Aaron van Dorn (00:00):

Welcome to AJP audio for August 2022. I'm Aaron van Dorn. This month on the podcast I spoke with Dr. Mark Shen, an associate professor of psychiatry at the University of Carolina at Chapel Hill and a researcher at the Carolina Institute for Developmental Disabilities. Dr. Shen and colleagues looked at the neurodevelopmental patterns in infants at risk for autism spectrum disorder, along with infants with fragile X syndrome. Through longitudal imaging between six and 24 months, the researchers looked at subcortical brain development to see what differentiated the two conditions, and whether infants at risk for ASD showed unusual brain development prior to the onset of clinical symptoms and ASD diagnosis. Afterwards, I'll speak with American Journal of Psychiatry editor in chief, Dr. Ned Kalin, on this paper and the rest of the August issue of AJP, which focuses on neurodevelopmental and neurodegenerative conditions.

Aaron van Dorn (00:49):

Dr. Shen, you looked at a longitudinal cohort of infants from six to 24 months, some with diagnosises for fragile X syndrome, infants with high likelihood for autism spectrum disorder who were either later diagnosed with autism spectrum disorder or who were not, as well as control patients. What did you find?

Dr. Mark Shen (01:03):

So we found four primary findings. One is when you look at the cognitive development or the behavioral development of these babies, we found important differences between the babies with fragile X syndrome and the babies who would eventually get an autism diagnosis. That is that really at the earliest age that we studied, at six months of age, the babies with fragile X syndrome already showed cognitive deficits, and those cognitive differences were maintained in fragile X through six, 12, and 24 months of age. Wherein autism, or the babies who would eventually get an autism diagnosis, they showed a different pattern of cognitive ability, which was that at six months of age their cognitive levels were relatively typical compared to controls. But between six and 12 months of age, there was a slowing of cognitive ability in autism, so that by 12 months infants who later developed autism had lower cognitive ability compared to those what typical development.

Dr. Mark Shen (02:02):

And so even just when we look at behaviorally, we're seeing a difference in the development of fragile X and in autism. And that behavioral development really actually mirrored what we found in the brain. So for example, in autism, the amygdala was typically sized at six months of age, but in babies who developed autism between six and 12 months, there was this rapid growth of the amygdala compared to controls, such that by 12 months of age the amygdala was too large in those babies who developed autism and that enlargement was maintained through 24 months of age. We found that brain growth pattern of the amygdala may be unique to autism, because babies with fragile X syndrome show a completely different trajectory of brain development, similar to their different trajectory in behavioral development. So babies with fragile X syndrome showed no differences in amygdala growth compared to controls, but they showed enlargement of a different brain structure called the caudate . And that enlargement of the caudate was found at all the time periods in infancy from six to 24 months of age. So that was the third major finding.

Dr. Mark Shen (03:18):

The fourth was that the babies who developed autism and the babies with fragile X syndrome also had distinct behavioral associations with their brain growth patterns. So for example, in autism, we found that the faster that the amygdala grew in infancy, the more social difficulties the child with autism showed when they were diagnosed with autism a year later. And in fragile X syndrome, we showed that the enlargement of the caudate was associated with a different behavior, increased repetitive behaviors. And so, together what this shows is that babies with fragile X syndrome and babies who develop autism really show this unique and distinct brain growth patterns that mirror different associations with behavior, and this double dissociation between autism and fragile X really shows that these babies are developing differently, both in brain and behavior.

Aaron van Dorn (04:20):

Why did you choose to look at patients with potential ASD diagnosis in conjunction with patients with fragile X syndrome?

Dr. Mark Shen (04:26):

So most brain imaging studies in autism compare children with autism to those with typical development. And one of the novel parts of this study is that we ask the question when brain development in autism deviates from typical development, like in other brain imaging studies, our study asked, well, is that specific to autism or is it present in other neurodevelopmental disorders like fragile X syndrome? So I believe this is the first MRI study to do this, at least in infancy.

Dr. Mark Shen (04:59):

We included a fourth group of babies, babies with fragile X syndrome, which is a genetic condition that has been long associated with autism and shares some behavioral characteristics as autism. As I mentioned, we found that MRI can differentiate between autism and fragile X in infancy, and each of those show distinct brain growth patterns. And I think this is important because as we start moving towards developing, hopefully, targeted and more individualized therapies, we need to be able to understand what brain growth patterns are really unique to autism. And one of the ways that our group has approached that is by doing a heads up comparison with other related conditions like fragile X syndrome.

