Aaron van Dorn (00:07):

Welcome to AJP Audio for September 2024. I'm Aaron van Dorn. On this episode of the podcast, I spoke with Dr. Jessica Salvatore, Associate Professor of Psychiatry at the Rutgers Robert Wood Johnson Medical School. Dr. Salvatore and colleagues have a paper in the September issue of AJP looking at the impact of peer social genetic effects on substance and alcohol use, anxiety and major depressive disorders on adolescents. Afterwards, I'll speak to Dr. Ned Kalin, Editor-in-Chief of the American Journal of Psychiatry, about that and the rest of the September issue of AJP.

(00:34):

Dr. Salvatore, your paper looked at substance use, major depression and anxiety disorders in adolescents through the lens of peer social genetic effects. It may strike people as counterintuitive. How can a peer's genetic makeup have an effect on someone else's mental health outcomes? So why don't we start with what is meant by a peer genetic effect and what constitutes a peer in your study?

Dr. Jessica Salvatore (00:52):

Absolutely. So I'm actually going to back that question up even a little bit further. To start with, how do we know that genes influence behavior and what's the conventional understanding of how genetic predispositions impact risk for psychiatric and substance use disorders? So typically when we think about how genes influence behavior, we think about how our own genetic predispositions influence our own traits and behaviors and in turn likelihood of developing a complex disorder like alcohol use disorder or major depression. But we also of course, are embedded in social environments and those environments matter a lot too. We know from [inaudible 00:01:34] work that in adolescence, the characteristics of our peers also impact our risk for a variety of behavioral outcomes. And of course, our peers and our social environments all have their own individual genetic predispositions.

(01:50):

So what we were able to do in this study and what we were really trying to investigate is how those genetic predispositions that our peers have in our broader social networks and how those predispositions influence major depression, anxiety disorder, alcohol use disorder, and drug use disorder. And so what's really meant by a peer social genetic effect is the influence or association between a peer's genetic predisposition and one's own risk for a particular outcome. So in the context of this study, the genetic predispositions of peers in adolescence, both at the classroom level in schools, but also geographically defined peers, so peers who live in the same neighborhoods or the same counties, how those peers and their own predispositions influence one's own likelihood of becoming registered for one of these disorders.

Aaron van Dorn (02:49):

With that understanding, what did you find? Did the genetic makeup of people in the cohort have an impact on others' outcomes for the conditions you've looked at?

Dr. Jessica Salvatore (02:56):

Yes. So we did find evidence in this work for peer social genetic effects across the four disorders that we were examining. Again, alcohol use disorder, drug use disorder, major depression and anxiety disorder. Again, in this particular study, we defined peers in a couple of different ways. We defined them both by geography and we were able to define peers based on school-based information. And of course, to some extent those social groups overlap or those peer groups overlap. And statistically we controlled for that sort of cross-classification, the fact that the same individual might be a peer at different levels of

sort of one social or peer network. And we did find an association between the genetic predispositions of one's peers in adolescence and one's own subsequent risk of developing those psychiatric and substance use disorders in adulthood. And importantly, these effects held even after we statistically controlled for the individual's own genetic risk and genetic predispositions for these disorders. There's something unique above and beyond our own genetic predispositions about the genetic predispositions of our peers that's associated with risk for these disorders.

Aaron van Dorn (04:12):

So even if you are less predisposed towards a given genetic condition, if someone in your peer group is more prone to it, you could have an effect on you and pushing you towards those conditions.

Dr. Jessica Salvatore (04:21):

Yeah. And in fact, that was sort of another angle that we took in this particular study to look at how one's own genetic predispositions might interact with these peer social genetic effects to sort of amplify the risk. And that's indeed what we find, that individuals who are themselves at higher genetic risk for these conditions, if they also have peers with higher genetic predispositions for these disorders, that their risk is further increased.

Aaron van Dorn (04:51):

As we were just discussing, your results found greater social genetic effects for drug and alcohol use disorders than for anxiety disorders and major depression. And you also found that the effects were stronger in older children, those in upper secondary school, than for younger peers. Wouldn't it make more sense to say, "Well, these are kids who are being exposed to social pressures." What do you gain by looking at these results through the lens of genetic makeup instead of, say, peer social pressures?

