Aaron van Dorn (00:07):

Welcome to AJP Audio for February, 2023. I'm Aaron van Dorn. This month's issue of the American Journal of Psychiatry features a lot of interest in new research and we'll be highlighting two articles of interest in this episode. First up, I spoke with Dr. Nate Harnett, an Assistant Professor of Psychiatry at Harvard Medical School about the impact of diversity and stressors on the racial disparities in brain development in black and white children in the United States. Following that, we'll hear from Dr. Ziv Ben-Zion, Post-Doctoral Associate at Yale University. Dr. Ben-Zion and colleagues performed a non-exec replication study of an earlier article by Stevens et al, published in AJP, looking for biomarkers that could potentially guide treatment of patients following trauma.

(00:41):

The paper by Stevens and colleagues was featured in the November, 2021 episode of AJP Audio and you can find a link to that earlier conversation in the show notes. Finally, we'll stop in with AJP Editor-in-Chief, Dr. Ned Kalin to see how those two articles fit together with the rest of the February issue.

Dr. Harnett, your study looked to racial disparities and exposure to measures of adversity compared to race related differences in brain structure in a large longitudinal cohort of adolescents from across the United States, focusing on black and white children. What did you find?

Dr Nate Harnett (01:05):

The major finding of our study was that there are very clear racial inequities in how much adversity children are exposed to, and that these inequities contribute to differences in the size of brain regions that play a pretty big role in trauma and stress related disorders. The lead author Natalie De Mornay and I were really interested in trying to understand what the neuro-biological impact of racial inequities could be. In some of our prior work, we found that developmental histories of exposure to adversity really accounted for differences in how black and white young adults responded to threatening stimuli. And we thought that these sorts of neuro differences may begin earlier in development like childhood. So we used data from the adolescent brain in cognitive development study, which is a large multi-site study of about 12,000 children in adolescents that began about half a decade ago. We looked at several different indices that could tell us a little bit about the participants' exposure to different adversities like trauma exposure, conflict within the family, material hardship like ability to pay bills, levels of income, caregiver education, and how relatively disadvantaged the neighborhoods were that these children came from.

(02:11):

As you might expect, black children generally came from more disadvantaged neighborhoods and their caregivers had less access to resources compared to white children. And when we looked at the brain structure in these kids, specifically the volume of gray matter in specific brain regions, we saw that black children also had lower volume compared to white children. The volume of brain regions, like the prefrontal cortex, the insula and amygdala also varied with our indices of adversity. But critically, when we actually controlled for the racial disparities in these levels of adversity, we saw a reduction in just how large the race related differences in brain volume actually were. And I think these results really highlight both the impact of essentially structural racism on our children, and has serious implications for how we think about inequi`ties in development and how we study the brain basis of psychopathology.

Aaron van Dorn (02:56):

It seems obvious that factors like poverty, malnutrition, violence, and exposure to pollutants would have an impact on brain development in childhood, but how to list tangible factors like trauma, stress and exposure to violence impact brain development.

Dr Nate Harnett (03:07):

We've known for a long time that different environmental exposures have an almost obvious effect on neuro-development. If you're poor and don't have resources to buy good food, you're not getting enough fuel and that impacts really basic functions that grow and repair your body. Even toxins like lead directly affect neural growth and you see these effects in different neurocognitive assessments, but other types of traumatic experiences that we don't often think about in terms of physiological damage, can directly impact the body. Witnessing highly stressful or traumatic events can bring about intense reactions of fear and can elicit the same fight or flight reactions that are related to activation of the autonomic nervous system.

(03:45):

For kids in particular, these stress exposures aren't controllable and they're not always predictable even when they can occur in a context where they're more likely to happen. So one view then, for what actually happens is that, because of this need to engage processes to deal with potential threats, there's actually an acceleration of brain development in circuits that help us to regulate our emotions. And this makes perfect sense. You need these processes to come online sooner to deal with the potential harms in your environment and deal with them so that you can both survive and also thrive. But there's really no free lunch when it comes to development, and this kind of accelerated maturation in certain circuitry may come at the cost of delaying development of other circuits or potentially shifting typical physiological functioning to deal with the sort of toxic nature of the stress that they're encountering.

Aaron van Dorn (04:32):

Your study found that a significant portion of the gray matter volume differences between black American children and white American children reflect disparities and toxic stress, which you just mentioned. What do you mean by toxic stress?

