

PLOS Science Wednesday: Hi Reddit, we're Joel and Charlotte, and in our PLOS ONE study we identified an EEG signature that may help guide clinical research into autism and other neurological conditions impacting children – Ask Us Anything!

PLOSScienceWednesday¹ and r/Science AMAs¹

¹Affiliation not available

April 17, 2023

Abstract

Hi Reddit, My name is Joel Frohlich and I am a neuroscience PhD student at the University of California, Los Angeles (UCLA) in the lab of Dr. Shafali Jeste. My research uses “brain waves” or neural oscillations to identify quantitative, biological markers (biomarkers) of autism and neurodevelopmental disorders. These biomarkers can be used to guide treatment or inform outcomes in patients. Our lab places electrodes on the scalp to measure neural oscillations in children, a technique known as EEG. My name is Charlotte DiStefano and I am a postdoctoral fellow and clinical instructor at UCLA. My research focuses on cognitive and language development in children with neurodevelopment disorders, including autism spectrum disorder and related neurogenetic disorders. We recently published a paper titled “A Quantitative Electrophysiological Biomarker of Duplication 15q11.2-q13.1 Syndrome” in PLOS ONE. Dup15q syndrome is a neurogenetic disorder caused by partial duplications of chromosome 15. It is one of the most common genetic duplications that causes autism spectrum disorder, and it also confers high risk for epilepsy (i.e., seizures) and intellectual disability (ID). We used EEG to measure a particular frequency of neural oscillation called beta in children with Dup15q syndrome and found that beta oscillations distinguish children with the disorder from other children with autism and ID, as well as healthy children. Remarkably, this EEG signature looks just like the EEG signature seen when a person takes benzodiazepine drugs that bind to and modulate inhibitory neurotransmitter receptors called GABA_A receptors. Because several genes that encode these receptors are duplicated in Dup15q syndrome, we think that this EEG signature might be indicative of GABA_A receptor subunit expression. For this reason, the EEG signature we've identified might be useful for guiding clinical trials that target these neurotransmitter receptors. My colleagues and I will be answering your questions at 1pm EST (10am PST). We're looking forward to discussing our work with these awesome kids. Ask Us Anything! Don't forget to follow Joel Frohlich on Twitter @joel.frohlich.

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PLOSSCIENCEWEDNESDAY [R/SCIENCE](#)

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We recently published a paper titled [“A Quantitative Electrophysiological Biomarker of Duplication 15q11.2-q13.1 Syndrome”](#) in [PLOS ONE](#). Dup15q syndrome is a neurogenetic disorder caused by partial duplications of chromosome 15. It is one of the most common [genetic duplications](#) that causes autism spectrum disorder, and it also confers high risk for epilepsy (i.e., seizures) and intellectual disability (ID). We used EEG to measure a particular frequency of neural oscillation called beta in children with Dup15q syndrome and found that *beta oscillations distinguish children with the disorder from other children with autism and ID, as well as healthy children*. Remarkably, *this EEG signature looks just like the EEG signature seen when a person takes benzodiazepine drugs that bind to and modulate inhibitory neurotransmitter receptors called GABA_A receptors*. Because several genes that encode these receptors are duplicated in Dup15q syndrome, we think that this EEG signature might be indicative of GABA_A receptor subunit expression. For this reason, *the EEG signature we've identified might be useful for guiding clinical trials that target these neurotransmitter receptors*.

My colleagues and I will be answering your questions at **1pm EST** (10am PST). We're looking forward to discussing our work with these awesome kids. Ask Us Anything!

Don't forget to follow Joel Frohlich on Twitter [@joel_frohlich](#).

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CORRESPONDENCE:

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Hi Charlotte and Joel, and thank you for doing this AMA. I found this idea interesting:

this EEG signature looks just like the EEG signature seen when a person takes benzodiazepine drugs that bind to and modulate inhibitory neurotransmitter receptors called GABA_A receptors

So it sounds like the participants in your study had an EEG that mimicked what is seen in people taking benzodiazepines, which are agonists of the GABA-A receptor.