Dr. Jessica Salvatore (05:12):

Yes, and this is absolutely something that we were interested in exploring as part of our study asking this question like, "Okay, well, peers who have higher genetic predispositions are also probably more likely to be themselves affected by drug use disorder or alcohol use disorder or major depression or anxiety disorder." And so what we were able to do with our data was statistically control for whether or not the peers were themselves affected. And we continued to see evidence that peers' genetic predispositions continued to be associated with the target individual's likelihood of being registered for one of these disorders across time. And that the effect was a bit attenuated, but it didn't completely go away even after we controlled for whether or not the peers were themselves affected by these disorders. But yeah, I mean, I think that it's a very relevant and salient question. What is the sort of value added at looking at this question from a genetic perspective?

(06:13):

And to that, what I would say is that the fact that we continue to find an association between peers' genetic predispositions and likelihood of registration for these disorders suggests that there's something beyond the peers' what we call phenotype or sort of diagnosis itself or registration itself for these disorders that matter. So these are probably subclinical traits and behaviors that become part of the socialization that any particular person is exposed to that is in turn increasing their risks. We know, for example, that genetic predispositions for externalizing disorders like alcohol use disorder and drug use disorder, that those are also genetically correlated with subclinical traits like impulsivity and other sorts of personality traits that become part of the environment in which someone is sort of growing up, and that even those subclinical traits and behaviors can increase one's risk for developing these disorders.

Aaron van Dorn (07:17):

What were the limitations of your study?

Dr. Jessica Salvatore (07:18):

I guess I wouldn't say it's a limitation per se, but I think it's important to talk about how did we index genetic predispositions in this particular cohort, for these analyses? And so what we used to index genetic predispositions in this particular study was what we call a family genetic risk score. And a family genetic risk score is basically using information about extended family pedigrees to make inferences about an individual's genetic loading for these disorders. So let's say if you consider someone's family tree, if they have many first degree relatives who are affected by a particular disorder, we make assumptions, again, based on genetic relatedness, that particular person has a higher genetic loading for that particular disorder. In contrast, someone who has a large family tree and maybe only a few people in their family who are affected by a particular disorder, but they're distant fifth degree relatives, that person in comparison based on degree of genetic sharing between a focal individual and then they're affected for fifth degree relative is comparably lower.

(08:32):

The biostatistical team for this work has been exceptionally careful in terms of developing these family genetic risk scores, conducting simulations to demonstrate, for example, that the family genetic risk score, because families, of course, share genes and environments, that there are statistical controls built into the generation of these family genetic risk scores that control for what we call cohabitation effects. So we feel very confident that what's being captured in these scores is indeed genetic risk as opposed to the broader familial environment risk that can go along with having many affected relatives with these different disorders.

(09:13):

And one thing that also comes up as a question with this particular study which was conducted in a Swedish national registry data, is how sort of generalizable are these findings going to be? And I'd say the question I get most is to US-based population. Encouragingly, there are other studies using other methodologies that have looked at peer social genetic effects in adolescents, particularly looking at cigarette smoking, that have found a very similar pattern of effects to what we found here. So of course, science is a cumulative business. No one study is the definitive answer on any particular question. So the evidence that we have and the set of findings that we have, it is consistent with a growing body of work on social genetic effects in adolescents.

Aaron van Dorn (10:05):

Are there immediate clinical implications for your findings?

Dr. Jessica Salvatore (10:08):

The big take home for me as far as what do we do with this information next, and the answer that I always think of when I get asked that question is that it makes us really rethink how do we think about genetic risk as it relates to the development of these disorders. So kind of how I started off speaking about, typically when we think about, "Okay, how do genes influence psychiatric and substance use disorders?" We think about, "Oh, this particular set of genetic predispositions that I might be carrying is influencing other traits and behaviors that I have or the wiring of one's brain or sort of the chemical neurotransmitter levels and whatnot." And what we're demonstrating in this particular study is, of course, that the environment also has a genotype because our social environments are made of people.

And so to me, what this means for sort of translational implications and what do we do with this knowledge is to think about at what level do we intervene?

(11:16):

And a lot of, of course, interventions are at an individual level. How do we sort of attenuate or mitigate the risks associated with certain tendencies that a person might have, like catastrophic thinking or not being able to reflect and restrain one's own impulsive behavior. But I think that what this really points to in this work is that we're going to have potentially a bigger impact, or at least some impact when we consider especially school-based groups, because that's a logical level on which to intervene or conduct preventive interventions, is that disrupting some of the behaviors that are being rewarded or reinforced within peer groups in adolescence and in high school is probably going to be a really effective way to sort of, I don't want to say kill two birds with one stone here, because you're going to be addressing both the individual predispositions or tendencies, but also disrupting some of how those tendencies play out within broader peer and social groups. So to me, it really points to the level on which interventions and preventive interventions in particular are going to be valuable.

