NeurOnAir Podcast

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Transcript of Episode 6
Guest: Dr. Kundakovic

Time Stamps:
00:00 - Intro
02:30 - Dr. Kundakovic's research questions at a broad level
03:16 - Epigenetic regulation in the Brain
06:03 - Current projects in Dr. Kundakovic's lab
10:48 - Techniques in neuroepigenetics
13:53 - Dr. Kundakovic's path to research
16:35 - Menarche to menopause: Increased female risk for anxiety and depression
19:31 - An underrepresented majority: females as research subjects
23:03 - Changes in the female brain: genes to synapses
24:50 - Epigenetic priming: increased susceptibility for psychopathology
27:04 - Susceptibility and strength: females overcoming obstacles
31:08 - Lessons for the next generation: Inclusivity
33:03 - Outro

Tori Lovallo: Our DNA expression controls nearly if not everything that we are. It informs how we look, the diseases we are susceptible to, and shapes our personality. It even sets the bar for our risk of developing anxiety and depression. In recent years the world has been hyperfocused on discussing depression and determined to fight it to help people lead enjoyable lives. Females are twice as likely as males to develop these symptoms, and we have yet to find why. Naturally, socio-cultural factors have been considered as the root cause of this difference across sexes… but one must wonder if there are underlying biological factors at play. The primary biological suspect of female vulnerability to depression is the drastic hormone fluctuation that goes hand in hand with the menstrual cycle. Throughout the process, estrogen and progesterone levels change, opening a line of questioning about how sex hormone levels can mediate mental health - and make menstruators more susceptible to anxiety and depression. In today's episode, we speak with Dr. Marija Kundakovic, assistant professor in Neuroscience at Fordham University where she studies the epigenetic basis of behavior. Her work focuses on the hormonal and environmental factors that mediate sex differences in depression, anxiety and drug abuse. Her findings can open the door to development of new diagnostic tools, and new preventative and therapeutic approaches addressing female mental health. She offers a multidisciplinary insight that gets right down to the question that keeps all of us scientists up at night: how does it work?

Claire Ward: In this episode, we sit down and discuss the exciting projects that Dr. Kundakovic is heading. We'll also talk about the importance of keeping females in mind when designing scientific studies. You are listening to NeurOnAir, brought to you by the next generation of neuroscientists at Albert Einstein College of Medicine in New York. We are your co-hosts for today, I am Claire Ward, a graduate student in neuroscience.

Tori Lovallo: And I am Tori Lovallo, a neuroscience research trainee.

Claire Ward: Hi Dr. Kundakovic, I'm Claire.

Tori Lovallo: And I'm Tori. Thank you so much for joining us today. I'm really eager, we are both really eager, to get into sex differences in the brain. Let's start by having you introduce yourself, please, and then offer us a brief synopsis, an introduction to your work.

Dr. Marija Kundakovic: Sure, so just to introduce myself, my name is Marija Kundakovic and I'm an assistant professor in the Department of Biological Sciences at Fordham University. My lab actually focuses on the epigenetic basis of behavior and psychiatric disorders--and we particularly are focusing on hormonal and environmental factors that are driving sex differences in anxiety disorders, depression, and drug abuse.

Claire Ward: Oh okay, epigenetics and neuroscience is a creative combo, so we were hoping that you could explain to us more specifically about epigenetics and how you apply epigenetics to your work.

Dr. Marija Kundakovic: I like to actually dissect this, first of all, to just maybe explain what epigenetic regulation is, I think. So we are interested in trying to understand the epigenetic regulation in brain cells, particularly in neurons. And this is important because, in each cell in our body, DNA is packaged in this very specialized structure which is called chromatin, right? So we have the DNA that is wrapped around these histone proteins and this is important because DNA in each cell is like around six and a half feet and you have to basically package it into this very small nucleus that is not even visible to our eyes, right? And so it's packaged around these histone proteins, and then there is like a higher order organization, and this is not important only for packaging, but it is important because this can also regulate expression of our genes, right? So you need regulatory parts of the genes, to be open for some factors to bind and for genes to be expressed.

Tori Lovallo: So this is the field of epigenetics. We have a lot of DNA, but which genes are expressed at what time? You are looking specifically at chromatin dynamics in neurons. What's so special about neurons?

