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**Julia:** Hi everyone. Thanks for tuning in today to the rehabINK Speaker Series Podcast: a collaboration between rehabINK—a student-led online magazine focused on rehabilitation research and innovation—and the Speaker Series—a bi-monthly event at the Rehabilitation Sciences Institute at the University of Toronto.

**Kyla:** My name is Kyla Alsbury.

**Julia:** And I'm Julia Rybkina.

**Kyla:** And we're graduate students at RSI. Today we'll be discussing the Speaker Series event we hosted on Woman and Brain Health that took place on March 25th, 2019.

**Julia:** The goal for the Speaker Series and the podcast is to bridge the gap between academia and the community, and to share some of the incredible research that's happening at RSI and U of T.

**Kyla:** We were grateful to host three prominent speakers at this event: Professor Gillian Einstein, Melissa Biscardi, and Dr. Reema Shafi.

**Julia:** Professor Gillian Einstein is the Wilfred and Joyce Polsuns Chair in Women's Brain Health and Aging, Professor of Psychology at the University of Toronto, and Guest Professor of Gender and Health at Linköping University in Sweden. Her broader interests encompass sex and gender, memory, dementia, and the long-term effects of hormone treatment and loss. Professor Einstein has served as a member, and then Chair, of the Scientific Advisory Board for the Institute of Gender and Health of the Canadian Institutes of Health Research, and is now, again, Chair of the IGH Advisory Board as well as a member of the CIHR College of Reviewers and Lead of the Women, Gender, Sex, and Dementia Program of the Canadian Consortium on Neurodegeneration and Aging.

**Kyla:** Melissa Biscardi is a Research Trainee at the University of Toronto Rehabilitation Sciences Institute. Melissa has a Bachelor of Science in Nursing, and she recently finished her Master's focusing on long term reproductive changes in women following traumatic brain injury. Her research interests focus on women's brain health and include neuroendocrine changes that may occur after traumatic brain injury, optimal brain performance over the lifespan in both brain-injured and non-brain-injured individuals, and functional neurological approaches to brain injury treatment. Melissa works in a busy clinical practice with a focus on concussion treatment, brain health, and mobility in adults and older adults.

**Julia:** Lastly, we also featured Dr. Reema Shafi. She's our very recent RSI alumna. She holds a Bachelor's in Occupational Therapy and a Master's in Psychology. As an Occupational Therapy clinician, she has over 20 years of clinical experience in adult

neurology with a special emphasis on delivering community rehabilitation programs to facilitate functional reintegration for brain injury survivors. Her research interests, however, lie in understanding the functional organization of neuronal networks and to investigate their influence on functional capacity post-injury and with aging. Her doctoral work explores the sex-specific impact of concussion on neural networks and assessed the functional impact of an assault-induced brain injury on time away from work.

**Kyla:** So, as you can tell, we were really lucky to have such a diverse and experienced group of scientists with us for our first event. The Speaker Series focused on the broad topic of Woman and Brain Health, touching upon some important themes in research and their implications on health care in the real world. I think my biggest takeaway, Julia, was really the definition of what sex and gender is and why it's important. And I think as students, you know, that's something that we've been exposed to but we're still learning about.

**Julia:** For sure, for sure. I remember being introduced to the difference between sex and gender late in my undergrad, and I was surprised that it was so late because it's such an important distinction. Especially as us now doing research, it's very important to take the two into account. So, for our listeners, it would be good to define the two. According to our speakers, sex and gender are very differently defined. Sex is often defined in terms of biology. As Dr. Einstein refers to it, it's an XX chromosome making up the female individual, and the XY chromosomes making up the male individuals. And then there's also gender.

**Kyla:** Yeah, so gender is a little bit I think more confusing for some people. Gender is more socially constructed. It's more about how you present yourself. It can also be related to the types of roles that you take on in a family, or the types of jobs that you apply for and those kinds of things, so it's a little bit more nebulous, I would say, than sex. Sex seems to be a little bit more clear, but even then that can be confusing too.

