Welcome everyone to Navigating Neuropsychology, a voyage into the depths of the brain and behavior. I'm Ryan Van Patten.

And I'm John Bellone. And today we're bringing you our conversation with Dr. Jeffrey Wozniak. Dr. Wozniak is the head of the psychology division at the University of Minnesota and is a clinical child neuropsychologist. He is the past President of the Fetal Alcohol Spectrum Disorder Study Group and has a lot of clinical and research experience in this area.

Fetal alcohol spectrum disorders, or FASD, is an umbrella term that includes multiple
syndromes nested within it. We will ask Jeff to define these related but distinct conditions so I won't get into them now. You'll hear us most frequently use the terms prenatal alcohol exposure, which is when a fetus is exposed to some degree of alcohol through maternal consumption. FAS is a specific diagnosis resulting from prenatal alcohol exposure, includes a characteristic facial morphology, neurobehavioral sequelae, and other symptoms, and FASD. Again, we will be using FASD in the broadest sense to refer to any possible phenotypic effects of prenatal alcohol exposure. In addition, the term teratogenic effects is important in this context. It refers to the negative impact of in-utero exposure to a wide range of potential toxins. Alcohol is only one example of a teratogen, but there are many others that we could talk about. However, because there's so much to unpack just with FASD, today's discussion will be limited to alcohol. John and I both know that working through jargon can, at times, come off as dry and uninteresting, but we think that it's really important to establish a shared foundation before we move forward into more interesting and engaging information. So hang in there with us while we plow through some terminology. Many people associate FAS with a triad of facial features, and appropriately so. There is a distinctive facial morphology that can result from prenatal alcohol exposure. Jeff does get into this later on and there are a few areas that will be repeated, but we think that this repetition can actually be really helpful for learning and retention. The three common signs of FAS are - number one is short palpebral fissure lengths. This is the distance from the inner corner to the outer corner of the eye. So the eye has less width. Number two is smooth philtrum, which is a vertical indentation in the middle area between the upper lip and the nose. As you're listening to me describe this, I would suggest just trying to picture what this looks like. Then, the third associated feature is simply a thin upper lip.

John Bellone 01:25

It might be helpful if you're not driving or if you have access to a computer to also look up a picture. There have been recent updates to the diagnostic guidelines for FAS and FASD. Specifically, a 2016 paper by Hoyme and colleagues in the American Academy of Pediatrics described FAS as the following: One is the characteristic minor facial abnormalities that Ryan just mentioned. Another one is height or weight equal or less than the 10th percentile, brain abnormalities such as seizures, structural brain abnormalities, low head circumference, and neurobehavioral impairments such as cognitive impairments that are greater than 1.5 standard deviations from the average on standardized tests. This paper includes criteria for documentation of prenatal alcohol exposure, which the number of maternal drinks in a particular length of time. Finally, it includes a helpful diagnostic algorithm in the form of a flowchart. So we're going to include the full reference in our show notes for this episode, if you're interested. Keep in mind that FAS and FASD are much broader than simply those three symptoms we mentioned. The facial features can be helpful diagnostic markers, but many cases of FASD go undiagnosed because of an over reliance on those visual abnormalities. Also, an under appreciation of the broad behavioral, cognitive, and socio-emotional symptoms resulting from prenatal alcohol
exposure. We will discuss this in much more depth with Jeff. Another important basic question here is: How common is FASD? As in many neurological and psychiatric conditions, it’s really tough to pin down a specific prevalence rate due to the heterogeneity in terminology, and the variety of research methods used, but we have found that FASD is likely present in about 2% to 5% of school age children. Just a couple other quick, relevant descriptive stats pertaining to the broad impact of FASD. The estimated lifetime cost of health care for each child born with FASD is close to $2.5 million. In 2005, children with FAS incurred average medical expenses that were 9x greater than those without FAS. Because FAS is only one condition under that FASD umbrella, the true economic effects of FASD is much greater. The projected cost of raising a child with FASD is 30x higher than preventing the syndrome in the first place, which makes prevention and intervention that much more important.

Ryan 04:36
Those healthcare costs are really staggering. Let's transition now and talk about mothers for a few minutes. Of course, it's the child who has FASD but the mother's an important part of a syndrome. Women who binge drink prior to conception have a higher likelihood of unintended pregnancy and are also more likely to engage in risky behaviors in general, which includes drinking during pregnancy. Heavy alcohol use, in women, and binge drinking in particular is a risk factor for later FASD in their child. According to the National Institute of Alcohol Abuse and Alcoholism (NIAAA), binge drinking is a pattern of consumption that results in a blood alcohol concentration of .08 grams per deciliter or greater. This is usually the equivalent of about four drinks for women and five drinks for men within about two hours. It's also important to be aware that prenatal alcohol exposure is frequently unintentional in that it occurs early in the first trimester before the woman knows that she is pregnant. It's vital that we both educate people on the teratogenic effects of alcohol during pregnancy and be sure not to stigmatize women who have a child with FASD. The more negative societal energy that is directed towards mothers of children with FASD, the harder it will be for those mothers to report early signs and symptoms. The easiest path in this situation would be for the woman to ignore, downplay, and deny. Who wants to be the subject of all of that stigma and negative energy? In contrast, if we are supportive and inclusive, rather than judgmental and exclusionary, then we will really open the door to honest endorsement of alcohol use and reporting of early signs and symptoms of FASD, all of which will help both the child and the mother. Another important issue is the question of a lower threshold of alcohol consumption. This is something else that we get into with Jeff a bit, but I do want to talk about it here just to prime you. The recommendation in terms of a lower threshold is clear. Harmful effects are well documented for moderate or heavy drinking. While the data for FASD regarding mild levels of alcohol intake are mixed. But still, there is no amount of
alcohol intake that has been documented as safe for the developing fetus. It is strongly recommended that women abstain from alcohol entirely while they are pregnant. To add some supporting data to this claim, a 1984 JAMA paper by Mills and colleagues prospectively examined over 30,000 pregnancies and reported an increased risk of infant growth retardation, even when alcohol intake was limited to just one drink per day. I think that's a strong finding and those results can really take it home for us to know that there's really no lower threshold of drinking that's safe. Okay, now that we've gotten that part said, we can move on to risk factors. I already covered maternal binge drinking. John, why don't you run through a list of additional risk factors for our listeners?