Dr Nate Harnett (04:41):

The idea behind toxic stress is that certain types of events or experiences in our lives can be incredibly physiologically damaging in a way that can have significant long-term health effects. Everyone has stress in their lives and things that cause stress and a little bit of stress can probably be good for you. You might have a report due soon or someone wants to interview you about your work, that can be stressful, but also might motivate you to get your tasks done and prepare for something that you're going to have to encounter.

(05:08):

However, extreme stressors that begin in childhood, things like abuse, neglect, poverty, and malnutrition, factors beyond your control that you still have to respond to, can lead to these intense responses that then shift how you might respond to things in the future. The systems that control how someone responds to stress become highly dysregulated, and this can impact hormonal, heart and brain systems responsible for keeping us healthy. And so, the long-term effects of these stressors can be especially bad in childhood, because it can impact growth patterns, contribute to increased inflammation and heart problems like heart disease or high blood pressure, and increased risk for behavioral issues or psychiatric conditions. And in that way, the toxic and toxic stress then is actually very fitting in the way that it impacts the body.

Aaron van Dorn (05:54):

Your study looks specifically at the hippocampus, the amygdala, and the prefrontal cortex regions of the brain. Why did you choose to focus on those regions specifically?

Dr Nate Harnett (06:01):

There's really two reasons we chose to focus on these regions, and they're both related. First and foremost, there's a lot of research to suggest these regions play a major role in trauma and stress related disorders like PTSD. These regions are highly involved in threat or fear conditioning, they support appraisal of emotional stimuli, and they regulate our responses to emotional events, and we've seen across animal models and human work that variability in the biology of these regions is linked to the cognitive and emotional dysfunction that we see in PTSD. And so, we really wanted to keep our analyses focused on regions where there is this really strong priori theory and research to help guide our interpretations. And I think the reason that's so important to do that is that, we are really looking into and discussing a very sensitive topic, and that is race-related differences in the brain.

(06:50):

Psychology and psychiatry have a controversial and sometimes problematic history when it comes to the intersection of mental health, the brain, and looking at race related variability. Part of that history has resulted in reifying fairly racist views related to behavior and cognition between groups. So for us, it was really important not to contribute to that history by over-interpreting the data or extrapolating beyond the framework that we were going to use. Obviously the brain is pretty big and there are other regions that we could have looked at and we likely will look at them as our reason expands, but I don't think those interpretations here would necessarily have been as strong or as nuanced as I think they need to be to avoid contributing to potentially racially problematic viewpoints.

Aaron van Dorn (07:34):

There's been a lot of research recently looking at the effects of systemic racism in the United States at least, looking at areas, for example, of the health effects of redlined areas on people who live there. But your data didn't really touch on that because you weren't able to drill down to the granular location level of people who were involved in the study, correct?

Dr Nate Harnett (07:50):

Yeah, that's right. The ABCD study had previously geo-coded participants and provided indices of neighborhood deprivation through the area deprivation index and associated metrics. Having to request zip code data and regional data can present a little bit of a privacy issue for participants. And so, we chose not to try to ask for that data and go down that road, even though I think that regional variability is really important to consider in terms of racial and ethnic variability in exposure to adversity and brain function and structure. One of the other reasons we didn't want to go down that road is because this is such a sensitive area, we wanted to make sure that we were using data that was widely available and wasn't as subject to individual interpretations on how the data should be transformed. And so, we're using ABCD data that's publicly released.

(08:45):

We give the digital object identifier for which specific data that we use, so that this way if there are questions about whether our results are going to be replicable, people can actually go to that data and look exactly at what we used. And we think that sort of transparency is going to be really important for

making sure that if there is a slightly different way that we could have done the analysis that people can go through and really double-check the work that we've done.

Aaron van Dorn (09:10):

What were the limitations of your study?

Dr Nate Harnett (09:11):

Well, since it's my study, there are obviously no limitations. No, there are some pretty important things to consider when interpreting our work. First and foremost, this is a cross-sectional study. We don't have data from before the participants were nine or 10 years old, and when we started the study, we didn't have any longitudinal data either. We really don't know how the inequities in adversity and the inequities of environment may be affecting brain development earlier in childhood or into the teenage years.

