[MUSIC PLAYING]

SPEAKER: How many neonatologists in the crowd? Oh, OK. So my disclosure is that I am not a sleep medicine specialist but I am going to talk about sleep. Another disclosure is I'm actually here representing Renee Shellhaas, who is the PI of all of these studies of pediatric neurologist. But she is also not a sleep medicine specialist, but at a sleep meeting out in Boston right now. And so Renee delegated this one to me, which I am happy to do, because we've been collaborating on this for a long time. Right And also on behalf of other faculty in our group, and besides that, on behalf of many students and fellows who worked on these projects.

So traditional evaluation of brain function of a newborn is we wake babies up, and we assess their tone and reflexes. And we may or may not apply some kind of a scoring system to that. It's actually a pretty limited way to evaluate brain function in a newborn when you think about it. It's pretty limited.

And I remember early on when I was learning the neurologic exam, pediatric neurologists making the point to me that everything you're seeing in this normal baby could likely be replicated by a baby with hydranencephaly. So the point being, you don't need a lot of cortex involvement to do the things that we think of as being normal neonatal neural behavior. And that's what we call our neonatal neurologic exam. And when they do have abnormalities, they're fairly nonspecific. They can't tell us much.

So why would we study neonatal sleep? So that would be because newborns spend most of their time sleeping, which means if they're spending 16 to 18 hours of the day sleeping, then probably, a lot of their normal brain development is happening while they're asleep. And another reason to study sleep is that it is actually a complex and highly regulated neurologic function, which we don't think about much, because we're asleep when we're doing it. But it might turn out to be a lot more informative than the neurologic exam, because this is something that actually does involve the cortex. In a way, it's a more sophisticated thing than what we're asking babies to do when we wake them up.

Another reason to study it could be that it's an interesting question. And we wonder, is it different when babies are sick? And we ask that in the NICU all the time. We don't ask it as much as we used to when I was a fellow, when the lights were on 24/7, and we played rock and roll music on transistor radios, which tells you how old I am. That's out of fashion now.

But this question has hardly been analyzed. What is being sick? Never mind having brain injury, but just being sick and in an ICU doing to sleep. For any of us who have been an inpatient or in an ICU, we can imagine that if it's not good for us, it might not be good for them, either.

So our two hypotheses that underlie the work that we've been doing for the last several years, one is that sleep could be a useful biomarker of brain function. And the other is that disruption and disregulation of sleep might be modifiable, at least that this is an interesting question that we ought to ask, if it turns out that we're messing up baby's sleep when they're in an ICU, whether we're trying to or not.

What's the evidence of this idea that sleep is a biomarker of brain function? Several lines. So one is, at least in the neonatology world, that sleep-wake cycling has become thought of as a good prognostic indicator. Now, mind you, this usually means really cyclicity seen on an amplitude EEG, which is a cerebral function monitor, one of those things where there's two electrodes or four electrodes. It's not a full EEG. It's not a polysomnogram. But in normal babies, you see cycling on that that we think is a manifestation of sleep cycling in some way.

And so in babies with HIE, or in neonates with sepsis, or just preemies, either the presence of this cyclicity or how soon it recovers in babies with HIE is a good prognostic indicator. And in one of the few studies actually published with full polysomnography in babies in a NICU, a study from Israel reported that abnormal sleep physiology, whatever that is, in pre-term infants is associated with adverse neurodevelopmental outcomes. And in babies a little bit older than our population, but I bet not too different from a lot of your infant cardiac population, snoring in infancy is associated with worse cognitive scores.

And when I heard this from Renee, my response was, who knew that infants snored? But apparently some of them do, just not my two kids.

[LAUGHTER]

So that's associated with worse cognitive scores. And in sleep medicine, I think in older populations, there's a big worry about sleep disordered breathing causing all kinds of bad things-- effects on your brain, effects on your pulmonary vasculature, et cetera. So these are reasons why it's plausible to think it's a biomarker of brain function.

Now, could sleep be related to outcome? And so this is a tricky question. What we're wanting to ask is not just, could sleep be related to outcome, but if sleep abnormalities were related to outcome, is there anything that we could do about that that might improve outcome? And another question is, even among children who don't have a preexisting hit to their brain, is the impaired sleep physiology a risk factor for adverse neurodevelopmental outcome?