**John Bellone 09:43**

Sure thing. Maternal markers that increase the likelihood of a child to prenatal alcohol exposure include a mother's past history of alcohol or drug use problems, little or no prenatal care, unemployment, transient lifestyle, incarceration, or a partner or family member who was a heavy drinker. Again, these are all just risk factors. Published guidelines suggest that frontline medical providers such as primary care physicians consider FASD whenever a child has those characteristic physical signs that we talked about before, or has poor growth, developmental delays, behavioral concerns like ADHD or poor performance in school, history of adoption, especially from a low SES environment, history of involvement with U.S. child social service systems. There is also parental abuse, neglect, abandonment, or history of out of home or foster care placement. Again, this doesn't mean that the child has FASD. They're just risk factors for FASD. We're going to wrap up this introduction with just a couple other quick helpful facts that people may not be aware of. Unfortunately, children with FASD are not explicitly designated to receive special education services in the Individuals with Disabilities Education Act. Another fact is that the 2010 Federal Legislation Child Abuse Prevention and Treatment Act requires that health care providers report FASD to Child Protective Services systems. So all the clinicians listening should find out about the specifics for reporting in your location. I think that was a long enough introduction. [laughs]

**Ryan 11:30**

I certainly hope so.

**John Bellone 11:31**

So we hope you enjoy our discussion with Dr. Jeff Wozniak.
John Bellone  11:45
Jeff, welcome to NavNeuro. We're sorry that we couldn't fly you out to San Diego like you wanted us to, but I hope it's not too cold there in Minneapolis right now [laughs].

Jeff  11:55
Well, being from Minneapolis, we always ask that question [laughs]. Happy to be here. Happy to have the opportunity to talk about FASD.

John Bellone  12:03
Great. So, as we typically do, we'd like to start with some core terminology. We have given listeners an overview in the introduction, but I think it'll be good to just touch upon the main terms here with you as well. So fetal alcohol spectrum disorders or FASD. It's kind of the umbrella term that includes multiple syndromes, including fetal alcohol syndrome (FAS), alcohol-related birth defects, alcohol-related neurodevelopmental disorder, or behavioral disorder associated with prenatal alcohol and we can go on and on [laughs].

Ryan  12:37
Please stop there [laughs].

John Bellone  12:39
So Jeff, can you just help us here delineate some of these and define them? We were also just curious what terminology you prefer to use?

Jeff  12:46
Sure. That's a very good question to start off with because this is actually one of the key areas where there really does need to be some development in the field of FASD. Most of us in the field now recognize that this is a spectrum disorder. In the truest sense, that we have a very well-defined phenotype and that is fetal alcohol syndrome, which has very specific criteria that are almost universally agreed upon. However, we know that that's an imperfect phenotype because partially how that diagnosis is made. It depends on physical characteristics that are only present in a small portion of people affected by prenatal alcohol. So we have this whole other spectrum that we recognize is related to prenatal alcohol, but can't be diagnosed at the level of FAS. That's where these other
diagnostic entities have evolved, things like partial FAS, which is basically what it sounds like. These are individuals that have some of the features, but not all of the features. Other various names for things like alcohol-related neurodevelopmental disorder, another partial condition, but containing even fewer of the diagnostic characteristics. Without spending too much time, maybe I can summarize this a little bit by saying that all of these various diagnoses and systems of diagnosis, look at four different criteria. The first one is alcohol exposure itself. In many of these systems, for many of these diagnoses, there was a requirement that there'd be some documentation that the child was exposed, or the individual was exposed prenatally to alcohol at a level that would be considered risky, and we can come back to talk about that. That's one characteristic. The second characteristic has to do with growth. We know that growth impairment as a result of prenatal alcohol exposure is associated with effects on the brain. The physical growth, height, and weight is a characteristic that goes into the diagnosis. The third area has to do with facial characteristics. So there are some very specific phenotypic facial characteristics that go along with FASD. We can get into those if you want to, but they basically define the syndrome and they can be present in lesser levels in some of the other diagnoses. And then the fourth characteristic has to do with cognition and that's the one that's most interesting to neuropsychologists. We can kind of spend some time delving into that. Maybe I'll stop there and see if that's clear so far.

John Bellone 15:41
Yeah, it sounds like FASD is kind of the preferred umbrella term, right?

Jeff 15:47
Yes, FASD is definitely the preferred umbrella term. Typically, when we make these diagnoses, we specify beyond that and actually give the individual diagnosis whether it's going to be FAS itself, partial FAS, alcohol-related neurodevelopmental disorder, etc. Maybe this is a good place to point out that these diagnoses are in the ICD system, the International Classification System for diagnoses, but they're not in the DSM, the Diagnostic and Statistical Manual. Typically, when we are making a DSM diagnosis that is related to prenatal alcohol exposure, we're using the neurodevelopmental disorder and then specifying what the actual diagnosis is, if we can specify within the FASD realm. There is discussion of FASD diagnosis called prenatal alcohol exposure. They're under a mental disorder and that's in the appendix of the DSM. So that is a diagnosis under study, essentially. It's not an official diagnosis and there has not been a consensus on how to kind of move that into the main part of the DSM.
Ryan 17:04
Interesting. Do you have thoughts on that yourself, about whether it should be moved into the neurodevelopmental disorders chapter? If so, how should we define and delineate FASD in the DSM?

