NS 112 FINAL PROJECT

EVOLUTION OF SLEEP

NS112: Evolution Across Multiple Scales
Minerva Schools at KGI

Yutaro Shimizu
December 2020

Word Count: 1983 (excluding the grant proposal, addendum and appendix)

NS112 FINAL PROJECT

Introduction

Sleep is a common behavior across all animals. Samson et al. (2015) quote “if sleep does not serve an absolute vital function, then it is the biggest mistake the evolutionary process ever made”. All animals spend a significant amount of time on sleep which seems to imply the biological significance of sleep whose underlying mechanism awaits to be unpacked. Sleep serves many complex functions such as energy restoration, immune repair, brain metabolic homeostasis, neural ontogenesis, and cognitive and emotional processing (Walker, 2009, 168). While the general functions of sleep are ubiquitous across all animal kingdoms (Langille, 2019, 2), for mammals, sleep has two subcategories: non-rapid eye movement sleep (NREM) and rapid-eye-movement sleep (REM).

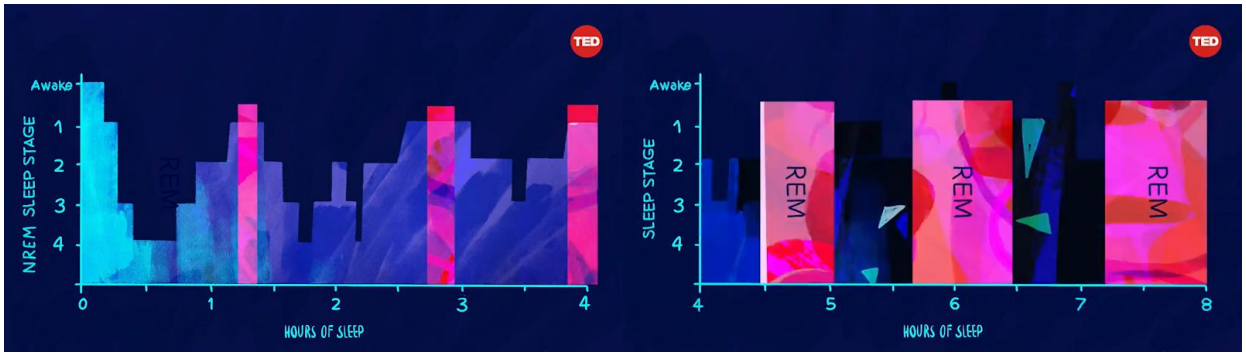

Figure 1. The division of NREM and REM during sleep hours (Walker, 2019). REM hours increase towards the end of sleep for humans.

The functions of NREM and REM connect to the high cognitive function of mammals. While NREM is associated with physiological rest (e.g. inactive brain, decreased heart rate, and low body temperature), REM is when the brain becomes very active (i.e. faster theta rhythms) despite the body's complete paralysis. During REM, the brain exhibits electroencephalographic (EEG) pulses that resemble pulse patterns during the awake state (Samson 2015, 226). This is when the brain becomes very creative and we see the most vivid dreams. Human sleep oscillates between NREM and REM every 90 minutes, with increased REM towards the end of the sleep hours (fig.1). This aligns with our own experiences of remembering more dreams just before we wake up. A recent study by Santa Fe Institute (SFI) showed that both brain size and brain metabolic rate are better predictors of sleep time than body size, indicating sleep's significance on the brain.

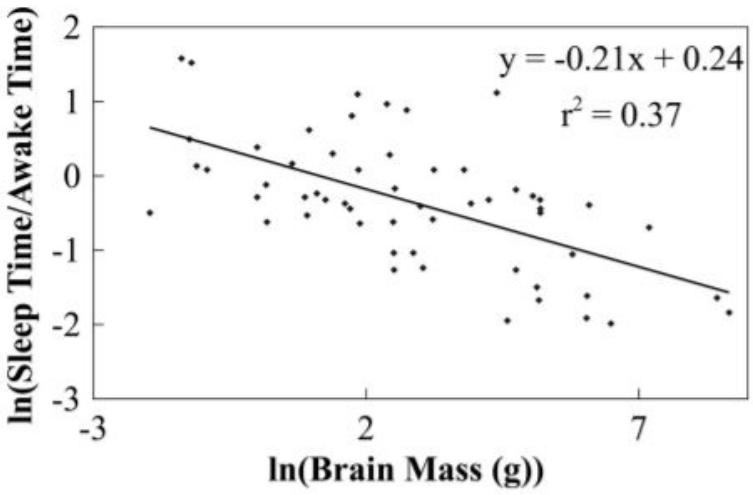

Figure 2. The logarithmic regression model reveals a close association between brain mass and the ratio of sleep time and awake time (Savage et al., 2006).