Dr. Marija Kundakovic: While in the other cell types, typically after differentiation, the chromatin really becomes quite stable, because we know which sorts of genes should be expressed and which should not. Neurons are very dynamic in terms of gene expression, and this is important because neurons have to be able to respond to both internal and external environment and which at the end allows us to you know, to respond to our environment to learn, to have a reaction to our environment, right? And for this, you have to have this plasticity of this chromatin so you have to be able to repackage the DNA to open certain genes at certain points and close the others right, you know. So this is important for the normal function of neurons but sometimes this can also lead to some problems (right) if there are changes in response to let's say stress or in response to hormonal changes like I'll tell you a little bit more in a moment. We believe that these changes that are happening might actually lead to changes in brain structure and behavior that might actually contribute to psychopathology, for instance, right? And this is something that you want to understand, right? We want to understand how, for instance, hormonal changes, particularly in females, or how early life stress, for instance, can lead to changes in this DNA packaging and how this can change gene expression, and as I said, contribute to these neuropsychiatric disorders.

Claire Ward: Oh okay, so hormonal changes could lead to changes in the epigenome, interesting. Could you tell us a bit more about your research?

Dr. Marija Kundakovic: One of the projects, like the project that is actually currently the most important, we just actually got the big NIH grant for this. It is actually trying to understand how hormonal changes in the females, which are basically periodic changes--we all know that, during the reproductive period women actually have these changes across this menstrual cycle in humans (or in rodents it's called the estrus cycle) where there is rising in estrogen and falling in estrogen and rising in progesterone, falling in progesterone, and this is really absolutely necessary for normal reproductive function. However, we do know that, you know, these changes are also associated with plasticity in the brain, for instance, there are changes in the spine density in rodents but there are also changes in gray matter in human females. And while this plasticity in a way can be something that someone can consider as something positive, there is a complexity to the female brain, and I like to actually just understand the physiology of that, on the other hand, we do know from epidemiological evidence that these hormonal changes can actually increase female risk for anxiety and depression. And this is particularly important because we know that women are at twice higher risk for these disorders than men are, right? And while this epidemiological piece of evidence, it is probably one of the strongest pieces of evidence that we have in epidemiology, very little has actually been done to understand the biological basis of this. And I think this is like a really missed opportunity. I think one of the biggest reasons for this is that a lot of particularly preclinical studies were done in male animals only, so if you study depression or anxiety related phenomena in male animals only you're in a way, addressing only a third of the population.

Dr. Marija Kundakovic: So I think we're expanding on these studies, and like doing studies in specifically on the female brain, and trying to understand how these hormonal changes are affecting the things such as let's say chromatin, in this case we are interested in in this particular molecular mechanism, we can actually start thinking about some kind of sex specific drug targets and like how we could specifically target some more female specific phenomenon that are important for depression and anxiety. So this has been the major project, the project that we have I would say now developed most strongly in a way. And we published recently a manuscript in Nature Communications (that was in 2019) where we described, for the first time, that there are changes in the chromatin organization across the estrous cycle and that these changes are of the same magnitude as if you compare, for instance, females and males, right. And, I think this is actually the starting point for something that we want to do in the future, and to try to better understand this regulation, to better understand the regulators of these changes in order to actually start thinking about some, as I said, sex specific treatments.

Tori Lovallo: Congratulations on your paper, that's really cool! You mentioned that you also look at the effects of early life stress on depression. What do you have going on so far in that regard?

Dr. Marija Kundakovic: We also have a project that is dealing with early life stress and how the early life stress can increase risk for both anxiety and depression and cocaine addiction in particular. And this is actually another project that is still not as much developed but we really have some really interesting data and hopefully maybe in a couple of months we will have the first manuscript out. And again, we are having the same kind of theme here, right? And we are seeing again sex specific effects. We know that estrogen is involved in the brain reward system and that the effects of drug abuse are different in males and females. But again, we don't really understand much about the molecular mechanism behind this. We started with this idea that there are chromatin changes in the ventral hippocampus, which is important for emotional regulation that we previously showed. But now we are showing, you know, these changes in the brain reward system in relation to cocaine exposure and something so we have a lot of interesting new [data]. But, if you're thinking about the lines of research, [there are] these two big lines of research; one is more related to anxiety and depression and another to drug abuse.

Claire Ward: Those are really cool projects that you have going on. We are interested in how you study this, could you tell us a bit about your techniques?