(09:39):

Given some of the effects that we've seen in some of our prior work in young adults, I worry that the magnitude of race related differences may in fact get larger over time as the cumulative burden or toxic nature of these inequities becomes larger. And that's something we really need to know as we think about systemic changes we might want to implement, to mitigate these brain differences that we're seeing. Second, we really only looked at a few indices of adversity. There are many types of things that could also have been aversive to participants that weren't included and other aspects of the neighborhood that we could have looked at as well. So for example, one thing that we didn't look at is racial discrimination and the impact it can have on children's brains.

(10:18):

There's been quite a bit of work from some of our colleagues, like Negar Fani and Sierra Carter, showing that the impact of racial discrimination on brain structure and function is in the same regions that we see here, in adults. So trying to see how discrimination might impact childhood and adolescent brains would be really important. And finally, we really focused on the bad things that participants experienced, and really didn't look at positive factors or potential resiliency factors that might also be playing a role. And we didn't look at community integration or how congruent their self identities were or things of that nature. And I think trying to understand how positive factors might buffer the effects of early life adversity is really important going forward.

Aaron van Dorn (10:57):

What's next for your research?

Dr Nate Harnett (10:59):

There are a couple loose threads in the study that we really want to tug on. We really want to probe into what happens in the brain over time as these racial inequities and adversity persist. Do we see a growing effect on the brain over time? Does it in fact lead to some sort of accelerated or decelerated maturation? And is that circuit specific? I think answering those questions is going to be important for getting a clear picture of the extent of the problem of, how are the inequalities in our country disenfranchising groups of people, and what are the consequences of that?

(11:29):

Another thing we're really trying to understand is how these race related differences might impact the generalizability of different biomarkers and treatment options that we might want to develop for

psychiatric conditions. As we move towards precision psychiatry and personalized medicine, I think it's important to figure out if, for example, the biomarker or biotypes that we identify for certain conditions are going to be equally applicable across groups, or if our results might be confounded in some way. So I think both identifying the neuro-biological consequences of structural inequities and how we use that to develop better biomarkers for psychiatric disease, is going to be a big part of our work moving forward.

Aaron van Dorn (12:07):

Is there anything else you'd like our listeners to know about your study?

Dr Nate Harnett (12:10):

I think one thing that I come back to, and I don't know how nuanced this is, is that in some ways I don't think the results are entirely surprising. We've known for a long time that there are racial issues in this country that have plagued us historically over time. I think one thing that's especially salient here though is that, what we're looking at are effects on children.

(12:35):

These are individuals who have no choice in the adversities that they're exposed to, who don't get to choose where they grow up, who don't get to choose where their parents come from. They have very little choice in their exposures, and yet we're still seeing these not huge, but noticeable differences in the way that these different groups' brains are developing. And I worry about what that means for their future, for the future of other kids and for just what this means in terms of their development going forward. And I think it should highlight to a lot of us that the systemic issues that we have in this country are something that we really need to intervene early on for people and really start to rectify that we don't have such huge disparities going forward.

Aaron van Dorn (13:24):

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

Dr Nate Harnett (13:26):

Thank you for having me.

Aaron van Dorn (13:28):

Up next, Dr. Ziv Ben-Zion. Dr. Ben-Zion, your study aimed to replicate a recent study by Stevens et al, published in AJP, that was looking for biomarkers that could be of help in determining treatment for recent trauma survivors. What did you find?

Dr Ziv Ben-Zion (13:39):

Indeed, as you stated, the aim of our work was to try and replicate a very promising study by Dr. Jennifer Stevens and colleague that was published in the American Journal of Psychiatry in 2021. We were looking to actually use identical methodology to the one that they used and using a different independent data set of recent trauma survivors, that is coming from a large scale study that I conducted in my PhD at Tel Aviv, Israel. And we were very interested to examine whether the findings of Stevens and colleague could replicate to a similar, but yet a bit different sample, in a study with different methodologies and some other differences.

(14:28):

So basically our main findings is that we found four clusters of individuals that we could classify or differentiate at one month post-trauma, based on neural activity, reflecting retroactivity and reward reactivity, using simple tasks in the FMRI, very similar to what was done in the original work. However, the four clusters that we found were not identical to the previously identified brain-based biotypes by Stevens and colleagues, and were also not associated with future clinical symptoms of PTSD or anxiety, as was found in the original work.

