Aaron van Dorn (00:07):

Welcome to AJP Audio for January 2023. I'm Aaron van Dorn. Today on the podcast I spoke with Dr. Stefanie Russman Block, a clinical assistant professor of psychiatry at the University of Michigan at Ann Arbor, Dr. Russman Block and colleagues have a paper in the January issue of the American Journal of Psychiatry, looking at the use of neuroimaging as a predictor for treatment effectiveness in patients with obsessive compulsive disorder. Afterwards. I'll again speak with Dr. Ned Kalin, editor-in-chief of AJP about the rest of the January issue and what it can tell us about neurodevelopmental disorders.

Dr. Russman Block, Exposure and Response Prevention or ERP is a first line treatment for obsessive compulsive disorder while associated with substantial symptom decline. ERP treatment has a large variability in treatment response. Your study looked at neuroimaging as a means of predicting treatment response for patients undergoing ERP, what did you find?

Dr. Stefanie Russman Block (00:51):

Thanks, Aaron so much for having me. Let me first start by explaining what obsessive-compulsive disorder or OCD is as well as why we use exposure therapy. So, OCD is a condition in which people repeatedly have intrusive or anxiety-provoking thoughts that they find difficult to dismiss, and then they develop these behaviors or what we call rituals that they try to use to lower their anxiety. And unfortunately, while that helps in the moment, it ultimately makes anxiety worse in the long run. So, let me give you an example. One subtype of OCD that a lot of people have heard about is called contamination, where a person might be afraid of contracting germs or getting sick. So, I have two little kids and I often take them to story time at the library and during story time, all the families sit on the floor while they listen to the librarian.

(01:43):

And if I had contamination related OCD, I might find that to be very difficult and I might even avoid taking my kids to the library entirely, or I might develop a ritual that makes it easier for me to sit on the floor in the moment such as maybe when I go, I wear a certain pair of clothes and then when I get home because I feel like those clothes are dirty or contaminated, I might feel like I have to change them or wash them immediately. And as you can imagine, that can become very impairing and can start to grow and affect other areas of one's life. So, Exposure and Response Prevention or ERP is a fancy way of saying facing your fears. And the idea is to try to break the cycle between that anxiety-provoking thought and the ritual. And the idea behind this is that when you do something that you're afraid of, your anxiety naturally goes down over time.

(02:38):

That's just part of your what happens in your body. And you also learn that what you're afraid of is usually less likely to happen than you think it will. Or if something does happen that you're afraid of yet you might be better able to handle it or cope with it than you expected. So, if I were in therapy, I might practice with my therapist repeatedly sitting on the floor for increasingly longer periods of time, and then I would have to not use any of the rituals I would normally use. So, it would be important for me to continue going about my day in the same clothes that I wore that touched the floor. So, for anyone who's tried to face their fears, you can imagine that this can be quite difficult. It requires quite a lot of engagement on behalf of the patient. And at the present, this is one of the most effective treatments for OCD.

(03:27):

However, a substantial number of patients don't receive as much benefit from it as we'd like. Thus, in our study, we were hoping to use brain imaging to better understand what factors might relate to better treatment outcomes so that we could hopefully in the future use this information to improve success in treatment. So, in our study, we had adolescents and adults with OCD undergo an fMRI brain scan. Prior to doing 12 weeks of individual psychotherapy, we looked at what's called resting state functional connectivity, which is how different brain regions talk to one another when they're not actively engaged in a task. And this is a great way to probe and understand brain function. Just like we know from previous work, we did find that ERP, the exposure therapy was more effective at reducing OCD symptoms than our control therapy, which was called stress management treatment.