Dr. Marija Kundakovic: So this is how we do it, right? Okay, as I said, like we are focusing on a certain brain region, because we know it is very important for emotion regulation. It's called the ventral hippocampus and in mice it has been shown previously that, if you do a lesion to this brain region or you actually optogenetically activate neurons in this area that you can change these anxiety related behaviors. This was the main reason why we chose to work on that particular brain region, right? So, then what we do is we actually sort and we isolate the neuronal nuclei because, as I said previously, the epigenome, this chromatin is actually cell type specific so we want to actually increase the resolution of our assay. So we do flow cytometry, like a fluorescent based assay, where we can actually sort and purify the neuronal nuclei. So, and then we use this method that is called ATAC-Seq that is based on the activity

of the enzyme, that is called transposase, which can then cut the DNA only if chromatin is open, so if the chromatin is closed the DNA is inaccessible. This enzyme cannot cut the DNA, right, but if the chromatin is open the enzyme will bind. And it's actually specifically engineered that once it binds it can actually insert sequencing adapters into DNA. So this actually allows you to select and enrich for that open chromatin or DNA, you know. That is connected to this open chromatin so, then you can do the amplification using a PCR and then you can do the next generation sequencing. So, we are doing the genomics assay, which means that you are not looking at specific genes. We are actually looking within these neurons that I said are the ventral hippocampal neurons; we look throughout the genome, right. So we do that, from [CW2] the animals that have high estrogen they're called proestrous animals, from the animals that have low estrogen, which is called diestrus, and then we do it from the animals that are male animals just age matched right.

Dr. Marija Kundakovic: So what we were able to find is actually that globally there are these reorganizations of chromatin, and this is really significant. We absolutely didn't expect this degree of change, which is like around 30% of the genome that actually shows changes in chromatin organization. Okay? And what was really important here is that, when we did some bioinformatics analysis, we were able to show that these changes are enriched within genes that are important for neuronal function. And, specifically, also within some pathways such as serotonergic pathway, that I actually just mentioned previously, that we know is actually changing across the cycle, right? So this actually gave us for the first time, some kind of a molecular basis of how these changes in serotonergic transmission can be happening, right? This is basically the underlying mechanism, so that was one of the most important findings that we had.

Tori Lovallo: You know, how did you get into this? Was it something that you studied previously in other labs and brought to your lab? I guess what I'm asking is, How did you decide to tackle these research questions about hormones and epigenetics and psychological disorders?

Dr. Marija Kundakovic: Yeah. So this is, I think, an interesting question. Because like it's a little bit, you know, of a complex question because sure, you know, I've been informed by what I studied previously. But I do also want to say that, in general, this specific interest in fluctuating hormones and anxiety-depression was in a way also partially informed from my personal experience. And, I think it's always an interesting story to tell because people always think how you do start being interested in something. When I was in my early 20s I started having some, you know, I like to call it like a stronger PMS and I think everyone knows what PMS is. It's like a premenstrual syndrome, right? And honestly like around two thirds of women actually have some sort of like a premenstrual syndrome, whether that's more physical like bloating like, you know, breast tenderness. Some women are more sensitive, they see emotional changes and stuff. And I think I was in the second cohort of this like. I did feel like some kind of emotional changes, so then it was really interesting because it came, it would come suddenly and then it would disappear, every time I get my period. It took me, maybe a couple of months to understand what was going on. You know, I'm a scientist and I was just trying to understand how can I relate to these changes because that's really like something quite interesting to me and quite intriguing. So when I

realized that this is actually related to my period, then I did some kind of research and I realized there's really this drop in sex hormone levels, just before then [period]. And, I was, I started thinking if I have this feeling, how strong this is, for instance, for someone who has already some kind of predisposition, you know, genetic or some other factors that are contributing. So this actually interest started from my own personal experience, where I felt the drop in sex hormones can really have an effect on the emotional well-being in a way. And, this never really affected me to the point where I couldn't go through my day or something, but it was obvious and I kind of had this thinking about like, you know, this is something that should be really understood, right? And the contribution to the mental disorder should be understood and I was like joking with friends of mine like, you know, I have to research this PMS, like I have to do that.

