). After overnight recovery from sedation, HR recordings started at approximately 07:00 am. HR was recorded for 24h as beat-to-beat intervals (IBI) at a sampling rate of 250 Hz.

HR analysis followed the Task Force Guidelines ("Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.," 1996). The 24-h IBI-data were decomposed into hourly intervals (clock hours) followed by calculation of an artefact rate per interval and the root mean square of successive differences (RMSSD). RMSSD was selected as the HRV measure as it has previously been shown to be a stable and valid indicator of parasympathetic vagal activity that is less affected by respiration and artefacts from body movement than other HRV measures (Penttilä et al., 2001).

2.2.3. Physical activity—Physical activity was assessed simultaneously by recording movement viaaccelerometry (ActiGraph GT3 × Triaxial Activity Monitor analyzed with ACTILIFE-Desktop Software, Pensacola, FL) (Shively, 1998). A portable actigraphy unit was attached to each nylon mesh protective jacket. After a 24h recovery period, activity was recorded for the next 24h, and the average activity over each hour was calculated for statistical analyses. Activity quantified during nighttime hours only (12:00–6:00am), was used as a surrogate measure for sleep disruption.

2.3. Statistical Procedure

Multilevel mixed effects linear regression models were calculated with maximum likelihood estimation to determine the association of depression (N/Y) and time of day (hour) on RMSSD, including an interaction of depression and time of day. A two-level hierarchical structure with hourly RMSSD estimates nested within monkeys was modeled. Time of day (hour) was additionally included with polynomial terms (quadratic, cubic and quartic) to approximate the diurnal variation of RMSSD. Bivariate (descriptive) and predicted were plotted including their according confidence interval to aid interpretation of these complex models. The model fit improvement was formally assessed using the likelihood ratio test. Analyses were performed using the linear mixed model (mixed) command in Stata version 14.2 SE (StataCorp. 2017, College Station, TX: StataCorp LP). The distribution of RMSSD was right-skewed and log-transformed accordingly to meet the assumptions of modelling. Two-tailed tests with alpha set at .05 were conducted.

3. Results

Sample characteristics of the monkeys are depicted in Table 1. There were significant group differences: monkeys showing no depressive behavior appear to have higher body weight and lower mean HR compared to their behavioral depressed counterparts. There were no differences in overall and night time activity counts.

Descriptive graphical analysis of RMSSD and daytime by depressed vs. non-depressed monkeys showed higher RMSSD in depressed monkeys compared to non-depressed controls (Figure 1). The model comprised on average of 29 observations on Level 1 (hours) nested in n = 42 female monkeys (Level 2). The main effect of the binary indicator of depression was not statistically significant (Model 1). Model fit was significantly improved by adding hour and the interaction term ($\chi^2_{(3)} = 23.67$; $p<0.001$) and the interaction term was statistically significant ($\chi^2_{(1)} = 4.01$, $p=0.045$). Adding the polynomials of hour further improved the models (LR-Test $\chi^2_{(6)} = 107.76$; $p<0.001$). Plotting the model prediction of RMSSD by DS revealed the underlying diurnal variation (see Figure 2) with the polynomials of hour approximating the diurnal variation. The grand mean by group was estimated to be RMSSD = 125.13ms and RMSSD 148.09ms for the non-depressed and the depressed groups, respectively (horizontal lines in Figure 2).

4. Discussion

This is the first study to address the association of cardiac vagal activity, indexed by 24h HRV in behavioral depressed vs. non-depressed female cynomolgus monkeys (Macaca

fascicularis). Female non-human primates classified as behaviorally depressed showed increased vagally-mediated HRV compared to non-depressed controls. These results replicate previous findings (Jarczok et al., 2016; Verkuil et al., 2015) in non-clinical human samples in support of a positive association between HRV and DS in females. Experimental studies have shown that human females show increased HRV when regulating their emotions by either suppression or reappraisal (Butler et al., 2006) and that amygdala activity and HRV are positively correlated in women but negatively correlated in men (Nugent et al., 2011).