Aaron van Dorn (15:12):

What were the challenges of running a non-exec replication study done by another group of researchers? How did you determine what factors you were going to replicate and which you would have to differ?

Dr Ziv Ben-Zion (15:20):

That's a great question. To be fully transparent, study that we used was, as I said, we used the longitudinal study of recent trauma survivors that was performed in parallel at the same time as the AURORA study, which is reported in the paper by Stevens and colleagues. These studies are very difficult to perform. They're very time consuming, money consuming. So obviously we didn't just read the paper and then started a five-year neuroimaging study of recent trauma survivors. So we didn't have many options to choose or change the study design or methodologies, but fortunately, we had a lot of similarities between the two studies. We both recruited individuals arriving to the emergency department of a general hospital following a traumatic event. We both had clinical and neuro assessments in the FMRI closely or shortly after trauma, and also going all the way to six month in the AURORA study and all the way to 14 months in our study.

(16:32):

And that's the data set that we chose to use. And to the best of our knowledge, this data set that we acquired, the Tel Aviv, is the only data set that is comparable to the AURORA study, that again I must state, it's a very big and important study that took a lot of efforts from many different great researchers. The challenge is obviously, we had some differences between the study. So from the beginning we had several possible confounds or explanations that we knew that if we would not replicate the results, it can be because of the fact that it's a different populations, because the FMRI tests were not the same because it was conducted at different times, but different people. But nevertheless, we thought that it's important and if there are really neuro-signatures of post-traumatic stress disorders, maybe they will overcome the differences between the study.

(17:34):

Initially, I didn't want of course to get into trouble with anyone else, I would say, especially not with other researchers that are some of the best researchers in my field. But fortunately, when I contacted Dr. Jennifer Stevens, which is the leading author of the previous paper, she was very generous and very supportive of my replication attempt. I must say that she and her team helped me send me their code, their regions of interest, and answered all of my questions. And I think they were genuinely interested in replicating the results and they were very transparent and supportive. And I think this is really setting up an example for other people, and this is the way that science should be, but we know that sometimes it isn't.

Aaron van Dorn (18:29):

You mentioned that there were differences between your dataset and also some differences between methodology, but were there other limitations on your research?

Dr Ziv Ben-Zion (18:35):

I think the main limitations were, as I already noted, differences between the studies that all of those are potential explanations for the inability to replicate. But again, I think that replications and specifically non-exec replications are very important in science. They represent a fundamental part, because they lead us to greater confidence in previous findings. And I think those replications are particularly relevant and important to both neuroimaging studies, because we know they have a large degree of analytical variability. And also for the field of psychiatry, which we know is a very heterogeneous field. And I think it's important to us to conduct replication and non-exec replications also, because we want our findings to be more generalizable to different populations, not only for the specific study and sample and FMRI tasks and people that we chose, we want them to have broader implications.

(19:44):

One other limitation that I can think about, and I think it's a general limitation of replication studies or attempts, is that engaging in replications is often undervalued, because many people and even many journals actually want to publish novel insights or at least to publish successful replications of previous work. And those, when you start a replication attempt, there will be a chance, like in our case, that the results would not replicate, and then it might be conceived as less interesting and it might be harder to publish.

(20:24):

And also, I have to say, it has less direct incentive for researchers. Usually you don't get research grants or money just to conduct a replication. People are trying to look for new things. But nevertheless, I want to state that I'm very happy and proud of this publication. And I'm also thankful for the American Journal of Psychiatry for agreeing to publish a non replication or even selecting to publish a non replication, because I think this sets up an example, and this publication shows that the American Journal of Psychiatry supports transparent research, and this could be a model for others I hope, to declare interest in replications and try to advance that field in that way.

Aaron van Dorn (21:14):

Continuing on with the subject of replication studies, do you think there's a way for researchers to design their studies to make replication studies similar to yours easier? Or does that risk putting a thumb on the scale? To what degree should researchers look at study design with replication in mind?

Dr Ziv Ben-Zion (21:26):

I think the best way for researchers to design their studies is using open science practices, exactly like Dr. Stevens did. And I think people should encourage other individuals to replicate their findings and not to be afraid of the fact that other people would try to replicate or even will fail to replicate. I think the basis for good research is to be open and transparent, to share your data, to share your code, to report all the analysis you have done, all the results you've got, both the significant and the not significant result. This is how science will work, and this is how science makes progress. I think that in general, our field is going for a positive change, and I think open science is growing and growing, but it still has a way to go. And I think researchers should definitely put in their minds the issue of replication even when designing a study, because they should keep in mind that everyone else that would read their paper should be able to understand well enough to replicate, should understand enough in order that you would be able to replicate the study.

