Published in final edited form as:

Appl Anim Behav Sci. 2017 December ; 197: 62–67. doi:10.1016/j.applanim.2017.09.002.

Rhesus macaques (*Macaca mulatta*) displaying self-injurious behavior show more sleep disruption than controls

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Abstract

Self-injurious behavior (SIB) is a pathology observed in both humans and animals. In humans, SIB has been linked to various mental health conditions that are also associated with significant sleep disruption. In rhesus macaques, SIB consists of self-directed biting which can range from mild skin abrasions to wounds requiring veterinary care. However, only one study suggests possible sleep disruption in macaques with SIB. We evaluated sleep disruption using a noninvasive system (infra-red camera and a video surveillance program) which created videos for every movement over the nighttime hours. Nighttime activity was examined in 13 macaques (three females) of which six were classified as having SIB (one female). Each monkey was studied for a total of 6 nights spanning a period of 4 months. Measures included total movement time (TMT), time moving in the first hour (HR1), time moving in the last hour (HR11), and number of videos <10 secs, 10 secs, and 30 secs in length. Overall, SIB monkeys had higher TMT ($p < 0.01$), higher HR1 ($p < 0.001$), and generated more videos 10 secs ($p < 0.01$) and 30 secs ($p < 0.01$). Thus, SIB monkeys showed significant sleep disruption. A four-fold difference between SIB and control monkeys in the 30 secs videos revealed many more significant awakenings in the SIB group. Overall higher nighttime activity, in the first hour but not in the last hour, is consistent with sleep-onset insomnia in humans. Whether increased nighttime activity contributes to the SIB condition during the day or, conversely, SIB causes higher nighttime activity remains undetermined.

Keywords

self-injurious behavior; nighttime activity; sleep

1. Introduction

Self-injurious behavior (SIB) is a serious condition observed in both human and non-human primates (Nock, 2010; Novak, 2003). In humans, SIB is usually termed non-suicidal self-

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injury or deliberate self-harm and typically involves cutting, burning, biting, or head-banging. The average lifetime prevalence of this pathology is estimated at 18% (Muehlenkamp et al., 2012). SIB is frequently, but not always, associated with clinical conditions such as borderline personality disorder (Krüger et al., 2014), anxiety disorders (Bentley et al., 2015), and developmental disabilities (MaClean et al., 2010). In the general population, SIB prevalence rates vary both as a function of age, being more common in adolescents and young adults (Swannell et al., 2014), and ethnicity, being more common among Caucasians than Arabs or African Americans (Kuentzel et al., 2012).

In rhesus macaques, SIB usually takes the form of self-directed biting, ranging from mild abrasions to wounds that require veterinary care (Novak, 2003). The prevalence of this condition ranges from 5–14% depending on the facility and methodologies used to assess SIB (Lutz et al., 2003; Rommeck et al., 2009). A decade of research on rhesus macaques suggests that there are commonalities with human SIB, not only with regard to prevalence but also with respect to etiology, triggering events, function, and therapeutic intervention (reviewed in Novak, et al., 2014).

Because only a small percentage of monkeys housed in similar laboratory environments spontaneously acquire this disorder, comparisons of those that develop SIB with those that do not provide insight into this condition (Novak, 2003; Novak et al., 2014). Based on our working model, at least two factors presumably play an initial role in the development of SIB in rhesus monkeys (Tiefenbacher et al., 2005): exposure to significant early life stress events (Lutz et al., 2003) in concert with differential sensitivity to stress as determined by the presence of gene polymorphisms associated with anxiety (Chen et al., 2010). The presence of both factors in the juvenile period can result in SIB, which once acquired is associated with increased responsiveness to anxiogenic drugs (Major et al., 2009) and elevated activity of the hypothalamic-pituitary adrenal (HPA) axis (Tiefenbacher et al., 2000, 2004), one arm of the stress response system.

One possible correlate of SIB, sleep disruption, has been examined in humans but is yet to be fully studied in macaques. In humans with developmental disabilities, sleep disruption is a common feature in those subjects who exhibit SIB as compared to those that do not (Brylewski & Wiggs, 1999; Chaney et al., 1994; Symons et al., 2000). Little research is available on the relationship between sleep disruption and SIB in the general human population. In one study, adolescents with SIB had shorter sleep duration, more insomnia symptoms, and greater sleep dissatisfaction compared to a non-injuring control group (Liu et al., 2016).