The observations of this study are relevant to human health because the neurobiological characteristics of nonhuman primates in general, and cynomolgus monkeys in particular, are far more comparable to humans than it is the case for other animal models of depression. Importantly, non-human primate models support the role and differentiation of cortical regions particularly the prefrontal cortex (PFC), anterior cingulate, and subgenual cingulate cortex which are critically involved in human depression and vagal activity. These regions are well represented in the macaque brain, but not present or only rudimentarily defined in the primary animal model i.e. the rodent brain (Preuss, 1995; Willard et al., 2015; Wise, 2008). In addition, the nuclear organization and connectivity patterns in the hippocampus, a structure also implicated in human depression, is highly similar between macaques and humans (Amaral and Lavenex, 2007). Likewise the serotonergic system which is central to the neurobiology of stress and depression shares large similarities in macaques and humans. These neurobiological similarities suggest strong translational relevance of the findings reported here.

Adult female cynomolgus monkeys that exhibit behavioral depression also exhibit pathologies in multiple systems. These systems include perturbed endogenous rhythms such as high overnight HR, hypothalamic–pituitary–adrenal axis dysfunction, and reduced ovarian function as well as disruptions in energy homeostasis indicated by lower body weight, body mass, and activity levels (Shively et al., 2005). Also, changes in social behavior occur such as increased body contact and less time alone (Carol A. Shively and Willard, 2012). Moreover, the risk for coronary artery atherosclerosis is four times more extensive and mortality is increased as well compared to their nondepressed counterparts (Shively et al., 2009; Willard and Shively, 2012). Finally, decreased 5-HT1A binding potential in multiple brain areas have been reported in both, depressed cynomolgus macaques (Shively et al., 2006) as well as currently depressed and remitted humans, (Bhagwagar et al., 2004; Drevets et al., 1999; Sargent et al., 2000) indicating that these alterations reflect potential trait markers of depression. Reduced 5-HT1A binding potential is inversely correlated with telemetered HR as well as atherosclerotic extent in behaviorally depressed monkeys (Shively et al., 2009), which provides evidence to support a relationship between serotonergic deficits and autonomic dysfunction in primates.

Previously observed changes in social behavior in female cynomolgus monkeys when behaviorally depressed (Shively et al., 2009) coincide with increased cardiac vagal activity in this study. In humans, seeking social-support e.g. in reaction to sadness or distress can serve as a strategy to regulate negative emotions and this behavior has been shown to coincide with higher cardiac vagal activity, too (Geisler et al., 2013). Geisler et al. found that participants with higher cardiac vagal activity reported more often to seek social support to

cope with distress and sadness (Geisler et al., 2013). Although speculative, the high female proportion in both studies (67% and 76%) might have played a crucial role for these findings. Previous research has proposed different coping strategies in men and women that may result in different peripheral output (i.e. cardiac vagal activity): While men tend to show the “fight or flight” response more frequently, women tend to show the “tend and befriend” response (Taylor et al., 2000), an oxytocin and endogenous opioid mediated behavior. However, depressive disorder in humans is particularly associated with social impairments and poor social functioning, including less support seeking behavior. In both animals and humans, social stress is known to induce depression (Shively et al., 2005; Carol A Shively and Willard, 2012) – although not all stressful events lead to depression in both species. Improving the understand of factors underlying the (non)development of depression after stressful events may help to define and explore new avenues for both prevention and therapeutic intervention.

The cortical areas and projection pathways, known to be critically involved in depression in human beings, appear parallel in nonhuman primates (Barbas et al., 2003). In humans, the underlying neurobiological correlates of stress regulation and adaptive response are detailed by the neurovisceral integration model (Thayer and Lane, 2009). Vagally mediated parameters of HRV have been suggested to serve as a measure of emotion regulation capacity of a central autonomic network (CAN) on both, the tonic (e.g. resting state data) and phasic (e.g. during laboratory tasks) level, that might be depleted – leading to subsequent deficits and failures in emotion regulation (Smith et al., 2011; Thayer et al., 2012). In both species, the CAN regions are reciprocally connected to the heart as well as the periphery via parasympathetic and sympathetic neural pathways. Through this neural network, structures of the PFC can exert inhibitory control on subcortical areas, providing flexibility and adaptation to changing situational and environmental demands (Barbas et al., 2003; Lane et al., 2009; Thayer and Lane, 2009). Importantly, ventromedial PFC activity can exert an inhibitory control over amygdala activity in both species (Barbas et al., 2003; Lane et al., 2009; Thayer and Lane, 2009), and consequently may aid the inhibition of subcortical sympathoexcitatory circuits (i.e., associated with the fight or flight response) (Thayer and Lane, 2009).