**Julia:** For sure, and so that's what the speakers-- I think all three of them unanimously would say that the two are very different and definitely understudied and underused in research.

**Kyla:** So why is this important? Why do we care so much about sex and gender?

**Julia:** Well, it can be as simple as 50% of the population are females or women. And it's important to make sure that—especially in healthcare when we're finding new treatments or investigating the efficacy or feasibility of new ones—it's really important to take into account who these treatments are meant to affect and study in greater detail how they affect them, and take into account their lifestyles, or their biological differences, or the hormones, and not base everything off of just the male, XY chromosome like it has historically been.

**Kyla:** Yeah, I think there's kind of a historical perspective that women are messy. Their hormones are messy, their cycles are messy, so it's easier just to take that mess out of the sciences. But, obviously, there's negative implications of that.

**Julia:** Yeah, and there's a great clip, actually, from Dr. Einstein. She addresses one of the problems with just looking at one gender or one type of sex, so take a listen…

**Dr. Einstein:** So, why should we think about women's brain health? Well, first of all, I think thinking about XX organisms brings new ideas. XX chromosomes end up leading to different phenotypic expressions, different gene expressions, different epigenetic signatures, and so it brings new ideas. It also leads us to ask questions about how life experience, hormonal milieu, and genetics, which are different than XY, how those get, I would say, instantiated. How they get put into the brain as different kinds of neural circuits, different types of behaviours, and how they're reflected in the central nervous system. And then I also think that studying XX organisms brings a broader dimension and more scientific rigour and repeatability, which is why the Canadian Institutes of Health Research, and also now the National Institutes of Health, are mandating that individual research projects—in animal experiments as well as human animals—take sex into account. And it also ensures that we can develop effective and safe treatments for XX people. So, I call this XX instead of men and women, XX and XY, because there are also some individuals who are XY but who are women, and some individuals who are XX who identify as men. And so, it's really important for us to think about the background upon which all of these genders are living.

Here's an example of sex differences. Maybe you've all seen this. I refer to it as the 'slide from hell' because it's so small (I'm sorry for swearing), but one thing to notice is that these are all drugs and all of these drugs prolong what is called the Q-T interval. They do this in XX people and they do this in XY people. And these drugs from being antimalarials to antiarrhythmics to antibiotics to antipsychotics, and many of them have been taken off the market. Why? Because they weren't tested in XX people, and when XX people started to use it, it turns out that women have a longer Q-T interval than men. This prolonged the Q-T interval and it actually led to an arrhythmia in women. They were taking it to counteract an arrhythmia, in many cases, but in fact, it led to them having heart attacks and death. So, they needed to be taken off the market because they weren't tested in XX people. And, in fact, between 1999 and 2001, 80% of the drugs were taken off the market-- sorry, 8 out of 10 drugs were taken off the market because they weren't tested in women first.

**Julia:** Great! And so, that's an excellent example of why both sex and gender should be taken into account, especially in the preclinical models. And it's not always so clear cut. I mean, for example, the LGBTQ+ community.

**Kyla:** Yeah, I think at this point we're all pretty aware that gender is not a binary and that people with varying gender identities will have varying experiences. And so, again, we need to consider this when we're looking at health. So, how do we study sex and gender?

**Julia:** That's a great question, Kyla. As Professor Einstein suggests, sex differences can be studied by considering hormones or other physiological differences, as she mentions here…

**Dr. Einstein:** And then another sex difference is that autoimmune disorders are as much as 10 times more common in women than in men. So, here you can see Hashimoto's thyroiditis: 10 times more common, primary biliary cirrhosis: nine times more common. If you get to lupus, which is the one I really like a lot: six times more common. I don't know how many of you ever watched the show House. I used to love House. And they were always diagnosing something in men as being due to lupus. And I thought, 'That is really unlikely! House ought to tell you that it's six times more common in women and you shouldn't even think about lupus right off the bat for men.' So, there are these differences in disease states.