Jeff 17:18
Yeah, ideally, it would be clean if we could move this neurodevelopmental disorder related to prenatal alcohol exposure into the DSM and have a very clear set of agreed upon terms. But DSM is a consensus document. So far, we haven't been able to reach consensus and research has not really been able to reach consensus on exactly how that should be defined. Right now, it's essentially up to the clinician to decide whether or not there's enough to call this a neurodevelopmental disorder. I am of the opinion that neurodevelopmental disorder is really the important factor. As a neuropsychologist, I'm less concerned with the facial characteristics and the growth because they don't necessarily have the same level of practical implications for the patient as the cognitive impairment. I'm of the opinion that diagnosing a neurodevelopmental disorder and characterizing it as best as we can with neuropsychology and good clinical evaluation is really the end result that I like to see.

Ryan 18:27
Yeah, I think that sounds like a reasonable argument. We've touched on several of the different FASD subtypes. You mentioned, the facial morphology that is characteristic of FAS specifically. We know that many children who have prenatal alcohol exposure don't have the FAS facial morphology and they tend to go undiagnosed, right? Because there aren't such obvious physical characteristics for us to look at and see so that they're not on people's radar so much. Do you do you have ideas as to steps that we could and should take, in order to reduce these false negatives? These misses?

Jeff 19:08
Sure, maybe I'll just start by kind of defining what the actual facial characteristics are for people who might be unfamiliar, and then we can kind of talk a little bit about how they relate to diagnosis. The main characteristics that we're looking at are small palpebral fissures, the eye width. The width of the eye is closely related to the development of the brain. It's kind of a window, a coarse window into brain development and there are normative data for these eye width measurements. An eye width measurement smaller than, say, the 10th percentile puts one in the category that it might be related to prenatal
alcohol exposure. The other two that are kind of specific and related are the flattening in the philtrum and this is the groove above the upper lip. That is significantly flatter in individuals who have FASD. Also, related is the circularity of the upper lip and we all have a feature called a cupid's bow that's sort of like a dip in the upper lip. That shape is altered in prenatal alcohol exposure. Those three facial characteristics together are definitive for FASD. Sorry, I should say are very closely associated with FAS and are pretty specific to FAS. Individually, those facial features occur across a whole range of genetic and environmentally determined conditions. This is where it gets a little bit challenging because sometimes people don't have all three of those facial characteristics. We know from the animal literature that these facial features do go along with brain effects, but they don't occur in most of the cases. We think that probably less than 10% of individuals who have some brain effects and some cognitive effects from alcohol have the facial characteristics or enough to make a diagnosis. Your question is, what do we do to sort of capture some of those people and reduce the false negatives? We are working on a number of strategies for that - one of which has to do with 3D facial imaging. One of the projects I'm involved with - it's a multi-center project - we have people who have expertise in imaging the face. We do that with 3D cameras and now evolved to the point where we can do that with even a smartphone or an iPad with some specific kinds of cameras. You can measure the face very carefully in a way that you can't do with the eye or with a simple ruler and that is one way that we might be able to get at some of these cases who have more subtle facial this morphology. The other way that we get at these is through this diagnosis of alcohol-related neurodevelopmental disorder where we don't have to have the facial features to make the diagnosis. This is based on impairments in cognitive functioning and also some indication that individual is exposed prenatally to alcohol. That's kind of how we get at those false negatives. As you might imagine, that is a more difficult diagnosis to agree upon because there are lots of reasons of course why people have cognitive impairment, even multiple cognitive impairments, and many of those might have alcohol exposure. Coincidentally, it may not be the cause, but that's an area where a lot of research is taking place right now to try to determine what are those characteristics that are specific alcohol?

Ryan 23:02
That's very helpful. Some of the facial imaging technology sounds really exciting and innovative, for sure. Can I back up a moment and ask a conceptual question? Do we know what it is about being exposed to alcohol prenatally that causes these facial dismorphologies specifically? What's the relationship between alcohol and then why does someone's face look different?
Yeah, that's a very good question. I spend a fair amount of my time in interdisciplinary circles with basic scientists who study these things in animal models and I have to say that after many, many years, I started to pick up a few of the pieces in terms of how the biology works. It's pretty complicated. I would say that there are many, many different biological mechanisms involved, apoptosis for one example. Cells have the built-in ability to stop themselves from growing or to destruct and that's a normal part of development. Alcohol has the ability to trigger that process of apoptosis inappropriately and so when you expose an organism or human to alcohol at the right time, during development, it can trigger that process. A lot of these effects are happening when critical things are occurring in the neural tube. At the very early stage of neural tube formation, where you're going to have all of this elaborate folding, and then coming together, you end up affecting the way the cells migrate through some of these damaging processes from alcohol. It's essentially tricking the biology into doing something it's not supposed to be doing at that particular point in development. It's pretty fascinating, actually, that when the way the neural tube forms that comes together and folds. This is why we have what we call "midline problems" in FASD. In the middle of the brain, some of the structures like the corpus callosum, for example, can be affected right along with features in the middle of the face. So you get this flattening in the midface, this flattening of the philtrum, and effects on the lip. It can occur in very severe levels, so you can end up with significant neural tube disorders, like spinal bifida that are even more severe. It's sort of a continuum effects that happen at this very, very early stage of development.

That's so fascinating.

It's really incredible to see some of this laid out in these animal models and it's very specific. The facial features come in some animal models on a single day of exposure. Let's say, day seven. Alcohol exposure will cause these facial features, whereas day 8 will not.

Sensitive period.
It's a very sensitive period and that's equivalent in humans to around the third week of gestation. So we're talking about really early in development at that point.

I have so many questions based on what you said. The first one is I'm assuming that the mechanism of cognitive impairment is also related to these neural tube developments, abnormalities, and the changes in cell migration that cause the facial morphology?

