Molecules, Memory, and the Mind: Psychedelics and the Future of Neuroplasticity

INTERVIEW WITH: DR. ANDREA GOMEZ

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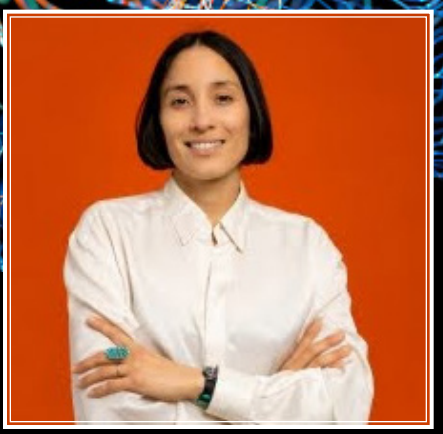

Dr. Andrea Gomez *is an Assistant Professor in the Department of Molecular and Cell Biology and a member of the Helen Wills Neuroscience Institute at the University of California, Berkeley. Her research explores neuronal circuits with a specific focus on synaptic plasticity and RNA regulation. Dr. Gomez investigates the underlying molecular mechanisms of cognitive functions and flexibility using tools from genetics and molecular biology. Her recent work investigates how psychedelics influence alternative splicing and long term neuronal function, providing insight into therapeutic applications for mental health disorders.*

BSJ: What initially sparked your interest in studying neurobiology and researching psychedelics?

AG: I like to say that I accidentally became a neuroscientist because that was not necessarily the path I had set on. My interest has always been in evolution. I was really curious about the rules for organization and how patterns are generated in life. My PhD was in developmental genetics and the developmental model that I was studying was synapse formation– the connections between neurons. That was the way I became a neuroscientist; I studied the structure that exists and serves as the communication between neurons.

Those of us who are in the field of synapse biology know that there are many perspectives. One perspective from developmental genetics asks: how do two neurons know how to connect to each other, and what are the rules for engagement? How does that structure change over time? The aspect of changing over time is fundamentally what synaptic plasticity is. The ability for that communication to change led me into the psychedelic world. Psychedelics have a structure very similar to serotonin, so much so they can bind to serotonin receptors that are located on our neurons. Serotonin, like dopamine, oxytocin, or noradrenaline, changes the timing of synaptic communication. There is the synapse itself, and then the neuromodulators, which affect the magnitude at which that synapse is communicating between neurons.

When I arrived at Berkeley and started my lab, my focus was understanding how synapses are organized. What are the rules? When asking questions about synaptic changes from a single event, the challenge is to find an event that is strong enough to elicit a change. In the summer of 2020, I was contacted by a clinician at UCSF who was running clinical trials with psilocybin. They asked to collaborate on a study that was trying to understand, from the cell and molecular perspective all the way to the human level, the basis of psilocybin-induced cognitive flexibility.

The reason I agreed to that collaboration relates back to my point: the challenge as neurobiologists is to find a stimulus that can induce plasticity with a strong magnitude enough to make measurable changes. Additionally, the psychedelic experience itself is quite remarkable for individuals. I am interested in linking a significant experience like this to long-term changes at the molecular level. That is what led me to begin working with psychedelics.

BSJ: You are from New Mexico, and are both of Pueblo and Chicana descent. How do you think different cultures have differing traditions surrounding medicine and healing? How do you think that your upbringing and culture has fueled your research and passions today?

AG: Anyone's experience affects their worldview, and I am no different. I would say that culturally, a lot of what we will call the value systems in which I hold informs the questions that we ask in my lab. So in my indigenous culture, we have this core concept around relationality in how things are related to each other and we consider the nature of these relationships as informing how each thing functions. I would say that is very easily translatable into the things that I am studying in my lab. For an example one way we can use this perspective directly to the questions that I am asking is that we are looking at the effect of psychedelics in a particular region of the brain called the prefrontal cortex, which has multiple different type of neurons and our question is really trying to understand each neuron type. Each neuron has particular types of functions; some may be excitatory, some may be inhibitory, some may connect short range,

some may connect long range. So, thinking about how psychedelics affect the way that these cells relate to each other over time I think is really inspired by this concept of relationality; how there will not just be one thing changing in isolation, but that everything is going to be changing relative to each other. Even if a neuron does not have a serotonin receptor that can bind to the psychedelics, if it is connected to another neuron that is affected or binds psychedelics, then that activity is going to change and then it is going to change the activity of the neuron that it is connected to it. Trying to understand how things evolve over time after a single dose or a single exposure to psychedelic compounds and thinking about this relationality is inspired from my cultural worldview.

