

### WHAT IS SLEEP? NOVEMBER 18-19, 2019 SUMMARY REPORT

Post-meeting Reflection by Presenter (Van Savage (UCLA/SFI)):

#### SFI WG Big Unanswered Sleep Questions

1. What is sleep? Behavioral definition? Phenomenological/experiential definition? EEG/physiological definition? Which metrics—fitbit, online, over what time span, Etc.? How closely matched in terms of time of onset? How closely matched in terms of functional or health effects? How do we separate sleep ability from sleep need? Do we need a species-specific definition and can we come up with a very general definition that abstractly covers everything? How strict should we be with definition of REM and SWS by voltage or time-scale and frequency characteristics across ages versus qualitatively similar behaviors? What are the building blocks of sleep? When do definitions fail? What breaks these definitions? Which questions correspond to which definitions? Can we make that mapping? Is there a universal rescaling of EEG or something else where sleep does look the same across species, life stages, etc?
2. What are the functions of sleep? Can we construct a phylogenetic tree of life and developmental stage tree of life for the function and features of sleep? Are all about evolutionary/energy optimization of processes that don't happen as well during waking? Restoring functions vs learning functions vs other
  - a. Feel rested/cure sleepiness
  - b. Performance of tasks
  - c. Emotional regulation
  - d. Metabolic function
  - e. Maintenance of brain and/or body
  - f. Immobility during dangerous times for predation etc.
  - g. Memory and information processing
  - h. Energy conservation, adaptive inactivity
  - i. Immune
  - j. Inflammation (molecular) and pain (behavior/perception)
  - k. Endocrine function
  - l. Growth (SWS)
  - m. Protein homeostasis
  - n. Endogenous sensory input with higher signal/noise than otherwise for neonates
  - o. Maintain mitochondrial function
  - p. CSF/glymphatics clearance
  - q. Synaptic homeostasis
  - r. Breathing and cardiovascular regulation
  - s. Sleep cycling for vigilance to monitor fires, danger, etc.
  - t. Appetite control
  - u. Increased/decreased predation
  - v. Allergies

- w. Kidney function
- x. To dream

Consequences of sleep. These would be costs/tradeoffs in an optimization function

- a. Reduced alertness
  - b. Reduced foraging
  - c. Reduced social contacts
  - d. Reduced activity
  - e. Fasting
  - f. Reduced information gathering
3. Does evolutionary origin for function of sleep correspond to current functions of sleep? Is one sleep function dominant and the rest subservient or piggybacking? Are all on equal footing now? How big is the selection pressure in terms of evolutionary theory and measurement? Is there a group-level selection for sleep? What is first common ancestor of sleep? Circadian rhythm came before "sleep".
  4. Do different functions compete for time? Which function has longest time constant, which is distinct from which is most important? How does this change with life stage?
  5. Are there different amounts of sleep time required for different functions of sleep? If sleep is limited, are these different functions competing for the available time? If you restrict sleep, what is the ordering and magnitude of loss of different functions? Much known for learning and memory but what about other functions?
  6. What are the characteristic time scales of sleep and what sets them? Which ones are invariant, and which ones change across size, species, developmental stage, brain region, task, etc.? What data already exist for this? What were our models predict? If you take differential equations models and parameterize by correct time constants (based on scaling of neuronal scaling and axon conduction velocities or based on physiological/allometric scaling or both), as you tune them what dynamical shifts or phase transitions do you see? Why does a 90 minute nap help more with learning tasks than 5 hours of sleep? Go from fastest (ripples) all the way up to long timescales. Can we list characteristics timescales for each function above?
  7. Do we mean mechanism or function? How are these all reconciled? All equivalent?
  8. If sleep is for repair, does whole body repair work differently or over different time scale than just for brain? Immune response, wound healing, and bone density connection to sleep and circadian rhythm? How to quantify?