Poor sleep quality has also been linked to increased HPA axis activity (Buckley & Schatzberg, 2005), consistent with our findings of a dysregulated HPA axis in monkeys with SIB (Tiefenbacher et al., 2004; Davenport et al., 2008). Support for the involvement of the HPA axis in sleep comes from several different sources. Patients with Cushing's syndrome (hypercortisolemia) show disturbed sleep in the form of a greater number of awakenings during the night (Shipley et al., 1992). Additionally, electroencephalographic (EEG) indices of sleep disturbance in human populations have been associated with elevated salivary cortisol (Hatzinger et al., 2008), elevated serum cortisol (D'Aurea et al., 2015), and a

reduced cortisol awakening response with a flatter curve across the day (Van Lenten & Doane, 2016).

Recent advances in sleep technology, EEG telemetry and actigraphy, permit the measurement of sleep/wakefulness cycles and sleep architecture in humans. EEG is the gold standard for measuring sleep architecture and sleep/wake cycles in humans and requires the use of a cap. Actigraphy is a non-invasive method of measuring gross motor activity using an actigraph unit (watch) worn by the participant. When EEG and actigraphy are simultaneously collected in humans, there is a high participant specific accuracy between the two methods (Ancoli-Israel et al., 2003; De Souza et al., 2003; Marino et al., 2013; Sadeh & Acebo, 2002).

However, the usefulness of these devices in unrestrained monkeys with stress-related conditions such as SIB may be problematic given that the measurements can include the use of skull caps and/or collars which by themselves might elicit SIB. EEG recordings can be obtained from scalp electrodes but the procedure requires daily placement of electrodes on to the scalp along with restraint in primate chairs during the period of recording (Attaheri et al., 2015). An alternative method requires surgical implantation of electrodes into the skull with an acrylic head cap (Woodman et al., 2007) or additionally implanted telemetry devices (Ishikawa et al., 2017; Rachalski et al., 2014). Actigraphy is less invasive and does not require restraint, but the actigraphy unit must either be affixed to a metal collar or implanted subcutaneously (Barrett et al., 2009; Darbin et al., 2009; Golub & Hogrefe, 2016). Furthermore, it provides only a gross measure of activity over the night without any indication of what the activity was.

In general, sleep ecology is difficult to study in free-ranging macaques as they prefer high sleeping places in tall trees (Albert, 2011; see Anderson, 2000 for a review). This antipredator strategy makes determinations of sleep versus wakefulness difficult to conduct in nature. However, some studies have demonstrated that macaques generally enter their chosen sleeping site at sunset and remain there until sunrise. Furthermore, free-ranging macaques modify the time they enter and exit their sleeping location to correspond with seasonal changes in photoperiod (Albert, 2011). Therefore, sleep in macaques seems to be driven by light-cycle.

Video scoring can be used as a non-invasive measure of nighttime activity in rhesus macaques. Unlike EEG, it cannot provide reliable information on sleep stages or sleep architecture. However, it provides more specific information than actigraphy inasmuch as videos of gross motor activity allow the behavior of the subject to be scored. However, manual scoring of hours-long videos of the nighttime period can be inefficient and time-consuming, resulting in few nights of data and possible human error.

Currently, the only examination of sleep in rhesus macaques with SIB was conducted in our lab a number of years ago (Davenport et al., 2008). In this study, nighttime activity was videotaped under low light conditions before and after a mandated relocation to another building, and the videotapes were scored once every minute for activity using a scale of 0–3, with zero representing no movement. Monkeys with SIB showed higher activity scores than

a control group. However, coding of videotapes was arduous even in the context of scanning only once per minute and the low light may have had differential effects on the SIB subjects given their heightened sensitivity to environmental change compared to non-injuring controls.

Recent advances in motion-activated surveillance software allow for accurate assessments of gross motor activity, similar to actigraphy, while at the same time allowing for streamlined scoring of behavioral data. This noninvasive method involves motion activated video capture using surveillance programs (e.g., ISPYCONNECT) which can operate in infra-red light not visible to rhesus macaques. The system is activated during each movement throughout the night. At the end of each night, it provides a summary of the total frequency and duration of nighttime activity, along with all videos of such activity. This activity can be then examined per hour, broken down into the frequencies of different length video bouts, and scored for behavior.