Aaron van Dorn (05:46):

As you mentioned, your study found that patients with a high likelihood for ASD had significantly larger amygdala volume compared with other groups, including those with fragile X syndrome. Similarly, the fragile X syndrome group had a larger caudate volume than other studied groups, including those with a high likelihood for ASD. Why are those findings important?

Dr. Mark Shen (06:02):

So these subcortical brain regions, like the amygdala and the caudate, are among the first in the brain to develop and are highly involved in the development of both autism and fragile X. The amygdala is highly involved in social behavior, and has been the focus of many previous studies of autism. For example, it's been long known that the amygdala is abnormally large in school-aged children with autism after they've already received an autism diagnosis. So our study sought to answer several questions. One, when does the amygdala start its overgrowth? Two, does overgrowth occur at an age before behavioral symptoms and before an autism diagnosis? Three does amygdala overgrowth have clinically significant consequences? And finally, is amygdala overgrowth unique to autism?

Dr. Mark Shen (06:58):

And so, as I mentioned, the way that we answered those questions was that, one, the amygdala starts its overgrowth precisely at a time between six and 12 months of age. And that overgrowth occurs before the hallmark diagnostic symptoms of autism are present and before autism diagnosis. We did find that this amygdala overgrowth does have clinically significant relationships because it is related to social deficits a year later, and we did find that amygdala overgrowth is unique to autism because we did not find it in babies with fragile X syndrome. Collectively, these results show an interesting pattern of timing in brain and behavioral development. In fragile X syndrome, brain and behavioral differences are exhibited early in life. Already, by six months of age, their caudate is too large and they show cognitive deficits. Whereas in autism, at six months of age, the amygdala is typical in size and there are typical levels of cognitive ability. But then in autism, there is this cascade of changes that occur between six and 12 months of age. During this period, the amygdala grows too rapidly, and between six and 12 months of age is when cognitive delays begin.

Aaron van Dorn (08:16):

Behavior's characteristic of autism spectrum disorder often don't begin to emerge until after 24 months of age, as you mentioned earlier, what would be the advantage of earlier detection of potential autism spectrum disorder diagnosis?

Dr. Mark Shen (08:27):

So the current study is actually one of several findings from our research group, that there are brain differences that are detectable by MRI in the first year of life in infants who will later be diagnosed with autism. And this period of time in the first year of life is what we're referring to as a "presymptomatic period in autism". So it's prior to the age when the diagnostic behavioral symptoms of autism, like social difficulties, are fully evident and then lead to the later diagnosis of autism. So currently, 24 months is generally the earliest that autism is diagnosed. Actually, in the United States, the average age of autism diagnosis is not until four years of age. So if we can detect risk of an autism diagnosis earlier, during infancy for example, then we could intervene earlier and give clinicians a possibly two to three year head start on providing behavioral supports to these children. The research is becoming very clear that the earlier you treat the better the long term outcomes are for the individual, really much like any medical diagnosis or behavioral diagnosis. So that's what largely motivates our work.

Aaron van Dorn (09:48):

What's next for your research? Are there clinical implications for your findings at the moment?

Dr. Mark Shen (09:52):

Well, the first step is to replicate these results. Any novel finding really warrants replication, and we are going through the steps to conduct the studies to replicate these results. So my lab has NIH funding to enroll babies with fragile X syndrome right now at the University of North Carolina, and we are acquiring brain MRIs in babies with fragile X longitudinally at the same time points as the study that we just published. We are doing the same in babies at high familial likelihood for autism, so those are babies with an older sibling who has already been diagnosed, and that is a nationwide network called the Infant Brain Imaging Study, or IBIS, where there are five universities spread across the United States where we're enrolling these babies, and the goal is to see if we can replicate all of these findings that show that there are brain differences that can be detectable with MRI in the first year of life in babies with autism that are distinct from the brain differences we're finding in babies with fragile X syndrome.