9. Does brain “saturation” cause sleep? Global saturation (no?) or local saturation? How are local limits set and what sets partition of space for each category, say physics versus French literature? Seems like it should be experimentally measurable/testable now. What exactly needs to be measured? Why don't we do it?
10. Do we need and can we get better developmental sleep data?
11. How do we include effects of temperature in sleep models? Via metabolism? Via loss of thermoregulation in sleep, hibernation, torpor in birds? What about sleep changes in total time, %REM, sleep cycle, etc across body temperatures in ectotherms, even for similarly sized organisms.
12. Is dreaming a way for brain to devise better computational algorithms for exploring large dimensional data or parameter space for theory? Why does this require sleep? Is it because it isn't accessible to our conscious brain because done by some other part of the brain and takes lots of energy so have to save energy from elsewhere? If it's so useful, why do we forget dreams? Maybe because their actual content isn't useful? Maybe if you remember too well, you start to confuse dreams with reality and that becomes big problem? Is there some wake correlate or default state or meditation or exercise in which something similar can occur?
13. What are the individual and Societal health implications of all the above?
14. Does sleep time change with city/community/social network/college size?
15. How can we best leverage large digital datasets? Can we align 23andme with fitbit and other data?
16. Can we develop a quantitative, mathematical, predictive, universal theory of all this? What would it take to do this in terms of data, assumptions, mathematical and computational tools?
17. How can we capture the heterogeneity of the data? Deviations from universal or described on its own terms or correlates and cross-effect for different features. Can we isolate which factors impact sleep? Gender, genome, SES, race/ethnicity, age, etc. Higher-order interaction effects.
18. How do recent experimental tools enable the answering of the questions above?

### What/Who are we missing?

- Ken Wright UC Boulder Metabolism and Microbiome
- Eve Van Cauter U of Chicago Metabolism and Immune function
- David Paydarfar UT Austin Engineering Mathematical Biologist and modeling of SIDS
- Rosemary Braun Northwestern Statistical Analysis of Circadian Phase from 1 or 2 samples
- Phyllis Zee Northwestern Sleep in elderly (bug picture thinker/ great at networking)
- Michael Perlis U Penn Insomnia and suicide
- Daniel Buysse (Sleep health)
- Sonia Ancoli-Israel UCSD sleep and chemo
- Laura Lewis Harvard Clearance of CSF during sleep
- Monica Haack Harvard Immunology/Inflammation/Sex differences
- Mark Opp (UC Boulder)
- More traditional Evolutionary Biologist
- Book audience more towards industry, Gates foundation, funding agencies, scientists, CDC,
- Present more scientific basis and evidence-based approach to importance of sleep and understanding it and its consequences.
- Mostly about basic science questions we've discussed throughout but with bullets at end of each chapter about implications and a chapter or two at end that is more focused on implications for health and policy.
- Make more focused in terms of modeling and timescales of sleep as theme of book.
- Data generated at many timescales, timescales can be organizing principle but must reconcile and synthesize them, modeling needed to reconcile and synthesize these timescales, this process actually unique vantage point for answering and asking big questions about sleep.
- Help bring model-resistant scientists to understand importance of modeling.
- Let's be provocative and say we can try to model dreaming!
- How does a brain calculate at the neuronal level which memories are valuable?
- How do we model sleep across timescales?
- Connecting machine-learning to modeling approach to make it better
- Importance of working and talking across disciplines
- How do a mapping from questions to appropriate scales? Hard to do it as just individual group or lab.

### Talk Notes (arranged by contributor)

#### **Susan Sara:**

Locus Coeruleus, Prefrontal Cortex, Sleep Spindles all increase about 2 hours after leaning task in rats. Higher LC firing rates even during Slow Wave Sleep, suggesting important learning and consolidation happening during sleep. LC is silent during REM sleep. Much more firing together during SWS than during wake. What sets time scales of 2 hours? It is task dependent because some take an hour. Does characteristic time scale change with species or brain size? What sets this time scale? Does it change across development? What is theoretical expectation? Any data? How to disentangle age effect from increasing difficulty of task being learned. Must be careful. Coordination and coupling of spindles and ripples. Which is first? How are coordinated? Which is functionally more important? Temporal relationships. Can replay happen without ripples? Replay in visual cortex is not related to ripples. Not clear ripples and replay are causative for memory. Maybe it's the subsequent ripple-spindling coupling that's disrupted instead of the present one.

#### **Gina Poe:**

Norepinephrine at Beta Adrenergic receptor is to increase/encourage long-term potentiation. Slow Wave Sleep goes aging with absence of Acetylcholine even in unihemispheric sleep in seals. Define sleep as a behavioral state but maybe that's hard because of dissociated states. Maybe sleep must be defined as functional question to ask what's needed or what counts. Is millisecond sleep enough to do something functionally? Lack of norepinephrine is required to erase memory so erasure can only happen in sleep. And targeted erasure (meaning targeting memory) can only happen in REM sleep thru depotentiation. Takes about 5 days or learning mazes for consolidation and reversal of learning. Again, what sets this time scale across task, species, development, or amount of brain involved? What tags or systematically decides what information you want to remember and what you want to forget? Firing rate lowest in REM sleep. Hard to see sleep in insects etc. because electric signals cancel out because not layered or striated or organized in way that gives clear signals.