Aaron van Dorn (12:39):

What's next for your research?

Dr. Jessica Salvatore (12:40):

Yeah, well, without saying too much, our group continues to be really interested in investigating the nature of social genetic effects and defining and investigating these types of effects across a variety of relationships across the life course. So of course, part of what our group is interested in are spousal social genetic effects. So looking at how a spouse or romantic partner's genetic predispositions might increase or decrease risk for these disorders, and you can think of a number of environments that might be interesting to explore, workplaces in adulthood. So yeah, so that's really where we're going next is continuing to investigate the variety of social environments across the lifespan for which these likely matter.

Aaron van Dorn (13:29):

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

Dr. Jessica Salvatore (13:31):

Thank you.

Aaron van Dorn (13:32):

Up next, Dr. Ned Kalin. Dr. Kalin, welcome back to AJP Audio for September 2024.

Dr. Ned Kalin (13:36):

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

Aaron van Dorn (13:38):

Earlier in this episode, I spoke with Dr. Salvatore on the impact of peer social genetic effects on substance use, anxiety and major depressive disorders in adolescents, once again from the Swedish registry.

Dr. Ned Kalin (13:47):

Yeah, so this is a really interesting, I think, idea, the idea that the genetics of your peers can affect your behavior or even your risk to develop a psychiatric disorder. It's not a new idea and it has been explored previously, but in this current paper, there are some unique features about it. It looks at a large data set and it tries to get at the demographic features of one's genetic risk and also looking at taking out of the equation the risk that you bring as an individual for psychiatric illnesses.

(14:21):

And in this large sample, what the investigators found actually was that yes, it's true for adolescents, there is a small increased risk for developing substance use, for example, alcohol use disorder or other drug use disorders, and even depression and anxiety if your peers are more likely to have that risk genetically. Now then when they talked about peers, it's not peers as you and I might think about them, like your friends, or your small social group. They looked at peers as sort of the group of folks that you went to school with, like your high school class and the overall risk in that group.

(15:01):

And they also looked at what they call geographical peers. They broke things down by geographical areas or regions. And so this is a much more sort of gross measure or broader measure of genetic risk in a group. But nonetheless, it's really interesting that this seems to impact the risk of a single individual in that group of having a greater risk to develop some of these problems. Now what's also interesting and sort of intuitive is that for things like increased risk for alcohol use disorder and drug use disorder, this peer genetic effect was greater for youth in the upper grades than the lower grades. So you can imagine how your peer influence may vary depending on your age and your developmental phase. Nonetheless, I think a really very interesting finding, not strong effects but real and significant effects.

Aaron van Dorn (15:54):

Next, we have a paper from Dalhuisen and colleagues looking at repetitive transcranial magnetic stimulation in comparison to current treatments for those who don't respond to antidepressant treatments.

Dr. Ned Kalin (16:03):

Yeah, Aaron, this is an interesting paper from a group in the Netherlands that was trying to understand where and when it's good to use transcranial magnetic stimulation and sort of the algorithm of treating depression. And what they do in this study is that they compare repetitive transcranial magnetic stimulation to changing an antidepressant or augmenting an antidepressant strategy in patients that were considered to be, quote, "moderately" treatment-resistant. And by that they meant that the patients had to have major depression and also had to fail at least one adequate clinical trial and also unresponsive to another medication in a trial. But that trial didn't have to meet full criteria for adequacy. That is length of treatment and adequate dose. But these are relatively treatment-resistant individuals that have depression. And what they did in these individuals is they basically did a open label study where the 89 folks that were involved, roughly half were receiving medication and got additional medication, a switch or augmentation, and the other half were exposed to 25 sessions of TMS that was applied to the left dorsolateral prefrontal cortical region.

(17:24):

Now this was, as I mentioned, it's an open-label study, and what the investigators found was that the individuals that received the TMS did considerably better than those that got a new antidepressant or had an augmentation antidepressant strategy. The magnitude of the effect was large. And an example is

that the remission rate in the TMS group was about 27% as compared to about 5% medication group. This is an important finding, but there are some caveats, and one of the major caveats is that it was an open-label study and that there are issues around patient expectation that can drive results.

