Marie: Hello and welcome to *The Parkinson's Research Podcast: New Discoveries in Neuroscience*. I'm your host, Dr. Marie McNeely, and I've partnered with The Michael J. Fox Foundation for Parkinson's Research to bring you to the forefront of the field of neuroscience to discuss the latest advances and discoveries with leading experts.

The Michael J. Fox Foundation created this podcast for researchers, clinicians, and industry professionals with the hope that these conversations and the resources that we share will advance your efforts and partnerships to improve brain health. And we're welcoming guests with a range of experiences and viewpoints. The views expressed belong to the guests themselves. Today, we are excited to welcome our guest, Dr. Amy Amara. So listeners, Amy is a professor of Neurology at CU Anschutz School of Medicine. And today, we are excited to hear more about her career, findings from her research on sleep in Parkinson's disease and her perspectives on future research in the field. So, Amy, welcome to the show. How are you?

Amy: I'm doing great. Thanks for asking.

Marie: Well, we're excited to have you with us today and looking forward to learning more about you and your work. So, can you start by telling us a little bit more about your background and how you found your way to your current position?

Amy: Sure. Well, I've always been fascinated with neurology. And when I started my neurology residency, I really fell in love with taking care of patients who have Parkinson's disease. It was always my favorite day if I had a Parkinson's patient to work with and talk to. And so I decided to go into movement disorders. And as I was considering that path, I learned more about the sleep problems that patients with Parkinson's experience and was really fascinated by REM sleep behavior disorder, which, of course, is a precursor to Parkinson's disease diagnosis in many cases. And so I decided to do a sleep medicine fellowship as well. And that led to some ongoing clinical research related to sleep in Parkinson's and really launched my research direction.

Marie: Oh, fantastic. And I love this area of sleep problems. I think it doesn't get the same airtime as a lot of the other motor features of Parkinson's disease, but it is a huge problem and has tremendous impacts on people's quality of life.

Amy: Yes, for sure. And it affects so many different aspects of sleep, both at night and then leading to a lot of daytime dysfunction too with daytime sleepiness and, you know, trouble doing activities because of those symptoms too.

Marie: Oh, absolutely. So perhaps let's start with the background and what we know at this point. Amy, can you tell us a little bit more about what are some of these

sleep differences that we do see in Parkinson's disease, perhaps compared to older adults who don't have Parkinson's disease?

Amy: So, one of the most common sleep problems is just sleep fragmentation. So just not being able to maintain consolidated sleep and stay asleep through the whole night. And so that can lead to reductions in many of the deeper stages of sleep, like the non-REM stage three sleep, which is also called slow-wave sleep, and then also reductions in REM sleep. And so that can lead to, as I mentioned, daytime sleep symptoms. But we also know that good sleep and those deeper stages of sleep are really important for cognition and other healthy processes. So, those things can be disrupted when the sleep at night is not good.

We think the sleep fragmentation is caused by a lot of things. So, it can be related to the motor symptoms in some cases. So, if you have bradykinesia and rigidity of Parkinson's, it makes it hard to roll over in the bed. And so, you can have a brief arousal that then leads to a full awakening because you have trouble shifting your position in bed.

And of course, there's the exciting REM sleep behavior disorder. And it affects a lot of people with Parkinson's and can lead to, of course, unsafe behaviors during the night that can lead to injuries to the patient or their bed partner as they're acting out dreams. And then a lot of daytime sleepiness also. And sometimes people sleep a lot at night, but then still have daytime sleepiness. And that may be related to neurodegeneration in some of the areas of the brainstem that are important for alerting – that ascending arousal system. And so, those areas can undergo neurodegeneration as well. And that can lead to trouble staying awake, even if you got a lot of sleep during the night.

Marie: Absolutely. And I know with a lot of diseases, you know, there can be sort of the fundamental features of the disease that lead to sleep problems, but also considering the effects that treatments have on sleep. So, what do we know so far about what some of these PD treatments, whether it's the traditional levodopa medications or other treatment approaches – how those impact sleep?