**Julia:** Gender, on the other hand, can be studied by looking at the social differences such as hours spent at work and family roles, as Kyla alluded to earlier. For example, Dr. Einstein mentions here a gender issue in healthcare…

**Dr. Einstein:** Here's some gender examples. So, one gender example, and it's a wonderful example that comes right out of Gillian Hawker's work here in Toronto-- In Ontario, men are 22 times more likely than women to be referred for knee and hip replacement. I mean, most people don't even believe that number and they always cite it as two times. No, it's 22 times! They used actors who went in and claimed to have-- male and female actors claiming to have exactly the same kind of hip problem to male and female doctors, and the men were much more likely to be recommended for hip replacement. One possibility is that it's because doctors think about what men really want to go out and do. They really want to get out there and play golf. They really want to get out there. And they're not supposed to play tennis, but they might want to do their tennis game. And they think about-- this is my guess, although it's not been proven: they think about gender differences and think 'Well, the women are just going to go to lunch or they're going to meet with their friends, so they don't really need this hip replacement and it's really a lot of trouble.'

The other one (gee I hope this comes up… yes!)-- the average caregiver is a 49-year-old woman who works outside the home. She provides 20 hours a week of unpaid care to her mother. Female caregivers may spend as much as 50% more time providing care than male caregivers. Why is that?

**Kyla:** But it's also important to consider the combination of sex and gender, or how differences in lived life become biological. Professor Einstein had a really interesting quote. She said, "The world bites upon the body." And this really resonated with me. For example, someone who's living in poverty will likely have an increased stress response, or release of the hormone cortisol, which in turn can affect neurons in the brain and actually impair memory. It can also affect gene expression, so silencing or awakening certain genes. And I think this really comes back to the debate of nature versus nurture,

which is something everyone's probably heard of at this point: being whether or not it's your genetics that are important, or the environment that you're living in. Or is it really both?

**Julia:** For sure, and I mean this wasn't mentioned in the Speaker Series event itself, but the twin studies where you have identical twins who have exactly the same genetic material, but they just come out differently and they evolve differently. And that because of their varied experiences.

**Kyla:** Mm-hmm. Ultimately, XX (female) or XY (male), even though they might have started via the same cellular building blocks, they end up looking different due to gendered experiences which is pretty interesting.

**Julia:** Super interesting! Another interesting part is Professor Einstein also told us about a really cool study she performed with a psychiatrist—Sarah Romans—where they asked women to answer a series of questions on their mood and also asked if they were menstruating that day. Surprising to some, myself included, they found that there were no correlations between a phase of the menstrual cycle and their mood. And that's interesting because we commonly know of something that's called PMS, or premenstrual syndrome. It's a phase in the menstrual cycle where females can experience moodiness and other symptoms. Interestingly, this study would debunk the existence of this phenomenon. But thankfully Dr. Einstein had some advice for partners of menstruating females.

**Kyla:** So, what did we learn from Professor Einstein's talk? Well, in summary, sex and gender are very different but related concepts and we need to consider both in research, especially when it comes to health.

**Julia:** Our second speaker, Melissa Biscardi, extends Professor Einstein's discussion of sex, gender, and health by talking about TBI, or traumatic brain injury. What you may not know is that how women and men are affected by brain injury can be very different, especially in their interaction with the endocrine, or the hormone, system. Melissa mentions in her talk that while brain injury occurs more often in men, the number of women reporting TBI has increased by 80% in the last decade.

**Kyla:** Yeah, I found that really interesting and I wonder why that is.

**Julia:** Me too. I know she didn't speak to it directly, but I think we can all hypothesize that perhaps it's due to females becoming more comfortable speaking out and reaching out to healthcare professionals regarding their brain injury. Also, maybe because of their entrance into the workforce they're now actually experiencing more brain injuries. They're now taking on more risk by being at work more.