BSJ: Your published article "Neurexins: molecular codes for shaping neuronal synapses," talks about Neurexins. Could you explain how the diversity of Neurexin isoforms are due to alternative splicing? And what challenges come with this in synaptic research?

AG: We can look at it from two perspectives. The first one is the one I mentioned previously, which involves how synapses are organized. The second is from a more clinical perspective - Neurexins are considered autism risk alleles. They are also associated with schizophrenia risk. When researchers looked into the function of these genes, they found that Neurexins are localized to the synapse. They belong to a family of genes called synaptic adhesion molecules. As the name suggests, these molecules have adhesive properties. They function across the synaptic cleft, which is a space between two cell membranes. In essence, a synapse is a tiny communication device that is organized so that communication between two neurons can occur. This communication is a chemical reaction, not electrical, which is very fast.In a chemical transmission which is slower, synaptic vesicles must fuse with the membrane to release neurotransmitters, which are the molecular currency of cells- the language of how cells communicate with each other.

The released neurotransmitter needs to bind to a neurotransmitter receptor, which induces a conformational change which then allows a tiny influx of current.

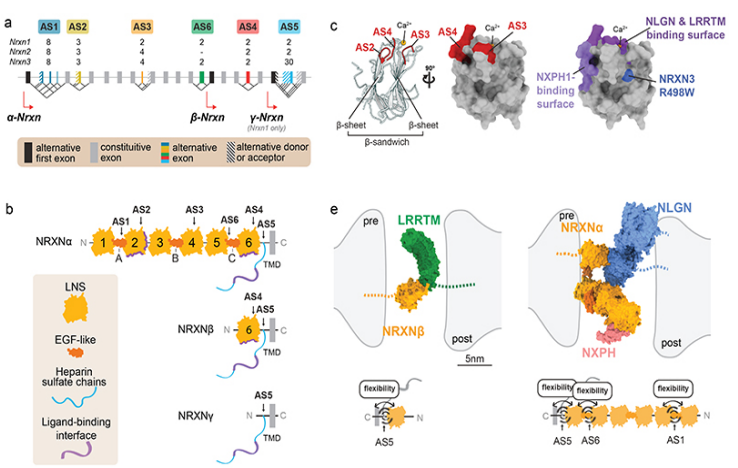

Figure 1: Structural diversity and interaction mechanisms of Neurexins. (A-B) Neurexzins undergo extensive alternative splicing at six canonical sites, generating α-, β-, and γ-Neurexin isoforms with distinct domain compositions. (C) Splice variants affect surface topology and logan binding. (D-E) Different Neurexin isoforms engage specific postsynaptic partners depending on their structure and flexibility, influencing synapse identity and function.

However, neurotransmitters released outside of the cell can easily diffuse away. Their ability to bind to a neurotransmitter receptor depends on proximity. What brings the neurotransmitter receptors and the neurotransmitter itself, or rather the synaptic vesicles, close to each other are synaptic adhesion molecules. These molecules organize the synaptic vesicles and ensure they are adjacent to the neurotransmitter receptors on the other side of the membrane. They function bidirectionally to coordinate this signal transmission and organization.

This is the functional role of Neurexins. When they were first discovered, researchers were cloning and sequencing genes to identify those that are responsible for these processes. It was found that there were many versions of the same gene. Therefore, it was found that Neurexins were alternatively spliced.

Why does that matter? In order to understand the function of a protein, one must examine the role of its individual domains. If a protein has various shapes, then each version may serve a distinct function in organizing components at the synaptic cleft.

Over the past two decades, researchers realized that different versions or isoforms of Neurexin have different sticky properties. Some make the molecule more or less sticky to specific binding partners. These variations can change the flexibility of the molecule. Neurexin is both a large gene and a large protein. If stretched linearly, it would essentially poke through the other side of the synapse. It has an ability to fold over and exist inside of the synaptic cleft, and it is these regions that are alternatively spliced. Another way to think about it is a Swiss Army knife. You can have multiple functions and you can create multiple things that the Neurexin can do by changing the exons that are included or excluded at the RNA level.