So you get into a lot of chicken and egg questions when you want to get into this. And how you can sort this out, it's not going to be straightforward. And part of why I'm here, you'll discover, will be advertising for the idea that maybe this should be something looked at it more than just a single center. So let's see if I can get this-- Oh, the chicken and the egg yet again.

OK, so how do we study neonatal sleep? So there's a bunch of ways you could do this. You could just hire students to sit at the bedside 24/7, and score them. And in some parts of the world, people did this because you could get a draft deferral by doing that in certain countries, not ours. OK, so that's one way to do it, exploit people.

[LAUGHTER]

Another would be just looking at cyclicity in the traditionally EEG. Like our previous speaker was talking about, if you're doing 24/7 video EEG monitoring anyway, can you infer about sleep just from looking at that without having to do anything additional fancy? Or you could just look at the cyclicity and amplitude EEG. Is it there or not? Try to score it in some way.

You could even look at cyclicity as cerebral nares. Hands up how many people put NIRS on your kids in your CVICUs? Whoa, a lot of hands. Actually, I'm not surprised. But the reason why Renee and I got interested in this that was an incidental finding in a NIRS study we were doing in babies with HIE. We noticed that there was cyclicity in the NIRS tracing, which actually turned out to be in the kids who were going to do better. But that's part of what got us interested in this question.

Or you can do the official thing, which is attended polysomnography, or PSG, which is easy to say in a talk. And there are actually standard neonatal criteria, which I didn't realize. And shockingly, they're from 1971, which is before even I went to medical school. And so you have a registered sleep technologist who scores it. And for the studies I'm going to talk about, we are fortunate to have one person who scored all of them. And then it was reviewed and finalized by somebody board certified in sleep medicine.

So how do you do polysomnography in the NICU? So this looks even scarier than the picture of EEG that you already saw from the previous speaker, because not only do you have the whole hat and the wrap with almost as many EEG leads, but you have a lot of the other stuff that they rely on for EMGs, and so on here. This baby also happened to have NIRS on, which we don't include in the studies anymore, which makes it look even more cluttered.

So the things that we're measuring are-- many of the things AHI, the Apnea-Hypopnea index, central and obstructive apnea frequency, means, saturations, and so on that you would see in a sleep study on any of us, too. And we also asked them to look at specific apnea episode duration of greater than 20 seconds, because olds neonatologists like me used to think, ah, we only care about apneas greater than 20 seconds. And why do I mention that? Because I'm going to talk a little bit now about the primer on polysomnography that Renee kindly provided.

So for neonatologists, this is a really shocking definition of central apnea. And most of my colleagues mock and laugh when they read this one, the people who are used to, it has to be 20 seconds or it's not a real apnea. So here, you can see that. Read that first definition. So it doesn't take as much for something to be called a central apnea as might have been the case back in the good old days when I trained and read what we call nomograms in that era, as a fellow. And their standard definitions for obstructive apnea, for hypopnea, for central hyperventilation, and so on. And these were the definitions used in our studies.

So some of the steady study questions we've worked on so far, which is just the beginning, are to ask questions like, in neonates, if they have impaired sleep physiology, does that correlate with the neurological exam? And the reason why that's important is because questions 2 and 3 are more important questions. So any time in neonatal neurology, we think we have the latest whiz-bang tool for prognosticating after neonatal brain injury, be it the latest MRI sequences, or the latest fancy neurophysiological thing.

One of the early questions we have to ask ourselves is, is this fancy thing that costs more to do and uses a lot of technology any better at predicting neurologic outcome than the neuro exam that we do when the baby is seven to 10 days old? And if it isn't any better than that, then why do it?

So therefore, if we want to ask this question, is impaired sleep physiology associated with poor neurodevelopmental outcome like at 18 months, then we also have to know, does impaired sleep covary with an impaired neurologic exam? Because if it does, then you really have to ask a question three, as well, which is, does the impaired sleep add predictive value after you correct for the neonatal neurologic findings? And we'll get to the results of that later. And finally, the thing that I think is most interesting so far is, does the NICU environment actually disrupt their sleep?

So for the first question, we recruited a bunch of babies in our NICU. And you have to know that these babies got into the study by first having had a clinically indicated EEG, which means there was some A priority reason to be worried about their brain. So we weren't looking for normal newborn volunteers to hang out and have all of this done for 12 hours. They were babies who are already in the NICU for reasons either neurologic or that there were incidental neurologic concerns. And they were late pre-term or term infants.