The study outlined two main hypotheses for why animals sleep:(i) cortical reorganization and processing associated with memory and learning; or (iii) cellular repair in the body or brain (Savage et al., 2006, 1051). Plotting logarithmic values of sleep time/awake time (tS/tA) against brain and body mass (Mb) revealed how brain mass is more associated with sleeping hours (body mass also showed a similar r-squared value, however, the slope of the linear equation was more important to determine the association). Considering multitudes of variables that affected the sleep strengths, the researchers generated an equation that related body/brain mass with sleep duration.[1]

$$\frac{t_s}{t_A} \propto M_b^{-1/4}$$

The group theorized that the brain metabolic rate influenced sleep time more, because sleep is devoted to the restoration of the brain (Savage, 2007), supporting the first hypothesis. Their inference is supported by another theory that sleep regulates the stress and restores damaged neurons (Reimund, 1994). The SFI group further tested how the sleep hours can be differentiated into REM and NREM, to determine the nuanced functions of "brain restoration".

[1] The specific value for the exponent was empirically derived by comparing brain size to the mass of other organs in different mammalian bodies.

Ratio	Measured exponent	REM reorganization prediction	NREM reorganization prediction	Repair prediction
t_S/t_A	−0.33 ± 0.07	NA	NA	0.20 to 0.60
t_R/t_S	−0.60 ± 0.06	**−0.87 to −0.07**	NA	0
t_R/t_A	−1.00 ± 0.05	**−1.20 to −0.40**	NA	NA
t_{NR}/t_A	0.09 ± 0.09	NA	**−1.20 to −0.40**	NA

Table 1. Summary of the results of the sleep hours ratio with reference to REM/NREM predictions (Cao et al. 2020).

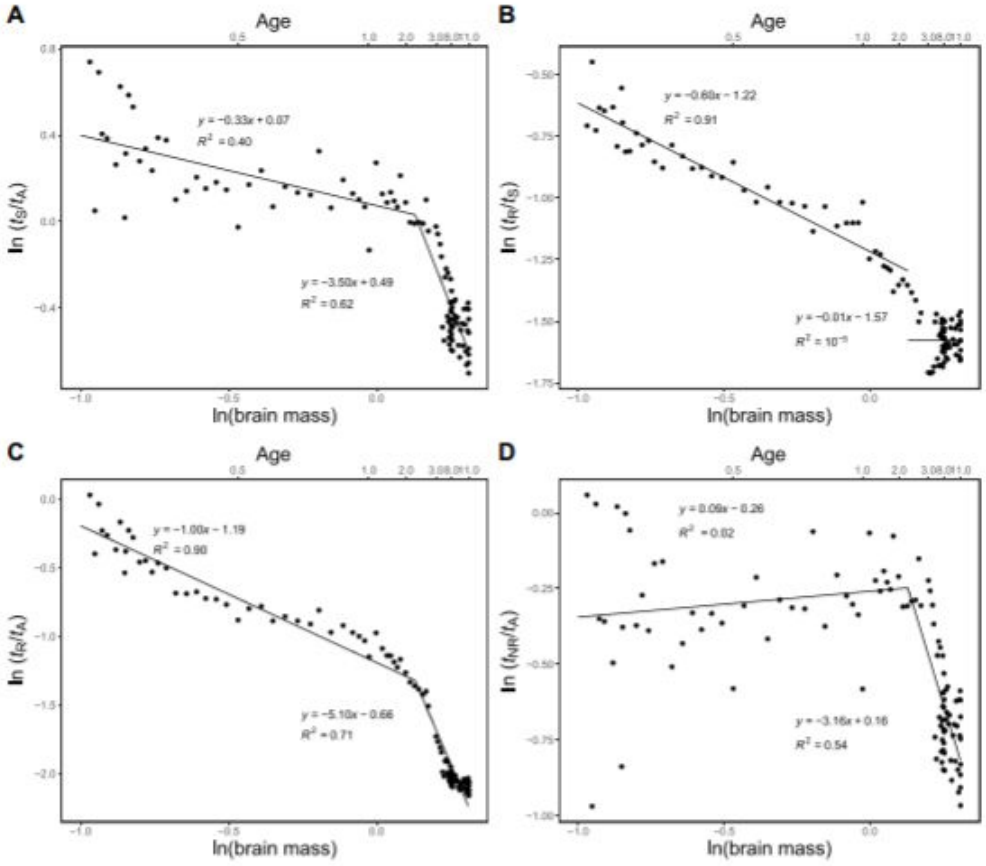

Figure 3. Plotting sleep hours ratio against age reveals a drastic transition in the sleeping function after 2.4 years for humans (Cao et al., 2020).[2]

[2] The slope of the graph corresponds to the power of the exponent which was more indicative of REM/NREM significance.