Dr. Marija Kundakovic: You know, like it came to some point that I started also looking into literature and I realized that when people tell you that women are at twice of a risk compared to men, no one really says--rarely people actually explained that this is not throughout life. This is actually pretty much happening only during reproductive period, right. So if you compare boys and girls, the risk for depression and anxiety is pretty much the same and they do develop depression, anxiety, maybe even nowadays, even more than before. And then, if you look at postmenopausal women, when there are these very stable low estrogen or progesterone levels, the risk between postmenopausal women and men of the similar age is actually also very similar right, so we are really seeing this jump in increase in female risk just around the first menarche when girls get the first period and their hormones start fluctuating and then this actually is quite stable two times higher risk throughout the reproductive period. And then during the perimenopause, when you have really like even the bigger fluctuations, you actually then start seeing even higher risk and further jump in females, right. So this is actually something that when I looked at this evidence, I was just like oh my god this is like a revelation for me.

Tori Lovallo: Interesting, so you took this experience of having a stronger PMS and in a way turned studying how these fluctuations in hormones can lead to anxiety and depression into a whole career.

Dr. Marija Kundakovic: When I was at Columbia University, I was actually teaching the psychopharmacology class and one lecture was on sex and the brain. And I kind of realized that this has to be understood, right? So it took me until I got my own lab to actually really study this, right? And but, you know, then the technical part and the molecular basis of this actually came from my previous experience because, like from my PhD throughout my final postdoc, actually I was studying the, you know, epigenetics of psychiatric disorders. And, I have to say that I've been in this field from its inception literally. When I started my PhD in 2003[CW4] , There were literally five papers on neuroepigenetics. I know, for you guys, it is probably very confusing to hear that, because you know everyone is now talking about epigenetics. People talk about epigenetic inheritance across generations, trauma inheritance and stuff, and so, nowadays, people are accustomed to that. But this idea that this could be dynamic like what we are seeing now, like in mice this happens over like 24- or 48-hour period, it's a couple of days within we see these huge changes in chromatin. These people would think you're insane...

Claire Ward: So neuroepigenetics was really at its inception when you started out. You also were at the forefront when it comes to research in female animals, right?

Dr. Marija Kundakovic: This is like a whole new field that we are now opening, you know. Because people are still thinking about sex differences in general, and not to mention all these female specific dynamics. Because if you're now also still going to go and look into some really high profile papers, you will understand that whenever there is like a first piece of evidence showing that there are [for instance], chromatin changes in response to neuronal activity, this is primarily done in male brain only. Right, so this what we are now showing is not only that there are sex differences, but there is like a female specific dynamism which I feel like it's really something that actually shows the complexity and something that should be embraced rather than kind of ignored.

Claire Ward: Let's take a moment to talk about the recent NIH mandate for the use of both males and females in pre-clinical and basic research. In the early 1980s, there was increasing awareness about the lack of research in women's health resulting in a push to include equal numbers of men and women in clinical studies that covered health issues that could affect both sexes. This is important because females may have different symptoms of disease, side effects to treatments, and overall risk than males. These standards were signed into law in the 1993 NIH Revitalization Act. This same standard of equal inclusion of the sexes in clinical research was not extended to pre-clinical and basic science research until in 2015 when the NIH formally mandated that sex as a biological variable is factored into research designs, analyses, and reporting as a condition for funding unless there is strong justification for the use of just one sex.

Dr. Marija Kundakovic: And you know, like this might not be very convenient for many people. I talked to one colleague of mine, he was saying 'what you're showing is inconvenient truth', you know what I mean? Sometimes what we are showing is that if you are putting these two female groups together, for instance, what we are now typically doing, like we are studying things across the estrous cycle and I do want to emphasize that we are studying these [processes] in mice right and mice have something that is called estrous cycle, which is similar to the human menstrual cycle, but it's actually shorter; [it] is only four to five days, but the hormonal profiles are very similar: like you have high estrogen, low estrogen [and] you have high progesterone, low progesterone. So we take these two extreme groups which are actually mimicking the follicular phase in humans and luteal phase in humans, and then we typically compare them and then compare them to the male brain. And I maybe should be also very specific, we're looking in the ventral hippocampus that we know is very important for emotion regulation. And then we actually purify neurons because, you know, there is cell type specificity of the epigenome so you want to actually be as cell type specific as possible. So, when we isolate these neurons, we actually compare two female groups with males and again sometimes we just know if you put together these two female groups you'll lose a lot. Maybe sometimes you are not going to even be able to see something, to claim the sex difference because once you put together these two female groups there is actually a lot of noise happening, and things cannot be really distinguished then.

Tori Lovallo: Hmm, so the male and female brain are actually dimorphic at the level of chromatin dynamics, and not only are there differences between males and females, but also between proestrus and diestrus females. Do these epigenetic changes translate into any changes at the structural level (pun intended)?