Dr. Mark Shen (10:59):

But if these results replicate it points to greater evidence that MRI could be used as an additional tool in the tool belt to detect autism risk in the first year of life. Infancy could be an optimal time to begin supports for children who are at the highest likelihood of developing autism in the first year of life so that we can improve early precursors or antecedents of social development, such as improving sensory processing, in those babies, possibly even before those social difficulties arise, and then ultimately improve the long term outcomes for those individuals and improve quality of life.

Aaron van Dorn (11:41):

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

Dr. Mark Shen (11:44):

Thank you so much. I appreciate the invitation.

Aaron van Dorn (11:46):

Up next, Dr. Ned Kalin.

Aaron van Dorn (11:48):

Dr. Kalin, welcome back to AJP audio for August 2022.

Dr. Ned Kalin (11:51):

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

Aaron van Dorn (11:52):

This month's issue of AJP looks at a number of articles focused on neurodevelopmental and neurodegenerative illnesses, including autism fragile X disorder or dementia. Earlier in this episode, I spoke with Dr. Mark Shen about his study looking at the development of the brain in children at high risk for autism spectrum disorder prior to when ASD is usually detected. What can you tell us about that article?

Dr. Ned Kalin (12:10):

Well, this is a really very interesting article and potentially important paper, Aaron, because this study follows children from a very early age of life beginning at six months of age, and then longitudinally doing brain scans at 12 months and 24 months to understand the development of brain systems that are part and parcel of the development of autism spectrum disorder. And also the authors compare this to the development of brain systems in relation to fragile X syndrome, which is a different neurodevelopmental disorder, has different genetics, but also shares some features from the standpoint of social deficits, intellectual impairments, and even some autistic features.

Dr. Ned Kalin (12:56):

What the researchers were particularly interested in, in relation to autism, was the development of the amygdala. And the reason that's important is because the amygdala has a lot to do with fear and anxiety processing, reactivity to stress, and also social interactions and social anxiety, all of which can be

enhanced in individuals that have autism. It's well known and very well established that individuals with autism have very high levels of comorbid anxiety types of problems.

Dr. Ned Kalin (13:25):

Basically, what these researchers found was that there are differences in the development and the growth of the amygdala that were associated with autism and autism spectrum disorder, and this was in the children who are at risk that actually went on to develop autism spectrum disorder. And what was most important is that these more rapid growth rates of the amygdala could be detected prior to the onset of significant symptoms. And so in relation to autism, this suggests that one could identify individuals where this pattern of development of the amygdala is aberrant early in life, and then having more of an understanding of their likelihood of developing the actual syndrome, and also thinking about ways to intervene in life to modulate the development of the amygdala in ways that might have a positive effect for the outcome for people that have this risk to develop autism spectrum disorder.

Dr. Ned Kalin (14:24):

Interestingly, what they found was that this was not the case for fragile X syndrome. Fragile X syndrome individuals, when they were studied early in life, had a very different pattern of altered brain development, and this actually involved other brain regions, including the caudate and the basal ganglia. And so while they didn't show the abnormality in amygdala development, they showed an abnormality in another brain region, and both of these abnormalities were also predictive of individual differences in symptoms. And so for the ASD kids, the autism spectrum disorder kids, greater alterations in this development of the amygdala were associated with more social deficits later on. And in relation to the fragile X kids, greater alterations in the development of the caudate, or the caudate volume, at 12 months of age was predictive of greater numbers of repetitive and stereotypical types of behaviors.

Aaron van Dorn (15:21):

Along the lines of infant brain development, there's also a paper by Girault and colleagues that was looking at infant brain development in autism spectrum disorder. What did that paper find and how does it differ from Shen and company?

Dr. Ned Kalin (15:31):

So this is a related paper. It also gets at looking early in life at brain development in children with autism spectrum disorder. Also, interestingly enough, using the same data from the same sample, it's called the Infant Brain Imaging Study Network. These researchers were particularly interested in trying to understand how the heritable risk to develop autism manifests early in life in the brain. They are also interested in brain regions that have to do with visual processing, because visual processing has been identified to be involved with some of the features and symptoms that autism spectrum disorder children have, especially in relation, again, to some of the social types of deficits that are found in kids with autism spectrum disorder. So the authors of this paper had a unique design. What they did is they looked at sibling pairs, of which the older member of the pair definitely had autism and the younger member was at risk because of the familial nature of autism, and then they followed these children, at risk children over 24 months, and established which subsets actually developed autism and which didn't.