The group subdivided “brain restoration” into two purposes, neural reorganization and repair, then determined which of REM and NREM was more involved in either process. The neural reorganization is related to high plasticity accompanied by ongoing synaptogenesis while the repair is concerned with “declining plasticity, slow synaptic pruning… and stabilizing connectivity” (Cao et al. 2020, 8). The group added another term to the previous equation to account for the REM sleep time (tR) to the brain reorganization.

$$\frac{t_R}{t_S} \propto {M_b}^{2(1-\alpha)} \frac{t_A}{t_S}$$

The group accounted for the controversy on whether REM or NREM was responsible for neural reorganization, thus predicted another complementary case by switching tR with tNR in the equation. After curating empirical data on humans up to 15 years old, the result showed that 2.4 years after birth is the “transition point in the function of sleep from reorganization to repair in the brain … that corresponds to transitions in brain development” (Cao et al. 2020, 8) (fig.2). This result supported that REM reorganization theory of sleep before the early transition. This is in line with the evidence that synapses grow quickly which are then pruned away as part of the neural organization during the early development. These two consecutive studies highlighted how human cognitive development is closely associated with the greater portion of REM

in early development. Both studies also highlighted the need to test whether these studies also apply to other mammalian animals.

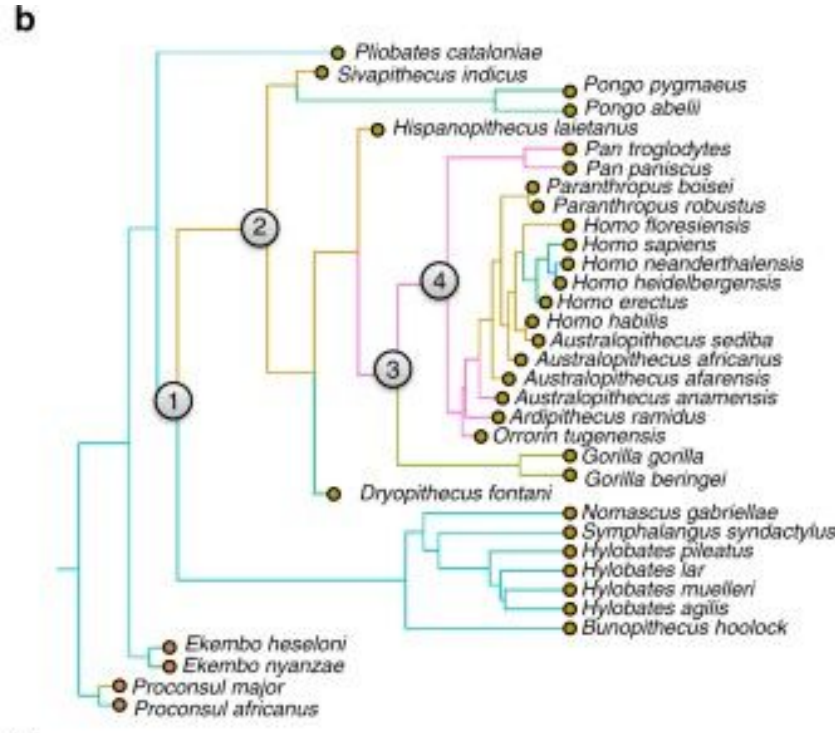

Figure 4. Hominoid phylogenetic tree constructed with Ornstein-Uhlenbeck stabilizing selection models to phenotypic species data[3] (Grabowski. 2017, 4)

Therefore, I hypothesize that the infant chimpanzees *(Pan troglodytes)* experience a greater REM ratio during early development than orangutans (*Pongo pygmaeus)*, due to the greater brain size. I chose these two species, because they both are primates, but occupy different spaces in the phylogenetic tree with respect to humans. In particular,

[3] It was not obvious to me from the paper, under which phylogenetic construction method OU model fitted into.

orangutans serve as an outgroup for the lower clade after node 2 (fig. 4). If only infant chimpanzees had a greater REM ratio, then that would indicate a homologous sleep pattern in the clade proximate to humans. We could then attribute this unique sleep behavior as the evolutionary factor for human intelligence. Alternatively, if orangutans also had a similar REM pattern then that would suggest similar cognitive behavior across the clades.[4]

Study design

Hypothesis	The infant chimpanzees *(Pan troglodytes)* experience a greater REM ratio during early development than orangutans (*Pongo pygmaeus)*, due to the greater brain size.
Type of research design	Observational study (cohort-study) Quasi-replication (conceptual)
Sampling strategy	Multistage sampling: simple random sampling of zoos in the United States and stratified sampling on species.
Treatment(s)(if applicable)	None, since this is an observational study.