The current study differed from the previous approach (Davenport et al., 2008) in four ways. First, nighttime activity was examined in a new group of SIB and control monkeys to determine if the previously reported sleep disruption could be replicated. Second, these monkeys had only a mild form of the pathology which involved self-directed biting without producing wounds requiring veterinary care. Third, the data were collected on monkeys that had been maintained under the same conditions for several years in contrast to the previous study in which the monkeys were relocated to a new building. Finally, the methodology was much more precise and specific, and even small movements, such as head turns, were recorded.

2. Materials and Methods

2.1 Subjects

Thirteen rhesus macaques (three females) housed at the University of Massachusetts Amherst Primate Laboratory were the subjects of this investigation. At the start of data collection, all the macaques were adults between 10–25 years of age, with a mean age of 16.2 years. Six monkeys (one female) displayed the biting pathology. This designation was based on two considerations. First, we determined the presence of self-biting behavior in behavioral samples conducted on every subject 5 days per week. Subjects were observed for two 5-min periods from 09:00–10:00 h and from 16:00–17:00 h, for a total of 160 samples per subject (80 morning samples and 80 evening samples). Second, additional information was obtained during veterinary health exams in which the skin was examined for abrasions in the areas in which monkeys typically bit themselves. Even though no wounds were produced, minor skin scarring was present in these areas. None of the monkeys, SIB or non-SIB, received any medical treatment during the course of this study.

The monkeys were exposed to an automated 13 h light/11 h dark cycle, with light offset at 20:00 h. Seven subjects (three with SIB) were housed indoors in Allentown cages (6 × 2 × 5 ft) where they had access to both the upper and lower quadrants. The remaining six subjects (three with SIB) were maintained indoors in floor-to-ceiling pens (8 × 4 × 6 ft). Four of the subjects had grooming contact and the remaining nine subjects were housed individually

within colony rooms where they could interact with other monkeys at a safe distance. Individual housing was necessitated either by repeated pairing failures or by substantially increased rates of self-injurious behavior during pairing. All work complied with the ethical standards outlined in the Institutional Animal Care and Use Committee (IACUC) and all subjects were housed in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals.

2.2 Apparatus

The Video Recording of Nighttime Activity (VRNA) system was designed to be a naturalistic measure of nighttime activity. It used an infrared (IR) light to film in complete darkness and a motion-sensing program to quantify nighttime movement. The VRNA system consisted of four components: an 850nm infrared light (model IR34, Super Circuits; Austin, TX), a webcam (model C920, Logitech; Newark, CA) modified to detect IR light, receiving laptop (Inspiron 3000, Dell; Round Rock, TX) connected to the webcams, and the motion sensing and recording program ISPYCONNECT (www.ispyconnect.com). IR light at the wavelength used (850nm) is not visible to rhesus macaques or humans (Jacobs, 1996). The webcams were modified to ensure the reception of IR light into the camera by removing a small piece of glass from in front of the lens that typically filtered out light in the IR range. Infrared light 550 nm or greater is not hazardous to the eyes (Sliney & Mellerio, 2013). Both the IR light and the webcam were placed a minimum of 4 ft. from the monkey's enclosure in a configuration which maximized visibility in total darkness.

For the purposes of capturing nighttime activity, the cameras only recorded during the period in which the lights were off in the colony rooms (20:00–07:00 h). The threshold for video detection was set to detect 0.001% pixel change on the computer screen. The webcams recorded at 30 frames per sec and began recording 0.03 secs after a movement had been detected. The program continued to record video until 5 secs after movement had ceased.

The use of the VRNA system was based on its ability to capture videos that were an accurate representation of the nighttime movements a subject displayed. Good quality images were produced and monkeys were visible inside of their cages (Figure 1). Very short videos (less than or equal to 5 secs of activity) were used to ascertain whether the system falsely recorded movement. Four observers, blind to the purpose of their observation, watched 15 randomly chosen videos 5 secs or shorter in length to determine whether movements were detectable. There was a 100% rater agreement for all videos indicating that movements did occur in the shortest videos produced by the system and were typically small shifts of head or body position.

2.3 Procedure

Two computerized systems were available, enabling the study of two subjects per night. A block randomized procedure was used within each trial to determine the order that the subjects would be tested. Monkeys had been thoroughly habituated to the use of cameras prior to the beginning of testing. Lights and cameras were placed in the colony room facing the subject's cage in the late afternoon before a nighttime collection. A computer, connected

to the cameras, was placed outside the colony room door. The VRNA apparatus was removed every morning approximately an hour after light onset.