(22:50):

Otherwise, it is not very helpful. In the end, we don't rely on one study and go to treat PTSD or any other mental disorder just based on one study. We want to find something that is strong enough that will be replicable and consistent for our different studies. I think even for me personally now, when I design my own studies since this publication, I always think about replication in mind. Again, I want to encourage people to try and replicate my studies. I will be happy if people will attend replication, both if they will succeed or not succeed, because it's important to emphasize that the fact that I did not replicate the findings by Stevens and colleagues, does not mean that their findings are not true or worthless. It could happen the other way around, that I would publish something first and then they would not replicate my study.

(23:50):

And again, I want to thank them for their collaboration. I think Dr. Stevens and all of her colleagues in the AURORA study really showed a great example of how science should be, and without them, it wouldn't be possible to even try this replication. And she and her team were very supportive throughout the whole process and even congratulating me and supporting me when this work was published, which I think is not trivial.

Aaron van Dorn (24:22):

What's next for your research?

Dr Ziv Ben-Zion (24:24):

I'm currently working on several new exciting projects, which I hope you'll be able to see in future publications in the American Journal of Psychiatry. One really exciting project that I'm currently working on is actually a direct result of this non replication work. So we are now collaborating with Dr. Jennifer Stevens and her team and other individuals in the AURORA study, and we are collaborating. We decided to look at both of our data sets together, both from the study of recent trauma survivors conducted in Tel Aviv as part of my PhD and AURORA study that was conducted here in the US, in order to try and find neural signatures that do replicate in both of these cohorts, despite the differences that I've mentioned, the differences in study population, the country of study site, the methodologies.

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So I think this work was first of all, very important for publication and for the general public to see, but also it was really important for me personally and for both of these groups, because now it made more sense to us and it's clear that we should not try and find things separately, but to work together, combine our data sets, and try and really through collaboration and through open size, try to get to some new exciting findings. And as I said before, I think publishing this work also changed the way I look at my own studies and the way I designed them.

(26:09):

Now more than ever, I always have replication in mind. I want other people to be able to try and replicate my work and of course to report whether they were able to replicate it or not. What I'm doing next and what the field should be doing is focusing more on finding more stable and generalizable neuroimaging subtypes or biotypes of psychiatric disorders, because I think we don't want 100 different studies that each one will claim that they found a new biotype of disorder X, but would prefer 100 studies that will try and replicate the same biotypes maybe in different populations with a little bit of different methodologies, with the possibility to identify something which is more stable and generalizable.

(27:05):

And that could actually lead to treatment or even to examine one biotype and see that it does not replicate and then try something new. But again, instead of trying to invent the wheel all over again, and instead of each team working on their own dataset with their own specific method and their own specific population, I think we should try to collaborate more to combine datasets to practice open science, to try replications. And I think this will be the key to really get meaningful insights.

Aaron van Dorn (27:41):

Dr. Ben-Zion, thank you for taking the time to speak with us today.

Dr Ziv Ben-Zion (27:44):

Thank you very much for having me.

Aaron van Dorn (27:46):

Next up, Dr. Ned Kalin. Dr. Kalin, welcome back to AJP audio for February, 2023.

Dr Ned Kalin (27:51):

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

Aaron van Dorn (27:53):

This month's issue looked closely at issues surrounding race related disparities in childhood diversity, trauma and stress related psychopathology. I spoke earlier with Dr. Harnett about the differences in exposure and impact of toxic stress in other forms of adversity in the development of brain structures of black and white children in the United States. What more can you tell us about it?

Dr Ned Kalin (28:08):

This is a very interesting and I think important study, and I'm sure Dr. Harnett reviewed for you some of the important findings, but just to say a few words about this, basically this study demonstrates that the differences in brain structure, that in the past have been sometimes related to race related differences, really are due to differences in adversity that result from the effects of racism and other influences that have put black American children at a disadvantage from the standpoint of their early environment. What this study shows is that there are a number of changes in the thickness of the cortex that are related to early life adversity, and that the reason that black American children have bigger effects is because they have greater levels of adversity. And these, of course can be tied directly to the influences of structural racism and systemic racism, from the standpoint of the early adversity and disparities in early adversity that black American children have and are currently dealing with.