BSJ: Your Neurexin research suggests that Neurexin mutations are linked to some neurodevelopmental and psychiatric disorders. Can you elaborate on the molecular mechanisms that translate into such conditions or more shortly, how do you think that understanding Neurexin function could impact our knowledge of neurodevelopmental disorders?

AG: If you remove or alter the way that the synaptic adhesion molecule is sticky, then it is going to change the way that synaptic transmission occurs. It could potentially make things really sticky and really recruit a lot of synaptic vesicles opposed to neurotransmitters. It may make it more dispersed and not have the communication as strong.

It may not completely remove the connection between the neurons, but it can alter the way the chemical signal is not only sent to the other neuron but also how it is interpreted. When we consider contexts in which different versions of Neurexin are linked to conditions like schizophrenia or other neurodevelopmental disorders, we can imagine that the communication at those synapses might be slightly different. It does not necessarily eliminate the communication, but it changes how information is transferred from neuron to neuron throughout a neural circuit. With that in mind, it becomes easier to understand how someone with one of these genetic variants might perceive the world differently—how they process sensory input, internal information, and how they form their internal states. Even slight changes in synaptic communication can influence how a person feels and experiences the world around them. So, I think that's probably the most direct way in which Neurexin variation can impact development.

BSJ: What aspects of neuronal synapse research do you think are most important to explore in future?

AG: I think research that focuses on understanding how the diversity of communication is generated in nervous systems is one of the most important questions in synaptic biology. Embedded in that question are several key ideas: how diverse synapses are formed, how they are maintained throughout life, and what that tells us about the brain's capacity for change. How much can synapses change over a lifetime? What's the magnitude of that change—and what are its limitations?

After all, millions of years of evolution have shaped a complex combination of genes and synaptic diversity that enables us to interpret and interact with the natural world. Looking ahead, a fundamental question becomes: what allows for even higher levels of understanding and interaction with our environment? I believe the answer lies in how many different types of synapses the brain can generate. This diversity directly influences how information, in the form of neural activity, flows across neural circuits.

BSJ: Transitioning back to more of your psychedelic research, could you explain the relationship between psychedelic treatment and neuroplasticity?

AG: To define neuroplasticity, it is the brain's ability to change itself. This can be at the structural level or the functional level. They are obviously intertwined, but I think when you consider this space where the brain needs to be both flexible and somewhat rigid– I call it a plastic plasticity paradox– if things were too flexible, then our memories would vanish, and if things were too rigid, then we would never learn.

What I like about this concept is that we can start to imagine what biological entity can contain both of these features. I am a biologist, so I will point to the central dogma– DNA, RNA, and protein. When we think about any type of change that occurs in a neuron and more specifically when it occurs at the synapse, we refer to it as synaptic plasticity.

Let us say that we want to change the way that neurons are communicating. As I described before, this can be done by changing the amount of neurotransmitter released, or altering the number of neurotransmitter receptors that can bind to those neurotransmitters, to either weaken or strengthen the synapse. That is the basis for changing information flow across neurons– literally, synaptic plasticity. They can also change the amount or timing of neurotransmitter release.

Psychedelics bind to their receptors, which can change the number of neurotransmitter receptors present in the synaptic cleft. They can also change the amount or timing of neurotransmitter release. By fundamentally altering components of synaptic communication, you can directly draw a direct link between how psychedelics function and changes not only in perception but also in long-term outcomes, as suggested by clinical trials. In these trials, individuals with major depressive disorder or PTSD are given a single dose and often experience not only but also persistent relief.

BSJ: In one of your more recent articles, your research found that there were dramatic changes in alternative splicing, lasting up to a month following psychedelic exposure. What led you to investigate this? And why do you think it plays such a significant role in psychedelic induced plasticity?