Is familiarity versus episodic memory two separate states or is it a continuum? Familiarity might be the feedback to the hippocampus that this can be erased. Seems like two separate states. Why do we want to forget? Storage limitation, not useful, scary/traumatic, updating of previous thought like Santa Claus, etc. Danger of seizure from overload or saturation but seems like little evidence for this. Maybe saturation is only at the local circuit level. Flips questions around to ask why do we partition brain memory in way we do and why we do give this chunk of memory to this specific task. Nobody has looked at this question experimentally but could be done now. Maybe not really forgetting anyway but more like down weighting certain memories compared with others. Very modular structure and organization to cholinergic and adrenergic systems. Perhaps people with super memories have less redundancy of memory. Would they forget more in old age? Is this observed?

**Sara Aton:**

Foot shock creates fear memory that isn't consolidated if transcription/translation is disrupted, neuron firing is blocked, or sleep is not allowed. Increase in theta and ripples (so oscillations in general) after learning event across sleep. If you induce similar pace (7 Hz) oscillations you recover consolidation even without sleep. Not clear of side effects of what happens to other functions of sleep if this is all you do. Use of optogenetic tools to do cool experiments. Able to make it so there is fear response but without awareness of what they're afraid of. Correct time scales of rhythms are main thing needed for appropriate spike timing and that happens during sleeps and that's why sleep is needed for memory consolidation even if that's not primary function (although it could be). Is the 7Hz timescale task dependence, species dependent, developmental dependent, etc? Going from rate code to phase code to renormalized rate code and strengthening connections to propagate information through circuit. Thinks 7Hz is circuit dependent and circuit frequency is tag in that way that depends on wiring. Like a resonance frequency. She thinks phase matters but not frequency but not clear. Could you decipher or reverse engineer these codes to read out dreams or other things that are happening. Seems like there are experimental tools where we could start to do that. Circuit itself and post-synaptic partners are themselves making decision of what to remember or forget. Is certain cells can't keep they are in some sense filtered (probably literally) out? Could at least ask this question theoretical and see what happens. Does lag time correspond to spindles?

Slow oscillations are 0-1 Hz. Delta is 1-4 Hz. Slow oscillations go much deeper that allows for calcium rebound. Slow oscillations are more global and Delta are more local. Even individual cortical column or relay neuron can exhibit Delta by itself. Spindles are 10-15Hz layered on top of these other waves. Ripples are 80-200Hz on top of spindles. Gamma are 40-80 Hz and occur while awake. Only 15% of spindles coupled to oscillations even though learning relates to total number of spindles in sleep. Seems like paradox. 200mV for waves. Most power is in slow waves. How much of the brain's metabolic rate does this take? A lot or a little?  $1/f$  power happening for this. Measures of fractal dimensions of these time series? Do follow a power law. These are like temporal correlations. What about spatial correlations (using calcium imaging) or overlap in temporal and spatial correlations? What percentage neurons contribute to this? About 5% of hippocampal cells involved in a learning task and memory. 30% have place fields. About 20% decrease in glucose and oxygen consumption during sleep. About 37% decrease for humans in NREM. Would these timescales change across species? Similar in mice, rats, and humans. Calcium imaging could say more.

**Kimberley Whitehead:**

Looks at spindle bursts that's different from sleep spindles because also happen in wakefulness. People are now claiming to see spindles in adult. Maybe these two things aren't that different and we just haven't realized that yet. Help refine sensoricortical maps. If you prevent bursting, barrel cortex doesn't get organized properly. Sleep-wake state on the scale of minutes for humans. Pre-term baby has loads

of delta in all their sleep. Higher power in pre-term. Role of nREM becomes more important as you grow. Maybe phasic and tonic REM sleep have different roles. Sub-sleep state in scales of tens of seconds. Active sleep movement on scale of seconds. Sleep oscillations important for sensory cortical organization in gestation and early development. Log normal for frequency of wake bouts and active sleep bouts. Role of benefits of wakefulness versus benefits of sleep and which are more important for survival and selection. Sensory experience more intense during sleep than during wakefulness so reverse of sleep model for information input proposed in paper (Cao, Herman, Poe, West, Savage). Wakefulness set more by time to birth than time to gestation age. Why not plot versus body weight instead of age? Age explains more of the variance. It's experience dependence response and processing which seems like the generic definition of learning, not just laying the substrate for it. Surge to breathe, arousal, etc at birth so that's enough to switch dynamics of wakefulness and sleep.