2.4 Data Collection

A total of six nights of data were collected on each subject. The VRNA system generated a video for every movement performed by a subject. The morning following nighttime recording, a preliminary check of the videos generated during the night was performed to check for any movement that was not produced by the subject; no such examples were ever detected. To quantify nighttime activity in rhesus macaques, we focused on six measures described in Table 1.

2.5 Data Analysis

Initially, all video bouts were corrected by removing 5 secs (the amount of time the program added on at the end of each bout). Because there were no substantive changes across trials, only the main variable of interest, SIB status, was analyzed. Averages were created for each subject across all 6 trials. The nighttime activity measures TMT, Hour 1Time, and Hour 11Time, and longINACT were analyzed for duration (secs), whereas < 10s Videos, 10s Videos and 30s Videos were analyzed for frequency. The data were subjected to an Analysis of Variance (ANOVA) with SIB status as the between subjects variable using the SYSTAT statistical package. The data were also examined for deviations from normality with the Shapiro-Wilk Test and for deviations from homogeneity of variance with Levene's Test. For all six measures, the assumption of homogeneity of variances was met. For five of the measures, the data were normally distributed, while one measure, number of videos 30 secs, was not ($W = 0.77$, $p < 0.001$). This measure was examined further using the Mann-Whitney nonparametric test. Because monkeys were housed in different kinds of cages (pens vs. Allentown cages) with SIB subjects equally spread across both cage types, we also assessed the effects of cage type on nighttime activity. The same measures were analyzed using an ANOVA with cage type as the between subjects variable. For all six measures, the data met the assumption of both normality and homogeneity of variances.

3. Results

3.1 Behavior and Sleep Postures

No episodes of biting behavior were seen in any of the subjects during the nighttime videos. The majority of movements consisted of scratches, self-grooming, body stretches, and brief shifts of position, either in place or by locomoting to a new location. Three different sleep postures were observed over the course of data collection: 1) sitting upright (including sitting in hammocks), 2) lying on one's side (lateral recumbency), or 3) lying on one's stomach (prone). None of the subjects slept in the supine position. All monkeys were observed sleeping while sitting upright (13 subjects). Lateral recumbency was the next most common position (10 subjects), with the prone position being the least common (5 subjects). Seven out of the 13 monkeys slept in all three positions, whereas three monkeys used only two sleep postures (sitting and lateral recumbency). The remaining three monkeys slept only in the sitting position. Subjects overwhelmingly preferred the uppermost parts of cages and

pens for sleep, with only one subject occasionally sleeping on the floor of an Allentown cage.

3.2 Effects of SIB status

Overall, SIB subjects showed greater nighttime activity and scored significantly higher than controls on four measures (see Figure 2 and Table 2 for statistical summary). Over the entire night, SIB subjects spent more time engaged in movement (TMT) compared to controls ($F_{(1,11)} = 10.12$, $P < 0.01$). In addition, SIB monkeys appeared to take longer to achieve sleep, generating more movements during the first hour (Hour1Time) after light offset compared to controls ($F_{(1,11)} = 18.04$, $P < 0.001$) but did not differ from controls in the hour before light onset (Hour1Time) ($F_{(1,11)} = 3.03$, $P = 0.11$). SIB and control subjects also did not differ on the length of their longest period of inactivity ($F_{(1,11)} = 0.72$, $p = 0.42$).

In terms of activity bouts, all monkeys generated equivalent numbers of short (<10s) videos. However, SIB monkeys generated more 10s videos ($F_{(1,11)} = 12.32$, $P < 0.01$) and more importantly produced a larger number of 30s videos, an indicator of significant sleep disruption ($F_{(1,11)} = 10.01$, $P < 0.01$). Because this last measure was not normally distributed, the data were analyzed using a nonparametric test, the Mann-Whitney Test. The number of 30s videos remained significant ($U = 2.00$, $P = 0.01$), with a mean rank of 61 for SIB monkeys compared to the mean rank of 30 for the control monkeys.