(04:21):

And with regards to the brain, we found that connections of a particular circuit that's previously been implicated in fear learning and emotionally driven behavior predicted who would have greater symptom decline to ERP. Specifically, we found that weaker connections between the ventral medial prefrontal cortex and the thalamus and caudate predicted greater symptom improvement to ERP, while the reverse pattern was true for those in the stress management group. So, this could mean that those with weaker connectivity at the circuit are somehow better to engage in those difficult fear-provoking exercises that are done in ERP. What was interesting was that we also found a large set of connections that predicted symptom decline for both treatment groups, meaning they weren't specific to exposure. So, specifically connections involving cognitive control circuits, which are processes that are involved in planning overriding impulses and acting in line with your goals predicted more symptom decline to psychotherapy in general. Not surprisingly, those are all skills that are probably very important when you're doing any type of therapy and trying to learn a new way to manage symptoms.

Aaron van Dorn (05:35):

As you mentioned earlier, your study was divided into two arms with one group assigned to 12 sessions of ERP and the other assigned to a similar number of stress management therapy sessions. Why did you choose to use an active comparator and why SMT in particular?

Dr. Stefanie Russman Block (05:46):

Yeah. It's, a great question. So, in this study, stress management therapy or SMT was considered the control therapy group. So, if we didn't include this and we had only had participants undergo ERP, we wouldn't know if our findings reflect a specific response to exposure therapy or just a psychotherapy more generally, and in stress management therapy, patients have the same amount of contact with a therapist as they would in the exposure group, and they're also taught active types of coping skills that are used in other forms of therapy. And because of that, we could then know that our findings regarding the ventral medial prefrontal cortex are not related to those common elements of psychotherapy and are probably more specific to the exposure element that we're interested in.

Aaron van Dorn (06:35):

So, what did you find in the differences between ERP and SMT?

Dr. Stefanie Russman Block (06:38):

So, we did find that in terms of therapy more generally, not considering the brain findings that ERP is a more effective, we did find that it was a more effective treatment at reducing symptoms than SMT, if that's what you're asking.

Aaron van Dorn (06:52):

You also divided your study population between children aged 12 to 17 and adults age 24 to 45. Why did you choose to differentiate between the groups and what differences did you see among the populations?

Dr. Stefanie Russman Block (07:02):

So, ERP is a first line treatment in OCD, not only for adults but also for kids. And we intentionally recruited these two groups of participants in these two distinct age groups in order to compare a period of more developmental neuroplasticity. So that would be the adolescence to a period of greater neuro stability that would be the adults because there's a thought that maybe intervening early when these brain areas are still more malleable, might explain why kids might respond better than adults. We actually did not find that kids responded better than adults in this particular study, but we did find that there were neural differences as to what predicted who would do better in terms of adults versus adolescents.

(07:51):

So, we found that in particular, connectivity of the nucleus accumbens was a differential predictor of adults versus adolescents. And the nucleus accumbens is a region that's particularly known for being involved in reward and we found that stronger connectivity of the nucleus accumbens was important for treatment response in the adolescent group specifically. So that might suggest and support the notion that the nucleus accumbens is particularly important for adaptive functioning during adolescence compared to other age ranges.

Aaron van Dorn (08:27):

Are there near-term clinical implications for your findings?

Dr. Stefanie Russman Block (08:29):

Mm-hmm. Great question. So, as I stated earlier, our hopes for the future would be that we could try to find ways that we could enhance people's treatment response when they're undergoing ERP with these findings. So, since we found that there were certain connections that predicted greater symptom decline, one idea might be in the future to try to have people do some type of a short or priming intervention before they do ERP in hopes that that might maximize their response. So that could be some very targeted, for example, computer game that we know involves and or activates that circuit. There's also different ways of more directly modulating those regions.

(09:16):

So, for example, there's some more recent work looking at something called neurofeedback where people can actually learn to modulate their own brain connectivity by receiving information about that in real time. So, we would hope that in the future those would be some things we can do, but we're still a long ways away from that. We really need to replicate these findings and look in other groups. For example. Another implication might be since we did find differences between the different age groups, that perhaps the treatments need to be tailored differently for adolescent sources adults, but we really need to look at a larger age range too before we can jump from our findings to direct clinical changes.