Amy: That's a great point. So, levodopa can actually help sleep because of improving the motor symptoms like we talked about before. But then there are some people who feel like levodopa leads to a little bit of insomnia, and it also actually acts as a REM suppressant. So, in some situations that can be helpful, like it might reduce the amount of REM sleep behavior disorder because you have less REM periods. But then again, it's important to get REM sleep. So, we don't want to reduce that too much.

And then, of course, there's a lot of attention to the dopamine agonist medications and how they can lead to daytime sleepiness and sudden onset of

sleep during the daytime after taking those medicines. And so that can lead to disability also.

Marie: Absolutely. And perhaps next, we'll talk about some of these frontiers in research on sleep in Parkinson's disease. Do you know, Amy, what are some of the hot topics in the research area at the moment?

Amy: So, one of the most exciting things is REM sleep behavior disorder because it does show us people who are at risk for Parkinson's before they develop the motor symptoms, and might identify people, you know, many, many years before they're diagnosed or recognized as having risk for Parkinson's. And so, that is a potential area where we could intervene with neuroprotective therapies. And as we've learned, both through Parkinson's and Alzheimer's disease research, early intervention is key because if you wait until the disease process is well underway, you may not be able to change that forward trajectory and cause some change in the outcome.

Marie: I think this REM sleep behavior disorder is particularly interesting because you can have it without ever developing Parkinson's disease. And many people with Parkinson's disease never develop this REM sleep behavior disorder. So, can you talk a little bit about this relationship? It's pretty complex.

Amy: Yeah. So, about 30 to 50 percent of people who have Parkinson's disease also have REM sleep behavior disorder and dream enactment behavior. And so, the number of people who have Parkinson's with RBD is a little bit less than in some of the other synucleinopathy conditions such as multiple systems atrophy and dementia with Lewey bodies. But there's quite a big association between having REM sleep behavior disorder and going on to later develop a synuclein disorder. It's probably upwards of 70 to 80 percent in most of the longitudinal studies that have been done.

And so there's a clear association. And as you said, though, it's not 100 percent, and other things can lead to acting out dreams. For instance, REM sleep behavior disorder is present in people with narcolepsy, and that's not thought to be in any way a risk for Parkinson's.

And then it also can happen in people who have changes in the brain unrelated to Parkinson's. Or sometimes there's a condition called arousal parasomnia where you can get dream enactment behavior because you have untreated sleep apnea, for instance, that affects you more heavily during REM sleep when you're dreaming, and your body happens to wake up before your brain does. And you lose the paralysis of dream sleep while your brain is still dreaming a bit. And so that can lead to something that mimics REM sleep behavior disorder.

Marie: Oh, that's very interesting. Now, Amy, do we know yet what's happening sort of mechanistically with these synucleinopathies that really leads to this REM sleep disorder?

Amy: The neurodegeneration in key areas of the brain. The sublateral dorsal tegmental nucleus is one key area that seems to be important for sending the signals to the spinal cord and the muscles during REM sleep to maintain that REM sleep atonia. So, those are the things that are happening, and that neurodegeneration is present before it moves on to the substantia nigra and leads to the motor symptoms of Parkinson's. And so, that's why it's a prodromal feature.

Marie: And I know you're doing a lot of very interesting research on a number of different questions within this area of EEG, sleep, Parkinson's disease, and other disorders as well. So, do you have any particular projects, I guess, that you're most excited about at the moment that you'd like to share with us?

Amy: Yeah, so we are doing a big project that's a randomized controlled trial with exercise as an intervention to see how it affects both cognition and sleep. And we had prior work where we looked at relationships between slow-wave sleep and cognitive performance in Parkinson's disease. And there was a big correlation, particularly in areas of cognition that are predominantly from the frontal parts of the brain. So, executive function, processing speed, language, and to some degree, memory as well. And we found that there was a correlation between those cognitive performance areas and the amounts of slow-wave sleep that people have at night. And interestingly, we also had another study that showed exercise increases slow-wave sleep, that non-REM stage three sleep.