3.3 Effect of Cage Type

Housing environment (pen or Allentown cage) had relatively little impact on nighttime activity. The only significant measure was the length of the longest bout of inactivity. This bout was significantly longer in monkeys housed in Allentown cages compared to monkeys housed in pens ($F_{(1,11)} = 10.46$, $p = 0.01$; Allentown cages = $3184.8s \pm 51.1$ vs. Pens = $2084.4s \pm 24.96$).

4. Discussion

The hypothesis that monkeys with SIB would show higher levels of nighttime activity was confirmed and replicated in a new group of monkeys with this pathology. The use of motion-activated surveillance software enabled the collection of precise data on the timing of nighttime activity across an 11 hour period, with the added benefit of being able to identify the nature of the activity itself. Although monkeys with SIB had a higher overall total movement time, indicative of reduced sleep duration compared to controls, two additional features stand out. First, monkeys with SIB had more movements in the first hour after light offset than controls, but did not differ from controls in the hour before light onset. Second, SIB monkeys experienced nearly four times as many significant awakenings across the night (defined as generating videos of 30 secs or more in length) than non-injuring controls.

Difficulties in falling asleep, also known as sleep onset insomnia, appeared to be more prominent for monkeys with SIB than controls. Sleep onset insomnia has been associated with several mood and stress-related disorders in humans, including depression (Nowell and Buysse, 2001; Sivertsen et al., 2014), anxiety (Leblanc et al., 2015) and post-traumatic stress disorder (Brown et al., 2017). Additionally, a recent report extends these findings to self-

harming adolescents in Norway (Hysing et al., 2015): in a study of 10,200 adolescents, long sleep onset latency was a significant predictor of self-harm.

Repeated nocturnal awakenings commonly occur in conjunction with other forms of sleep disturbance such as delayed sleep onset. In this study, monkeys with SIB averaged 12 significant awakenings per night compared to 3 such awakenings for the control monkeys. This relationship was also observed in the Norwegian study of adolescents where repeated awakenings after sleep onset also resulted in higher odds of self-harm (Hysing et al., 2015).

This study extends the finding of sleep disruption in macaques with SIB to a more mild form of the pathology: biting which did not yield wounds that required veterinary care. In the previous study (Davenport et al., 2008), all the SIB monkeys had a veterinary record for self-inflicted wounds. Taken together, these two studies suggest biting may be the better indicator of this condition in rhesus macaques than wounding by itself.

The discovery of significant sleep disruption in macaques with SIB provides researchers and colony managers with an additional target for therapeutic intervention. Currently, existing treatments for SIB typically involve maintenance on psychoactive drugs targeting the serotonergic (Fontenot et al., 2009), noradrenergic (Freeman et al., 2015), GABAergic (Tiefenbacher et al., 2005), or endogenous opioid systems (Kempf et al., 2012). However, drug treatment is not effective in all individuals and may actually exacerbate the condition in some animals (Tiefenbacher et al., 2005). Additionally, these drugs can have adverse side effects (e.g., sedation), produce tolerance in the long-term resulting in increased dosages, and have a substantial risk of relapse once the drug has been removed. Thus, monkeys are often treated chronically with these drugs rendering them unsuitable for many research protocols.

Given the replicated finding of significant sleep disruption across two populations of monkeys with SIB, it is possible that treatment with a sleep aid (e.g., melatonin) will reduce self-injurious behavior. Importantly, the effectiveness of melatonin in improving sleep quality has been studied experimentally in three species of macaques. Oral doses given 2 hours before light offset led to significantly earlier sleep onset and longer periods of sleep compared to vehicle-treated monkeys (Zhdanova et al., 2002). Additionally, MPTP-treated monkeys, an animal model of Parkinson's disease, showed reduced sleep disruption with melatonin (Belaid et al., 2015). These findings suggest that melatonin might be an effective treatment for monkeys with SIB by accelerating sleep onset and reducing nighttime activity.

Although this study demonstrated that monkeys with SIB have disrupted sleep, there are two limitations that must be considered. First, there is no way to determine cause and effect, either in human or monkey populations; it is possible that sleep disruption led to the development of SIB, but it is equally plausible that SIB led to significant sleep disruption. Even this relationship has to be placed in the context of the many variables that are connected to this pathology, including both increased anxious behavior (Major et al., 2009) and heightened activation of the stress response system (Davenport et al., 2008). How all of these factors fit together is currently unclear.