(29:13):

So again, a very important finding and important study pointing us to, I think two important conclusions. One is that we've known all along that adversity early in life has negative impacts on health, on wellbeing and on brain development, and also the impacts of disparities in adversity on brain development playing out in relation to structural racism. And I think this is a real call for psychiatrists to be very explicit about these findings and to force and to get behind changes at a societal level that will tackle and hopefully reduce the structural racism that we currently have in our country and the impacts of that.

Aaron van Dorn (29:57):

We also have a paper from Baldwin and colleagues looking at childhood maltreatment and mental health problems. What can you tell us about that?

Dr Ned Kalin (30:02):

So this paper is related, because it again gets at early adversity. And in this particular paper, the investigators did a meta-analysis using a design that allows you to think about the causal influences of early adversity on the development of psychopathology. And in this case, the researchers, Baldwin et al, were very interested in looking at maltreatment and early abuse in children. And what they found was consistent with what we know, which is that there's no question that early adversity in the form of abuse and neglect results in higher levels of psychopathology. But what also is a bit new here is that when they did this causal analysis, that is, they asked the question, to what extent do these early adverse experiences actually lead to and cause the development of psychopathology?

(30:53):

The effect was much smaller, which is a little bit surprising. So the association between early diversity and the development of psychopathology is high, but the extent to which there's a direct link to causality is lower. And this suggests that there are other factors that are related to early abuse and neglect that may be modulating or modifying this relationship. So an important finding, reiterating for us the need again, to be thinking about early development and improving the environments in which our children live in, and especially in relation to severe trauma in the case of emotional abuse and institutional neglect as examples.

Aaron van Dorn (31:32):

Up next we have a paper from Cleary and colleagues looking at polygenic risk scores and social support and the ability to predict depression under stress.

Dr Ned Kalin (31:38):

This paper is interesting because of the samples that were studied, two different samples were studied. One was doctors who were just doing their first year of internship, and they were assessed throughout the year of internship, which is known to be a very stressful time related to all the things that you can imagine related to being a medical intern. And they also assessed in a separate analysis, a sample of over 400 individuals that were recently widowed, lost their significant other. And what they did is, they looked at the polygenic risk scores for depression in these individuals and asked the question, how does that interact with the levels of social support that they got during these periods of stress? And what they found was a couple things that were not surprising, which I'll mention, and then a really interesting finding out of all this. The not surprising findings were that if you have higher depression and polygenic scores, you're going to be more likely to develop depression in the face of these ongoing sort of persistent types of stressors.

(32:39):

The other thing that was interesting is that during the year of internship for the medical interns, the levels of social support actually decreased, whereas during the period following loss for the individuals that were widowed, the levels of social support actually increased. So that I think is a nice example of how different types of stressors, different populations and different contexts play out in relation to social support. But most interesting, what they found was that if you have a high polygenic risk score for depression, you tend to be more sensitive to the influences of social support, both from the standpoint of whether you have more social support or less social support. So the way this plays out is that if you have a high polygenic risk score for depression and you have low levels of social support, you're more

likely to get depressed. But interestingly, if you have higher levels of social support, you're less likely to get depressed.

(33:32):

And what's interesting about this is that, you might have argued that if you have a high genetic loading for depression, that higher levels of social support would not mitigate the influences of your genes. And this was not found for individuals that have low polygenic risk scores. So the idea here is that if you have high genetic risk for depression, you're more sensitive to social influences in a bidirectional way. This is interesting for the standpoint of thinking about implications from the standpoint of psychosocial interventions in individuals that have higher levels of polygenic risk for depression. And one of the conclusions is the possibility that these individuals would be more sensitive to these types of interventions than individuals who have lower genetic loadings.

Aaron van Dorn (34:15):

Dr. Ben-Zion is another author I spoke with earlier in this episode. He and his colleagues conducted a non-exec replication study of an earlier paper published in AJP by Stevens et al, that aimed to reproduce the results in finding biotypes to guide treatment following trauma. What can you add?