(18:00):

In fact, the researchers gave the participants what's called the credibility expectancy scale, which is basically asking the participants what they expected as far as outcomes go, and maybe not surprisingly, those that received TMS had more positive and greater expectations about having a good treatment outcome. So it's an interesting study, but there is that caveat and there's a really nice editorial by Drs. Castor and Blumberger from the University of Toronto that delves into this in more depth and talks about the implications in relation to this through the algorithm of treating patients who have [inaudible 00:18:38].

Aaron van Dorn (18:38):

Isn't that always going to be an issue if you're treating people who have already tried multiple antidepressant rounds, that you're going to enter some novel intervention that they haven't used before that it changes the modality that they're going to have a greater expectation of success?

Dr. Ned Kalin (18:51):

Yeah, I think that's true. I think that with medications, there are other types of medications that can be tried, and one of the questions is how far do you go with switching medications and trying different classes of medications? And for sure, TMS, I think is a good strategy and this is data that really supports that as going to TMS perhaps more rapidly than others might do in thinking about how they stage the treatments for some [inaudible 00:19:16].

Aaron van Dorn (19:16):

Next up, we have Hess and colleagues looking at entactogen effects of ketamine treatment in a reverse-translational study.

Dr. Ned Kalin (19:23):

So this is an interesting study, and I think it's an important one. It combines human data with also data from a rodent study. Again, I think the ability to work across species to try to hone in on a question or an issue can be helpful, and this is a really nice demonstration of how that can work. The investigators were quite interested in the effects of ketamine on behaviors beyond antidepressant response, and were particularly interested in whether or not ketamine promoted empathy-like behaviors, positive social interactions, and what are known also as pro-social behavior. In the human side of the paper, they analyzed data from roughly 70 individuals, actually 68 individuals, that had major depression that had previously participated in double-blind randomized ketamine IV studies for the treatment of depression. These are sort of standard studies, and what they looked at though was a rating scale that had been collected and that had not been reported on before, which is called the Snaith-Hamilton Pleasure Scale.

(20:31):

And this scale is designed to look at hedonic responses. And as you know, anhedonia is a major component and a core component frequently of depression. But it also moves beyond that and has questions about do you enjoy looking at other people's smiling faces? Do you enjoy being with family or friends? Do you enjoy helping others? And they considered those questions to be questions that are more related to empathy. And what they found was that the patients that received ketamine had more

of a response on those questions. That is, those issues all improved. So that is an indication that in fact, the ketamine may be impacting not just depression, but also some of these pro-social or empathy-like behaviors.

(21:16):

On the other hand, when the investigators did a statistical analysis where they took into account the antidepressant response in each patient, the effects on these particular questions sort of washed away from the standpoint of them being significant, which shows what you would intuitively think, that is that these are all sort of intermingled effects, that you get better from depression, you are more likely in general to be more social, and maybe to take more time in relation to helping others and things like that because you have more energy that's outwardly directed. And you also are experiencing more pleasure from a variety of things, including social interaction. So in a way that's not particularly surprising, but it's nice to demonstrate that.

(22:00):

I think what's interesting though is in the animal experiment that was done, they also looked at how ketamine might affect so-called pro-social, in this case, behaviors, not feelings because we can't look at feelings in animals. We can look at behaviors and then interpret those behaviors in relation to what we think about symptoms or emotions. What they used in the rat study was a model called a Parme avoidance paradigm. This is an interesting model, and the way it's set up is that one rat learns to press a lever to receive a reward or to receive food, and that rat that's doing that can also see another rat that at the same time receives a mild shock. And so the conundrum for the rat that's receiving the food reward is that every time it receives the food reward, it visualizes a response that is uncomfortable from the standpoint of its partner getting a shock.

(22:57):

What the investigators did is that they gave ketamine or saline to rats and then waited seven days and then put them in this paradigm. And what they found was is that if rats had received ketamine previously, they were less likely to press the lever for reward, knowing that when they did that, they saw their partner getting a shock. And so the idea here is is that the ketamine administration may have made those individuals more sensitive to the experience of their partners when their partner was experiencing some painful stimulus and thereby sort of decided to accept less reward in the face of experiencing their partner having less of an adverse experience. And that was interpreted as being a possible empathic-like response. So it's an interesting paper. It combines the animal model with the human data, and it does suggest that when we think of ketamine as its antidepressant response, we can begin to break down some of those components and think about its direct impact on more pleasurable experiences and also outward experiences towards others that are more pleasurable [inaudible 00:24:05].

Aaron van Dorn (24:05):

Another paper drawing on a national registry this time in Denmark is from Frochiar and colleagues, looking at the association between hormonal IUDs and depression risk.

