

Science Studio Vol 021 (Guest: Jamie Tyler)

Scents, Senses, and the CNS

Have you ever noticed how a whiff of some perfume can throw you backwards in time: a flashback of the hottest date ever or maybe just your grandmother's loving hug? Assistant professor and neuroscientist Jamie Tyler shares his insights about two sensory domains and the brain: how odors are processed in the central nervous system and can alter how the brain processes information and memory, and how sensory information, through the medium of hypersonic sound waves, can be harnessed as potential drug free, non invasive cures for serious central nervous system (CNS) disorders, such as Parkinson's.

[music]

Peggy Coulombe: Hi. This is Peggy Coulombe, and welcome to Science Studio. I took a class last week with a massage therapist who blends her own natural aroma therapy products. What surprised me most was how these chemicals, each one with a really strong scent, could influence moods, behaviors, even memories. How is it possible for an airborne molecule to have such an influence?

Our guest, Jamie Tyler, is going to talk with us a bit about the effect that activity in the olfactory bulb, where neurons reside that respond to scent, can have on the central nervous system, and some of the other technological wizardry that he's been involved in that may create some of the first noninvasive, drug-free cures for CNS disorders. Welcome, Jamie.

Jamie Tyler: Hi.

[laughter]

Peggy: So, tell me. We have sight, hearing, touch, taste, smell. And I think that studies about how smell effects behavior in the central nervous system haven't taken off until more recently. Why is that?

Jamie: Well, in 2004, Linda Buck and Richard Axel were awarded a Nobel Prize for their discovery of olfactory receptors and kind of the way the olfactory system is organized. Before that, we weren't really sure how olfaction occurred. The general hypothesis was that odor molecules basically bind to odor receptors, kind of like a lock and a key.

But what Buck and Axel really found was that there's a large part of the genome, in rats, it's about one percent of the entire genetic code is devoted to making very specific olfactory receptors. And each one of these olfactory receptors binds one particular odor molecule. And so, with their discovery, it really opened up a new field, something that was always a black box.

We learned a lot about the organization of the olfactory system, and we started to be able to employ molecular genetic techniques to study how olfaction occurs across many different levels, ranging from a molecular level all the way up to how it regulates the behavior of an organism.

Peggy: So does that mean one molecule, one type of receptor?

Jamie: Yeah. So, basically, we can just discuss primarily the rodent olfactory system. So, in rats, rats have about 1,200 different types of odor receptors, and each one of those odor receptors binds an odor molecule, an individual molecule. And so, odors, the way we think of odors, are typically complex stimuli.

So if you think about the odor of coffee, for example, there's probably about 10 different distinct odor molecules. And each odor molecule is at a different concentration in the coffee, and that really gives rise to this overall perceptual awareness of the odor “coffee.” And so what happens is those 10 to 12 different odor molecules each bind to their receptors, and then it's basically integrated in the olfactory bulb and projected to the other higher centers where it's processed and gives rise to the awareness that “I'm smelling coffee.”

In the mouse, there's about 900 different receptors. In humans, we have probably between six and 700 different receptors. So the olfactory system is really unique, for a couple different reasons, and one of the reasons that it's unique is that we do have this large diversity of distinct receptor subtypes.

Peggy: So how does a molecule taken in through the nose cause a change in the central nervous system?

Jamie: Well, essentially, the molecules bind to their olfactory receptors. And the olfactory receptors are in the nasal epithelium. So one thing that's really interesting about the olfactory bulb and the olfactory system is that it really provides the most direct pathway between the environment and the organism. There's no other sensory system that has such a direct pathway directly to the brain.

You hear people refer to the eye as the window of the brain, but the number of synapses that have to process visual information before it gets to the brain itself is actually on the order of seven to 10. In the olfactory system, there's actually only one synapse, right?

So what happens is an odor molecule binds to its receptor, which is distributed throughout the olfactory epithelium--so, inside your nasal cavity. And then that basically elicits an action potential. Which then, it basically passes that information from the odor environment directly to the brain. So it's basically, the action potential is carried by the olfactory receptor neuron, and then the olfactory receptor neuron releases a neurotransmitter onto a post-synaptic cell, which is located in the brain itself.

Peggy: So does this mean when a scent molecule binds that it elicits an immediate response?

Jamie: It is fairly immediate. There's a couple properties about the olfactory bulb and the way that it integrates the information across time, particularly in that the response is immediate, but there are other types of temporal processes that really influence the way that we perceive odors. So, it's like we have adaptation or habituation. So, if there's a persistent odor stimulus in a very short period of time, right?