[4] #testability: I concisely describe how the hypothesis leads to testable predictions and discuss their explanatory consequences. These predictions are later followed up in the paper with presumed observations.

Independent variable(s)	Brain sizes, age
Dependent variable(s)	REM hours/total sleep hours ratio
Control(s)	Orangutans-negative control (less brain mass)
Potential confounding variable(s)	Exhaustion, external stimuli during sleep, sleep environment.

Table 2. Outline of the study design.

To test the hypothesis, I conduct an observational study on the relationship between the brain size and REM and total sleeping hours ratio, during early development. There is no treatment since brain size is not subject to manipulation. While there were some labs that recorded sleep of chimpanzees[5] and orangutans[6], the duration of recording was too short or missed brain sizes thus making the data suboptimal for this study.[7] Therefore, we conduct a cohort-study to independently collect data on REM ratio and brain size of the primates. This will reveal how closely the two variables are associated over time.

[5] Mizuno, Y., & Takeshita, H. (2020). *Behavior of infant chimpanzees during the night in the first 4 months of life: smiling and suckling in relation to behavioral state.* Primate Research Institute, Kyoto University. https://langint.pri.kyoto-u.ac.jp/ai/en/publication/YuuMizuno/Behavior_of_infant_chimpanzees_during_the_night_in_the_first_4_months_of_life.html

[6] Center for Academic Research and Training Anthropogeny. (2020). *AMOUNT OF REM SLEEP*. Human Uniqueness Compared to "Great Apes". https://carta.anthropogeny.org/moca/topics/amount-rem-sleep

[7] #constraints: I identify how the current dataset issues that cannot be overcome and suggest that we independently collect data. This assessment of the problem led to my decision on choosing prospective cohort study to collect the most suitable data for the study.

According to Riopelle, chimpanzee's infancy lasts for about one to two years. To buffer some individual differences, we will prospectively track each primate sample for three years.[8] This study is also a quasi-replication experiment where we attempt to generalize the result gained by Cao et al. Their group tested on humans, and we aim to expand the hypothesis to broader primates. This is a conceptual replication since the same hypothesis is applied to broadly defined biological phenomena across many species. The extent of the hypothesis' generalizability will provide an evolutionary explanation of how sleep is associated with human's high cognition. Since the original study that inspired this quasi-replication has been tested in multiple SFI papers alongside other evidence, I believe our study can still yield sound inference (Nakagawa et al. 2015).[9]

The hypothesis outlines two variables to be tested: brain size and age as the independent variables and the REM sleep ratio as the dependent variable. I chose chimpanzees and orangutans because they have different average brain sizes which help us naturally vary the independent variable. On average, chimpanzee's brains are 390 cubic centimeters (Harding, 2020) whereas orangutan's brains are 375cc (Bone Clones Inc., 2020). According to the equation by Savage et al., this seemingly minor size difference is significant enough to change the sleeping hours.

[8] #plausibility: I justify my choice of the study setup with reference to the aging characteristics of the primates. Throughout the paper, I support my argument with some scholarly evidence to ensure that all assumptions are plausible.

[9] #studyreplication: I contrast my study with the original hypothesis and discuss how the prior validation of SFI studies lead to confident quasi-conceptual-replication whose generalizability can produce nuanced evolutionary explanation on sleep behavior.

To mitigate the sampling bias, we apply multistage sampling by randomly selecting zoos then conduct stratified sampling of chimpanzees and orangutans. To ensure statistical significance, we collect fifty (n>30) samples for each species. Sampling primates in the wild is not realistic, since we will have to record videos of the infants who move freely around the forest.

Some confounding variables are exhaustion, external stimuli, and the sleeping environment. If the primates are active during the day, they may experience NREM sleep since they need more physiological recovery. Also, other researchers noted that "compared with data obtained in the wild, the isolated chimpanzee infants in the laboratory showed longer sleeping phase durations" (Mizuno et al. 2006. 234). However, by limiting the sleeping environment to only artificial enclosures, we can standardize sleeping duration.[10] The morphological differences between chimpanzees and orangutans remain subtle while they are in the early stages of development. We minimize the influence of morphological difference on sleep hours, by measuring the ratio of REM to total sleep hours, rather than taking absolute values. This helps us standardize the scale of measurement.