Aaron van Dorn (10:00):

What were the limitations of your study?

Dr. Stefanie Russman Block (10:02):

So related to that, while I mentioned before that resting state connectivity is a great way of probing brain function, it's important to remember that when people were spanned, they were not actively engaged in the task. And so, this does not speak to how the brain might be functioning when people are actively engaged in different tasks, and it doesn't preclude that there could be other connections that are involved or important treatment response that we didn't examine in the study for the findings that were common across both psychotherapy groups. Because we didn't have any group of patients that didn't undergo any treatment, for example, they were scanned and then followed up after 12 weeks without any therapy. We really can't rule out the possibility that those findings are just simply due to the passage of time. Maybe that's just what happens after 12 weeks. So that might be interesting to look at.

(10:54):

And we also didn't have anyone who was doing pharmacotherapy, so it would be very interesting and unknown to know if these findings hold for other types of interventions that are not psychotherapy for the age-related findings. We did require that both the adolescent and the adult group have a childhood onset of symptoms, but that also meant that the adults had had OCD longer than the adolescents, which is not really something that could be controlled for but is something that could have affected the results. We also would love to do this in a more diverse sample to really understand if this holds across different populations. And like I mentioned before, we had these two very specific age groups, but it might be interesting in the future to look at young adult that are between the ages of 18 and 24 that we didn't have in the study to see if similar findings held.

Aaron van Dorn (11:51):

You mentioned quite a few narratives of potential research, but what's next for your research? What are you actually working on right now?

Dr. Stefanie Russman Block (11:56):

Yeah. Great. So, there's definitely I think a lot of avenues. So, one avenue would be, like I said, looking at how these brain areas could be modulated. So, we're starting to, I did develop some of those neurofeedback studies to see if people can directly modulate these brain regions. We're also looking to see if connectivity in these regions change with therapy. This study only looked at baseline connectivity, meaning how the brain was before anybody did any treatment would be really interesting to know if those regions are the same as what actually changes when people then undergo treatment. And we're also looking at other populations. So, exposure therapy is also effective for anxiety disorders. So, we're also looking at to see similar predictors occur for those groups as well.

Aaron van Dorn (12:49):

Well, Dr. Russman Block, thank you for taking the time to speak with us today.

Dr. Stefanie Russman Block (12:51):

Yeah. Thank you so much for having me.

Aaron van Dorn (12:53):

Next up, Dr. Ned Kalin. Dr. Kalin, welcome to the first AJP Audio for 2023.

Dr. Ned Kalin (12:57):

Thank you. It's a pleasure to be with you.

Aaron van Dorn (12:59):

This month's issue looks at childhood and neurodevelopment related psychiatric disorders. I spoke with Dr. Russman Block earlier on, her and her co-authors paper looking at how predictive resting state connectivity in the brain was for treatment response in adolescence and adults with obsessive-compulsive disorder.

Dr. Ned Kalin (13:12):

That's a very interesting study and we wanted to highlight the study in the journal because it gives us a glimpse of the future from the standpoint of being able to potentially use brain imaging measures to make predictions about treatment outcomes. And in this particular case, as you mentioned, the study is in adolescents and adults with obsessive compulsive disorder. It's a relatively small study and it compares an evidence-based treatment for OCD exposure response prevention with an active comparator treatment that is not necessarily evidence-based for OCD, but should theoretically be somewhat helpful, which is stress management therapy. What the investigators found, not surprisingly, was that the exposure response prevention did better from the standpoint of outcomes than the stress management therapy. But the aim of the study was really to not demonstrate that because that is expected, but rather to find out if they could find some neuroimaging predictors of treatment response.

(14:12):

And what they found was different measures of connectivity with regions of the brain that have to do with habit formation and have been identified with OCD. The cortico-striatal-thalamic circuits were individual differences in the function connectivity of those circuits was somewhat predictive of outcomes for either treatment as well as some outcomes that were specific to the treatments. So, really interesting early study, relatively small sample, but highlighting the potential for the future from the standpoint of using imaging measures to help us think more about personalized medicine approaches.