**Kyla:** Mm-hmm. I know also in health, you know, how we define something changes over time as well. Sometimes we come up with better and better outcome measures or

ways to diagnose or label certain health conditions too, so it could also be a terminology issue as well.

**Julia:** For sure, for sure. Maybe we are better at recognizing it and diagnosing it. In the past it's been overlooked due to more prominent or significant or more visible conditions and now we know to address this as well. And Melissa shares her thoughts on this as well.

**Melissa:** … these can be disruptions in growth hormone, testosterone, estrogen, follicle-stimulating hormone, and growth hormone is the most commonly reported disturbance, and that's followed by the gonadotropins (such as testosterone or estrogen). In women, changes in the menstrual cycle are a key indicator that there is a disruption in the neuroendocrine system, in particular the hypothalamus-pituitary-ovarian axis. And this is in comparison to other symptoms that might be reported, such as a headache or dizziness. So, one interesting feature—which is important for rehab professionals working in this population—is that disruptions not seen in the acute phase, so right after injury, may actually develop over time. So, looking for these disturbances right after injury is not enough. Disturbances not seen at three months may actually present themselves at six months. In Canada, the mean age that women sustain a traumatic brain injury is 31 years old, and this is well within reproductive years. Women who've had TBI compared to age-matched controls will report more issues with the reproductive system, such as menstrual changes, amenorrhea (so lack of period for two or more months), and more problems in the postpartum period, such as postpartum depression. Research involving biomarkers or blood samples looking at estrogen, luteinizing hormone, follicle-stimulating hormone, does exist but is limited by small sample size and a short follow-up time. Previous research has indicated that premature menopause may be a risk factor for Alzheimer's disease, and previous research, although mixed, suggests that traumatic brain injury may be a risk factor for cognitive decline. Despite this, little is known about the relationship between traumatic brain injury, menopause, and cognitive decline.

So, this is kind of where my research interest lies. Specifically, do long-term disruptions in reproductive hormones put women at risk for early menopause and cognitive decline. So, how would we study this? Well, there's a hormone called anti-müllerian hormone and it is the gold standard test for time to menopause. It's a great hormone to do research with because it does vary over the menstrual cycle, unlike estrogen. It's released by the growing follicles in the ovaries and produced by the granulosa cells. It decreases as we age, so the lower the hormone the more we're approaching menopause. And there's a sharp decline at age 35 which, as many of us will know, our fertility decreases after 35. Preliminary research from our lab for my master's thesis looked at anti-müllerian hormone, menopausal symptoms, cognition, and distress. We had a small sample, a clinical sample, of 10 pre-menopausal women with persistent symptoms, and they were one or more year post-injury. We had some very interesting findings. In terms of menstruation, 60% reported new menstrual variability, so that means where they're periods were "normal" before, they had new changes. And that may have been periods getting closer together, further apart, a missed period,

amenorrhea. Those were some of the reported changes. And this is despite them being between one and five years post-injury. These are changes reported in the last year. In terms of anti-müllerian hormone levels (so this is a “no tweet” slide, please), 50% were in the lowest 10$^{th}$ percentile or lower for their age. So this means either they were in the lowest 10% or they were actually low and out of range, which would mean they are approaching menopause at a faster rate than other people in their age range.

**Julia:** In terms of menopause symptoms, like depression and joint pain, Melissa’s lab split their clinical sample of post-concussed women into two groups: by under 35 years of age and over 35. They report that both of these age groups had much more menopausal symptoms than the general population.

**Melissa:** So, it really is interesting that the under 35 was still very symptomatic on the scale. In terms of cognition, we had some interesting findings here. Women with the lowest levels of anti-müllerian hormone also scored very low on cognition, and we actually had some participants that were in the lowest 1% compared to the population. So that means 99% of the population would score higher than them for their age. In education, all participants had post-secondary education or higher, so it wasn’t necessarily education related. In terms of distress, as would be expected, those with more menopausal symptoms were more distressed, and those who were more distressed scored lower on cognition, in general.

