Aaron Van Dorn (00:07):

Welcome to AJP Audio for October 2023, I'm Aaron Van Dorn. Dr. Luis Farhat and Dr. Guilherme V. Polanczyk, both in the Department of Psychiatry at the University of Sao Paulo in Brazil, are authors on a study looking at how the impact of socio-environmental factors, emotional dysregulation and other factors impact neurodevelopment in children. Following that, I'll once again speak with Dr. Ned Kalin, editor-in-chief of the American Journal of Psychiatry, about what else you can find in the October issue of the journal. I hope you'll give it a listen.

(00:32):

Dr. Farhat, past studies have identified multiple associations with neurodevelopmental traits such as ADHD, Autism spectrum disorder, its socio-environmental stressors with depression in children, adolescents, and young adults. However, many neurodevelopmental traits are highly correlated with each other and looking at any one trait in isolation could confound other associations. Your study aimed to untangle some of these associations and lead the way in taking them into account. What did you find?

Dr. Farhat (00:54):

Thanks for your question, Aaron. Yes. Several studies have looked at this question previously and the sort of hyper-typic trajectory in which individuals with neurodevelopmental disorders, or if we look at the general population considering neurodevelopmental traits, are linked with the development and the occurrence of depression and depressive symptoms over the long term. So this is relatively well established, but as you noted very well, usually neurodevelopmental disorders and neurodevelopmental traits in the general population tend to occur. When we looked at several neurodevelopmental traits simultaneously, as well as co-occurring difficulties that often occur in the context of neurodevelopmental difficulties, we found that first, because we know these traits are highly correlated with each other, simply focusing on one and not looking at the others is not ideal and leaves a little bit of room for improvement. And second, neurodevelopmental traits and difficulties are usually associated with socio-environmental factors that could also contribute to the development of depression.

(02:05):

So kids who have ADHD also have trouble with their peers. They may do worse at school, and usually as they grow older, they start to notice they are lagging behind their peers. And this may contribute to the development of depressive symptoms and depression. And this, although we didn't look at the sample of clinical cases and we are focusing on general population, this is what we somewhat expect as well, considering ADHD symptoms or autistic symptoms in the general population. So what our study adds is exactly by using network analysis, which is a tool that sort of maps out how different symptoms are associated with each other after accounting for the other symptoms in the model. Our study adds to this discussion by showing that while neurodevelopmental traits may be associated with depressive symptoms across development, disassociation could be explained by the socio-environmental difficulties, such as having problems with peers and emotional dysregulation. It's a finding that could have potential clinical implications, as I'm sure we'll talk about a bit later.

Aaron Van Dorn (03:22):

What kind of comorbidities and associations did you see?

Dr. Farhat (03:24):

Yes, so we looked at ADHD, we looked at a broadly defined neurodevelopmental traits following the neurodevelopmental disorder definition by the DSM and the American Psychiatric Association. So we looked at ADHD, autism, general cognitive performance correlate for intellectual ability, and we also looked at communication and learning abilities. For the co-occurring difficulties, we examined having trouble with peers, having difficulty at school, and we also looked at emotional dysregulation, which is a very broad concept, but could be perceived as a general difficulty to regulate affect, behavior, and sort of cognition. Of course, we looked at the depressive symptoms across the development. So while these factors were mostly neurodevelopmental and social factors were mostly constrained in childhood, we also wanted to look at depression across the development. So not only focusing on childhood, but also looking at adolescence and young adulthood because usually emotional problems and emotional depressive symptoms can appear more often in adulthood than necessarily in childhood. So we also wanted to examine that time span.

Aaron Van Dorn (04:47):

Your study looked at two UK-based cohorts, the Twins Early Development Study, and the Avon Longitudinal Study of Parents and Children, both large population-based datasets. Why did you choose to look at these datasets in particular, and what did looking at the two together tell you?