Conclusions

This is the first study to show a positive association of behavioral depression with cardiac vagal activity, indexed by HRV in adult female cynomolgus monkeys (*Macaca fascicularis*). These results replicate similar findings in human females, and provide cross-species evidence for psychophysiological alterations in depression. These findings may inform future research on the etiology, diagnosis, course, and treatment of DS in humans.

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Highlights

- investigating 12 month behavioural depression and circadian variation of vagal activity
- depressed female monkeys show increased vagal activity
- replication of results in humans in an animal model
- cross-species evidence for psychophysiological alterations in depression

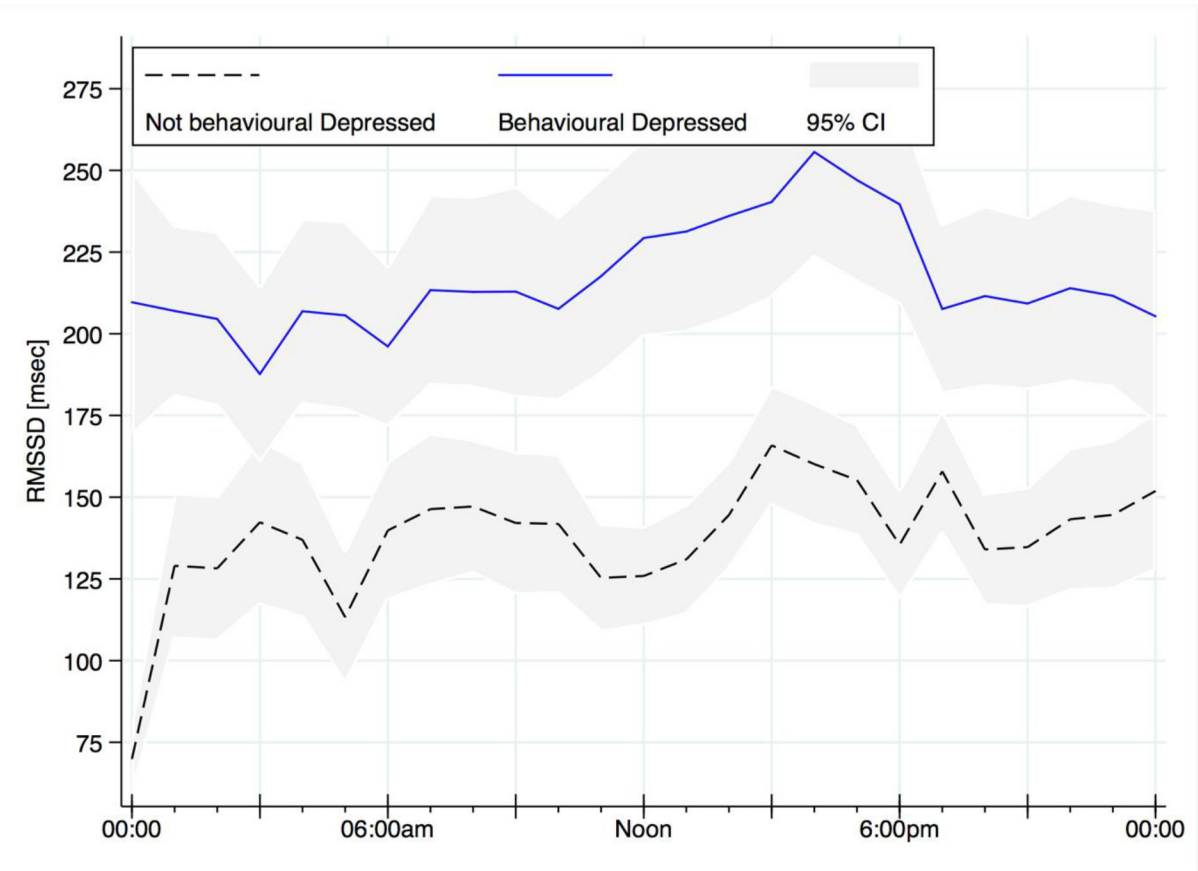

Figure 1: Descriptive average RMSSD by Depression (N=42)

Average RMSSD in behavioral depressed (solid line; N=19) vs. not depressed (Dashed Line; N=23) female adult cynomolgus monkeys across time of day