I guess the obvious question is, are there good inverse agonists of the GABA-A receptor and have they

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been tried in Dup15q syndrome?

Further, which alpha subunits do you think are most relevant to Dup15q? My understanding is that inverse agonists targeting $\alpha 5$ -subunit-containing GABAA receptors are in clinical trials for Down syndrome. I believe the $\alpha 2$ - and $\alpha 3$ subunit containing receptors are thought to be targets for modulating anxiety disorders without inducing sedation.

[SirT6](#)

I guess the obvious question is, are there good inverse agonists of the GABA-A receptor and have they been tried in Dup15q syndrome?

Great question, we are considering exploring something along these lines.

Further, which alpha subunits do you think are most relevant to Dup15q?

GABRA5, which encodes the alpha5 subunit, is duplicated in Dup15q syndrome.

Another question for you:

Do you see abnormal EEG responses in children with autism who do not have Dup15q syndrome? Related follow-up: What percentage of children with autism have normal EEGs, and what does it mean to have autism but a normal EEG?

[slowlyslipping](#)

Great question. EEG signatures that are as clear as what we see in Dup15q syndrome are very rare. It is likely that children with other forms of autism have EEG features that would be useful as biomarkers, but they are probably much more subtle.

It's hard to talk about a "normal" EEG because there are different ways of analyzing EEG. Clinical EEGs are read qualitatively and examined for unusual activity. Research EEGs are more often quantitative EEG (qEEG), which is analyzed digitally with a specific hypothesis in mind (like what we did in this study). Many researchers examine the EEG frequency spectrum using Fourier transform to look for abnormal EEG oscillations, for example. A growing trend in the field is also to examine the complexity of the EEG signal, for which there are many measures. For instance, [this study](#) was able to distinguish infant boys at high and low risk for autism using EEG complexity as measured by multiscale entropy.

In terms of clinical EEG findings, about 20% of children with ASD have epilepsy (at least two unprovoked seizures), and "abnormal EEGs" are reported in up to 50%. Abnormal EEG in this case just means that there was something unusual noted on the child's clinical EEG, so it's not just one specific signature. We don't have a great understanding yet of what this high rate of abnormal EEG means, especially since it varies so widely across individuals.

So to answer your follow-up: many children with autism do not have a clear or overt EEG signature, but this likely means that we need more innovative techniques for unlocking the information in the EEG signal.

Hi there! Thanks for talking with us today! Although the dup15q variant confers a strong risk to autism, explaining a small but significant portion of autism cases, I think it would be helpful to our readers to understand a little bit more about the complexity of the risk that this locus confers. What is the penetrance of the dup15q variant? How varied are phenotypic outcomes for carriers? Ed Cook had a nice (if old) [paper on effects of maternal vs paternal inheritance](#), is more known today about what

underlies these observations?

[p1percub](#)

Charlotte: Estimates vary a little bit, but about 75% of individuals with dup15q syndrome have ASD. The characteristics associated with dup15q vary quite a bit. In addition to ASD, we most commonly see intellectual disability, epilepsy and motor impairments. However, this can range from a relatively mild impairment to individuals who have significant delays all areas of development (e.g. don't develop spoken language). We recently published a paper looking at the clinical characteristics of children with dup15q syndrome, and how they compare to a sample of children with non-syndromic ASD. In our sample all of the children with dup15q met criteria for ASD on a common diagnostic assessment (the ADOS), but our sample likely skewed a little bit to the more impacted end just due to the nature of kids we see in our clinic. You can read more here if you're interested!

<https://www.ncbi.nlm.nih.gov/pubmed/27158270>

In response to your last question, dup15q syndrome is generally maternally derived. It doesn't appear that paternal inheritance leads to the disorder, although it's possible that the paternally derived duplication leads to an extremely mild phenotype that just isn't ever diagnosed because there aren't any noticeable impairments.

Hi Charlotte/Joel

Do you think this discovery will help improve neurotherapy techniques for the treatment of autism? In what ways do you think this could be implemented?