Dr. Ned Kalin (24:14):

So again, I think this is an interesting finding. It also gets at risk for developing a psychiatric illness or depression. It looks at women that are using hormonal treated IUDs, which are quite common. And in this Danish population, they looked at almost 150,000 women between the ages of 15 and 44 that were first time users of hormonal IUDs for contraception. Now, it's important to keep in mind that these women did not have a history of psychiatric illness or a history of use of psychotropic medications. So

it's a population that as far as we know, had no other psychiatric problems or maybe even less risk. And what they did is they basically looked at the incidence of having depression or using or getting prescribed antidepressants as a proxy for depression in these women that were prescribed these IUDs. And the IUDs contained a progesterone-like drug called Levonorgestrel.

(25:19):

And this is important because progesterone is commonly used with IUDs or progesterone-like compounds. And we also know that sex hormones like estrogen or progesterone when they fluctuate, have impacts on mood and can increase or decrease the risk of depression. And in fact, a progesterone-like compound allopregnanolone is used now for the treatment of postpartum depression. An analog of that zuranolone was recently approved by the FDA as an oral medication for depression. So there's a lot of evidence that hormonal treatments affect mood and can affect depression. In this case, looking at the risk for increased depression.

(25:55):

And what the researchers found was that there was an overall increased risk that was dose-dependent. So the more of the hormone that was used in the IUD, the greater the likelihood. And the absolute risk ranged from about 1.2% up to 1.84% for the highest group. Now, what's important to keep in mind here is that these findings are associational. They don't necessarily tell us that the hormonal IUD was causing the problem. To understand that you need to do a prospective planned controlled study. But they do suggest in fact that there is this association, and it could be that these could be [inaudible 00:26:34].

Aaron van Dorn (26:33):

And finally, we have a Priority Data Letter from Frohlich and colleagues looking at a closed-loop transcranial alternating current stimulation for the treatment of major depressive disorder.

Dr. Ned Kalin (26:43):

This is an interesting study too. It's a very early study. We published this study because of some unique features that it has, but the caveats are that it was done in only 10 individuals, and also that it was an open-label study. So the findings have to be, I think, taken with those caveats in mind. People have been very interested in different ways to modulate the brain with electricity and also with magnetic fields. And there's been a lot of work done using direct stimulation of the scalp with electricity to see if that actually alleviates depression. What's unusual about this paper is that this was what we call a closed-loop paradigm. And so here what the investigators did is that they applied alternating current to the frontal lobes of patients that had moderate depression, and they related this to alpha activity or alpha brain waves. And the reason that they did that is that at the alpha frequency, which is in the eight to 12 hertz range and is associated with resting wakefulness and relaxed states, has also been implicated in depression.

(27:54):

And there's been imbalances sometimes in the alpha frequency waves in the left and the right prefrontal cortex, and that has been thought to be associated with depression in some individuals. And so the investigators basically used a method where they thought that they could modulate alpha waves in the prefrontal cortex and by so doing, hopefully alleviate depressive symptoms. Now, what's unique about this and interesting is that as I mentioned, it's a closed-loop method. And what this does then is it uses the electrical signals from one's own brain to trigger the delivery of the alternating current. And so they had an algorithm that when there was a certain fluctuation in alpha waves and our alpha power in the frontal regions of the brain, that would then trigger the AC current to be given and to then modulate

this. And without getting into a lot of the details or further details, what the investigators found was that there was a pretty dramatic reduction in depressive symptoms when participants received this closed-loop [inaudible 00:28:59] stimulation for up to 60 minutes a day for five days.

(29:03):

And so this is really quite interesting. It's interesting because it allows us to think of more personalized treatments, that is to sort of begin to deliver neuromodulation based on one's own brain physiology, which may be different in one person than the next, but it also needs to be really cautiously interpreted because of the caveats that I mentioned, the small sample size and the open label. There's a really good editorial by Dr. Donel Martin from the University of New South Wales that talks about in general using electrical stimulation for depression, the history of that, and focuses on some of the potential advantages of a closed-loop method that was used [inaudible 00:29:43].

Aaron van Dorn (29:43):

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

Dr. Ned Kalin (29:47):

You're welcome. It's a pleasure.

Aaron van Dorn (29:48):

That's all for this month's episode of AJP Audio. Be sure to check out the rest of the APA's podcasts, including Psychiatric Services From Pages to Practice at psychiatryonline.org or wherever you get podcasts.

Speaker 4 (29:58):

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.