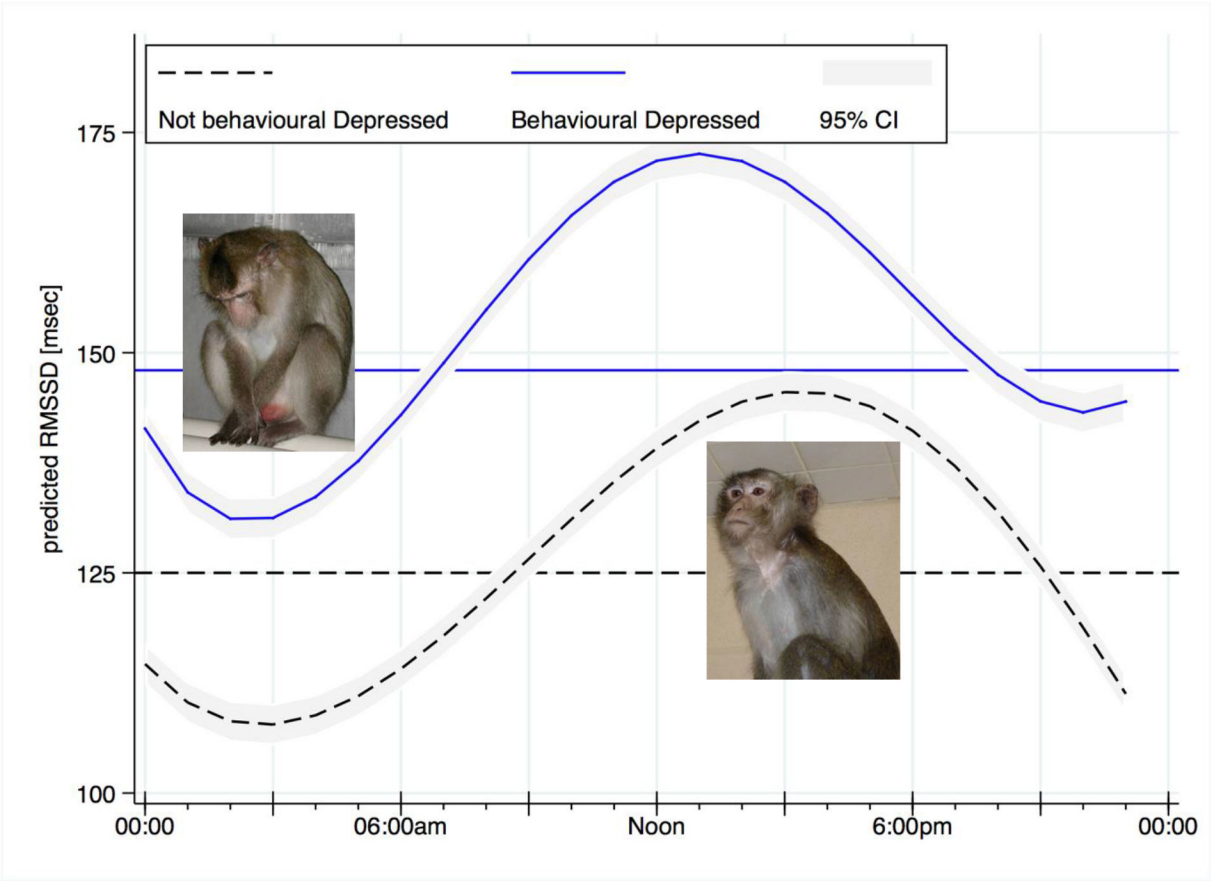

Figure 2: Predicted RMSSD by Depression (N=42)

Predicted RMSSD in behavioral depressed (Solid line; N=19) vs. not depressed (Dashed line; N=23) female adult cynomolgus monkeys across time of day. Shaded area represents the 95% confidence interval

Table 1:

Sample characteristics of N = 42 monkeys shown as mean and SEM

Variable	Nondepressed (N=23)	Depressed (N=19)	p-value
Body weight (kg)	4.0 (0.01)	2.9 (1.25)	<0.001
Mean HR 24h (bpm)	135.2 (3.05)	148.8 (4.34)	0.01
Mean rate Depression	0.0 (0)	1.7 (0.10)	0.002
Mean % time Depression	0.0 (0)	0.6 (0.19)	0.002
Nighttime activity count (12–6am)	11,475 (1,952)	14,373 (4,421)	0.52
Total activity count (24h)	285,912 (6,269)	218,917 (27,709)	0.21

Group differences assessed using two sample t-test.