So, we thought that perhaps if we can increase slow-wave sleep with exercise, we might also be able to increase or improve cognition. And so, our current study is looking into that. And we're looking at one potential mechanism that may drive some of those changes being related to glymphatic clearance. So, the glymphatic system is a fairly newly-described proposed system of drainage of lymph or toxins from the brain. And so the glymphatic stands for glial lymphatic. And we think that that might increase during exercise, and it has been shown to increase during slow-wave sleep in both animal models and in humans. And so, perhaps the mechanism is that exercise is increasing slow-wave sleep, which then improves our glymphatic clearance to get rid of the dangerous neurotoxins, which then can lead to improvements in cognition.

Marie: Absolutely. And I know exercise is a broad term and you can sort of bucket it in different ways. But, I guess, what kinds of exercise are you finding are particularly beneficial for sleep?

Amy: It looks like high intensity exercise is probably important. There have been some studies in early Parkinson's disease, including the SPARX trials, which currently there's the SPARX3 trial that's going on that's enrolling early Parkinson's patients who are not yet on treatment. And they're comparing moderate-intensity treadmill training to high-intensity treadmill training. And that's based on how high the heart rate goes. And that's been shown to improve motor symptoms, but also cognitive function as well. And then in our research, we've used high-intensity resistance training exercise. So, we have people doing weightlifting exercise, but they're also moving fairly quickly from task to task and not having many rest periods. And so, they really get their heart rate up and maintain a higher heart rate throughout the exercise session. And that's also what we found to improve sleep and what we hope will improve cognition as well.

Marie: Oh, interesting. So, do you think this resistance piece is sort of a critical ingredient for improving sleep?

Amy: I don't think we know for sure yet. They haven't been compared head to head — the resistance versus aerobic training. I think probably they are both beneficial. And one thing that our current project is looking at is to see if there may be differential responses to exercise in individual people. Because as we know, Parkinson's disease is a very heterogeneous disorder.

Like we said, you know, 30 to 50 percent of patients might have REM sleep behavior disorder, but then many people with Parkinson's don't. And what are the differences in pathology that lead to those types of changes? And there are differences in genetic backgrounds as well as clinical features. Like some people have more tremor and others have more balance problems. So, we think that exercise may work the same way. There may be some people who benefit more from resistance training and others who benefit more from aerobic training. And so, one step in our study is that if people don't improve their slow-wave sleep in the first 12 weeks of the trial, we change them from that resistance training over to an aerobic intervention.

Marie: Oh, that makes a lot of sense. And I think the sleep research is fascinating. And I think, you know, just thinking about the sleep data for people who aren't sleep specialists, specifically out there who might be listening.

When you think about the EEG, it's sort of a signal coming in from every electrode that you might be measuring. What specifically are you looking for when you're sort of evaluating sleep? What are some of these quantitative sleep EEG key measures or metrics that you're looking at in these studies?

Amy: Well, we're really interested in both sleep spindles and the slow-waves that really predominate that slow-wave sleep. And that's where it gets its name, of course.

So, delta sleep or those frequencies less than one hertz is one area to look at the slow-waves. And then the delta frequencies are one to four hertz. So, those areas seem to be important for cognition. And those are really present more predominantly at the beginning of the night. And then the most common stage of sleep is called non-REM stage two. And it's got a lot of sleep spindles. And that's one of its characteristics. And sleep spindles seem to also be important for cognition and memory consolidation. And we found in our research that people with REM sleep behavior disorder and Parkinson's have a lower density of sleep spindles during their non-REM sleep. So, they seem to have fewer sleep spindles.

And we also found that, as has been reported many times, the people with REM sleep behavior disorder and Parkinson's tend to have worse cognitive performance than people with PD who don't have RBD. And that is thought to be driven by the RBD. But in our research, we found that the spindles were more responsible for the cognitive dysfunction than the presence of RBD.