Thanks

[wetnax](#)

Charlotte: Thanks for your question! In order to improve treatments for ASD, we really need a better understanding of the mechanisms behind the deficits we observe. Right now, our treatments are based on behavioral symptoms. E.g., a child has a difficult time with social interactions, so we do social skills intervention to try to improve their social abilities. While this works great for some kids, unfortunately it doesn't help us understand why some kids DON'T make a lot of progress with intervention, and what we could be doing differently with them. Although one genetic disorder only accounts for a small percentage of cases of ASD, research like this helps us understand what some of the neurobiological mechanisms might be that underly the deficits we observe. That in turn will help us understand why we see so much variability in terms of children's development and response to intervention, and will hopefully help us develop and target interventions that will work best for specific children.

Hi Joel and Charlotte,

Thank you for visiting [/r/science](#). In what manner will the EEG signature you've identified be useful in guiding clinical trials? Ideally, what is the next step in your research -- is it confirming GABA_A subunit expression or something more?

[adenovato](#)

Joel: Thanks, this is a great question. We think that this EEG signature would be a very promising measure of target engagement in future clinical trials. In other words, by measuring this biomarker, we could perhaps infer whether a drug is actually engaging the GABA_A receptors that the treatment is targeting. Furthermore, because physiological changes should precede behavioral changes, we could use this biomarker to perhaps tell whether neural circuit changes are occurring, even if the trial does

not last long enough to see the behavioral changes that might take much longer to observe.

An important next step, of course, is to do preclinical work in animal models of Dup15q syndrome that will correlate this EEG biomarker with GABA_A receptor subunit gene expression. We also want to correlate the EEG biomarker with clinical traits in humans with the disorder. By learning what clinical traits the biomarker is possibly associated with, we will know what aspects of the disorder might be improved by a treatment that alters this EEG biomarker.

Hi Joel & Charlotte, thanks for doing an AMA!

Beta band activity is fairly 'broad'. What specific frequencies were observed within this group, and at which sites were the abnormalities recorded?

Also, were there any specific aspects of autism, or particular behaviours (measures) which were more closely linked to the biomarkers you have pinpointed?

I really love research uncovering links between EEG correlates and behaviour/psych outcomes. Cheers!

[Takre](#)

Joel: Great point, beta is very broad, usually defined as 12-30 cycles per second or Hz. In this case, the signature was strongest toward the higher frequency end of the beta band (sometimes called beta2), with a peak around 23 Hz, which you can see [here](#). The beta finding was very diffuse across the scalp, but strongest in frontotemporal regions. We also observed lower delta (1-4 Hz) activity in the children with Dup15q syndrome, which is interesting because patients with deletions of the same region actually have elevated delta activity.

We have yet to correlate this biomarker with autism severity or ADOS subscores, but that is an exciting direction for this work. In this paper, though, we did show that the EEG biomarker is associated with epilepsy.

Glad that you're excited about our work!

Hi there. When you talk about kids with autism who also happen to have seizures it seems you're focusing on the more severe end of the spectrum. But what about the more mild end, for someone who has Aspergers?

I'm aware that as of 2013 it technically doesn't exist anymore in the DSM but I still feel that it there may very well be some inherent, quantifiable biological difference between traditional autism and Aspergers. Any information on that that?

[ASD Project](#)

Charlotte: That's a good question. You're correct that within the ASD population, epilepsy is associated with intellectual disability. However, individuals with more "mild" ASD also have rates of epilepsy that are higher than the general population. A meta-analysis from 2008 found that among individuals with ASD who do not have intellectual disability ("high-functioning", although I don't like that term), 8% had epilepsy. That's a lower rate than in kids with ASD and intellectual disability, but much higher than the general population (.5%).

Given that ASD is such a heterogeneous condition, it's likely that different genetic and biological mechanisms contribute to the very different characteristics that we see.

Hi there. When you talk about kids with autism who also happen to have seizures it seems you're focusing on the more severe end of the spectrum. But what about the more mild end, for someone who has Aspergers?