[10] #testability: I discuss how testability of the hypothesis in practice may be influenced by some confounds and assess how we can abbreviate their effects.

Since we cannot apply any treatment to change the brain size, I included orangutans as the control group against chimpanzees since they have different brain sizes. This way, naturally we can manipulate the independent variable. The video is recorded every month for over three years (36 data points per individual).

Technology	Gross Measure	Specifics	Invasive
Actigraphy	Active/nonactive states	Can measure activity at 1-sec interval resolution; in humans, algorithms may generate NRME/REM states at 90% efficacy	No
Videography/ Eularian magnification	Behavioral signatures	Can measure respiration and gross body motor movement; in apes, shown to differentiate between NREM/REM states at 80% efficacy	No
Piezoelectric	Active/nonactive states	Automatically records data; can measure breathing rhythms	No
EEG	Gold standard "brain wave activity"	Automatically records data; can differentiate between NREM/REM states and measure delta and theta wave states	Yes

Table 3. Methods to record primate sleep with reference to their accuracy and invasiveness (Samson, 2015, 235).

The sleep will be measured by videography/eulerian magnification to ethically treat the animals. The golden standard of sleep recording of animals is to implant electroencephalographic (EEG) recording devices with surgery, however this method is extremely invasive. Though implanting the device inside an animal head may produce

the greatest utility of the study due to better measurement accuracy, I think it is also important to recognize that animals also have lives and treat them with respect.[11] Eulerian magnification is an alternative approach to measure sleep by amplifying the sensitivity of video recordings, such as slight physiological patterns unique to REM and NREM.[12] This method has proven to be 80% accurate which is high enough to compensate for resolving animal pain (Table 3). We will use this method to record the duration of the total, REM and NREM sleep.[13]

[11] #ethicalconflicts: since this is not a paper on ethics, I concisely weigh utilitarian and Kantian moralities and identity which one is more suitable for this scenario. I consider how different measuring methods can compensate for the Kantian choice of treating animals to balance ethical integrity and scientific rigor.
[12] I was initially hoping to use datasets from Dyriad, but noticed how many contained vivid descriptions of surging mice brains to implant EEG devices inside their skulls. To ethically treat animals, I instead decided to generate an alternative null data. For your reference, this is the dataset I was initially considering: https://datadryad.org/stash/dataset/doi:10.5061/dryad.rv15dv45r
[13] #responsibility: during class discussion, it came clear to me that you as a squirrel researcher values ethics when treating animals. Through this class, I learned how this HC is not restricted to local team dynamics which was the scenario this HC was introduced to me in CX class, but carries a much broader consequence of my own action. In this paper's context, I realize that my choosing EEG could promote animal suffering across the research field, thus propose an alternative to responsibly encourage more ethical practice within the whole natural science discipline.

Result

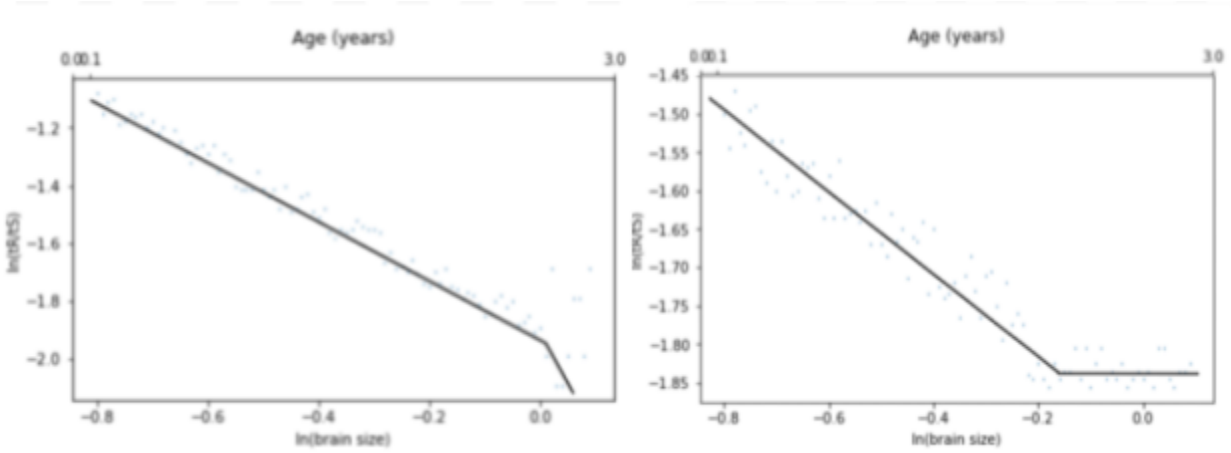

Figure 5. The REM ratio against brain size and age for chimpanzees (left) and orangutans (right), generated by pseudo-data (Appendix).