That's a very good question and we could spend a lot of time on that one too. Maybe I'll summarize by saying yes, and. So certainly, if you have effects at the level of this basic neural tube formation, you can have really coarse effects on brain development. The brain can be smaller than normal. It can be smooth. One of the studies that I published recently had to do with looking at cortex, and the alcohol can actually affect the processes that cause the cortex to fold. We've seen in our samples that kids with FASD have smoother cortices. It can also affect these midline structures like I was talking about. We've seen cases where the corpus callosum is partially absent or mostly absent. In other cases, we can detect abnormalities using microstructural MRI techniques. The bottom line is that alcohol exposure early on in pregnancy can result in these facial characteristics and the full FAS syndrome. But the brain is developing throughout the rest of gestation so alcohol is going to have different biological effects on those different processes whether the synapses are forming or whether the neurons are migrating. All of these different developmental processes can be interrupted by alcohol.

That's fascinating. Definitely the window into the basic science, as you said, is helpful for us to at least have an idea as to what the biological mechanisms are that are causing this. As you mentioned, Jeff, we're neuropsychologists. We can maybe move forward, talk a little bit about phenotype in terms of behavior and cognition. In my background readings for this conversation with you, I noticed that the list of neurocognitive, social, and behavioral effects documented through prenatal alcohol exposure is extensive, to say the least. I found citations for essentially all the major neurocognitive abilities potentially being impacted and that children who had previously experienced significant prenatal alcohol exposure tend to have a very high occurrence of psychiatric problems, including depression, anxiety, ADHD, learning disabilities, intellectual disability, autism, and others.
It feels like we’re sort of listing all the possible cognitive and emotional issues that could be present or sometimes present in kids with FASD. My question is how do we define the FASD profile? If everything can be impacted, how do we know what FASD looks like compared to something else?

Jeff 29:26

This is a very challenging issue as I think you hinted at and I would say right off the bat that there is no FASD profile, unfortunately. But we can talk specifically about how we approach assessment. Maybe I'll start a little bit talking about why I think there is no profile and it actually relates to some of the biology that we were just talking about. If you think about a brain that is affected at the level of neuronal migration, you end up with a brain that is really effective at a coarse level. So the structure doesn't even form correctly. Imagine a smoother than normal cortex. That's a major disruption to the communication system in the brain and the processing system. Imagine a brain that is 1.5 to two standard deviations smaller than normal, or a brain that has a major hippocampal abnormality, or a corpus callosum abnormality. All of those kinds of effects are going to be different when it comes to cognition. The corpus callosum abnormality, for example, might affect the individual's motor functioning and their processing speed. You might have to do some sensitive measures of looking at the cross-hemisphere functioning in order to detect that, whereas a child who has a major anomaly might have sort of global cognitive impairment and have a low IQ. Then, there might be other effects on things like myelination. Some of my work is really focused on the white matter and, in those individuals, we typically expect attention problems and processing speed abnormalities. It really can be all over the board. I would say that almost the universal area that's affected has to do with attention. That's not surprising because you can disrupt attention by having a white matter effect by having an effect on cortical functioning by having a gross structural kind of effect. So attention is one of those functions that are so highly sensitive and so distributed that you can disrupt it in lots of different ways. That is what we see in FASD that many of these individuals have the attention and impulse control problems that you would see in a lot of other conditions, including ADHD. If there's anything characteristic about FASD that would be relevant to neuropsychology, I would say that adaptive functioning is one of the areas that stands out. Many times adaptive functioning is sort of dissociated from the rest of the cognitive profile. You may very well have an individual with an average IQ or a slightly below average IQ, but you're going to see big impairments in adaptive functioning. That's one of the characteristic things about the behavior of kids with FASD or adults with FASD - the judgment is impaired, the ability to handle abstraction is impaired, and it shows up in the adaptive functioning pretty routinely. There can be some specific kinds of effects that we sometimes see in memory functioning. There's a whole literature on hippocampus and how it's affected by alcohol...
exposure. I usually look pretty carefully at memory functioning when I'm thinking about FASD as a clinical diagnosis. Bottom line is that we recommend and we do very comprehensive neuropsychological evaluations of these patients, and that includes sort of the full range of domains, as well as their emotional, psychiatric functioning, and adaptive functioning.

**John Bellone 33:32**

The diagnostic guidelines for FASD define cognitive impairment as greater than 1.5 standard deviations below the mean, right? Is that a hard cut off? What kind of tests are usually used? I mean, you kind of answered that with your typical battery, I guess.

**Jeff 33:52**

There are multiple different diagnostic systems and they have slightly different cutoffs, but generally, we're looking for somewhere in the 1.5 to 2 standard deviation range. Usually, we're looking for at least two to three or more different domains of cognitive impairment. Domain is typically what you would think of so executive functioning, memory, motor functioning, as opposed to a specific subtest or something like that. You're looking for multiple different domains to be effective in order to meet that criteria.

**Ryan 34:31**

Can I follow up, Jeff? You talked about adaptive functioning. Clearly, that's very important and maybe that is a domain that is particularly impacted in FASD. Then, you referenced judgment, some executive functions that we often don't test very well. As you were talking, that's what I was thinking. Well, so maybe if we had better tests or maybe we could use a Tower Test or the NAB Judgment to maybe focus cognitively on some of these areas that maybe are more impacted by FASD that then lead to poor adaptive functioning. Do you think if we use the right tests we can pick up on those or that we just don't test those skills very well?

**Jeff 35:12**

Well, I think sometimes it's relevant to their adaptive functioning or the day to day functioning and we do see that often times in people who have very significant executive functioning impairment on some of our measures, like planning, organizing, and working memory. However, I will say that we have published and others have now published on this effect, whereby there's not a strong correlation between real-world measures of
executive functioning tests like the BRIEF and in office measures of executive functioning. There’s another effect where their adaptive functioning is often highly correlated to other aspects of their behavior and will involve executive functioning too. So the self-report measures, parent-report measures, teacher-report measures of executive functioning, seem to correlate more highly with the rest of the individual behavior than they do correlate with their actual executive functioning on some of our specific tasks.