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Joel: I'd like to add that autism is, in a sense, really dozens of different disorders. The reason that Asperger's and autism were consolidated into autism spectrum disorder (ASD) was because there is so much heterogeneity within this spectrum that no one knows where to draw a meaningful line. Yes, I absolutely expect that we are going to find quantifiable, biological differences between different forms of ASD, and one of the goals of biomarkers is to stratify ASD into meaningful subgroups.

One reason we focus on Dup15q syndrome is because we already know the genes involved, so it is likely more tractable to treat. There are many, many genes involved in autism. Some forms of autism are caused by copy number variants like Dup15q, where deletions or duplications of a handful of genes have a large clinical impact. Other forms of autism are also caused by mutations in a few important genes. But very commonly, autism is driven by many different mutations in one person, each mutation individually having a modest impact. The sum of all these mutation, though, may converge on autism.

So returning more to your question, we are starting with the most tractable forms of ASD with the goal of eventually being able to understand the heterogeneity within the spectrum and to offer treatments for as many of these different clinical subgroups as possible.

Sorry, I haven't read the paper yet and don't know much about autism or Dup15q. I am postdoc studying cortical interneurons in development (rodent somatosensory cortex model) so I have some knowledge on cortical function. How reliably are you able to discriminate between Dup15q, ID, and autism? What brain areas give the best discrimination? Would you be able to speculate on whether these are GABA receptors on excitatory or inhibitory cells?

[philosochu](#)

These are all great questions. Because Dup15q syndrome is a very rare disorder affecting about 1 in 10,000 individuals, we did not have a large enough sample to do machine learning classification. But the effect sizes here were very large, $d > 1$. We have not yet done EEG source localization, so we don't know where in the brain the signal is being generated. As measured here, it's smeared across the scalp. Any guesses about cellular mechanisms would be highly speculative at this point, so there's a lot of exciting research to be done.

I don't know if I am clever enough to understand anything you say, but will this research help people currently living with ASD, or will it help prevent autism in future?

It is one of the most common genetic duplications that causes autism spectrum disorder

Here you say it causes ASD, but is it a causality or just a correlation?

[KesTheHammer](#)

Joel: Thanks for your question. Some genes duplicated in this syndrome, such as [GABRA5](#) and [UBE3A](#), cause autism-like behaviors when their expression is disrupted in animals. Obviously, we can't do the same experiment in humans where we change gene expression and observe behavioral effects. But the whole logic of treatments that target proteins encoded these genes would be that they are causing the disorder.

What we still need to learn is *which* specific genes in 15q11.2-13.1 are responsible for *which* symptoms. Most of the research has focused on UBE3A, which is also deleted in Angelman Syndrome, but I think the role of the duplicated genes encoding GABA_A receptor subunits has been under-emphasized. The fact that the EEG signature we've described looks so much like what is seen in drugs that modulate GABA_A receptors suggests that they might be important, but the exact relationship between these GABA_A receptor genes and autism or intellectual disability is uncertain.

Is there the possibility that other disorders could impede normal readings? - e.g. i adopted a young boy who has (due to a difficult upbringing), severe trauma, complex attachment issues, underdeveloped parts of the brain to allow regulation of behaviour and ADHD. with complex issues such as these and the fact they "cross over" in terms of outward symptoms, would they impact readings at a level like this?

[kennethmci](#)

Charlotte: Great question! Yes, there are lots of things that can contribute to the EEG signal. For that reason, research generally tries to be pretty rigorous about the participants who are included - we want to avoid as many confounds as possible. In our studies, we generally exclude any participants who have had significant neglect/abuse in early childhood (e.g. were adopted from an orphanage), have sensory impairments (significant vision/hearing loss), or had birth trauma. We also carefully document seizures and medications, since those can affect the EEG signal as well. It's not perfect, but we do our best to disentangle all of these potential confounds from the variables that we're actually interested in (in this case, genetic diagnosis).

Hello and thank you so much for taking the time to speak with us.

How will EEG signature help guide autism research? Can you elaborate on where you go from here?