Dr. Farhat (05:00):

There is a reason why we chose the two cohorts. Definitely there are more research accessibility related factors in that the TEDS dataset, at least, is more open to collaborations. The ALSPAC dataset is also open to collaborations. It does require a fee, but we had collaborators that had access to that data, so we had the capability of accessing those cohorts. But they also offer a very unique perspective to this point because we are estimating several small associations simultaneously. And when you're doing that, you usually need very large number of individuals, and the clinical cohorts all be possibly more interesting from clinical psychiatric point of view. They usually have much smaller numbers, and this would preclude our approach to estimate so many associations simultaneously. So the general population cohorts were chosen for that reason. And of course these neurodevelopmental difficulties are distributed across the population, so they also offer potential to examine neurodevelopmental processes, or at least neurodevelopmental symptoms. And not only focusing on the clinical side, but also looking at how things happen in the population, broadly speaking.

Dr. Guilherme V. Polanczyk (06:24):

And in these two cohorts, the TEDS study and the ALSPAC study, besides having wonderful collaborations, there are researchers in these two studies, we have very rich measures that are present in these cohorts across development from ages seven to the twenties. And what is very interesting is that we found very similar measures across these two cohorts. So we have harmonized measures, and then in this way we were able to replicate what we found in one cohort in the other cohort as well. So this is really important and gives us more confidence in our results.

Dr. Farhat (07:13):

And this is a great point from Guilherme because these models we estimated are somewhat exploratory. So having the two cohorts gives us a little bit more confidence in what we're finding. And reproducibility is a big thing and replicability is a big thing in our fields, so it was good to get that done.

Aaron Van Dorn (07:33):

What were the limitations of your study?

Dr. Farhat (07:35):

So first limitation, right off the bat, is this is a general population sample. So whether these findings that we are reporting, how much they extend to clinical samples, it's a little bit unclear. As I said, general population cities with neurodevelopmental traits are relatively common and we believe they all extend to the general population, but that needs additional replication in clinical samples. That being stated, our study sort of provides a nice hypothesis that can be tested in more limited sample sizes from clinical population. We also have a lot of trouble with measures. Sorry, maybe Guilherme you were going to say something?

Dr. Guilherme V. Polanczyk (08:16):

I would say that although we have several measures of neurodevelopmental traits and all sorts of socio-environmental stressors, it is possible that there are others that we haven't measured, although we understand that the most important ones are considered here.

Dr. Farhat (08:34):

This is a usual problem we have with these large cohort studies because usually the measures are more broad and try to capture, not in this specific, but more like there may be other instruments that would be used in clinical practice that we aren't using here because of the fact that this is done in a scale of a large study with thousands of participants and they're being followed up over time, multiple times, so they provide several waves of data. So for instance, I think there has been quite some debate on the autism and the autistic symptoms, how much they really reflect, specifically autistic symptoms. And we did have an interesting finding with a general cognitive ability that we didn't find an association between them. So that wasn't expected, and maybe explained possibly because of the measures we had.

Aaron Van Dorn (09:29):

Are there immediate clinical implications for your research?

Dr. Guilherme V. Polanczyk (09:32):

I think this study has a very interesting, in fact, clinical implication. We are demonstrating here that emotional dysregulation and stressors in childhood are the ones that probably are most related to depression over time. So of course, we always think that how can we help these children? How can we prevent the depression over time? So one clinical implication in this way would be to intervene in these symptoms as they appear in childhood. So irritability and emotional dysregulation are already understood as target of treatments at this age, but maybe this is something that we should consider even more now that we understand that they are in the origins of depression over time.

Dr. Farhat (10:27):

And there has been some interesting open-label randomized trials, or actually uncontrolled trials. Nonetheless, they showed that psychotherapy programs focused on family relationships and emotional dysregulation could be promising approach to reduce depressive symptoms in youth with ADHD across a relatively okay time of follow-up. So it's an interesting approach that maybe should be examined further in ADHD and also other neurodevelopmental disorders.

Dr. Guilherme V. Polanczyk (11:01):

I also think that when we emphasize that all these traits are correlated between them, and when we actually do our best to include all possible traits in our model to understand the independent association with depression, I understand that in this way we are sending the message to clinicians that they have to always see the patient and see the children in a broad perspective and try to understand, not only the reason, because the families bringing the children to clinical attention, but all other possible traits and conditions that are associated at that point in time.

Aaron Van Dorn (11:47):

What's next for your research?