John Bellone 36:24
That is interesting. If we can maybe talk a little bit about the comorbidities that are involved, in addition to FASD. Because it is quite high, the rates of comorbidity. In terms of ADHD and learning disabilities, I've also come across FASD can sometimes look like autism. There are also qualitative differences between FAS, FASD, and Autism Spectrum Disorder (ASD). Can you talk us through differential diagnosis here? How you distinguish these?

Jeff 36:55
Sure, I think an important element of those diagnoses has to do with kind of the full developmental picture. I think it can look different in FASD versus autism spectrum condition. Not always. There is some overlap between these conditions. Certainly, having prenatal alcohol exposure doesn't protect you from having autism and it probably increases your risk, somewhat. The social and communication elements are probably one area of distinction. Often times, individuals with FASD are not socially affected in the same ways that someone with ASD might be affected. So you don't necessarily have a lack of interest in social interaction, core problems with joint attention, core problems with perspective taking, or affect recognition. The type of things that you see that we really think of as core to the social functioning of someone with autism aren't not necessarily present in the typical FASD kids. I think evaluating those elements that I just mentioned can be a useful part of the process. Again, looking at the developmental history is also important and knowing something about the alcohol exposure itself can be useful. We tend to think of these these evaluations as not just a static evaluation, but a sort of multiple time point evaluation to really get a full picture of what's happening with development.

Ryan 38:34
Yeah, it's helpful. If you wouldn't mind, Jeff, I'd like to take a stab at sort of summarizing the general behavioral and cognitive effects of FASD. Then, you can give me feedback if
I've got it, right.

Jeff  38:45
Sure.

Ryan  38:47
Children with FASD tend to have broad impairments in cognition, behavior, and emotion such that there's really not a strong FASD profile that we can delineate. Cognitively, they tend to be impacted across the board. Maybe slightly more so in memory. You mentioned testing that quite strongly, but adaptive functioning might be the domain that tends to be most impacted. Behaviorally and emotionally, there are a lot of co-morbidities. All of the heavy hitters developmentally are more likely as a result of FASD. There are similarities to other conditions like ASD, but there are also some differences. Is that a decent summary? Did I miss anything?

Jeff  39:29
Yeah, just to reemphasize the area of attention as being one that we see very disrupted in FASD almost across the board and sometimes very significantly. One other thing I'll mention is that in the area of academics - mathematics seems to be an area where there are some specific difficulties. Some people who have done a fair amount of work on this, including developing some educational curriculum around math, have shown that it might be related to some of the core features of FASD. There may be some breakdowns in nonverbal processing. Things related to magnitude comparison, numeric operations, and also the attention and working memory component that makes it very difficult to learn math. We oftentimes see that that kids with FASD struggle more with math than we might expect for their level of IQ.

Ryan  40:33
That's a helpful bit of information. We're going to keep moving along. I'd like to talk a little bit about neuroimaging in FASD. I know you've authored and co-authored multiple papers on this topic, including recent work such as the multi-site study, the collaborative initiative on FASD. If you don't mind for us and our listeners, if you could just start from the top and give us a summary of the state of the literature on neuroimaging and FASD. What brain regions and developing neural networks tend to be the most vulnerable to the effects of prenatal alcohol exposure?
As you might imagine, it's a pretty broad literature at this point. Some of the earliest studies looking at gross pathology and FASD demonstrated that some of the things we talked about already, like corpus callosum anomalies. The animal literature pretty clearly shows us that hippocampus can be affected and we've seen that in some of our MRI studies. There are effects on both white matter and grey matter. I mentioned already the cortical gyrification or cortical folding abnormality that we've seen. A number of studies have shown the white matter is abnormal at the microstructural level. We think that might be related to myelin, but it could also be related to how the white matter is constructed or laid out, the structure of it. There are a whole range of effects that can happen, but don't necessarily happen often, that are kind of other structural anomalies that happened in the brain. I think that the literature is pretty clear that the white matter is significantly affected, in many cases, even when the brain doesn't look abnormal. So we know that networks are going to be affected. As far as which networks, I don't think it is a regionally specific effect when we're talking about white matter. It's more of a whole brain effect because of the way the white matter forms. As far as pulling out networks from neuroimaging studies, there hasn't been too much of that yet but we've seen anomalies in memory processing. In fMRI studies, we've seen anomalies in math processing. So I think it is a widespread kind of effect. Going back to what we talked about earlier, which is that people use alcohol differently throughout the pregnancy. Some are using it in the early stages only. Some use it in the early stage and then throughout the pregnancy. Some use it and then discontinue. So you're hitting, as a population of people, with all kinds of different developmental systems and it's not surprising that we see a range of effects on the brain.

It's not just that first trimester alcohol exposure is bad and then you can drink as much as you want after that. It's really throughout the whole pregnancy the fetus is vulnerable to the effects of alcohol.

Exactly and in different ways because different developmental processes are unfolding.

Random question. Does that also apply to breastfeeding mothers?
Jeff  43:54
There have been a few studies that have been published, including one very recently that show there are some small effects from breastfeeding. Obviously, the brain is still developing at that point. But you can imagine that some of the major effects happened very early in the pregnancy because we're talking about an organism that is really just a collection of cells. It doesn't have a liver, for example, to deal with alcohol. It's just "bathing" the cells and something that is disrupting these basic biological processes.

John Bellone  44:32
Is there a dose dependent relationship with the amounts or frequency of prenatal alcohol consumption with the neuroanatomical effects?

Jeff  44:45
Yes, but it's also timing dependent. It is gene dependent. It is nutritionally dependent. There's a lot of interactions that we sometimes don't think about. For example, timing. I mentioned that we can produce these effects on animal models with a difference of one day, either producing effects or not producing effects. In terms of eye development, there's a very clear dose relationship between the alcohol exposure and the amount of effect on the eye and on the brain development. I mentioned genes. We know that there are different strains and animal models. You can produce these effects, to more or less extent, depending on something is as basic as a single nucleotide polymorphous. So a genetic difference, can can contribute profoundly to how one is affected by alcohol or not. Nutrition is another factor. If you have a nutritional deficiency, like an iron deficiency. That is going to magnify the effects of prenatal alcohol exposure. In humans, you start to get a sense for just how much variability there's going to be with the outcome. That's one of the reasons why we will never be able to say "Here's a safe level of alcohol exposure. It's X number of drinks." Because there's so many other factors that interact.