Have there been any recent breakthroughs in autism research in the past year or so?

In what ways can the layman better understand autism to avoid any stereotyping?

Thank you again!

[FillsYourNiche](#)

Charlotte: Your first question has been covered in a couple of other replies, so I'll just answer the others. :)

Yes, lots of exciting research happening in the ASD world! Here's a nice summary that Spectrum put together. <https://spectrumnews.org/features/special-reports/2016-year-review/> I think we're developing a much better understanding of the heterogeneity within ASD, which is hopefully going to improve our ability to target interventions and really improve outcomes for individuals with ASD.

In terms of better understanding ASD, I think the most important thing is to be aware that it's a large and diverse spectrum. It's diagnosed based on broad categories of symptoms (e.g. impairments in social communication, the presence of repetitive behaviors and restricted interests), but how those symptoms manifest is extremely variable. The one stereotype that I'd love to change is the idea that

children with ASD don't like social contact, or aren't affectionate. Individuals with ASD often have difficulty with social interaction, but can still be very interested in being with people!

Hello, I am an EEG tech who regularly works with people with autism. I'm curious if the beta frequencies you saw were frontally located or if they were generalized? And what were the ages of the test group? Thanks.

[Aurora1098](#)

The beta activity is virtually everywhere, but strongest frontotemporally. You can actually see the scalp plots of beta activity [here](#). In the first part of the study, where we measured beta activity and compared it to controls, we looked at children from 16 months to 12 years. It's a rare disorder, so hard to look at a specific age. In the second part of the study where we correlated the beta activity with age, duplication type, and epilepsy, we looked at an even broader age range, including two adults. You can see the exact ages in Table 1 of the paper.

While the post title suggests it is useful in children, would this also be able to potentially be used in adult diagnoses, assuming the general efficacy could be proven? As a BA Psychology, I'm aware some things don't necessarily translate well between neurological developmental stages, would this be one of those things?

[jddbeyondthesky](#)

Joel: Thanks for your question. We imagine that this biomarker would mostly be used to guide treatment rather than diagnosis. Since these kids already have a partial chromosomal duplication, there are very straight forward genetic tests for diagnosis. And since Dup15q syndrome is a neurodevelopmental disorder, I would expect any treatment would be most effective in children for whom developmental trajectories can still be altered, but of course we want to work towards findings that benefit anyone and everyone with this disorder.

In your conclusion, you note that studies like this help parse out specifics from what is often diagnosed as a spectrum or range of disorders. How can research like this help us better understand the heterogeneity of autism? Do you anticipate that in the future we'll think of it less as a spectrum and more as specific and somewhat different disorders?

[firedrops](#)

Joel: Thanks for your question. I definitely anticipate that in the future, we will think of autism as many different but related disorders. To stratify autism spectrum disorder (ASD), we need biomarkers that relate to disease mechanisms. In this study, we have identified an EEG signature that likely relates to the overexpression of GABA_A receptor subunit genes that are duplicated in Dup15q syndrome. Other individuals with autism might have more subtle aberrations of GABA_A receptors, such as point mutations. They might also have a more subtle form of this EEG signature. By relating this and other biomarkers to various causal mechanisms, we can move towards an understanding of autism that is rooted in distinct mechanisms with distinct treatments.

Hi Charlotte and Joel, thanks for doing this AMA!

Can EEG be used to help in the diagnostic of other neurodevelopmental disorders such as ADHD?

Even though there are studies trying to associate ADHD with physiological differences on how certain genes are regulated and how parts of the brain works, the current ADHD diagnostics is mostly behavioral, relying on analyzing the responses of the patient to a series of questions and it's own behavior during the interviews (at least mine was like this). I am curious if, based on your results, EEG could be used as a confirmatory exam in order to rule out "false positives".

[pedroivo000](#)

Joel: [The FDA has actually approved an EEG test](#) to guide the diagnosis of ADHD, but it is very controversial. Our work on EEG biomarkers is more focused on biomarkers that guide treatment and inform outcomes rather than diagnosis.