If someone were to spray perfume in the room, initially we would smell it. It would be very, very small. But then it would decrease over time. And we're talking about the order of minutes here. So there's other types of plasticity that we see in the olfactory bulb that are over the orders of days, and it depends on the stability of the odor and the odor concentration in a particular environment. So there's all types of temporal dynamics that really influence the way that we smell, the way that we perceive our odor environments.

Peggy: I think your graduate training was looking at neuronal activity in the hippocampus. Is that right?

Jamie: Yeah. So I studied how neuronal activity in the hippocampus might play a role in learning and memory. And to do this, I basically focused on this one protein, brain-derived neurotrophic factor, or BDNF, which is one of the most powerful regulators of synaptic transmission on the nervous system. And so I looked for structural and physiological changes that were exerted through BDNF signaling pathways, and then tried to postulate some hypotheses regarding the way that BDNF could play a role in memory consolidation.

Peggy: And so did this work underlay the work that you went on to do in the olfactory system in your post-doctoral fellowship at Harvard?

Jamie: No, it really didn't. So, I became interested in studying the way that synapses process information, really, when I was an undergraduate. And so my work as a graduate student really opened up a new field for me: to be able to examine kind of the cellular processes that underlie central synaptic transmission.

When I went to Harvard to conduct my post-doctoral studies, I decided to stay with synaptic transmission and plasticity, but I chose to focus on how environmental experience influenced the regulation of synaptic plasticity. And to do this, I focused on the olfactory bulb. The olfactory bulb, for many reasons, provides us with one of the best model systems for studying the way that experience can influence synaptic plasticity.

Peggy: So, in your research, you described an effect that explains something I've always wondered about, and you touched on it a little earlier. When I traveled to Micronesia, I was strongly struck by how it smelled like garbage. But after like 17 days, I didn't even notice it. What causes this effect, and what kind of function would such a process serve evolutionarily?

Jamie: I think that you touched on something that I previously alluded to in that there's temporal dynamics. The way that the olfactory system responds to environmental signals can be regulated across time domains ranging from seconds to hours to minutes to days. And so the type of experience that you just described in Micronesia would be an example where we see this long-term, this change to a persistent, stable odor stimulus across time.

What I found, during my post-doctoral studies, was that relatively stable changes in odor environments or odor activity across time can induce a type of plasticity that we refer to as synaptic homeostasis. And homeostatic plasticity, or synaptic homeostasis, is essentially that neurons are thought to operate within some optimal set point. And if the activity impinging on that neuron is either driven too high or too low, the neuron can

basically go in and regulate the total integrated strength of the synapses impinging on itself so that it gets back to its optimal level.

And so, what I found in the olfactory bulb of rats is that if one were to go in and deprive a rat of olfactory experience from anywhere -- I found the shortest time period that I found this effect was across three days, but up to 14 days -- then what we see is that the strength of the synapses responsible for processing the odor stimuli are actually stronger. And so, if it is a true homeostatic process, we would expect the opposite to be true.

So what you described in Micronesia is that you went there, and initially you found this really bad odor, this garbage smell, existed. But after 17 days, you didn't notice it anymore. So what I would predict, based on my findings, is that the synapses that are responsible for processing the odors associated with Micronesia, whatever they may be, basically the synaptic strengths are down-regulated. So the information can't get in as easily. It's not as reliable coming into the nervous system.

Peggy: That's very interesting. You also give me a new view on camping, how you're out in the woods, and, all of a sudden, that coffee smells so much better than it did [laughs] when you were home.

Jamie: It does. And that's another interesting part about the olfactory bulb. There's lots of interesting things about olfaction. I don't know that I'm necessarily interested in olfaction as much as I am how experience influences plasticity or synaptic transmission. But like I said, the olfactory bulb really provides a unique model, so when I started thinking about using it as a model system, I started studying.

So one of the interesting things that you just pointed out, say, if you're camping, and the coffee smells much better, right? It's really because, at any given time, your olfactory receptors are not just processing the odor of the coffee; it's the context of the environment. So it's also in relationship with other odor molecules that are also binding to other receptors at the same time.

So you have, in humans, like six or 700 olfactory receptors, and at any given time, you could have two or 300 of them active. So you can imagine that the way that the olfactory system provides input to the brain is it basically goes through a lot of arousal and affective areas -- areas that control emotion, areas that control overall arousal. And there's even recent evidence that there's some direct projections from the olfactory bulb directly to the hypothalamic regions that actually control ovulation in females.