Dr. Marija Kundakovic: There is also one piece of data that people are shocked when they see that, and this is like, you know, this phenomenon where you see that dendritic spine density changes across the estrous cycle. So literally, there is an increased dendritic spine density, during the high estrogen phase and then, you know, there is a reduction of the dendritic spine density after this. So and now, when you start thinking about this--Okay, so there is a structural change, and then you find the human papers where they're showing that there are changes in the gray matter across the menstrual cycle. It's like you have to understand that this is important, you know what I mean, and that we should think about that, particularly if you want to understand sex differences and why there are some changes. But, regardless of the psychopathology I think just understanding these in general is super interesting and important and this should be studied and understood only from this, you know scientific point of view, I think it's quite interesting. And when you say how many individuals are menstruating? I was reading somewhere where they said if women are constituting 50% of population, at least 50% of women are in the reproductive period, right, so it's a huge huge percentage of population that we should be talking about, then, and again I do want to say that I do want to be inclusive - it is not only women, it is all menstruating individuals basically, right?

Claire Ward: So hormone fluctuation can lead to increased risk for anxiety and depression. But not everyone who menstruates has the misfortune of being clinically depressed or having an anxiety disorder. What do you think helps turn this susceptibility into an actual disorder?

Dr. Marija Kundakovic: Hormone fluctuation, you know, hormone fluctuation by itself, they're not sufficient to induce psychopathology, right[CW5] . So, they might be actually increasing the risk, they might actually lead to the vulnerability, but I do believe you need another hit, whether that's going to be genetics, or some environmental factors. So, I think this is important to keep in mind. And, (sometimes when) because what we study is primarily this physiological model of changes across the cycle. Sometimes, what we are seeing (is actually) might be sort of like what I like to call priming, where there are some changes that, for instance, like if I look at the chromatin changes that we're seeing across the estrous cycle . Some changes lead to changes in gene expression, as you would expect, as some functional change. There are a lot of changes in chromatin that we are seeing that do not necessarily translate to changes in gene expression. And I do believe that there is something about that, that I like to see as some sort of like a priming effect. That there is an increase in this risk, there is also, you know, molecular priming for something, so if you have another hit, that that hit might actually lead to some functional changes that can contribute to phenotypic changes like a psychopathology. So that said, I see our estrous cycle study as like almost like a model of vulnerability, rather than a model of anxiety and

depression, because the animals that we are studying are really... you know, they're just normal animals; we didn't do anything to them, they're just showing this natural variation in anxiety levels, I would say. I do believe that, looking at these interactions of other risk factors together with this will actually be critical in the future if you really want to understand the contribution of these hormonal changes to increased female risk in anxiety and depression.

Tori Lovallo: In talking about the susceptibility of females to anxiety and depression, I wonder whether these vulnerabilities could be used to support ideas that menstruating individuals might not be suited for high stress positions?

Dr. Marija Kundakovic: Well, I'm glad you asked that question because I feel that there is still a kind of resistance to these ideas, maybe that like, you know, we are now trying to [do]. And I'm not saying that I'm trying to push anything, in particular, because I am drawing the ideas for my preclinical work, from clinical evidence. But, I'm glad that you asked, because I feel that there were some fears in emphasizing this vulnerability to stress and how these hormonal changes are affecting emotion regulation in women. There were some fears in the past that this might affect the actual image of women and how much they are actually able to do the serious work, right. I think we are way past that, right? I think we really don't have to even have this conversation whether women can do these high pressure situations, whether they can be great leaders. We actually see that nowadays in the countries where the women are leaders, the pandemic was actually managed in a better way, if you want to be honest about that. We also have seen women, you know, we also have seen women actually doing amazing jobs during their pregnancies and these periods where there is really even more vulnerability. So I actually reject even these ideas that like we should really have a conversation about this. I think this is important to understand that there are really like the women, women might have certain vulnerability, but also some strength that actually allow for overcoming these obstacles, and like being able to actually perform very highly, regardless of the situation. What I think is important, because we are way past that, we now have to go back and like focus on these problems women are actually afraid to talk about. Because I think if you don't talk about... you know, like there has always been some shame associated with periods right, I mean always like since you got your first period you're like you just don't talk about that. Women don't talk about , you know, pregnancy in general and , like you know, menopause. And I think, considering that we have 50% of the population that is dealing with this, you know, like a female specific like, you know, female unique experiences, I think, really, we should now embrace this and not try to hide it under the rug and be like, you know—"this is not something that affects us, we are cool, hormones are not important”--I think it should be different. We're able to do all of this, regardless of some kind of difficulty that some women are experiencing. I don't even want to say like, you know, when we think about, for instance, a PMDD, right, there are only 5-8% women that really have a diagnosis and need to actually take, you know, some treatments for this, right? So I think we should really embrace this and be trying to understand how these hormonal changes, how these things that are female unique, can actually help us understand the psychopathology or brain disorders even better and start to actually think how we can use this information to actually improve our treatments. But, I really reject the idea that we should have this conversation whether women are able to perform at high level and work under high pressure or not. I think this is being confirmed.