They, with parental consent, had the 12 hour PSG. And then we did a standardized neurologic exam at about a week of age. And the particular one we used is something called the Thompson score. And I have the citation in there. It's a simple score that even I can do. It's only one of many, but it's the one that we chose to use. And a higher score equates to a worse neurologic exam.

So this was the question of, is sleep physiology correlated to the exam scores? And the answer was yes for some of the sleep indicators. So for quiet sleep, then babies who had a worse neurologic exam spent more time in quiet sleep. So it's a positive row in this Spearman correlation.

And then the next association that we found was that babies who had less sleep-wake entropy, less randomness in their moving around among sleep states, had worse neurologic scores in the neonatal period after we'd done the PSG. And then the other finding was that babies who had relatively low delta power-- so delta, that's the lower frequency EEG waves. So if babies had lower power in delta, which is the red dots you're seeing here, during quiet sleep, that was associated also with worse neurologic exam scores. And these correlations remained after adjusting for gestational age, because we had a range of gestational ages, and for their post menstrual age, how old they were in days after birth at the time of the PSG.

So to summarize all of this, then, babies at risk for brain dysfunction based on their neurologic exam may be showing us a tendency or some pressure to have more quiet sleep than would be normal. They're spending more time in quiet sleep. They have lesser intensity of delta power in quiet sleep. And they have less entropy. And they tend to spend more time going into quiet sleep from other sleep states. So that's interesting.

And then we get to the question of, well, could these objective measures be associated with a later neurodevelopmental outcome? So we tried to follow all of these babies with an 18 month Bayley in our neonatal follow-up clinic. And we were successful in having 29 of them out of the original 50 come back. And so first of all, of course, not all of the babies necessarily survived until 18 months. So we had some outcome data, basically dichotomous outcome, which is survival without severe disability on 40 babies. And we had full Bayley on 29 of them.

By the way, it's not mentioned on there in writing, but the babies who had the Bayley, these various characteristics, did not differ in the 29 who made it to have the Bayley exam from the overall population of 60 babies for things like birth weight Apgar scores, and so on. OK, so the way we analyzed this question was, first of all, were any of the neonatal sleep measures associated-- so these are as continuous variables-- with any of the Bayley subscale scores as continuous variables?

And then to analyze the question of, did impaired sleep add predictive power to the exam, is you would do the regression analysis with and without the Thompson score in the model. And just reminding you there why we wanted to put the Thompson score in the model, because of it's correlation and the neonatal period with some abnormalities of sleep. So the answer to this question, then, was that these associations remain significant, two of the associations remain significant, after adjusting for the Thompson score. And that was the increased percent of time spent in quiet sleep was associated with 18 month outcome, independent of the neonatal exam.

And this low delta power in quiet sleep was also associated with some abnormalities on the 18 month Bayley, not necessarily the same ones. Motor was an association for both of them, cognitive just for the percent quiet sleep, and language for the decreased delta power. And you might wonder why we put exposure to phenobarbital in there. We also thought having neonatal seizures-- and it makes sense from the previous talk-- would be an independent predictor of 18 month outcome.

And so being exposed to phenobarbital in this population, we were using it as a marker for neonatal seizures, because we don't use prophylactic phenobarbital in our NICU. So we figured that was a good proxy. And so these associations stayed true even when we adjusted for neonatal seizures.

Now, what does this phenomenon of the decreased delta power actually look like? So here's an example of how you might graphically display the sleep cyclicity. And all of these epochs are scored for whether they're awake, or in quiet sleep, or in active sleep. So quiet sleep is blue. So focus on the blue dots, and look where they are compared to the y-axis. It's the same scale on the y-axis and the upper and lower graph.

So this patient on average, the blue dots are higher up than on this one down here, where these rather more scattered blue dots are lower. So this is an example of a lower delta power in quiet sleep. And you can see that this baby's overall sleep architecture is just really different from this one. And it also looks like they're spending more time in quiet sleep.

So this gives you a graphical representation of the differences between the more healthy sleep pattern in the upper panel, and the not so healthy sleep pattern in the lower panel, that Joe Burnes, who's our biostatistician and signal analysis guru, came up with. Kind of cute.

OK, so why is this a plausible idea that abnormal quantity and quality of neonatal sleep would predict abnormal neural development? And it turns out it is. If you do sleep deprivation or restriction in immature animals, then this alters their synaptic plasticity and their neuronal maturation. So it alters this really important stuff that's still going on in the postnatal brain at the time that we have them in the NICU, or you have him in the cardiovascular ICU.