Dr. Farhat (11:48):

We're a group that does a lot of clinically oriented, I guess, research focused on neurodevelopmental disorders. We have different studies in the pipeline, mostly focused on ADHD. Guilherme also does great work with early infancy and child's development, normative development. At the moment, I don't know if we have any direct developments from this specific paper. I'm curious if Guilherme has any different thoughts on this.

Dr. Guilherme V. Polanczyk (12:20):

The relationship between depression and neurodevelopmental conditions disorders is a very important one. And as our patients and our cohorts mature, we can see how important depression it is for their development and for their quality of life and so on. So this is really a point that Luis is interested, and we are all interested in that. So understanding more of that is definitely a target and a name to our group.

Dr. Farhat (12:58):

It'll be interesting to see if we can continue collaborating. Here in Brazil with other investigators, but also abroad, in terms of trying to figure out a little bit further about the occurrence of depression in this context, for sure.

Aaron Van Dorn (13:13):

Dr. Farhat, Dr. Polanczyk, thank you for taking the time to speak with us today.

Dr. Farhat (13:16):

Thank you so much.

Dr. Guilherme V. Polanczyk (13:17):

Thank you.

Aaron Van Dorn (13:18):

Up next, Dr. Ned Kalin.

(13:20):

Dr. Kalin, welcome back to AJP Audio for October, 2023.

Dr. Ned Kalin (13:23):

Thank you, Aaron. It's a pleasure to be here.

Aaron Van Dorn (13:25):

Earlier in this episode, I spoke with Drs. Farhat and Polanczyk about their paper looking at the association between neurodevelopmental traits, socio-environmental stressors and emotional dysregulation in childhood. Let's begin there.

Dr. Ned Kalin (13:35):

Yes, thank you. So this issue of the journal has a lot of really interesting papers that are related to stress, heritability and genetic factors that influence development, depression, PTSD and suicidal behavior. And this particular paper is interesting because it gets at the early life antecedents of potentially depressive symptoms in children. And basically what this study does, is it looks at how a variety of early traits, that children come into the world with, are related to the later development of symptoms associated with depression. And so what the investigators did, as I'm sure they discussed with you, is they looked at a couple of samples of children. One was a sample of twins, Twin Development Study, which involved about 4,000 twins. And the other was a study of parents and children that involved about 10,000 individuals. And what they looked at were early neurodevelopmental traits, traits that were reflective of ADHD types of symptoms, autism spectrum disorder, intellectual issues, and disability and communication and learning disorders.

(14:50):

They also look at two socio-environmental stressors and measures of emotional dysregulation, which were collected a little bit later. And what they found was that, and as expected, that the neurodevelopmental measures, the trait measures, were predictive of individual differences in the magnitude of depression as children mature. So this was sort of a known phenomena and they found that, but the important thing that they also found was that when they took into consideration the effects of stress and also the emotionality and how individuals the children accumulated their emotions, this association between neurodevelopmental traits and later depressive symptoms went away.

Aaron Van Dorn (15:31):

Up next we have a paper from LOU and colleagues looking at the genetic contribution to the heterogeneity of major depressive disorder.

Dr. Ned Kalin (15:37):

So this is also a very interesting study because this study uses an extremely large sample to try to understand more about whether the different presentations of major depression have similar or different levels of heritability. This is a study that was done with a Swedish registry, a very large sample that caps into over a million and a half individuals. And this particular sample that was used, from that larger sample, from the Swedish registry, over 400,000 sibling pairs were used. Of those 400,000 pairs, about 46,000 individuals or roughly 10%, had a diagnosis of major depression. And then what they did is they looked at what they called the different types of major depression. They divided the major depression into a lot of different subgroups. This is DSM-5, but this is how they did it. They look at such factors as the severity of depression, the number of occurrences, the other comorbidities, whether or not the depression was accompanied by suicidality, how early the individual first got the diagnosis of depression and how impaired the individual was.

(16:44):

And what they found was that for these different subtypes, they could estimate heritability because of using this family tree from the SID pairs, they found that there was a range of heritability, ranging all the way from 30% almost up to 58%.