Okay. Recap: how premenopausal women age during traumatic brain injury really is a wide-open field and it’s an important area of research that we should be focusing on. Here, we saw most women experience new onset of changes in menstruation, despite being at least one year post-injury. And across all ages in the sample, reports of menopausal symptoms were higher than in the general population. There is a lot of overlap between symptoms of menopause and symptoms of post-concussion, so future research is going to have to tease out what’s coming from what. And, as expected, the stress in the sample was high and related to low cognition. This study provides some new, novel information about anti-müllerian hormone in women who’ve sustained a TBI. Definitely, more research is needed. It’s important that we are constantly increasing knowledge about the physiological changes that are happening behind the symptomology. So, we’ve known for a long time that women are experiencing menstrual changes post-TBI, so now this is giving a little bit of information into that. Yes, of course, the findings here are preliminary and must be expanded upon in a non-clinic sample, and also across all levels of severity. All of these patients were diagnosed with mild TBI. And, in the absence of clear clinical guidelines about who to screen, when to screen, rehab professionals can really just keep a keen and open eye—always asking about changes in menstruation and maybe employing some psycho-monitoring so that we can identify those women that should be referred for a more thorough endocrine assessment, and then intervene as necessary.

**Kyla:** So, this is something that Professor Einstein also touched upon. One of the key signs that something is wrong, or something has changed, is when there are changes to the menstrual cycle as a result of TBI. And this can also develop over time, not just in

the acute phases of the injury. If we think about it, the average age of injury is 31, which is well within reproductive years. We also know from the literature that premature menopause can also be linked to the risk of developing Alzheimer's, which is pretty concerning.

**Julia:** For sure, and Melissa's research specifically speaks to the fact that traumatic brain injury caused long-term disruptions in reproductive hormones in females, putting them at a higher risk of accelerated aging and cognitive decline.

**Kyla:** It's pretty obvious that we need more research to closer investigate the nature of the relationship between brain injury and menopause, but some preliminary findings show correlations between hormone disruptions after TBI and low scores on cognitive testing, as well as psychological symptoms (like low mood) when compared to the general population.

**Julia:** Melissa's talk provides a clear example of a sex issue. While the nature of the injury is the same, men and women can experience it differently and need different treatments with varying approaches just due to their biological differences.

**Kyla:** Moving on to Dr. Reema Shafi's talk, she discussed a specific type of brain injury—concussion—which is not uncommon, especially if you play sports. Have you had a concussion, Julia?

**Julia:** No. I've been lucky enough not to have a concussion.

**Kyla:** That's good.

**Julia:** But I think I heard that you did.

**Kyla:** Yes, I had one when I was about 10 years old and I was tobogganing in the wintertime at Bickford Park—which is the smaller park across from Christie Pits if you know Toronto—and I just spun right off the toboggan and I just remember feeling awful and nauseous. But thankfully I didn't have any lasting symptoms. So, it sounds like I was in the lucky 85% of concussions which typically resolve without any lasting impact. But if you're unlucky enough to be in that 15%, you could experience persistent post-concussive symptoms, such as mood changes, headaches, difficulties thinking, and other symptoms. I remember when I was in physio school at Queen's University we had someone come in to speak to us who had had a concussion, and he experienced significant personality changes and changes to his social roles and environment, and it was really quite traumatic.

**Julia:** Yeah, it seems scary. And the scary part is that it's so long-term. You can get it in the months after, years after, and there's a dearth of rehabilitation therapies available in those scenarios. And so then Reema got into the nitty-gritty details of some potentially sex-dependent changes in the brain as a result of mild brain injury. In non-injured individuals' brains, males are connected more intra-hemispherically—or more

connections within the right or the left half of the brains—whereas females are more connected inter-hemispherically—which means more connections between the right and left halves of the brain. And this may speak to some of the stereotypical differences between men and women, and perhaps be a result of hormones.