### **Elizabeth Klerman:**

Sleep-wake cycle and circadian cycle Homeostatic cycle and circadian cycle must be coupled. Must desynchronize two clocks to decipher effects of each one. Homeostatic is need for sleep overall and not just circadian. Clocks shift for 25 or 26 hour timing. Scored in 30 second chunks of sleep or wakefulness. Organized around core body temperature minimum that typically occurs a couple of hours before you wake up. No circadian rhythm in SWS but there is in REM sleep. Not understood physiologically why that is? Tononi's model is that SWS reverse buildup of LTP. SWS percentage is same regardless of sleep debt so total SWS decreases. Related I think to questions about %REM and %NREM across development and across species. Remember to ask this question during my own talk. Drive to wake strongest right before you go to sleep and drive to sleep is strongest right before you wake up. Like hanging on by your fingertips but need some force you're fighting against then. Needed to help you consolidate sleep is hypothesis. Humans can know time of day even as seasons change by adjusting melatonin levels up and down. People used to be seasonally reproductive. Children and adolescents have much faster buildup of sleep pressure than older people. People who are out in bright sunlight during day aren't as affected by devices at night. So, something to do with change in magnitude of light, but just current amount of light. Different models needed for short exposure to light and effects on phase delay. Additional process coupled to process L or some type of modification of process L. How do go from average- or group-level models to more individual-specific models? How does caffeine or other drugs affect it? How does aging, disease, mental disorders, etc. affect it? What is physiological analogue of the two variables for the phenomenological model? Some amalgam of the physiological factors? Maybe different amounts of sleep are needed for different functions of sleep? Maybe they are competing for the time they get?

**Cecilia Diniz Behn:**

Sleep depends nonlinearly on amount of sleep deprivation and timing in circadian clock. Characteristic time scales affect shape of circadian waveform that affects timing of sleep and wake. Can we get a more physiological perspective and include that in modeling framework? Network between SCN, Wake, REM, and NREM. Choose scale at which network is specified, ranging from neurons to whole-brain regions or functions. How do you choose scale and how that affect choice of math methods? Depends on what questions you're asking as to what scale you should choose. Time constants of homeostatic sleep for humans can be tuned to work. For rats' homeostatic sleep build up too quickly so can't compensate with circadian clock. Shows importance of time constants and that it can really give different effects and conclusions depending on what you think or use here. Could be order-of-magnitude difference between rats and humans. Populations of neurons can shift clock and likely mediated by electrical activity and firing in SCN. Can use Hodgkin-Huxley type models here. Circadian rhythm plays a role in sleep timing but not the ultimate clock! Feedback with other sleep clocks!

**Marishka Brown:**

It is a mandated program but funding is not mandated. Largely instigated with push from circadian researchers. Trans-NIH sleep coordinating committee to build partners across all the different parts of NIH. Starting to build with NIAID. Studies on fatigue and sleep and performance joined together for studies. Connecting also with Human Health and Services. Circadian, disease, development, understanding are big parts of funded NIH sleep proposals. Turning discovery into health is motto. We scientists need to communicate better with those who fund us and general public to explain why basic science is so important to even be able to have something to translate into clinical applications. Need to do a better job to verbalize priorities to get funding behind us. Sleep disturbance is one of the best predictors of suicide. Lots of effects on heart and other functions. Correlation between sleep deficit and every type of risky behavior of adolescents. Public is convinced about sleep, just not academic medicine. Sleep and circadian rhythms are fundamental to health and life. How does circadian timing (NIAID) and sleep restriction affect immune response and vaccinations? Funding opportunity now. Ideas about chronotherapy. Does timing of organ donor for transplant need to match circadian timing of recipient or does it not matter? How does sleep deprivation affect it? What about sleep and health disparities compared with woman, URM, low SES, rural communities, etc. Why do these differences exist? (Not just cardio event in AA adults.) DOD strongly aware of importance of sleep and funding for research for it. Big upsurge in funding over last 3 years. Funding connections with cancer are expected to grow stronger. Silos of sleep research based on citation networks. NIH wants to break that down and create more communication.

**Victoria Booth:**

Shortest time scales are bouts of minutes. (In principle, could this go down to even milliseconds because memories can form in that small of a time.) Wake durations are power law and sleep durations are exponential. Wake durations seem to follow Zipf's law. Sleep duration follows random Poisson process like radioactive decay. More fragmentation in sleep bouts happens towards the end of the night. How strict should we be with definition of REM and SWS by voltage or time-scale and frequency characteristics across ages versus qualitatively similar behaviors. Randler et al. 2019 in Sleep Medicine for time in bed across ages. 3 to 4 months for baby to get used to day-night cycle. Sleep is more fragmented with aging. Trying to use fine time-scale modeling to predict changes in sleep across development and aging. Both wake and sleep bouts start exponential and random but become power law for wake around P15. Is this same as pre-term to term? Lesioning SCN you don't see as much of the power-law behavior being established. By synaptogenesis P14 in rats is similar to about 3.5 years of age in humans. Younger subjects have longer tails than older subjects. Difference has a lot to do with NREM to REM transitions. Probability of waking up is much higher in older people so they sample the long-tail of the distribution and have longer individual waking bouts. LC develops early in fetus (Nakamura) and transitions/switches to alpha-2 autoinhibitory mechanism around P10 to P15. LC might be off in REM sleep. True in fetal rats but unclear in humans or other species? Diniz Behn and Booth (J Neurophysiology 2010) have physiologically-grounded model to investigate and explore this with and look at mean firing rate using ODEs. Stochasticity lengthens tail. Huge switch at 3 to 4 weeks to entering sleep in NREM phase. Can mode predict this?