Marie: Oh, very interesting. And We mentioned some of the impacts of medication in terms of how treatments affect sleep in people with Parkinson's disease. I'd love to talk about deep brain stimulation as well. And I know you've done some work here looking at the effects of DBS on sleep. What have been some of your findings so far?

Amy: Yeah, there have been a lot of studies, in addition to our own, that have looked at the objective changes, meaning how does the polysomnography or the actual sleep study change before and after DBS, or when we turn DBS on and off in people who already have it. And it does appear that in most situations, the deep brain stimulation does help people sleep better. And that may be through improvement of motor symptoms, or there may be some changes in the sleep architecture that we are still trying to learn more about. And recently, we did find that having the high frequency DBS, or the typical DBS settings, does increase those sleep spindles that are important for memory consolidation and cognitive performance. And so, it's possible that the effects of deep brain stimulation on sleep go beyond just improving the motor symptoms and therefore helping people sleep better.

Marie: Oh, very interesting. And what are some of the future directions or lines of research that you're pursuing then in terms of next steps to further investigate the effects of DBS on sleep?

Amy: So, we have seen that the beta frequencies that have been found to be important for the motor symptoms of Parkinson's are altered during non-REM sleep. And s,o that's one interesting area of research that I think deserves a lot more attention. And I have some colleagues who are looking into that.

Marie: Absolutely. And we touched briefly earlier on some of these connections or relationships between sleep, cognitive impairment, and some of these other measures or outcomes that you might be looking at. Do you have any other thoughts or findings in terms of, I know we sort of alluded to the fact that sleep impacts pretty much everything. I know when I'm tired, I am not functioning optimally. So, what are some of the other areas of research that you're investigating or questions that you're answering, kind of looking at the intersection of these different areas?

Amy: So, we have some interest in looking at heart rate variability during sleep. There's a fairly big differential between heart rate variability when you transition from non-REM sleep to REM sleep.

And we have some preliminary data suggesting that that difference is decreased in Parkinson's disease. So, that's called the sympathovagal balance because there's certain types of heart rate variability that represent more sympathetic function, whereas other aspects look more parasympathetic. And the parasympathetic activity tends to predominate in non-REM sleep and more sympathetic in the REM sleep.

And so that differential does seem to be less pronounced in Parkinson's. And so we'd like to look into that a little bit more and see what that looks like, and more sleep studies, and how maybe exercise interventions might affect that, or even deep brain stimulation.

Marie: Do you think this heart rate variability as the stages of sleep are transitioning – do you think having a lower variability would impact the quality of sleep? Or how does that, I guess, translate into outcomes?

Amy: It may impact quality of sleep, and then it may also have more daytime implications for autonomic function, which of course can be impaired in Parkinson's disease. That can lead to the orthostatic hypotension and constipation and things like that. So, whether the changes during sleep might represent a signal that those problems are present, or may be contributing to those problems, or other things, we still have to figure out.

And whether or not it's important for cognition, we haven't even delved into that area yet, but I could imagine that it possibly could be if it reduces some of the efficacy of the transition between non-REM and REM.

Marie: I know there's a lot of unanswered questions in this area still, but I'm curious, if we know that someone with Parkinson's disease or another disorder has EEG features that sort of signify “bad sleep”. Are there any evidence-based

approaches known to make sleep, or maybe specific sleep parameters, better or more like those of people without Parkinson's disease? We sort of hinted that exercise might be one of them.

Amy: Yeah, exercise definitely can improve the slow-wave sleep, and it helps with sleep consolidation as well. And there may even be, you know, if the sleep is more consolidated, there may even be downstream effects that are more healthy for the overall brain function. It's very important to make sure that there are not other common sleep disorders going on. So being willing to chase down sleep problems with a sleep study is a good idea because sleep apnea is so common in older adults, and it's very often unrecognized. And Parkinson's patients tend to have fewer symptoms of sleep apnea or at least not the typical symptoms. So, they might be less likely to snore, but still have the apnea events happening. Or they might be less likely to exhibit daytime sleepiness, specifically, but still have a lot of sleep apnea at night. So being willing to check for those things is important.