Dr. Ned Kalin (16:47):

What they did was they looked at the symptoms in the older sib that had autism and asked how are those symptoms, if at all, related to brain development, or brain alterations in the younger sib that was

either at risk to develop autism or actually developed autism. And so it's a very unique design, and this was their attempt to get at the heritable nature of the brain alterations with the idea being that the sibs that are concordant for autism spectrum disorder would be more likely to share brain abnormalities and have relations that cut across these two children from the standpoint of brain predicting behavior. And so the analyses that they did was they asked the question whether or not they could use brain alterations in the younger sib to predict behavioral alterations in the older sib. And so it's a bit of a complicated design, but a very interesting one.

Dr. Ned Kalin (17:40):

And what they found, basically, was that the younger sibs that went on to develop autism spectrum disorders, so the dyads of siblings that were concordant for autism spectrum disorder, this prediction could be made. And so, basically, what they found was is that, for example, in area the brain, the occipital cortical regions and also the part of the corpus callosum, where there was alterations in volume of those structures and the integrity of those structures, that that was predictive then of behavioral symptoms or emotional symptoms in the older sib. So a very interesting finding suggesting that these alterations in brain may actually be heritable because of their linkage within the family in relation to the dyadic pair that are concordant for autism spectrum disorder.

Dr. Ned Kalin (18:30):

So both of these papers taken together bring us to a better understanding of the very early alterations in brain function and structure, mostly structure in this case, that are identifiable in children that are either at risk or who will develop autism spectrum disorder, shedding light a bit onto the heritability of this, as well as, most importantly, allowing us to think about very early identification of brain systems that may have altered development that are associated with specific symptom patterns that could be early life intervention targets.

Aaron van Dorn (19:04):

Moving away from infants to the other end of the life spectrum, a paper by Gerlach and colleagues looked at the effort to reduce the use of antipsychotics and dementia treatment in VA nursing homes. What did they find?

Dr. Ned Kalin (19:13):

In the journal, in this issue, we have free papers that are related to dementia. One is the overview by Dilip Jeste on the management of the neuropsychiatric associated symptoms related to dementia. And then we have this paper and he had another paper, which we can talk about in a few moments, but in this particular paper, this was a survey looking at VA population that has dementia. And the survey was done over a period from 2009 to 2018. And the question that was asked was whether or not over this time period there was a reduction in the use of antipsychotics to treat the behavioral alterations that are associated with dementia in patients that suffer from neurodegenerative types of problems.

Dr. Ned Kalin (20:01):

The reason that this is of interest is because the VA and others have been suggesting that it's important to not overuse antipsychotics in this population. There are concerns about antipsychotic medications impairing function from the standpoint of their sedating aspects, and importantly, earlier work suggesting a small but real increased risk in the likelihood of dying in patients that have dementia who

are prescribed antipsychotics. So for those reasons, the VA set in place guidelines about reducing the use of psychotic medications, especially in their nursing home patients.

Dr. Ned Kalin (20:41):

And in this particular survey, the survey revealed that over this nine year period, there was roughly a 8% reduction in the use of antipsychotic medications in this population, from 33% to 27%, and also a reduction in the prescription, interestingly, of anti-anxiety agents from 34% to 20%. Now, at the same time, there was an uptick in the use of antidepressants, and also in the use of some other medications. This is important to note from the standpoint of these trends, but I think it's also important to note that while there was this reduction in the use of the medications and a switch to the use of other medicines like antidepressants, the evidence base best supports the use of antipsychotics and frankly not antidepressants for this population.

Dr. Ned Kalin (21:34):

So I think the editorial that was written by Dr. Lon Schneider from the University of Southern California, the point is made that we need to not be overly zealous about reducing the use of antipsychotics in this population, because the indication is there for their use, the evidence base is there for the use for behavioral problems and psychotic problems related to dementia, and the evidence is not there for some of the other medicines, which have actually appear, at least in this paper, to be used more frequently than they were in the past.

Aaron van Dorn (22:06):

Finally, we have another paper looking at antipsychotics in an elderly population, this time focused on Parkinson's disease, from Mosholder, et al. What can you tell us about it?