AG: This is one of my favorite findings in my career, honestly. The components themselves, across the synapse, are critical for the communication. They are the ones that facilitate communication. When I started the project, the reason why I wanted to use psychedelics was because they are a very robust stimulus. Using psychedelics as a tool to induce a stimulus and then observe the responses at the molecular level has been a challenge for a long time, especially for those who study alternative splicing.
In a dish, you can apply drugs and see the effects on splicing patterns or how RNA changes.You can look at which genes are upregulated or downregulated. But finding a stimulus that you can give to an individual– one that is time locked and restricted to a specific period– and then to expect to see molecular changes has been a challenge.

We have known for a long time that there are conditions, like seizures, that can induce changes in neural activity, but what happens in a healthy context? How does a single stimulus alter molecular processes? That is the fundamental motivation for using psychedelics: to examine whether they influence alternative splicing.

The biggest surprise was not that we saw alternative splicing; I expected that to happen. The surprise was that transcription had not changed that much. Gene expression levels– whether genes were turned up or down– after two days, one week, and one month, were very similar to animals that had not been treated with psychedelics at all. But at the level of alternative splicing, I had expected hundreds of changes. What was shocking to me was that we saw over 18,000 splicing events occurring over the course of a month. In particular, in specific cell types– namely, an inhibitory cell type called parvalbumin neurons (PV neurons) – we saw increased splicing activity. When we looked at the number of events that were occurring at two days compared to one week, there were more at one week. And then compared to one week, there were more at one month. It was as though the splicing activity increased over time. That was really surprising to us.

We do not know what that necessarily means. But what we like to speculate is that this is a way for neurons to consolidate or encode long-term memories without disrupting the transcriptional programs needed to carry out the basic functions of neurons.

I liken this to a filmmaker analogy—you collect the raw footage, which contains information, but also parts you do not want to include in your story. By cutting the silent parts and keeping the relevant ones, you can resequence it. What I really like about what our studies suggest is that the raw footage, at the transcriptional level, was not changing. But the different versions of that same story, at the alternative splicing level, were altered. This did not necessarily affect the core components at the synapse, but may have changed the stickiness of the molecules for example. That slight difference, triggered by a single psychedelic dose, was consistent across many animals, indicating it was not a spurious or random event.

These findings suggest that these alternate versions, observed only in psychedelic-treated animals, reflect the molecular encoding of the psychedelic experience.

BSJ: It appears you investigated two classes of psychedelic drugs. How would you interpret the differences in results for those and what might this mean for potential in real life applications?

AG: People who are familiar with psychedelics know that there are many different types. Those who have experienced the different types of psychedelics will tell you that they are not all the same, an LSD trip does not feel like a mushroom trip. What are the qualitative and quantitative differences? The other question: what are

the similarities and differences in the way that the neuron responds? That is the reason why we chose to study two types of psychedelics; to compare the distinct molecular features.

There are hundreds of psychedelic compounds, but they fall into two structural categories. One group is the phenylethylamines, which includes molecules like mescaline which is derived from psychedelic cacti, but also some synthetic, lab synthesized versions. The one that we use in our study is called DOI. The other group is tryptamines. Psilocybin falls into this category. Within tryptamines, there is a subcategory called ergolines, which includes LSD.

We selected one from each class – DOI (phenylethylamine) and psilocybin(tryptamine). A key difference between these two is the time that an individual experiences the subjective mind altering change. Psilocybin's effects last about six hours, while a DOI trip lasts about 24 hours or more. Some psychedelics can last up to three days. We found some interesting similarities, but most of the results were non-overlapping. However, at the transcriptional level, the patterns seen at one week after DOI looked similar to those at two days from psilocybin. Therefore, they should not be thought about as one entity. They have distinct properties, but there may be some overlap downstream in the biological response that may be shifted in time temporarily. This is the first molecular evidence that is observed. There has been behavioral evidence from Gül Dolan's lab here at UC Berkeley, suggesting that different psychedelics affect animal behavior in temporally shifted ways. There seems to be a temporal dependency that influences overlapping molecular programs, though shifted in time.

BSJ: What are the next key research steps to better understand how alternative splicing influences long-term psychedelic effects, and do you foresee potential for targeted interventions based on your findings?