**Jerry Siegel:**

Sleep changes across species. Argues it's driven by ecological factors. Argues sleep is adaptive in evolutionary sense. Perhaps animals are dying from repeated awakenings instead of loss of sleep for things like disk-over-water technique or experimental deprivations in general. Carnivores show little change in total sleep time with size. Recorded conditions aren't much like natural conditions so how much does that affect sleep results you get. For example, temperature regulation. Example of platypus believed to have no REM and then they built platypusariums and there was lots of REM. Sleep changes a lot during migration. Amount of sleep in wild typically less than in lab. Elephant sleeps half as much in wild as in lab so about 2 hrs. Do they sleep at best time to thermoregulate? Bats sleep a lot (~20 hrs) but also have a very high metabolic rate. Go into hibernation though SWS that gets deeper and deeper. Could REM sleep be happening while elephants are seemingly awake and walking around? Might it be happening in only certain parts of the brain? Could you see how Mom responds to meat in terms of speed and orientation to determine how lack of sleep affects her. EEG basis for REM sleep but not based on brainstem recording. Call to include more temperature effects in models. Temperature and light are correlated. How to disentangle which drives sleep? Janet Best has paper on how temperature drive sleep cycles.

**Geoffrey West:**

Body cannot have nearly perfect repair because of increase in entropy and second law of thermodynamics. But brain can be treated as not a closed system. It is an open system that draws from and drains off of resources of rest of body to keep nearly perfect repair. Lifespan and aging both about damage. Should be able to have formula in biology textbook for why we sleep 8 hours a day and live roughly 100 years.

**Alex Herman:**

Subcortical REM more important in relation to number of synapses.

- Does LC firing trigger upstate or is LC firing triggered by cortical down state?
- Can parameterizing models with anatomical distances and scaled time-constants lead to emergent behavior in dynamics of sleep wake cycles consistent with data?
- What is the history dependence of sleep states? Are all REM and NREM sleep bouts created equal over the course of a night?
- What
- Oscillations: What sets the intrinsic rhythm of a cortical area? What reads out the phase-ordered temporal sequence of spikes?
- Can animals have more localized forms of sleep?
- How are the electrophysiological signals of REM sleep related to its functions?
- How can animals with close phylogenetic relations show such different sleep patterns?
- Do we have a phylogenetic history of the different functions/phenotypes of sleep?

**Bob Stickgold:**

More creative after sleep or dreaming. Because new creations are explored then or puts brain in better space or configuration to then do exploring once you wake up. How does this relate to patients with narcolepsy because seems like they have higher levels of creativity or lucid dreaming? Function of dreaming is not to solve problems as much as to explore different solution spaces and find what's promising. Reminds me of trying to devise better computational algorithms for exploring large dimensional data or parameter space for theory. Maybe our brain has found good way to do this. Question is why does this require sleep to occur. Is it because it isn't accessible to our conscious brain because done by some other part of the brain and takes lots of energy so have to save energy from elsewhere? If it's so useful like this, why do we forget dreams? Maybe because their actual content isn't useful? Or maybe we unconscious access to them but not direct access. Or maybe if you remember too well, you start to confuse dreams with reality and that becomes big problem.

DISCUSSION:

**Big idea: consideration of multifactorial definition of and function of sleep**

**Susan Sara:** Hippocampal ripples are important for memory consolidation; how would the timing of increased ripple density post-learning change with species and/or development? Can this be connected to brain size/networks involved in memory consolidation?

**Gina Poe:** How are memories tagged for strengthening or weakening? What computational approaches could inform our understanding of this? Complexity of memory likely influences the time scale - how might we explore this experimentally or computationally?

**Sara Aton:** Mechanism whereby a rate code is translated to a phase code. How does modulation of neurotransmitter milieu affect the propensity of network to propagate particular rhythms? How does the power of rhythms relate to metabolic rate of the brain? Does synchrony play a role?