John Bellone  46:16
I could imagine that some women might be concerned that they might have had a glass or two of wine before they even knew they were pregnant. Should they be worrying about that?

Jeff  46:29
As these questions sometimes come up, and I've had these questions come up directly
when I've done radio shows and things like that and it's difficult. Usually my advice is we want to make the message clear that there is no safe level of alcohol exposure. At a public health level that has to be the absolute message and that is the message from Surgeon General and World Health Organization, etc. But at an individual level, development is complex and we have no way of predicting. What we do know for sure is that stopping drinking has a positive effect on the rest of the development. If a person knows that they have exposed alcohol, of course, the number one thing to do is to stop, and then to optimize the rest of the pregnancy. So to ensure that the person not getting prenatal care starts getting prenatal care. To ensure that the nutrition is optimized. To ensure that all other aspects of taking care of that fetus' development are attended to. We don't generally advise that people panic if they've had some exposure. There are many cases where there's alcohol exposure and there are no discernible effects. That doesn't make it safe, but that also doesn't mean that it's 100% likelihood of having an effect.

Ryan 47:58

Yeah, that's great advice. That makes sense in terms of how we might think about this issue of a lower threshold of exposure and how we might talk to patients about it. I'd like to switch gears a little bit. So Washington State has been touted as a leader in FASD diagnosis, prevention, and intervention. It seemed kind of random to me, but the state includes a diverse set of government initiatives, research funding, that are apparently well coordinated across institutions leading to better outcomes for children with prenatal alcohol exposure. Will you talk about some specifics? What's working so well in the Pacific Northwest and how might other states start to implement this system?

Jeff 48:43

It's a great question. Part of the reason why I think Washington is somewhat ahead of the curve is that there's a long history. This condition was essentially identified in the early 1970s at the University of Washington by Dr. Ken Jones and his colleague, and there was a simultaneous discovery in France at the same time. Then, they proceeded to start studying it so there has been a clinic that was initiated. I believe by Ann Streissguth and Sterling Clarren many years ago and that clinic has been carried on. Susan Astley runs that program currently and is very involved in having developed a diagnostic system for FASD, etc. They've done a great job of building a diagnostic capacity in the state. Tying that into referral streams and publishing the results of their diagnostic efforts and their clinical work to set the standard for the diagnosis for other states. If I can, maybe plug my own state a little bit. I'm in Minnesota and we have the good fortune of having had an organization started back in the 1990s that was previously called the Minnesota Organization on Fetal Alcohol Syndrome. It's now called Proof Alliance and this was
started by Susan Carlson who was a juvenile court justice, and she was married to the
governor at the time. This organization is a thriving organization that helps establish
diagnostic clinics in Minnesota and does a lot of public awareness work in the state, as
well as dealing with legislation. So we have a pretty progressive movement in this state
around alcohol. One other state that I would mention is Alaska - a lot of the effort at the
legislative level and at the public health level dealing with some of the problems that are
occurring with alcohol in Alaska. There's a few stand stand out places and I think the
combination of public awareness, integration with state and county services, and
integration across professions is really some of the reason for this.

John Bellone 51:19

It's also important to kind of talk about the social and cultural factors that are involved in
FASD that can affect outcomes, like how much parents are involved in the child's care,
special education programs in schools, and access to healthcare just in general. I know
there's a high number of these kids in foster homes, and I've seen it high as even 60% to
80%. Coupled with the typical neurobehavioral impairments that we were talking about
before, that really creates an increased risk for legal issues. These kids tend to get in
trouble more than other kids. According to a 2012 report by the Office of Juvenile Justice
and Delinquency Prevention, about 61% of adolescents with FASD have had a history of
legal problems and about 35% of those who were older than 12 had been incarcerated at
some point in their lives. One study showed that the crimes committed by the population
tended to be more impulsive, unplanned, shoplifting and theft, which makes sense, given
what we know about the cognitive factors and the social factors. I'm sure we can do a whole
episode on this as well, but how do you think we should approach treatment
recommendations with all of these multifaceted layers to consider, especially the legal
issues involved?

Jeff 52:47

Yeah, very good question. I think you've hit on the sort of key issue that the social
problems and legal problems that these individuals have are a result of things like impulse
control problems, judgment problems, and abstract reasoning difficulties, but also the
social environments. Some of the difficulties that they may have had developing good
emotion regulation skills because they had attachment problems or were bounced
around from foster home to foster home, and didn't have stability during those early
periods. It's a complex mix. I think as neuropsychologists, we can approach this in a
similar way that we might approach other neurodevelopmental disorders - helping
individuals and court system understand how these deficits play out in real-world settings.
Also, how these individuals need help in navigating the legal system. This has been an
emphasis in the last few years in terms of trying to put in place, in the court system, some awareness of this issue and this diagnosis, as well as some awareness of what special accommodations are needed. That could be as straightforward as having individuals familiar with FASD who can respond to complaints. In other words, the police, probation officers, and parole officers being aware of this diagnosis and taking into consideration when they're facing active situations. At the level of the courts, having appropriate guidance, coaching, and legal assistance provided to these individuals to make sure that an assessment is part of the proceedings. Part of the sentencing decisions, etc. It's really treating it as a neurodevelopmental disorder, like any other neurodevelopmental disorder. Maybe with a specific understanding that these folks have difficulty with judgment, impulse control, and those sorts of things.