Dr. Ned Kalin (22:13):

So again, this is a related paper to the other two papers that I mentioned related to neurodegenerative diseases. This particular paper is about Parkinson's disease and is a survey looking at the extent to which the use of a newer antipsychotic agent, pimavanserin, may be associated with less deaths than the more commonly used, at least in the past, atypical antipsychotics. Now, why would you use antipsychotics in Parkinson's disease? The reason is that Parkinson's disease is frequently associated with psychotic symptoms, with hallucinations, with dementing processes, and sometimes with behavioral problems. And so for the management of those neuropsychiatric symptoms, atypical antipsychotics have been commonly used. It's estimated that up to 50% of Parkinson's disease patients actually have hallucinations or delusions when the disease becomes advanced.

Dr. Ned Kalin (23:16):

Now, Parkinson's disease is a disease that primarily affects dopamine systems and dopamine neurons, many of which originate in a brain region called the substantia nigra. It's thought that the alterations in dopaminergic neuro transmission at least in part may be related to some of the psychotic symptoms that occur in patients with Parkinson's disease. Pimavanserin is a drug that is actually approved by the FDA for the treatment of psychotic symptoms in patients with Parkinson's disease, and it is the only drug that is approved for that, although it certainly is not the only drug that is used for that. As I already mentioned, numerous other atypical antipsychotics are used. Pimavanserin is somewhat unique. It binds at the 5-HT2A receptor and has both agonist and antagonist properties at this receptor, and it also has minimal effects that monoamine receptors, including the D2 receptor. So it's unique in that regard.

Dr. Ned Kalin (24:13):

In this particular study, that was a survey over a three year period from 2016 to 2019, the authors found that pimavanserin treatment was associated with a 35% lower mortality rate compared to the use of the atypical antipsychotics. Now, this sounds like a large effect, although I want our listeners to keep in mind that the likelihood of mortality with these drugs, it's there, but it's quite low. Now, what's also important to keep in mind here is that this effect seemed to be relatively short lived. So during the first 180 days of treatment, or the first six months, this effect was apparent, but when treatment continued beyond that, the difference between mortality rates in the pimavanserin group as compared to the other atypical antipsychotics was not significant. So an effect that is there, but appears to be relatively short lived.

Dr. Ned Kalin (25:09):

And then finally, Dr. Schneider, again, comments on the findings in this in his editorial and puts these findings into perspective. And really, I think it would be useful for our readers to take a look at this, because in his editorial he's cautious in thinking about the interpretation of the advantages that seem to be apparent from this paper for pimavanserin.

Dr. Ned Kalin (25:32):

To summarize, this issue is a really interesting issue. One of the things that I really like about this issue is that it involves thinking about new ideas for treatment, or new treatments, across the lifespan, starting in infancy in individuals that have neurodevelopmental disorders, such as autism spectrum disorder and fragile X syndrome, ranging all the way through later life, neurodegenerative disorders, such as dementias and Parkinson's disease. And so we get this really focus on neurodegeneration and neurodevelopmental problems with concomitant neuropsychiatric symptoms at the two ends of the life spectrum or the life range. And we get a lot of insights into thinking about the use of interventions that help with the behavioral and psychiatric manifestations that occur with them in dementias and Parkinson's disease, and also then insights into brain developmental abnormalities in the early lives of individuals that have genetic alterations that put them at risk for developing autism spectrum disease and fragile X syndrome.

Dr. Ned Kalin (26:45):

So very interesting. Lots of new thoughts about how we might proceed with some of these disorders, and hopefully, again, ideas about how we can begin to target brain systems and specific symptoms that have to do with both neurodevelopment and neurodegeneration.

Aaron van Dorn (27:01):

Dr. Kalin, thanks once again, and I hope you're managing to stay cool in this hot month.

Dr. Ned Kalin (27:04):

Thank you. You too. Appreciate it.

Aaron van Dorn (27:06):

That's all for this month's AJP audio, but check out the other podcasts from the APA. This month on Psychiatric Services From Pages to Practice, Dr. Dixon And Dr. Berezin speak with Dr. Bonnie Zima about the impact of the COVID-19 pandemic and school closures on utilization of childhood emergency mental

health services. For that and other podcasts, check out psychiatryonline.org/podcasts, or you can subscribe via Apple, Google, Spotify, or wherever you find podcasts.

Speaker 4 (27:30):

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