Claire Ward: I love that, “women might have some vulnerability but also some strength” And yes indeed, we have confirmed that women are able to perform at a high level under high pressure. We can let Dr. Kundakovic be our example of that.

Tori Lovallo: Are there any ideas that you want to impart on the next generation of neuroscientists?

Dr. Marija Kundakovic: I actually teach Neuroscience at Fordham University and students do not believe it when I say that a majority of studies are done in males only. They, I mean, they're just asking, “but why?”, so and it's really difficult to explain to people this was even possible before, right? So it was interesting because during this pandemic now I actually introduced their presentations, right, so just to make things more dynamic because it's an online course they should, you know, do their own research, find their own papers, and so we ended up, of course, with probably at least 80% of papers being done only in males and they were shocked. I think it's one thing to actually hear that from me, right, and another thing is that you now see like 20 students, they chose papers randomly right, that means like totally randomly. Not to mention that at the end at least 50% [of the students are women] I would say. We have actually more women in my neuroscience class than men. And you know, like somehow it's like, well, this ends up that it's mainly [males], you know. And then I really like when I hear from them something like, “But this is unacceptable not to include females or not to include both sexes”, I kind of have the feeling that, I really did a lot as a teacher, right? I mean not only for them in order to teach them, but for the bigger society, because I think until you understand that this is really an issue, I don't think we can really do much about it. Because I think understanding of this, you know, when the bigger population understands this, this is what can also push the policies.

Tori Lovallo: We’ve learned that females are at a two times greater risk than males for neuropsychiatric disorders such as anxiety and depression, and that this risk corresponds to the onset of the menstrual cycle. Dr. Kundakovic’s lab is exploring the epigenetic phenomena that underlies this susceptibility of females to these disorders. Epigenetic regulation determines which genes get expressed and at what time through restructuring tightly wound DNA, called chromatin. Neurons are a cell type that must quickly respond to the environment and as such, they are constantly needing to restructure their chromatin in order to change their gene expression. Dr. Kundakovic’s lab demonstrated how dynamic chromatin regulation is in neurons across the estrous cycle and that these changes correspond with changes in behavior.

Claire Ward: But how do we see what is going on in our heads? It's hard enough to understand our own behavior, let alone understand our behavior at a molecular level. This is where the mouse model comes in. In a cell culture dish, you can know a lot about how genes are regulated. In a human you can study how brain activity across regions underlies cognition. But in a mouse, you kind of have the best of both worlds. Female mice have similar reproductive physiology to humans, where there are phases of high and low estrogen & progesterone. Dr. Kundakovic’s lab looked at the difference in anxiety in male and female mice, separating the females into two groups based on the phase of their cycles, showing significant differences in anxiety-like behavior between the two female groups. To understand what

might underlie these differences, Dr. Kundakovic's lab looked at the chromatin dynamics in neurons from a brain region known to be associated with emotional regulation, called the ventral hippocampus. The changes in chromatin that they observed across the estrous cycle were linked to changes in neuronal gene expression and synaptic plasticity. These studies spanned all the way from chromatin to synapses to behavior.

Tori Lovallo: Your hosts for this episode were Tori and Claire. Thanks for joining us today! Visit our website neuronair.org for more resources about today's episode and our guest
Dr. Marija Kundakovic. You can visit her website at www.kundakoviclab.com and find her on Twitter @KundakovicLab. You can also follow us on social media @neuronaircast to leave comments on today's episode, or to get in touch with us directly, email us at neuronairpodcast@gmail.com. And finally, if you enjoyed the episode, please subscribe, and review us! See you next time!