(16:59):

And more importantly, what they found was that the higher her abilities were found for the major depression subgroups that were characterized by having higher levels of disability, and the children and those that had the early childhood or earlier onset, these her abilities were round in the 50%/ the lowest heritability, interesting enough, and not surprising when you think about it, were subgroups that were characterized by only having a single episode of depression, no comorbidity with anxiety disorders, and no comorbidity with other psychiatric disorders. So the less complicated depressions were associated with lower heritability than 30%. They also did an analysis where you can look at shared genetics or co-heritability, and they found that there was a large range across these different subtypes suggesting that some of the subtypes shared genetics and others had differential genetics. So this begins to give us some insight into the different presentations of depression, suggesting that these different presentations likely run in families and that they seem to be somewhat heritable.

Aaron Van Dorn (18:02):

Following that, we have a paper from Dr. D and colleagues, a GWAS study looking at a number of genome-wide loci associated with suicide attempts. What can you tell us about that?

Dr. Ned Kalin (18:10):

This is an important study. It's the study using the largest database now, to look at, basically, suicide attempts. The two samples that were used were the Million Veterans Program and also the International Genetic Suicide Consortium. The total combined sample, as I mentioned, was the largest ever that was analyzed. There were previous analyses of these separate data sets, but this was done together. There were roughly 43,000 individuals that had made suicide attempts in this sample and about over 900,000 controls that were used. Now, one of the really important features of this study is that there were enough multi-ancestry individuals that they could do analyses in subgroups, including individuals that had an African-American ancestry, those that had East Asian ancestry, those of Hispanic Latino ancestry as well. What they found was that in this sample of 43,000 individuals that made suicide attempts, there were actually 13% of these individuals actually died by suicide.

[NEW_PARAGRAPH]By looking at the GWAS for suicide attempts, they found eight significant loci or SNPs, single nuclear polymorphisms. They also found some specific findings related to the ancestry analyses, and actually found that more of the heritability could be accounted for by using the African-American sample than just using the entire sample. So this then gives us more insight into the specific genes that may be involved in suicide attempts. It also is noteworthy again, as I said, because it's not only the largest analysis that's been done, but it also has the highest percentage of individuals from African ancestry and Hispanic ancestry and Asian ancestry, allowing us to have greater insights into the [inaudible 00:20:08] of the findings from our GWAS studies, which have mostly been done in individuals with European ancestry.

Aaron Van Dorn (20:13):

Next, we have a paper from Chatzinakos and colleagues looking at gene expression and PTSD stress response.

Dr. Ned Kalin (20:18):

So this is a paper that takes advantage of post-mortem samples, from post-mortem brain banks, to analyze RNA in the dorsolateral prefrontal cortex of individuals that died, who had histories of PTSD and those that had histories of major depression. What this allows for then is an in-depth look, at a cellular level of gene alterations that may be occurring in the dorsolateral prefrontal cortex of these individuals. The reason the investigators chose to look at major depression and PTSD is because these are related illnesses, but they're also different. Both are related to stressors and both are also related to changes in physiology, some of which is shared and some of which is not. For example, the pituitary adrenal system, which is a stress related system that results in the release of cortisol is overactive in depression and appears to be blunted in individuals with PTSD. Now, the other thing that's really exciting about this study is that it used cutting edge techniques, including what we call single nuclear RNA sequencing.

(21:27):

I won't get into the details of this, but this allows the investigators to look at differential gene expression in single cells and to identify which cell types in the brain may be altered from the perspective of gene expression. So it's a complicated study from the standpoint of the methods, but the findings suggest that the expression of different genes is altered between PTSD and the individuals in a way that is interesting, and this particularly involves gene expression in expiratory and inhibitory neurons. And also they found some interesting finding in astrocytes as well.

(22:05):

The other finding that was important was they found that the genes in the stress-related glucocorticoid, or cortisol signaling pathway, were significantly enriched for individuals with PTSD, as far as their expression goes, but not so for individuals with major depression. And they also did some work using stem cells, where they showed that the pattern of changes that they saw in the PTSD patients were also similar to what happens in vitro, or in a test tube, in a sense, if neurons that are derived from stem cells are treated with high doses of a glucocorticoid like dexamethasone, further drawing similarities between alterations in this particular pathway and individuals with PTSD.

(22:52):

Now, the other finding that's interesting is that one of the gene regions that look to be involved was for the gene corticotropin-releasing hormone receptor one, and this is a gene that has for a long time implicated in stress responses for sure, and also in psychopathology, such as depression and stress-related psychopathology. And this looked to be also involved perhaps in PTSD.