And then there are a lot of body movements during sleep in Parkinson's. So, in addition to the amounts of REM sleep behavior disorder, people with Parkinson's also frequently can have movements of their legs during sleep that can be disruptive to sleep for both the patient and their bed partner. So, identifying those things would be important.

Marie: Absolutely. And you mentioned this a couple times now just, you know, poor sleep in one partner impacting the sleep of the other partner. Has much research been done in this area in terms of sort of making everybody's life a little bit better, particularly this partner who is perhaps experiencing disturbed sleep as a result of their partner's, whether it's REM sleep behavior disorder, just fragmented sleep, or other sleep disturbances.

Amy: There has been some work looking at the health of caregivers, showing that if the patient with Parkinson's or with dementia, for example, is not sleeping well, it can lead to a lot more caregiver stress and actually increases risk for a patient being put into a skilled nursing facility that needs more support that the caregiver can't handle. Because that disruption of sleep really does make it hard to function during the day.

Marie: Absolutely. And as we alluded to, there are still a lot of areas that are ripe for research within the sleep field. But I guess, you know, thinking about the work that you've done so far, you've made some amazing strides, Amy. What have been maybe some of the biggest surprises, or perhaps unexpected outcomes, that you've encountered in the work that you've done?

Amy: Well, we really were excited about studying slow-wave sleep and thought that that was going to be an important feature of cognitive performance. But the association with sleep spindles, I wasn't necessarily expecting that.

And so, it's been exciting to learn more about that area. And we have some preliminary data that suggests that the sleep spindles are really important for cognition, not only at the cross-sectional evaluation, but also longitudinally. And it looks like people who have fewer sleep spindles are more likely to develop mild cognitive impairment in Parkinson's disease.

Marie: So, is it fewer sleep spindles, or is it to do with the density of the sleep spindles?

Amy: Yes, the density of the sleep spindles. So, we measure that as the number of spindles per minute. So, having fewer of those seems to be worse for cognition. And also having fewer of those is associated with people who have REM sleep behavior disorder and Parkinson's.

Marie: Oh, that makes sense, Amy. And, you know, research, you're not able to do it alone. There are often tools, resources, collaborations, a lot of things that really help you and really move the field forward.

So, Amy, when you think about your own work, are there examples of tools that you've leveraged or resources that have been particularly helpful or just fantastic collaborations that you've had, whether it's with MJFF researchers, or others or these tools coming from MJFF or others?

Amy: Well, first of all, it's so important to have patients who are willing to participate in the research. And so, we couldn't do any of it without their efforts and willingness to contribute their time.

So, that's extremely important. And from the Fox Foundation, I've been very fortunate to have the opportunity to collaborate with many researchers who are involved, particularly in PPMI study. But also, we've done some work associated with Fox Insight.

And there's also a project that's led by Connie Marras and Ira Shoulson looking at the Parkinson's disease patient reports of problems, which is a way to allow patients to describe, in their own words, the symptoms that they're having and what symptoms are important to them. And so, that has been a really rewarding project to be a part of. PPMI is a fantastic resource for researchers with the ability to apply for obtaining samples. I haven't done that myself, but I think that's such an amazing resource. And then also the breadth of data that's being collected from the patients and the longitudinal aspect of that, and it's really helping us understand more about the changes in Parkinson's and what's important.

Marie: Absolutely. And Amy, how did you get involved with MJFF originally, if I may ask?

Amy: It was thanks to my mentor, David Standaert. So, he's the site investigator for PPMI at University of Alabama at Birmingham. And he asked me to be a part of the study when I was still very early in my faculty career. And then he also encouraged me to attend the annual meeting. And that's the way I met many of my collaborators and led to publishing some papers with PPMI data and helped grow from there.

Marie: That's phenomenal. So, for researchers who might be listening out there who might be interested in either getting involved with MJFF or taking advantage of some of these resources. Do you have any advice or any, I guess, thoughts on what your experience has been like?