**Kimberley Whitehead:** How do mechanisms for spindle-burst production relate to mechanisms for spindle production? What are appropriate comparisons for pre-term human infants and animal models of different species (rat, sheep, etc.)?

**Beth Klerman:** Seasonality is observed in the duration of the biological night as measured with melatonin expression; how does this relate to mechanisms for seasonality encoded in the SCN? Important new direction to take insights from groups and translate this to predictions for individuals? How do we handle missing data and investigate the tolerance of models to missing data?

**Victoria Booth:** What do changes in the structure of sleep tell us about changes in physiology? Blumberg showed a lack of consolidation of wake in OXKO infant mice emerged during development when WT mice were able to consolidate wake bouts to transition to a power-law-like behavior. We showed similar differences in a mouse model with acute orexin cell loss (Branch et al., SLEEP, 2016). What can we learn about sleep in development in the absence of orexin neurons? How would physical distance between neuronal populations and degree of myelination affect the time scales on which these populations interact? For example, would slower transmission allow more bistability between states? Neonates have more wake to REM sleep transitions. How would we understand this in terms of different network configurations for NREM/REM regulation? Would this be a useful constraint?

**Jerry Siegel:** Fur seals can switch between bihemispheric sleep and unihemispheric sleep. Modeling has suggested that this can be understood based on relative strengths of contralateral and ipsilateral connections between brain hemispheres (Kedziora et al., J of Theoretical Biology, 2012). How do predictions compare to anatomical evidence?

What other insights from physiology could we get from this system? Important to consider the role of temperature and thermoregulation in sleep dynamics. This has been explored a bit in a recent model (Banuelos et al., Effects of Thermoregulation on Human Sleep Patterns: A Mathematical Model of Sleep–Wake Cycles with REM–NREM Subcircuit, in Applications of Dynamical Systems in Biology and Medicine pp 123-147). What are other ways that these ideas could be included in mathematical models of sleep?

**Van Savage:** What can theory tell us about the quantities we should be measuring experimentally? For example, the theory suggests the importance of considering the ratio of time asleep to time awake rather than durations only.

**Geoffrey West:** Developing a theory that connects sleep duration and lifespan. Lifespan scaling is derived from ideas of sleep for repair; could we introduce a modification that involves a different role for sleep in development? How is this impacted by differences in species development/maturity? Can we understand this scaling in terms of the DNA methylation view of aging (e.g., converting dog years to human years: <https://www.sciencemag.org/news/2019/11/here-s-better-way-convert-dog-years-human-years-scientists-say>)?

**Alex Herman:** If synaptic density drives metabolic rate of the brain, is there also a role for different rhythms? Reporting a sharp transition in the relationship between the ratio of time asleep/time awake to brain mass. What else does this transition correlate with? Changes in behavior? What would this be abrupt and not graduate? What does synaptogenesis peak and how does it relate to this transition? Follow up with Junwu Can regarding her method for threshold detection of this transition.

**Bob Stickgold:** Different types of sleep for different types of learning; gist words - how does this relate to other measures of creative thinking? What is the role of forgetting for dreams and what is important about the dreams we remember? What about problem solving that can occur while sleeping/dreaming?

**Elizabeth Klerman** (Harvard Medical School)

- Add information/discussion about non-brain "functions" of sleep (e.g., metabolism, immune function) with their time scales
- Add Other brain "functions" of sleep to include are: mood/psychiatry; objective neurobehavioral performance; "cleaning" of toxic substances (glymphatics); neurochemistry
- What are target/pivot points for changing some aspect of sleep?
- How to define and then study sleep "need"? Is it different for each function? with age? How does it interact with sleep duration or timing of sleep?

- Feedback between sleep and circadian rhythms; not just one way circadian-> sleep
- Two comments from discussion:
  - Comment: Frame the “needs” of sleep not as competitive with each other but as parallel.
  - Comment: Not all functions of sleep bring you back to where you were before; some are to bring to a new state (e.g., learning, immune)

Gina Poe (UCLA) -

### Is sleep for remembering or forgetting?

I like starting our meeting “What is sleep?” with a session on function, because sleep looks different in different animals. so, to figure out what sleep is we need to figure out what it does, then figure out what is necessary (conditions) to do that function then look for those conditions across ages and species.

Of course, we have to start with some fundamentals and commonalities of sleep, even though we don’t know if they do - or should - define sleep or whether it is incidental-- a side effect, instead of an essential to sleep. I believe that thanks in part to the people here today, we have that starting point. We also have some basic functions of sleep identified, although it has been messy because until recently, we have not known enough about those functions to adequately test whether sleep is important to those functions. But, again, we are at the point where we have enough clues to start our reverse engineering phase.