**Kyla:** So, because traumatic brain injury is experienced mainly by men, preclinical models, as we mentioned before, tend to be based on XY or male organisms. However, women report more negative outcomes and seek out more care. Yet, somehow only 7% of all studies report findings stratified by sex, which means the other 93% lump XY and XX together.

**Julia.** Very concerning, and Reema discusses this in further detail:

**Dr. Shafi:** What is more alarming is that there's a critical gap in the literature. There's a lack of contextualization. So, we know there are known differences with respect to developmental changes, with respect to baseline sex differences, with respect to hemispheric asymmetries, particularly during the menstrual cycle. But when you look at the studies, when they've interpreted the data, they haven't really interpreted it within that context.

**Julia:** Reema's research is still underway, but the key takeaway from this field of research is that while females seem to have an advantage before the injury in their increased connectivity between the right and the left halves of the brain, they are at a disadvantage after the injury. A combination of structural disadvantage and pre-existing, sex-dependent differences in women make women uniquely vulnerable to concussion.

**Kyla:** Overall, this event raised some very important issues regarding the importance of taking into account both sex and gender when conducting health research. Some interesting sex-based differences in the way brain injury affects men and women were highlighted by Reema and Melissa, while Professor Einstein provided a detailed overview of this topic with some excellent examples. It definitely got me thinking more about how I can incorporate and consider sex and gender in my own research. What about you, Julia?

**Julia:** Definitely! It's not something I've had the opportunity to explore yet, as a first-year master's student, but our speakers had some great advice on how to get started. During the panel discussion at the end of the event, one student asked for any advice or recommendations for novice researchers looking to design a study investigating sex and gender differences. It was clear that all speakers unanimously agreed that students should try to study both sex and gender, if possible, depending on your research question. If there's past literature showing contradictions, definitely study it. Professor Einstein suggested a qualitative interview might be a great way to gather gender data. Oftentimes you'll also be using mixed methods in your analysis if you're studying both.

**Kyla:** And if you don't have experience in these methodologies, it may be worthwhile learning more about them to properly answer your research question.

**Julia:** Yeah, at times there are great courses or the CIHR, as mentioned, offers some great tools.

**Kyla:** We had another question from the audience: 'How has thinking in academia and approaches to research changes in terms of brain health as a gendered and/or sex-based topic, especially over the years?' Professor Einstein, who definitely has the most experience in this field, felt that it has improved over time, but we're still a long way from equal representation. And part of that is due to the way that funding for research is distributed. She highlights that not every problem in science is gendered or has sex differences, but we do need to do more research to check where there are differences and where there aren't. Many researchers also say that they lack the knowledge and experience conducting gender and sex analyses, and so they avoid it. But that kind of training should be more widely available for researchers, students, and grant review boards.

**Julia:** Mm-hmm. Our other two speakers, Reema and Melissa, also concur. As we're still far away from consistently addressing the question of sex and gender differences in brain health research, specifically, it seems like until grant agencies make it a priority—mandating gender and sex analyses to be considered, and ensure follow-through—all researchers will not be motivated to adopt it.

**Kyla:** So, if you're interested in learning more about sex and gender and how to apply this to your own research, there are some great modules online through the Canadian Institutes of Health Research (or CIHR). Definitely check those out. Those have been very helpful for me.

**Julia:** Me too! And that's all for today's segment. Thank you for listening. It's been a pleasure recapping this event on Women and Brain Health!

**Kyla:** We'd love to hear your feedback, questions, comments, anything at all. You can connect with us via Twitter (@rehabINK) or visit our website at www.rehabinkmag.com.

**Julia:** Thanks and until next time!

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