The result suggests a difference in the sleep pattern transition. For chimpanzees, REM seems to occupy greater sleep hours until around 2.5 years old, whereas for orangutans REM sleep flattens much earlier around 1.5 years. R-squared values for the two plots are 0.934 and 0.496 (Appendix). This means that for chimpanzees, the majority of the REM ratio is attributable to the brain size. Though the R-squared value for orangutans suggests the limited explanatory power of the brain size in relation to the REM ratio, this value may also be confounded by the stretch of flat regression after 1.5 years. This suggests the confounding in the orangutan's result due to the earlier transition from REM to NREM. 95% confidence intervals (two-tailed tests: [-0.260,-0.232] for chimpanzees and [0.157,0.242] for orangutans) for two groups narrowly capture the

general trend of the regression models (Appendix). These results show how the transition to NREM is dependent on the brain size which is in line with the hypothesis by Cao et al.

An alternative result would show no difference in when REM to NREM transition occurs, which would indicate that the human/chimpanzee clade's sleeping pattern is in fact not unique, but shared across the phylogeny.

Interpretation

The difference in the REM ratio corresponds to a neural organization taking longer for chimpanzees than for orangutans (Cao et al. 2020). Since chimpanzees require more REM ratio before the drastic transition around 2.5 years, they require a longer time to construct and prune neural networks inside their brains which is in line with chimpanzees' high intelligence. On the other hand, orangutans required less time to transition from REM to NREM, indicating that their brains require less time to complete initial maturation. The SFI model assumes constant neural development, thus this result may indicate chimpanzees possess denser neural structure which is reflected in their greater brain size. Given the orangutan's position as an outgroup for the second half of the clade after node 2 (fig.4), this result indicates that prolonged REM ratio is a homologous character for this particular clade which contain very few existing species (i.e. humans, chimpanzees, bonobos, and gorillas; other edges have gone extinct). This

could indicate how high REM sleep ratio was equipped as a result of high cognitive development.[14] This primary connection between neural restoration and high REM ratio could indicate how some sleep traits are in fact spandrels and not adaptations. For example, we discussed REM as the primary portion when we see dreams. We cannot attribute the evolutionary origin of REM if the dream was to be its primary purpose since its fictitious function does not seem to provide an obvious benefit. This would only start making sense if we attribute REM to synaptogenesis which provides a clear fitness advantage. Cao et al. mention that some physiological functions must have piggybacked into sleep since all animals spend a significant amount of time on it. Therefore functions like dream may be a consequence of another REM's primary function such as a neural reorganization.[15]

This study aimed to extend the REM/brain size model produced by Santa Fe Institute to determine its generalizability across primates. The hypothesis was in line with the result where chimpanzees and orangutans showed different REM/NREM transition patterns with respect to their brain sizes. Our phylogeny indicates the uniqueness of REM sleep within the proximate clade amongst humans. Our result implies a possible explanation for how some REM functions like sleep emerged as a side effect for another sleep mechanism.

[14] #evaluatephylogenies: I identify how the outgroup and homologous character are indicative of high intelligence, and how that could inform adaptation/spandrel assessment.
[15] #adaptationandspandrels: I discuss and apply four criteria of adaptations to sleep behaviors to determine whether they are adaptations. I also analyze evolutionary consequence of some functions not being adaptations.

Funding justification

This work is worthy of the federal grant because the study expands upon study replication which is rarely done in today's science. One of the reasons why replication is avoided is due to its lack of providing a new explanation especially if the replication is exact. However, our work is unique since it replicates the concepts of SFI studies to generalize how their hypothesis can be applied to other species. This generalization not only informs the primate's own sleeping patterns but it also helps us determine how the human sleeping pattern may or may not be unique. Sleep is associated with the neural reorganization and if a large REM sleep ratio is unique to primates close to humans, we could attribute REM sleep as one driver for the clade's high cognitive ability. This study is also unique for its ethical consideration. Traditionally, sleep research has implanted EEG recording devices in animals, but this causes extreme suffering especially for mammals. Since we use an alternative method that does not invade primate's sleep, funding our research will send a message to other researchers about the importance of ethical consideration for animals.