And so yes, messing with their sleep can actually interfere with important stuff, not stuff that you could see grossly at the level of white matter injury or decreased gray matter volume, necessarily, but at the synaptic level where there's a lot of forming or pruning of synapses happening at this age. And also both REM sleep and non-REM sleep are important for normal brain development, although we've been focusing mostly on quiet sleep here.

So then that final really interesting question to me, does the environment disrupt neonatal sleep? So we did this fun study that was really a spin-off and some of the PSGs that we collected in that previous study. And this is one of our neonatal fellows projects. So the objective was just to see, because we have a video that we recorded during the PSG, we could determine how often people were bugging the babies. Yes, it's just that easy. How often are we disturbing the babies? A polite way of putting that is hands-on care.

[LAUGHTER]

And what's the impact of that on sleep? Because we are obsessively evaluating their sleep during all of this. We have 12 hours worth of obsessive evaluation of sleep. And with this disturbing the baby, are their actual respiratory events, changes in physiology, that are associated with it? And so out of those babies, what we did was pick a really nice, clean, continuous, four hour chunk out of the entire 12 hour time.

And Jen and some of the students who worked with us-- bless their hearts-- sat and watched through the entire video tracing, scoring when all the messing with the baby was happening. And they actually tried to say, when is it a caregiver? When is it a parent? When can we tell which it is? I'm not going to go into that and talking about the results. But that's the level of detail they went into.

And then we looked into what was the relationship between those interactions and sleep physiology, and just how often were those interactions happening, which was the most interesting result here on the top line. The median time between contacts with these babies, 2.3 minutes. Yeah, holy cow. And so we thought we were one of these units where we turn down the lights at night, we do light cycling, supposedly we don't touch the babies unless we have to. Ha, I would just say, ha.

[LAUGHS]

Now, these are not the ELBW preemies where we're really supposed to obsess over that, and where we have the shroud over their incubator. But still, 2.3 minutes median time. The maximum duration between handling episodes per any individual infant, the mean was around 15 minutes, with a very broad standard deviation, as you might expect.

And handling occurred across all behavioral states. So we were not discriminating in terms of when we were bugging them. And arousals or awakenings occurred in the majority of these contacts. So whether we thought we were being stealthy or not, we weren't, I guess. Or the other way of looking at it is, we were being successfully stealthy 43% of the time.

[LAUGHTER]

Great, OK. So talking about all of those things that we measure in the PSGs, hypopnea, or apnea, or oxygen saturation occurred in not a lot of babies, but a reasonable sized minority of the babies. And hypopnea was most likely to occur following a contact when the baby was in active sleep, as opposed to the other sleep stages.

So the conclusion of this was that infants in the NICU are getting-- at least in the NICU, and I'm guessing maybe in your cardiac ICUs, too, then, are experiencing very frequent hands-on care. And it disturbs their sleep, and it disturbs some of their sleep-associated respiratory effort. And so there could be potential health and developmental impact of these disturbances. We don't know that, we can't assume that, but it at least merits studying. And it also raises this intriguing question is, could you develop a machine that goes ping? How many of you remember the Monty Python sketch, "The Machine That Goes Ping?"

[LAUGHTER]

OK, good. I'm glad to see that it's not totally linked to Y chromosomes. And so could you develop a machine that would help you monitor sleep at the bedside, and tell you, if you decided disturbing them in quiet sleep is the worst thing to do, wouldn't it be nice just to have a machine that had one color of light when they were in quiet sleep? So this is our rich fantasy live.

Whether that will ever be possible, I don't know. And just like I said for every other fancy technology, just because we can do it doesn't mean it's necessarily going to make outcomes any better. You'd have to have that, though, to answer the question. So limitations to all of this, the intensity of the monitoring means the sample sizes are small. A newer technology that was simpler would at least allow you to study this in a broader way. And also to remember we were not studying normal newborns here. There's all kids who are at risk in one way or another in an ICU.

And as always, there's the chicken versus the egg. Future directions are to look at, are there ways of modifying sleep in the NICU patients? And the other future direction is to think about recruiting collaborators. Because if we're ever going to answer some of these questions about, does bugging them make a difference for the rest of their life, we'll have to do that in some a multi-centered way to get a decent sample size. And I will just stop there, and escape, there we go.

[APPLAUSE]