In those early days we could not reverse engineer because we haven’t known what brain areas were responsible for what kind of learning and what neurotransmitters and electrical activity signatures were needed. But now, thanks to a horde of thousands, we know a few essential things:

- Theta, gamma,
- ACh, NE/DA
- Phosphorylation
- Potentiation/depotentiation, engrams, ARC, cFos, mRNA, protein synthesis,
- Circuits: what is interconnected. How specifically NE and ACh targets forebrain,
- Order of play: cortical registration, Hippocampal assembly, and eventual cortical strengthening...

Now we are ready to roll up our sleeves and figure out what sleep really is!

---

### Why awakening-based sleep deprivation is not great:

1. As Jerry Seigel points out, if you wait until an animal shows electrographic or behavioral sleep before you awaken it, then you get the arousal-response.
2. My 2016 Sleep paper shows (replicated by Duran et al., 2017) that cortical electrographic signs of sleep misses much subcortical sleep even normally... how much more when sleep pressure is high! We also show that hippocampus is in REM when the neocortex remains in NREM normally, but even more when the hippocampal homeostatic drive (learning-induced) is high. Thus, any sleep deprivation protocol that relies on posture, EEG, or muscle tone would and probably does miss a lot of sleep that goes on "locally". Thus, any negative finding, e.g., "REM sleep is not important for X learning task" could be completely wrong if we are not measuring that particular type of sleep from the area involved in that type of learning and/or memory consolidation. Recommendation: measure the amount of sleep from the actual structure essential for the function you are testing.
3. Some of the sleep deprivation studies use pharmaceuticals like caffeine or some other stimulant, which is good because it eliminates the awakening response discussed in point 1 above, but of course stimulants have their own effect on the function under study.

---

### On time variances of total sleep time vs sleep bout lengths-----

One function of sleep, like the memory process of sleep, may take only a few minutes or even seconds to accomplish, while other functions of sleep, like repair and clearance, may take much longer to accomplish, and be counterproductive to the learning function, and therefore sleep may need to intersperse the learning function at intervals during the longer sleep period in order not to lose, e.g., what you consolidated.

Either the undoing of one sleep state's function by another or the processes or side effect outcomes of one state requiring another sleep state to clean up after it may be why healthy sleep proceeds in an orderly fashion and unhealthy sleep, even if it is adequate in total length is disordered: REM sleep occurring too soon in depression, REM sleep occurring at sleep onset in narcolepsy, etc. If REM sleep serves to clean up synapses (strengthens those spuriously weakened but tagged for keeping, and weakens synapses spuriously strengthened by SWS or those ready to be erased now that slow-oscillation coupled spindles have consolidated them to their final place) then that would explain why the length of REM sleep is related more to the length of the prior NREM state than to the length of waking.

---

It may be that the cycles of sleep are timed as they and the states follow each other in order as they do because should our planned long sleep cycle be interrupted, we will at least get some of all of the different kinds of necessary work done. even though having only one cycle leaves it incomplete, it would be better than nothing. Interrupting a sleep cycle midway (e.g. being awakened out of SWS) may be like interrupting the wash cycle midway, leaving clothes soaked and soapy rather than rinsed and clean. A power nap with only stage 2 sleep may be like a quick rinse and spin-dry which is better than the dry but filthy state that the party of wakefulness has left us. But a sleep disturbed from slow waves may, like the middle of the wash phase with soap and soaking wet, leave our brains in a worse state than the previous dry filthy one.

---

**Susan Sara** (École des Neurosciences Paris Île de France) - Is sleep for remembering or forgetting?

The quest for a universal definition of sleep and an overarching function may be misdirected. There may be sleep functions that are species specific. Moreover, functions dependent upon sleep in one given species may be sleep-independent in another species (elephants sleep 2 hours/day and have good memories). Therefore, we need a more phylogenetic or ecological approach.

From an ontogenetic point of view, the function of sleep, especially REM sleep may change with development.

**Victoria Booth** (Univ. Michigan) (Notes on each presentation, by speaker)

Sleep is a variable state depending on species, developmental stage, available physiological markers:

- **Kimberly Whitehead talk:** In preterm infants, the active sleep stage fulfills a development function that is distinct from the proposed functions of sleep in full-term infants and adults. Namely to develop the somatosensory maps in the brain for processing external inputs like the barrel formations in whisker barrels.
- **Jerry Siegel talk:** Sleep in different species doesn't show same physiological markers as in usual lab animals and humans. Dolphin and killer whale unihemispheric slow-wave sleep – is it the same as human sleep? Brown Bat sleeps ~20h per day – is that the same state as other animals? Can we relate all animal "sleep" states to human sleep states?
  - **Summary:** the question of what is sleep is not fully answered. Sleep is different in different life stages and different species
  - What are key physiological processes that contribute to sleep timing, duration?
- **Jerry Siegel talk:** Body temperature has large effect on sleep durations, especially REM sleep occurrence. Should be considered in models