Second, this study was focused on nighttime activity as revealed by motion-activated surveillance software. We did not measure sleep behavior per se. However, the system was capable of detecting very slight head movements, and thus conservatively, it is reasonable to infer that when the surveillance system was not activated, the monkeys were indeed asleep (no movements detected). It is also possible that they were asleep during very short movements (< 10s videos). Monkeys with SIB did not differ from controls in the number of short videos generated. However, for movements greater than 10 secs, and more specifically for movements greater than 30 secs in which the monkeys were clearly awake, SIB monkeys generated an average of 12 videos per night as compared to control monkeys which only generated an average of 3 per night. Although we have no measure of sleep physiology, the greater number of long videos and seemingly significant awakenings demonstrated by SIB monkeys suggests that sleep may be more disrupted in SIB monkeys overall.

In conclusion, this study replicated and extended the finding of significant sleep disruption in rhesus macaques with self-injurious behavior. Furthermore, it established commonalities of sleep disruption across humans and rhesus macaques with this condition. For both species, self-injurious behavior was associated with sleep onset insomnia and increased nocturnal awakenings during the night. Further research is needed to determine if sleep disruption can be a target for treatment in these subjects.

Acknowledgments

The authors would like to thank the Research Assistants that assisted in data collection: Sarah Paugetee, Peter McGinn, Andrew Guresh, Abigail Campbell, Abigail Solomon, and Chelsea Sams. In addition, we would like to acknowledge Mark Menard, Research Technician, for his assistance on this project and Chris Hrasna, Computer Specialist, for his expertise with the cameras and the software program. This work was funded by the National Institutes of Health R24 Grant #OD01180 to M.A.N.

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Highlights

- Self-injurious behavior (SIB) is exhibited by some captive rhesus macaques
- Monkeys with SIB had disrupted sleep and greater nighttime activity than controls
- SIB monkeys were more active during the first hour after lights off than controls
- SIB monkeys had more significant awakenings across the night than controls
- Motion-activated surveillance can be used to monitor monkey nighttime activity

Figure 1.

Examples of screengrabs from video taken during the night by the VRNA system in total darkness; left photo shows an awake monkey in a pen stretching his arms out; right photo shows an awake monkey in an Allentown cage moving her head and arms.

Figure 2.

SIB Status Effects: **(A)** Average total movement time in a nighttime period, **(B)** Average total movement time during the first (20:00–21:00 h) and last (06:00–07:00 h) hours of a nighttime period, and **(C)** Average number of videos above 10s and 30s per night.

Table 1

Nighttime Activity Measures

Measure	Definition
TMT (total movement time)	The sum of the durations of all videos minus 5 sec $\times$ # of videos
Hour1Time	The sum of the durations of all videos during the first hour after light offset minus 5 sec $\times$ # of videos
Hour11Time	The sum of the durations of all videos during the last hour before light onset minus 5 sec $\times$ # of videos
10 sec Video	The frequency of videos equal or greater than 10 sec
30 sec Video	The frequency of videos equal to or greater than 30 sec; a measure of substantial awakenings often involving movement from one location to another
LongINACT	The duration of the longest period between videos; a measure of longest inactive bout

Table 2

ANOVA results of nighttime behavioral measures across SIB status.

Measure	SIB Status F ratio	SIB (mean + standard error)	Control (mean + standard error)
TMT	$F_{(1,11)} = 10.12$ $P < 0.01$	$1752.06s \pm 209.25$	$845.05s \pm 193.73$
Hour1Time	$F_{(1,11)} = 18.04$, $P < 0.001$	$616.72s \pm 48.69$	$334.95s \pm 45.08$
Hour11Time	$F_{(1,11)} = 3.03$ $P = 0.11$	$220.22s \pm 30.80$	$147.17s \pm 28.52$
LongInact	$F_{(1,11)} = 0.72$ $P = 0.42$	$2467.17s \pm 337.99$	$2856.67s \pm 312.92$
Short Videos	$F_{(1,11)} = 1.83$, $P = 0.20$	$153.03 \text{ videos} \pm 33.80$	$115.93 \text{ videos} \pm 31.30$
10s videos	$F_{(1,11)} = 12.32$, $P < 0.01$	$96.19 \text{ videos} \pm 10.57$	$45.64 \text{ videos} \pm 9.79$
30s videos	$F_{(1,11)} = 10.01$, $P < 0.01$	$11.86 \text{ videos} \pm 2.07$	$2.95 \text{ videos} \pm 1.91$