Addendum

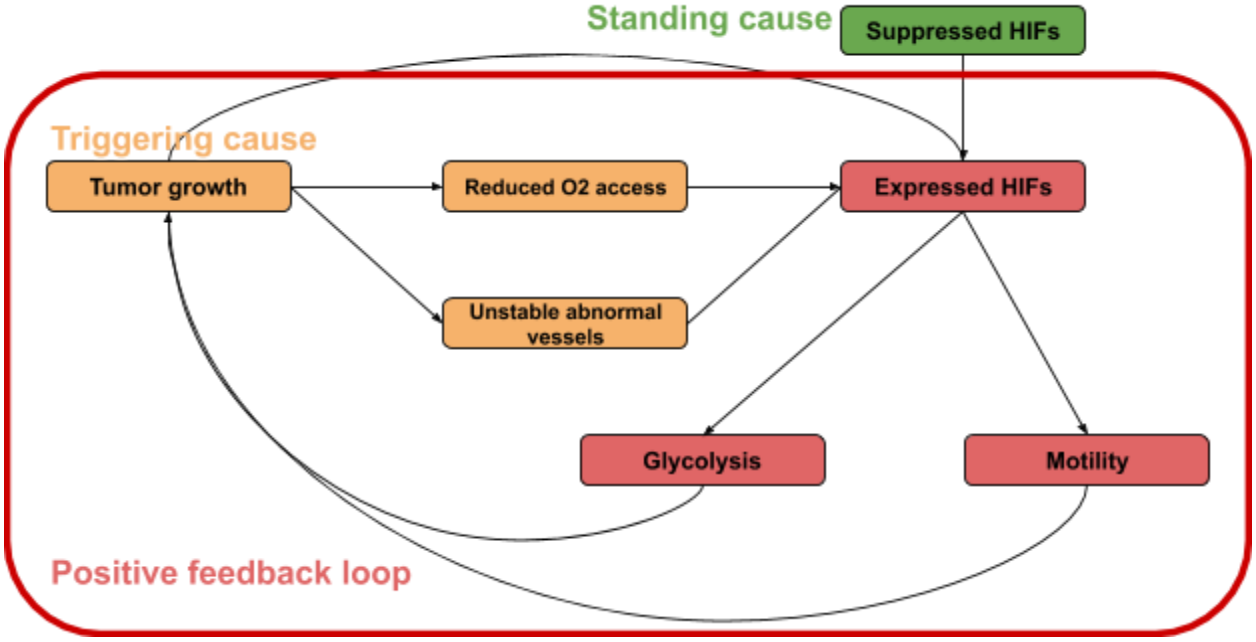

Figure 6. Cancer (organism) and the surrounding environment (microenvironment) go through complex interactions to reinforce bidirectional selective pressure.

Ibrahim-Hashim et al. (2017) draw acute connections between niche construction theory and cancer research. Their work is strong because it not only identifies the bidirectional relationship between carcinomas and the microenvironment but also characterizes the relationship as a positive reinforcement loop for the growth of cancer. The authors analyze how hypoxia does not negatively impact the survival of the tumor cells but in fact benefits them, because the tumors have a more selective advantage to this harsh condition than nonneoplastic cells. Hypoxia is caused when access to blood vessels get difficult due to neoplastic cells occupying more space. Tumors adapt to the

lack of oxygen by creating their own supplies, but the vessels cannot maintain steady blood flow due to their abnormal structure. These conditions promote somatic mutation of the hypoxia-inducible transcription factors (HIFs)[16] whose α subunits increase survival pathways as well as glycolysis, acid production, and motility. HIFs are usually suppressed by another protein and their effect only emerges in the presence of tumors. Therefore, HIFs not only help tumors survive in low-nutrient conditions but help them metastasize. As a result, tumors are selected by HIFs to spread around the host and select the environment by reducing the oxygen-level and inducing HIFs. This positive feedback loop is reinforced by the growth of cancer (fig.6). This work acutely exemplifies cancer as a complex system whose reinforcing interaction with the local environment serially benefits the progression of cancer. Previously, I mixed #nicheconstruction with the idea of sole "niche" and only identified the unidirectional benefit of immigrating octopus taking over a niche. Since this LO discusses the interaction between agents, I realized how I can apply the idea of complex systems to assess how the complex interaction between the microenvironment and cancer lead to the selective pressure for niche construction.[17] (300 words)

[16] The discovery of this protein led to the Nobel Prize in Physiology or Medicine in 2019.
[17] #multiplecauses: I identify niche construction as a form of positive feedback loop where each agent is a cause for another. I also characterize the causal relationship as a positive feedback/reinforcement loop with reference to the subtlety of the causes.