Aaron van Dorn (14:47):

Continuing with biomarkers, Dr. Webb and colleagues evaluated Kennedy EEG biomarkers, which might allow clinicians to guide children diagnosed with ASD towards more effective treatments. What did they find?

Dr. Ned Kalin (14:57):

So, in this issue, we have a number of papers that are related to autism spectrum disorder. We have a review that is from the American Psychiatric Association Research Council on biomarkers, and then we have a more specific paper, the one you're referring to looking at electroencephalography or electrical singles from the brain as being used as biomarkers for autism. And then we yet have another paper which we'll discuss a little bit later on autism as well. The important thing to note is that biomarkers are critical from the standpoint of developing quantitative measures that either are helpful with diagnosis or helpful with treatment selection or predict treatment outcomes. There's a tremendous amount of research in psychiatry searching for valid biomarkers. And in general, at this point in our evolution with the research, we have not found reliable biomarkers that are strong predictors of these types of outcomes.

(15:57):

And this study that's presented in the journal looks, as I mentioned, looks at EEG biomarkers, which is useful because EEG is a measure that's relatively easily obtainable when you think about it in relation to other measures such as neuroimaging measures. The investigators of this study did a really very good job of not only thinking about which biomarkers might be useful, but also trying to validate them. And by validation there are a number of things that we have to do, one of which is to show that the biomarker is related to the illness. Another is to show that the biomarker is stable across time. That is to say that within an individual, whatever you're measuring from one time point to another time point is relatively unchangeable. And to make a long story short, these investigators found evidence for one of the biomarkers that might be useful, and they really suggested that this should be investigated in greater depth.

(16:54):

And this was a biomarker that has to do basically with face processing. I mean, that's interesting because face processing is something that is frequently altered or changed in individuals that have social deficits who also have autism spectrum disorder. So, really strong study from the standpoint of being very careful, it's done in a relatively large sample of individuals children with ASD and also typically developing children. And the conclusion is that again, there more works needs to be done, but the one paradigm that looks like it would be useful would be to use EEG to monitor responses to face presentations as a potential reliable ASD biomarker.

Aaron van Dorn (17:37):

The other paper you mentioned that was looking at autism spectrum disorder is from Floris et al, which looked at the link between autism and sex related neuroanatomy. What can you tell us about that?

Dr. Ned Kalin (17:45):

Yeah. This is a really interesting paper with I think potentially important implications. ASD, you know, is a classic psychiatric neurodevelopmental disorder. And just to give you an example, in 2021, the prevalence in the US population was estimated to be around 0.2%. But what's important to keep in mind is that study after study has shown that there's a marked increased risk in boys as compared to girls. And in 2021, that was estimated to be a fourfold increase in boys compared to girls. And there's been a lot of work trying to understand why there's this sex difference and risk. Some studies have demonstrated that there seems to be an association between male related brain features and ASD interesting enough in both males and females. And this study actually went further and used lar very large databases to try to understand what features of the brain were predictive of ASD in both males and females.

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And by using sophisticated machine learning techniques with structural imaging data, the basic finding was is that that features that are predictive of male brain structure were more predictive of males with ASD and in females features that were predictive of female brain structure were not particularly predictive of ASD and females. In fact, even in females, the features of the brain that were more male related seemed to be more predictive of ASD. And so, this is further evidence that there is a sex related brain effect that seems to be predictive of autism spectrum disorder and that in both males and females, it tends to be the more masculinized the brain is in some of these regions, the more likely it is that an individual might have autism spectrum disorder. Now in females, what was found was is that greater male related brain features were associated with larger deficits and social sensitivity. And interesting enough, as we mentioned in the earlier paper, in relation also in relation to face processing.