- **Beth Klerman talk:** Circadian rhythm acts to consolidate sleep and wake episodes. At end of the wake episode, circadian rhythm generates a wake-promoting signal, the no-sleep zone. This acts to keep us awake longer so that when sleep occurs it lasts longer and is more consolidated. Similarly, the circadian sleep-promoting effects are strongest at the end of the sleep period, so that we stay asleep longer and the subsequent wake episode will be more consolidated. Also has new paper coming out in J Biol Rhythms on the phase shifting effects on circadian rhythm of very short light exposure in the dark period
- **Cecilia Diniz Behn talk:** Signalling of SCN to sleep-wake centers may not be 1-dimensional. In rat, requires both sleep-promoting and wake-promoting effects to account for SCN lesion data. In squirrel monkey, can be 1-dimensional effect perhaps because homeostatic time constants are longer relative to circadian rhythm than in rat.
  - Role of EEG signatures of sleep, such as spindles. Ripples, slow oscillations, theta range oscillations, depends on developmental stage and type of EEG event
- **Kimberly Whitehead talk:** In neonates, twitches are initiated in periphery and cause a spindle-burst that propagates throughout the somatosensory cortices. This is a signature of propagating activity throughout brain regions and contributes to constructing the neural map of the sensory system. In neonates, sleep oscillations subserve sensory cortical organization
- **Sara Aton talk:** Different oscillations occur in cortex and hippocampus in different sleep states. In NREM, have slow oscillations (different than slow waves) in cortex and have sharp waves and ripples in the hippocampus. In REM, cortex shows asynchronous activity and hippocampus shows theta oscillations. Oscillations are the substrate for temporal coding of information. The relative phase of cell firing to the oscillation peak sets the temporal frame for temporal coding. A rate code during wake and shift to a temporal code during sleep oscillation with most excitable cells firing first during the oscillation. The temporal code during sleep oscillation also support appropriate patterns of synaptic plasticity for memory consolidation.

**Kimberley Whitehead** (Univ. College London)

Common principles of sleep-related oscillations that subserve some form of 'learning', e.g. bursting on a background of neural quiescence - this definition would encompass the unusual features of sleep in early development. Very interested by a) Susan's reference to the Aston-Jones 1981 paper that shows attenuation immediately prior to firing as if to 'boost' the effect of the firing, b) that oscillations can occur but the ones that have many frequency bands coupled together are the most important for memory consolidation, c) Susan's quote 'synchronous activity during sleep provides a substrate for []' (the square brackets could be replaced by nearly all functions!)

Remembering: we need augmented oscillatory power for a stimulus to be learned (Sara's talk) and this can be artificially provided (Ognjanovski et al. 2018), how might this relate to augmented sleep EEG power post brain injury - is it possibly not just a biomarker of damage but a marker of the synchronized activity necessary to 're-learn' new circuits? If a neuron which has learnt something continues to stay more active, for how long? How does that link to the renormalization mentioned in final slide?

Forgetting: Is it REM sleep or forgetting or dreaming specifically for forgetting? Very interested by Gina's reference to Crick 1983 Nature paper - how could that relate to infants who have MORE REM sleep but probably don't yet dream like we conceive dreaming

Sleep oscillations as a spatial filter: because some neuronal ensembles can't keep up with the speed of oscillations, creates a spatial filter

Cortical region-specific projections from Locus Coeruleus (Chander et al. 2019 ref from Gina's talk): a way that sleep-wake states could differentially modulate sensorimotor areas in the developing brain, to help them to differentiate?

Durations of sleep: Bob's conceptual theory that 100ms of sleep would be sufficient to encode a memory e.g. a microsleep. Could that be reversed to think about some adaptive function of the extra-short WAKE durations pre-term infants have e.g. 2 minutes?

Body weight vs. age predicting sleep-wake bout durations: Following up on Geoffrey's question, I will go back to the literature to check those references that biological age is more predictive than body weight. But thinking about his question, my forthcoming project on intra-uterine growth restriction would be an ideal opportunity to look at this in more detail.

Other ways I intend to improve my practice following this meeting: report ambient temperature

Evocative metaphors!: 'Mountain of wakefulness'. Bob's 'Memory evolution', more dynamic than just consolidation which doesn't fully capture sleep's functions. 'Ground truth' - the challenges of establishing this in many aspects of sleep research