Appendix

```python
import matplotlib.pyplot as plt
import random
import statsmodels.api as statsmodels

xlist=[]
ylist=[]

for x in range(-80,0):
    c = random.randint(-5,5)
    y =-0.01*x-1.9
    yi= y+0.01*c
    xlist.append(0.01*x)
    ylist.append(yi)

for xi in range (0,10):
    d = random.randint(-2,2)
    y1 =-5.1*x-0.06
    y1i= y+0.1*d
    xlist.append(0.01*xi)
    ylist.append(y1i)


fig, ax1 = plt.subplots(constrained_layout=True)
ax1.scatter(xlist,ylist,s=0.20)
ax1.set_title("Age (years)")
ax1.set_xlabel("ln(brain size)")
ax1.set_ylabel("ln(tR/tS)")

ax2 = ax1.twiny()
ax2.set_xscale('log')
ax2.set_xaxis([0,3,0.01])

regressionmodel = statsmodels.OLS(xlist,ylist).fit()
regressionmodel.summary()
```

```python
import matplotlib.pyplot as plt
import random
import statsmodels.api as statsmodels

xlist=[]
ylist=[]

for x in range(-80,-20):
    c = random.randint(-5,5)
    y =-0.06*x-1.2
    yi= y+0.01*c
    xlist.append(0.01*x)
    ylist.append(yi)

for xi in range (-20,10):
    d = random.randint(-5,0)
    y1 =-5.1*x-0.06
    y1i= y+0.1*d
    xlist.append(0.01*xi)
    ylist.append(y1i)


fig, ax1 = plt.subplots(constrained_layout=True)
ax1.scatter(xlist,ylist,s=0.20)
ax1.set_title("Age (years)")
ax1.set_xlabel("ln(brain size)")
ax1.set_ylabel("ln(tR/tS)")

ax2 = ax1.twiny()
ax2.set_xscale('log')
ax2.set_xaxis([0,3,0.01])

regressionmodel = statsmodels.OLS(xlist,ylist).fit()
regressionmodel.summary()
```

Figure 7. This is the code that generated the pseudo data for the result section. To make the data plausible, I referenced the values gained in Samson et al. and Cao et al.papers. The left code is for chimpanzees, and the right code is for orangutans.

Dep. Variable:	y	**R-squared (uncentered):**	0.934
Model:	OLS	**Adj. R-squared (uncentered):**	0.933
Method:	Least Squares	**F-statistic:**	1251.
Date:	Fri, 18 Dec 2020	**Prob (F-statistic):**	3.41e-54
Time:	13:49:10	**Log-Likelihood:**	68.231
No. Observations:	90	**AIC:**	-134.5
Df Residuals:	89	**BIC:**	-132.0
Df Model:	1		
Covariance Type:	nonrobust		

OLS Regression Results

	coef	std err	t	P>|t|	[0.025	0.975]
x1	-0.2459	0.007	-35.368	0.000	-0.260	-0.232

Omnibus:	5.575	**Durbin-Watson:**	0.093
Prob(Omnibus):	0.062	**Jarque-Bera (JB):**	2.664
Skew:	-0.113	**Prob(JB):**	0.264
Kurtosis:	2.188	**Cond. No.**	1.00

Dep. Variable:	y	**R-squared (uncentered):**	0.496
Model:	OLS	**Adj. R-squared (uncentered):**	0.490
Method:	Least Squares	**F-statistic:**	87.60
Date:	Fri, 18 Dec 2020	**Prob (F-statistic):**	6.76e-15
Time:	13:53:52	**Log-Likelihood:**	-22.960
No. Observations:	90	**AIC:**	47.92
Df Residuals:	89	**BIC:**	50.42
Df Model:	1		
Covariance Type:	nonrobust		

OLS Regression Results

	coef	std err	t	P>|t|	[0.025	0.975]
x1	0.1998	0.021	9.360	0.000	0.157	0.242

Omnibus:	29.421	**Durbin-Watson:**	0.004
Prob(Omnibus):	0.000	**Jarque-Bera (JB):**	5.451
Skew:	-0.008	**Prob(JB):**	0.0655
Kurtosis:	1.794	**Cond. No.**	1.00

Figure 8. Regression analysis for the two datasets based on the pseudo dataset. Chimpanzees (left) and orangutans (right).

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