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So, this is evidence again pointing to a male related brain features in both sexes being related to the likelihood of having autism spectrum disorder. The investigators went further and used this data to combine it with data from the Allen Brain Institute, which is a repository of really great genetic and gene expression data to try to understand in the brain regions that were identified to be associated with autism spectrum disorder and that were also male related, what were the genes that are most expressed in those regions, and how do they overlap... how do those genes overlap with known autism spectrum disorder related genes?

(20:38):

And I won't go into the details, but so they found some very interesting findings, including some interesting sex differences in the genes that were overexpressed in these regions that overlap with the autism spectrum disorder genes suggesting that there may be different molecular pathways in males and females in these brain regions. So, interesting paper, more insights into perhaps the genesis and risk for developing ASD and more support for the idea that early life or even during fetal life, that sexual differentiation of the brain and the mechanisms related to that also may be related to the propensity to develop autism spectrum disorder.

Aaron van Dorn (21:17):

Next, Dr. Lese Martin and colleagues looked at the electronic health records from a large healthcare database to identify patients with neurodevelopment disorders such as ASD, schizophrenia, and bipolar disorder.

Dr. Ned Kalin (21:27):

Well, a large feature of this issue is dedicated to neurodevelopmental disorders and also to childhood disorders. And this is building on what we just discussed in relation to ASD because in this large healthcare population in which they had gene or genomic data, the question that was asked was if they search for rare genetic variants that are associated with neurodevelopmental disorders, is that predictive of the likelihood of having a diagnosis of a neurodevelopmental disorder or a psychiatric disorder? Now the reason this study is important is because it's in a very large healthcare population that was not selected for neurodevelopmental disorders. It was not selected for psychiatric disorders, but rather it was a survey of the prevalence of these rare genetic variants in this large population. And also, a question of what we talk about is penetrance, which is the extent to which those genetic variants are actually associated with an illness or a diagnosis.

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And most studies in the past have looked at more selected populations, for example, psychiatric populations or populations to samples that have to do strictly with people that have neurodevelopmental problems. And so, that doesn't give a fair sort of view of what's out there in the world, a broader sample of the prevalence of these mutations and also the likelihood that they'll predict disease or illness. And the findings in this paper demonstrate that roughly in this large sample of almost 100,000 individuals, I think it's 90,000 individuals that were surveyed of the 94 genetic variants that were searched for, that were known to be related to neurodevelopmental disorders. 61 genes I think were found that had these mutations in this sample. And the prevalence of these pathogenic genetic variants or gene variants was roughly 0.344%. Now the authors point out at an earlier paper that it was actually published in AJP, they looked at a different type of genetic variant.

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And when in the same population and when you put all this together, the overall prevalence of these rare genetic variants is around 1% in the population. Now that sounds very low, and it is on the one hand. On the other hand, this can provide some really interesting insights. As we've discussed in the past, the genetics that underlie or associated with psychiatric disorders almost always tend to be complex with polygenic or many, many genes being involved.

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What we're talking about here is a much more select number of genes that have mutations and because of those mutations are more directly related to the illness without having necessarily this polygenic risk background. The reason that's important is twofold. One is that it may suggest that we should be doing some genetic screening, but also it may suggest pathways at a molecular and a neural circuit level that are altered in relation to these very specific genetic mutations that also may be altered in other individuals that don't have these mutations but have the illness. From the standpoint of penetrance or the concept of what is the relation between having these genetic variants and then also having the disorder, what the researchers found was that, for example, a significantly higher percentage of individuals had a neurodevelopmental diagnosis if they had at least one of these pathogenetic variants compared to individuals that did not have one of the pathogenetic variants.

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And this was to the order of 34% of individuals that had one of these pathogenic variants had a neurodevelopmental illness. Whereas 40% of the individuals that had these neurodevelopmental disorders did not have a pathogenetic variant. They went on to look at schizophrenia and also went on to look at bipolar disorder. And what they found was is that if you had one of these genetic variants, the odds of having a diagnosis of schizophrenia or bipolar disorder or even ADHD was increased by about two to threefold. So, an important study giving us a better handle on the prevalence of these rare genetic mutations in a non-selected healthcare population sample, and also insights into the likelihood of those genetic variants predicting or being associated with a neurodevelopmental disorder or psychiatric diagnosis.