Dr Ned Kalin (34:29):

So this study, as you mentioned already is basically termed a non-exec replication, conceptual non-exec replication by the authors. And what they're basically saying is that they tried to use the same methods in a different sample to attempt to replicate the findings that were published earlier in the AJP in 2021 by Stevens et al. In the Stevens et al paper, the authors basically showed that they could use functional brain assessments using MRI to make predictions about the likelihood of individuals developing PTSD after they were traumatized. This was based on machine learning techniques to use the brain data to come up with what have been termed neuroimaging-based biotypes that then were associated with different types of symptoms. And then, one of which was more predictive of later likelihood of developing PTSD. The Ben-Zion study used a different sample.

(35:26):

It was done in Israel, it was done with individuals that were traumatized mostly from motor vehicle accidents, which was somewhat different than the Stevens et al paper. So the samples were somewhat different, and the imaging tasks that were used also had some differences. Now, what's really, I think, important to emphasize is that the Stevens et al group actually collaborated with Ben-Zion et al from the standpoint of sharing methods and statistical analytics strategies. As an example, I think of a nice way of thinking about how we work together across laboratories in the field to really understand better where the truth lies. The long and the short of it is that the Ben-Zion et al study was not able to fully replicate what the Stevens et al group found, that the Ben-Zion et al group did find some neuro biotypes, some of which were similar to what was reported by Stevens et al, but importantly, what they didn't find was they didn't find that these biotypes were predictive of outcomes in relation to PTSD.

(36:25):

I think the not so good news is that they were unable to replicate these really interesting initial findings, but importantly, I think this is an example of how we need to continue to work together to replicate findings, how we need to think about differences between studies that can explain differences in findings, and also clearly emphasizes we need to do more work in relation to this area as well as other areas when we're thinking about using neuroimaging and neuroimaging biotypes to make predictions about psychiatric illnesses and their treatments.

Aaron van Dorn (36:58):

Finally, we have a paper from Hien and colleagues, a meta-analysis comparing several behavioral and pharmacological therapies for individuals with co-occurring PTSD and alcohol and other substance use disorders. How does that fit into the issue?

Dr Ned Kalin (37:08):

So this again gets at the stress related kinds of ideas that are in this issue. This is a meta-analysis of a large group of, I think over 4,000 individuals that have PTSD or PTSD with sub-threshold symptoms, and also have alcohol use disorder or some other substance use disorder. Importantly, PTSD is highly comorbid with alcohol and other substance use disorders. And the purpose of this meta-analysis by Hien et al published in the journal, was to try to better understand which treatments are most effective for individuals that suffer from both PTSD and alcohol use disorder or other substance use disorders. And what they did here is, they used a method that they termed a virtual clinical trial where, and I won't go into the details by using some statistical methods, they tried to compare across very, very different studies and different patient populations to come up with conclusions about comparative efficacy of different treatments.

(38:08):

Basically, what they found, I think is affirming and not surprising, but important to know. What they found was that in relation to PTSD symptoms, the best treatments appeared to be were trauma focused therapies, along with other pharmacotherapy aimed at the alcohol or drug use issue that the individual had. And likewise for individuals that had for alcohol related symptoms, the best treatments were, again, trauma-focused therapy combined with, in this case, alcohol related pharmacotherapy. The conclusion is that, what works best is targeted evidence-based treatments for the two comorbid conditions. Again, not surprising, but I think important to confirm, because there's so many different treatments out there and combinations of treatments that haven't been really studied head-to-head, and this meta-analysis using this strategy of a virtual clinical trial allows us to begin to compare across these studies and ask the question, what's going to be the most effective treatment?

Aaron van Dorn (39:12):

Well Dr. Kalin, thank you once again for taking the time to speak with us today.

Dr Ned Kalin (39:15):

You're very welcome and it's good to be with you. Thank you.

Aaron van Dorn (39:17):

That's all for this month's supersized episode of AJP Audio. But be sure to check out the other podcasts from the APA. This month on Psychiatric Services from Pages to Practice, Dr. Dixon and Dr. Bearson spoke with Navdeep Kaur about racial and ethnic disparities and mental health treatment in the US since 2005. The views and opinions expressed in this podcast are those of the individual speakers only and do not necessarily represent those of the American Psychiatric Association. The content of this podcast is provided for general information purposes only and does not offer medical or any other type of professional advice. If you're having a medical emergency, please contact your local emergency response number.