Ryan  55:00
That's helpful. I like they're moving into interventions a little bit. I'd like to ask another specific question about those. In some of my reading, I found that, not surprisingly, multimodal symptom treatments tend to be most efficacious for these children. Hitting the issues from multiple angles, but I haven't found anything that seems specific to FASD. The techniques that seemed to work are things like orchestrating a supportive stimulating environment and providing social support. These sorts of things tend to be helpful for children, whether they have FASD or not, right? If we could give every single child the most supportive environment possible - tutoring, emotional health from parents and teachers, and things like that. It's just general good care for children. So it got me thinking, if the intervention choice doesn't depend on the diagnosis, then it reduces the ultimate utility of the diagnosis itself. I could certainly be missing something here, but maybe you can set me straight. Is there anything particular to FASD treatments that would not be relevant for a child who did not have this condition?

Jeff  56:12
I think there are a few minor things. For example, many of these kids have attention problems and impulse control disorders. Oftentimes, those are treated with stimulant medications. That can be a problem in these individuals. There's a whole literature on why that might be having to do with dopamine - how the developing dopamine system responds and how that plays out later in life. As a rule of thumb, the treatment with stimulant medications can work, but sometimes doesn't work effectively and sometimes has an adverse effect on kids with FASD. There are math interventions that I mentioned earlier that are specifically designed for FASD, so that might be one of the specific areas where an intervention would be diagnosis dependent. We are working on nutritional interventions. I have a study going with two to five year old kids where we are specifically
trying to nudge their hippocampal development with a single nutrient called "choline." We think there's hippocampal development still happening at the level that we could influence it with this. That's a couple of randomized control trials that are going on with that. This might be very specific to prenatal alcohol exposure because we know the effects on the hippocampus, but, in general, I think you're right. I think that because the effects can be so widespread or idiosyncratic to the person that the treatment plan really does need to be taking all of that into consideration.

John Bellone  57:53

That seems optimistic that there might be some of those specifics that you mentioned could be contributing to better outcomes and early screening might potentially identify those kids who are most at risk and could utilize those interventions. I'd imagine and I hope that medical professionals working with kids would know when to screen for FASD and that women who are educated and counseled around FASD are more likely to monitor their own drinking and to check for FASD signs and symptoms in their kids. Is there anything you wanted to expand on in terms of the importance of screening?

Jeff  58:32

Sure, I've been involved in some efforts to implement screening at the level of pediatricians, which is kind of interesting. We think the natural place would be with obstetricians, gynecologists, which of course is a great place to do screening. But pediatricians are also seeing patients who have kids - women and families who have kids - so there's an opportunity there to ask about alcohol exposure and potentially prevent another alcohol exposed pregnancy. We know that these tend to run sequentially so that exposing one child to alcohol raises the risk that another child is going to be exposed. So yeah, screening is very important and I think we've tapped into numerous different medical specialties. Screening can also happen at the school level and there's been some interesting efforts to look at developmental disruption, general developmental delay, and then to tag on questions about alcohol exposure. For example, when there are questions about development and that can be done very early at the preschool level.

Ryan  59:40

Yeah, early screening tends to be helpful in a lot of conditions, for sure. I like targeting the pediatricians. That makes sense. I'd like to circle back around to something we talked about at the beginning of this conversation, specifically image-based recognition of the FAS facial features. Can you tell us a little bit more about this technology, Jeff? How it
works? The overall state of the empirical literature? How it can help clinicians, patients, and their families?

Jeff  60:09
Sure, I have a couple of colleagues working on this one at Oxford by Michael Suttie and he’s carrying on the work of a previous researcher. They started with $50,000 3D cameras sitting on big tripods and we're now moving to the point where these cameras are handheld, which may now cost $15,000. Even to the point where you can use an iPhone with a two camera system to get a 3D image.

Ryan  60:41
You can do everything with an iPhone [laughs].

Jeff  60:42
Yeah, exactly [laughs].

Jeff  60:45
I'm an Android user myself so I guess I'm out of luck [laughs]! But the technology is really focused on some of the spatial characteristics that can be measured in very subtle ways - the flattening in the mid-face is a good example where you can discriminate between individuals who have FASD versus not pretty reliably with just a profile of the middle of the face. That shows some promise that this might actually be a high throughput screening tool. At least for catching the cases where there was early alcohol exposure, where the effects might be significant.

John Bellone  61:26
I can imagine a lot of clinicians are quite confident in their ability to diagnose FAS, but I'd imagine that this type of technology that you're talking about, the image-based recognition, is probably much more accurate.

Jeff  61:39
It's a little hard to know what's more accurate because what's the gold standard, right? We can't randomly assign people to alcohol and have a non-alcohol group and then do
our studies of specificity and sensitivity. So the gold standard tends to be a morphologist - the expert in facial morphology who does this for a living and knows all of these different genetic syndromes - who can identify the spatial characteristics. The 3D imaging is pretty good at matching that if not exceeding the sensitivity of the dysmorphologist, but the question is always "what's the gold standard?"

Ryan 62:20
Yeah. How could we say that the 3D imaging exceeds the sensitivity of the dysmorphologist, if there is not a gold standard?

Jeff 62:29
When I say that, I mean it can detect abnormal flattening, whereas maybe the dysmorphologist might not call it abnormal. But that's at a statistical level, right?

John Bellone 62:43
Yeah, I guess the real benefit to that would be that it's in the hands of more clinicians who maybe are not as expert at noticing those.

Jeff 62:52
Exactly. That's exactly right.

Ryan 62:55
Okay, this conversation has been very enlightening and helpful for sure. I'd like to to wrap-up FASD by asking you a little bit about what these children tend to look like as adults. We know, for example, that many children with ADHD grow out of it, so to speak, or become less symptomatic as they mature into adulthood. At the same time, there are many adults who have ADHD symptoms and we sometimes diagnosis it in mature patients. So I'm wondering, with respect to FASD, what is the standard developmental trajectory? Is there even a standard developmental trajectory? It might be so variable that we can't say. Can you speak to this issue?