Aaron van Dorn (25:55):

Finally, Dr. Brikell and colleagues looked at polygenic risk scores for ADHD, and along with 24 other risk factors associated with ADHD. What can you tell us about their findings?

Dr. Ned Kalin (26:04):

So, this is an interesting study, ADHD is known to be another developmental disorder, neurodevelopmental disorder that's known to be highly heritable. The heritability of ADHD is thought to be estimated around 75%, but also, again, numerous other factors, non-heritable factors presumably are associated with the risk to develop ADHD. Each may be perhaps conferring small risk, but real risk. Some of these are birth related, some of them are physical, some are psychosocial, some are demographic factors. So, some examples include low birth weight, maternal hypertension, and a variety of other factors. But what's interesting is that even though these are not traditionally thought to be heritable, there's some evidence to suggest that these other more environmental associated factors or factors in moms related to birth, there's some evidence to suggest that they also could be mediated by the same genes or be associated with the same genes that confer the risk to develop ADHD.

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And so, the idea here is that even though things are not thought to be strictly genetic, they still can be related to the same genes that have to do with the risk to develop an illness. And the only way you can

look at this is to look at it in a very large sample. And in this particular study, the large sample that was selected was from the Danish Psychiatric Research Consortium. And in this sample, there were roughly 20,000 individuals that were selected along with about 14,000 individuals who had ADHD. And what the investigators found was, first of all, that as expected, the polygenic risk score for ADHD was predictive of having ADHD. So, for example, if you were had the highest polygenic risk scores for ADHD as compared to individuals that had the lowest risk scores, the risk for developing ADHD or having that diagnosis was about fourfold greater.

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They looked at 24 other risk factors for ADHD, many of which I just enumerated or mentioned. And they also found that for 12 of these 24, that the polygenic risk score for ADHD was also associated with individual differences in exposures to those risk factors. So, this is now linking the risk score or the genes that confer risk for ADHD to also the risk to be exposed to a variety of these other risk factors, which also confer some risk to develop ADHD. That's a little bit complicated, but it's really quite interesting. Now, I need to point out that the relationship between the genes that confer the risk for ADHD and these other risk factors was small. It was significant but was small. Some of these factors that were also associated from the standpoint of the polygenic risk score were such things as gestational age, mom having an autoimmune disorder, and also other family psychosocial factors.

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Now, what's important is that in the statistical analysis that the investigators did, they were able to demonstrate that while polygenic risk scores for ADHD can further risk for ADHD and also for the exposures to these other risk factors, it seemed like the influences of these different risk factors were independently associated with ADHD and not necessarily as working through the polygenic risk score. So, it's a little bit complicated, but just to summarize, ADHD risk, polygenic risk scores predict greater likelihood of having ADHD is expected. ADHD polygenic risk scores are also associated with other risk factors including environmental risk factors that are associated with the risk to develop ADHD. But those associations are small, and also when you look at the combined influences of the polygenic risk score and these other risk factors, they seem to be acting independently even though there's this small significant association between them.

Aaron van Dorn (30:08):

Dr. Kalin, thank you once again for joining us.

Dr. Ned Kalin (30:10):

You're welcome. It's my pleasure.

Aaron van Dorn (30:12):

That's all for this month's AJP Audio, but the APA has other podcasts for you to enjoy. And the most recent Psychiatric Services From Pages to Practice, Psych Services Editor-in-Chief, Dr. Lisa Dixon, is joined by PS Editor-in-Chief Emeritus, Dr. Howard Goldman and Dr. Alison Cuellar to discuss everything you want to know about the peer review process, but we're afraid to ask. That and more can be found at psychiatryonline.org/podcasts or wherever you find podcasts.

Speaker 4 (30:34):

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