(23:15):

So what these studies do is they now get us down to the cellular level in the dorsolateral prefrontal cortex. The reason the investigators thought that was interesting is because that's a region where there's a lot of emotion, cognitive interface, and regulation of emotions and thinking has been implicated in altered function across various psychiatric disorders including PTSD and depression. And now at the cellular level, in specific cells believe, as the investigators are demonstrating, that we can identify alterations in how genes are working and that there are some areas that may be shared across MDD and PTSD, but also some distinct differences which shed light into the molecular underpinnings of these illnesses, how they're similar, how they may differ, and also begins to give us ideas about gene-related targets for thinking about the treatment of these illnesses.

Aaron Van Dorn (24:01):

Finally, we have a paper for Marr et al. It looks at the perinatal stress and its impact on the development of the amygdala in children.

Dr. Ned Kalin (24:06):

So this study gets back to development, like the earlier study we talked about. This involves two cohorts of mother-infant pairs, where the investigators tracked depressive symptoms and stress and anxiety, prenatally in pregnant women, as well as postnatally for a period of time about one month after pregnancy in moms. And looking now at how the baby's developed, from the standpoint of their negative affect and also their amygdala function, which is, as we've discussed many times, an area of the brain, deep in the brain and the temporal lobe, that is very involved with the fear response and anxiety and the modulation of emotional responses. So what these investigators did by tracking longitudinally these symptoms and stress, they basically were able to demonstrate that there are different patterns of exposure to stress over pregnancy that are related to outcomes in infants. And it turns out that it wasn't so much the magnitude of stress that a mother faced, that is the total amount of stress, but rather the pattern of stress over the pregnancy that looked to be important.

(25:22):

And what they found was is that there was one particular trajectory of stress and depressive systems and anxiety that looked to be important. And this was characterized by having production in that stress score in the middle of pregnancy, and then an increase late during gestation, towards the end of pregnancy. And in this particular group, what they found was is that there was an alteration in the development of the infants who came from these moms, from the point of their negative affect in a way that differed from the other groups. And what they found was, is that there was sort of a blunting or a flattening of the typical negative affect curve, growth curve, and infant from the age of 12 to 24 months. Now, it's hard to know exactly what this means, but the authors of this paper argue that that alteration in the normal development of negative affect may be related to some difficulties in infants acquiring emotion regulation strategies as they develop.

(26:21):

Now, this is complete speculation, so it needs to be taken with a grain of salt. Nonetheless, this particular trajectory of stress experienced during pregnancy seems to be related to this development of negative affect in infants. And then in this subgroup of infants, 60 of the infants from one of the cohorts, they had resting state functional connectivity measures collected with MRI in these children that were done at approximately one year of age. And they found that in a number of the children there was increased amygdala connectivity with a variety of regions, including the ventromedial prefrontal cortex in the anterior insula. This is interesting because this is a circuit that is likely very much involved with emotion regulation and emotional development. So this is beginning now, to give us some insights into the timing and pattern of stress and experience of stress that moms, or pregnant women are exposed to over the pregnancy, suggesting that different patterns of stress exposure may be related to different outcomes in infants, as far as their negative affect development goes.

(27:31):

And this also may be related to different patterns of development, of connectivity or function of the amygdala, which may be underlying the development of negative affect. Now, again, I'm using the word maybe because these are all inferences that have not been established, but are suggested by this work. Nonetheless, the two papers on development in this issue, which are fairly complicated, provide models of how to think about the development of negative affect and depressive symptoms in children and how this relates to early life factors, whether it's, in the first study we talked about, the traits and stress that an infant is exposed to, or whether it's the stress that a mom is exposed to and the trajectory of that stress over a pregnancy.

Aaron Van Dorn (28:16):

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

Dr. Ned Kalin (28:18):

You're welcome. It's a pleasure.

Aaron Van Dorn (28:19):

That's all for AJP Audio for this month. But be sure to check out our other podcasts offered by the APA, including Psychiatric Services from Pages to Practice, Psychiatry Unbound, and others at psychiatryonline.org/podcasts or wherever you get podcasts.

Speaker 5 (28:33):

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