AG: Given that we saw these shifts in time, I think it can really inform us on thinking about clinical interventions and when you would want to do that. Right now, a lot of the clinical trials have some type of follow-up after an individual gets a dose of psychedelics. Looking at our timeline of when things have the largest magnitude, that is when you would want to intervene the most if someone is dealing with a maladaptive stimulus that causes maladaptive behaviors That is how it helps inform us or translate what we understand on the molecular level to the clinical level. Of course, mice and humans are different, but just consider that there is a timeline that we would expect there to be a human-specific one and to think about how to create new protocols for clinical intervention in whatever context or if it is a disease context or if it is a conditioned context.

Now, considering splicing,and given that RNA is relatively short-lived, the question becomes: how are these splicing events sustained over such long periods of time? We observed that transcription was not changing significantly. Key factors like RNA-binding proteins or splicing regulators, which might typically drive changes in RNA patterns, also were not showing much variation. How, then, are these splicing events persisting for up to a month? We specifically chose the one-month time point assuming things would have returned to baseline, but to our surprise, in some cell types—not all—the splicing activity continued to increase. This raises a major question for my lab: what is driving these sustained changes if the RNA itself doesn't last that long?

Another possibility, which we find really exciting, is that this could represent a general mechanism neurons use to encode long-term memories or experiences—without altering baseline gene transcription.

The next big question is: what are these alternative splicing events actually doing to the proteins? That is where the bioinformatic challenge comes in. We now need to map which protein regions are being affected. The top three areas of interest for us include: (1) regions that undergo post-translational modifications, such as phosphorylation, which can drastically change protein function; (2) ligand-binding domains, which might alter how "sticky" a protein is—perhaps increasing or decreasing its binding affinity; and (3) regions involved in epigenetic modifications, such as those that influence how methyl groups are added to chromatin.

Essentially, anything that could change how a protein functions is now on our radar. With a list of over 18,000 splicing events showing dynamic shifts, our next challenge is to connect those molecular changes to changes in protein function—and ultimately, to biological outcomes. That is what makes this the most exciting next step for our lab.

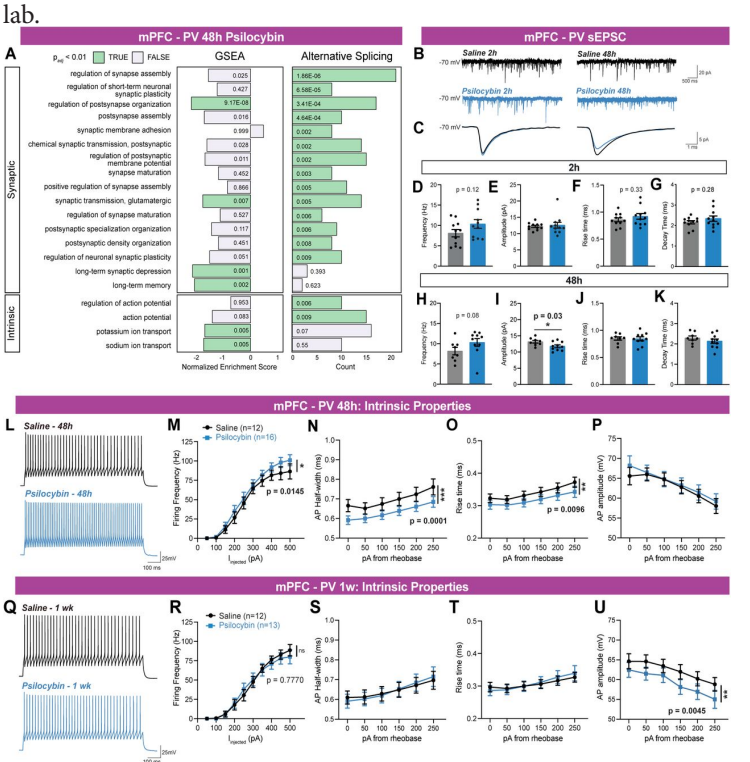

Figure 2: Psilocybin alters synaptic and intrinsic properties of PV interneurons. At 48 hours post-treatment, psilocybin changes gene regulation and alternative splicing related to synaptic and neuronal activity in PV interneurons of the mPFC(A). It decreases the strength of excitatory input (B-K) and increases neuron excitability, including faster firing and shorter action potentials (L-P). Most effects return to baseline after one week, except for a lasting drop in action potential amplitude (Q-U).

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