Amy: I think it's a very open-minded group. The whole purpose is to move research forward for Parkinson's disease. And so, there are many, many resources. And the data, of course, is open for anyone to download. And then there are also resources for the research individuals are doing at their own institutions, like the Fox Trial Finder and matching people up with interested potential participants. I think that's a fantastic resource too.

Marie: Absolutely. And I think, speaking of moving research forward, I think neuroscience is sort of inherently interdisciplinary. But I think there are advances or maybe gaps within neuroscience that we would like to see filled. And I think these interdisciplinary collaborations are key. So, when you think about your own work, Amy, are there advances, whether it's in neuroscience or perhaps other fields, whether that's instrumentation or technology, statistics, implementation, medicine, public health, whatever you can think of, that would really accelerate Parkinson's research, in your opinion.

Amy: I think incorporating more techniques related to neuroimaging is very important. I'm lucky to have some collaborators who are neuroimaging experts as well. And that's been very helpful in allowing me to ask different questions that I wouldn't have otherwise been able to think about. And then deep learning methods can also really expand those opportunities to look further into differences in EEG or even other aspects of biology that we don't understand just by looking at it on the surface.

Marie: Absolutely. I think there's tremendous potential there. And I know as we've alluded to throughout our conversation, there are many questions that remain to be answered, not only in your specific field, but in the field more broadly of Parkinson's research. So, in your opinion, what are some of the biggest

unanswered questions or maybe areas of opportunity in Parkinson's disease research?

Amy: So one definite area of opportunity is having people with REM sleep behavior disorder who are early in their disease process in whom we can intervene to try to use neuroprotective therapies to prevent Parkinson's disease from developing into that disorder. And prevent those motor symptoms from ever emerging. So, I think that's a fantastic opportunity.

And related to sleep, specifically, in Parkinson's disease, I think there are many opportunities to understand more about glymphatics. As I mentioned before, the glymphatic clearance in the brain – it's hard to measure it. And there are a lot of efforts going on to try to figure out different neuroimaging aspects for measurement of that. And so that's an exciting area of research, and one that we're hoping to continue exploring.

And the problem is that if glymphatic clearance is predominantly occurring during sleep, it's really hard to do neuroimaging during sleep, although some people are attempting it. So, a lot of challenges there too, but that makes it exciting to try to figure those things out.

Marie: And that was a perfect segue, I think, for my next question, which is, what are some of the biggest challenges, Amy, that you are facing in your research right now? Or maybe the biggest limitations that are keeping you from answering the questions you'd like to answer?

Amy: Recruitment is always challenging. So, we definitely appreciate when people can participate in research, but it's also a big ask because it takes a lot of time commitment. And so it is hard to sometimes get all the research participants that are needed to answer the questions and have enough power to statistically get to the right answer.

Marie: And I know you've been doing amazing work in the field, Amy. And of course, The Michael J. Fox Foundation is dedicated to bringing us closer to finding a cure for Parkinson's disease and improving life for people who are living with the disease now. So, can you talk a little bit more about how your work is really bringing us closer to finding a cure, or even contributing to those improved therapies for people with Parkinson's?

Amy: That's a great question. And I'm really excited about our work in exercise, because everyone has access to it. And we can hopefully at some point provide guidance on what the ideal types of exercise might be. And it has been so far shown to have so many good effects, but I think we can continue to optimize it.

And then as far as getting closer to a cure, I think working with PPMI has been one of the most rewarding aspects. And we'll also have potential for broadening our likelihood of achieving that goal. There are so many biosamples being collected and increased understanding from that data set. And I think that it's only going to continue to grow. And each time we answer a question, it allows us to figure out what's the next question. And so, that's really exciting.

Marie: Oh, I love that. Well, thank you again, Amy. It's been such a pleasure. And listeners, it's been great to have you here with us as well. If you want to know how The Michael J. Fox Foundation can help your research, please visit michaeljfox.org/research resources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. When you have a moment, please subscribe to our show to make sure you don't miss our outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast*.