Jeff 63:35
Sure. We know a lot less about adults with FASD, unfortunately. I just came from a
conference last week in Vancouver. There were a number of adults with FASD who attend that conference and their families, as well as mixed with researchers and clinicians. It's interesting to hear their stories and it's a range. Many of these individuals - if they were diagnosed with FAS and had, let's say, intellectual impairments - continue to have those intellectual impairments as adults, not surprisingly. As you said, some of the ADHD changes form. They may go from having hyperactivity as kids to having more executive functioning and organizational problems as adolescents, and then that carries forward into the adult years. Often times, they have these adaptive functioning impairments that we talked about. They may need help managing their finances or they may need help living independently, but many of these folks have good social functioning. They can learn get along socially, can hold jobs, can marry, and can even raise kids with assistance, similar to how you might think about other developmental disorders. So there are some challenges. One of the things we're starting to see is that prenatal alcohol is not just a brain specific teratogen. It affects other processes and development that may lead to other health problems. We've seen evidence so far of things like obesity as being possibly related. Some cancers possibly might be related to prenatal alcohol exposure. A number of orthopedic issues seem to crop up in these adults. inflammatory processes seem to be affected. So we're starting to think about this as really a whole body condition that we really need to think about health and the overall health effects of prenatal alcohol exposure.

Ryan 65:37
Great. Very helpful info. Well, this is where most interviews would end, Jeff, but we like to throw our guests a few bonus questions. So these apply to the field of neuropsychology broadly and not to FASD specifically. The first question is: If you can improve one thing about the field of neuropsychology, what would it be?

Jeff 66:02
One thing off the top of my head would be better access and shorter waiting times to access neuropsychological services.

John Bellone 66:12
Do you have any ideas for how to make that happen?
Well, I think we're in the era where technology can help and maybe is helping to some extent, but I feel like this is a field, in particular, since it's so measurement heavy, that there's a lot of room for improvement on automation. Everything from administering tests in a more automated way to reporting on those tests and putting data together in a format that other people can use. Not neuropsychology speak, but usable data output. I think would really help.

John Bellone  66:48

I like that a lot. What is one bit of advice that you wish someone had told you when you were in training or maybe someone did tell you that really made a difference? Just an actionable step that trainees might be able to take that they might not have thought about and that really could improve their training?

Jeff  67:05

That's a good question. What I did not know about when I was in training was what I would ultimately be doing. In fact, I'm doing something very different than I imagined I would be doing. As a trainee, I never would have imagined that I would focus my career on FASD, and that I would be federally funded to do research on this for many years. So the advice would be don't plan too far ahead. Try to be open to the experiences that you're having in your training whether it's at the graduate level, internship level, or post-doc level. Follow the path loosely as opposed to thinking that you can pick your direction and just stay on it throughout your whole career because many interesting opportunities will come up. If you are open to them, and if you are taking opportunities, you will land in a place that is interesting.

John Bellone  68:05

Yeah, we've heard that advice several times and I think it's awesome advice. Stay flexible. Be open to whatever comes your way because it might be something that is better than you had thought the trajectory of your career might look like. So I love that.

Jeff  68:18

One related thing I would say is stay involved with patients and families. If you can, do work that brings you into the realm of families. I do a fair amount of speaking and interfacing with the public on FASD and that has really enriched my career. Sometimes working in a lab setting, an MRI environment, or even in a clinical setting, you sometimes
miss that human impact. So getting out and interfacing with people at the level of families dealing with the conditions is a very positive thing for yourself and for the families.

**John Bellone  68:59**
That's awesome and that might be your answer to this next question that we're sneaking in here. Just to finish up by asking for advice for early career professionals. Specifically, we know the healthcare landscape is changing really rapidly and we want neuropsychology to remain relevant and useful. Once we're established, as neuropsychologists, do you have some advice about what steps can be taken to ensure that we're continuing to provide cutting-edge scientific and clinical services for decades to come?

**Jeff  69:31**
Yeah, that's a big question. We think about evidence-based interventions and we still have not made a lot of progress on evidence-based assessments, especially in neuropsychology. So I think the next generation can make a lot of advances in linking these assessment tools to outcomes and to paths along the way. How do these assessments inform, in an evidence-based way, what we actually do and what the outcomes actually look like? I like to encourage my trainees to not think of themselves with too much of a capital "N" in the neuropsychologist identity. Rather, to think of themselves as clinicians and people who know a lot about behavior as well as they know about neuropsychological tests. And to always put neuropsychology in the context of being a systematic set of tools, but also keeping it in the context of good clinical care.

**Ryan  70:39**
Great, excellent answers. Thank you so much for your time. Thanks for coming on NavNeuro, Jeff. We really appreciate it.

**Jeff  70:45**
I had a good time and I appreciate all the thoughtful research that you guys put into preparing this.

**Ryan  70:50**
Yeah, no problem. Thanks again.
Well, that does it for our conversation with Jeff. As always, thank you so much for listening and I'd like to put a plug in for a new project that John and I are launching here soon, which is what we're calling My Story. This is an opportunity for neuropsychologists and neuropsychology trainees to share - with anyone who's interested - your story, your narrative about what got you interested in neuropsychology, your passion. What initially was that spark, for you, that put you on this path to where you are today? As neuropsychologists, we are a very diverse group of people. We all have our own unique story about how we got to where we were and we're always interested in having more people join us in the field of neuropsychology. So people who are not in the field would likely be really interested in reading about our stories. All you have to do, if you're interested in helping us out with this, is go to our website at NavNeuro.com/MyStory and tell us a little bit about how you got to where you are. We'll remind you again at the beginning of the next episode, but I'll just say that John and I are really excited about this project. We think it could be really helpful for anyone who's interested in this and we're thrilled to see where this goes. Join us next time as we continue to navigate the brain and behavior.

John Bellone  72:47

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Ryan  72:59

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