And so we're starting to understand that there's all these pathways that olfactory receptors bind. They bind odors in the olfactory epithelium, it's transmitted to the olfactory bulb, and from the olfactory bulb it's dispersed and distributed throughout the brain, and so it can regulate lots of different levels of behavior.

Here's a good example. If you go into a coffee shop and it's also a bakery, and they're baking muffins and bagels or whatever they bake, and cooking egg sandwiches, whatever they bake in the bakery, the cup of coffee isn't going to have the same type of input, because it's in the presence of all these other odors, right?

But if you're in a natural environment, where there's not as many odors bombarding your olfactory system, then the cup of coffee might carry a higher saliency, right? Because then it's like you can really, really identify with the specific elements that are giving rise to the odor of the cup of coffee.

Peggy: So if you're going on that hot date and you're bringing flowers and chocolate, it may pay off.

Jamie: If you roll the windows down.

Peggy: If you roll the windows down. Yeah, OK.

[laughter]

Peggy: I'd like to shift gears and talk a little bit about the other direction your research is taking, which centers on the development of some novel, drug-free, noninvasive treatments for CNS disorders. One technique you've termed "hypersonic neuromodulation." First off, can you tell me what hypersonic energy even is?

Jamie: Well, hypersonic energy is essentially sound: cyclic energy that's above the frequency which we're capable of hearing. So, humans are capable of hearing sound frequencies ranging from about 20 hertz up to about 20 kilohertz. So anything that has a higher frequency range, higher than 20 kilohertz, we would refer to as ultrasound or hypersonic sound. So there's nothing really magical about hypersonic sound; we just can't hear it.

Peggy: I know one treatment that utilizes another modality, light, to correct, for example, seasonal affective disorder. How is it that energy from outside the body can cause changes in our nervous system to the extent that it could be used in the potential treatments of things like depression or anxiety or coma?

Jamie: Our nervous system is really designed to perceive stimuli from the external environment. So if you think about touch, right? We have specific receptors that are designed to process touch. We have specific receptors that are designed to process temperature. And these are only the receptors that we know about, right? There's other types of receptors.

So the example we were talking about, using blue LEDs or blue light to treat seasonal affective disorder, we don't really know a lot of the receptors that are there or why this blue light may be working; we just have evidence that it works. For example, in the central nervous system, we have vagal nerve stimulation has been used extensively to treat depression. And this is basically where they wrap an electrical coil around the vagus nerve and then stimulate the vagus nerve. So we just know that it's stimulating activity.

Another example is deep brain stimulation, where they implant electrodes in particular nuclei in the brain, and then you wear like a pacemaker. So you have electrodes implanted in your brain which basically controls the electrical activity. But it's actually been shown to alleviate many of the symptoms associated with Parkinson's disorder. There's also repetitive transcranial magnetic stimulation, all these things.

One of the most interesting things is, recently, a study was published in "Nature." There was a patient who was in a coma for six years. He was actually mugged and beaten badly and left for dead, and then neurologists went in and implanted electrodes in his brain, into his thalamus. He had some types of conscious activities, so every now and again, he might be able to blink or respond. So there was some level of activity, but for the most part, he was basically in an incapacitative state.

So neurologists went in and implanted electrodes into his thalamus and began stimulating. And over a short period of time, he made not a complete recovery, but he began to be able to talk. He began to be able to recognize people, to feed himself, to watch TV without falling asleep. For the most part, he made, really, a miraculous recovery.

And we're not really sure that we understand the mechanisms that are at play. The thalamus, the area that they stimulated, is basically a gateway. It's the sensory gate, so it allows what gets into the cortex. And if there's some disconnect between the cortex and the thalamus, we may expect that stimulating the thalamus might give rise to this. But on the other hand, I think it's completely unexpected that we can just deliver this type of bulk activity without any type of particular pattern. So it's just activation.

So it's interesting that there are all types of energies that the body processes, and we're not really sure how it happens or why it happens, but we're starting to become more and more aware that it is possible to control some of these neurological and psychiatric diseases using energy from outside the body.

Peggy: But in the last one you described, you were talking about implanted electrodes.

Jamie: Right.

Peggy: So what about hypersonic neural modulation, which, you don't actively hear it, but some part responds to it?

Jamie: Right. So, just to give you some background, I've been working with an engineer, Mike Fensterwald, who I consider to be a really, really bright engineer. He's a sound transducer engineer, so he builds ultrasound transducers. He designed the ultrasound transducers that GE is now using to perform ultrasound imaging. I met Mike through a fortuitous set of events. It was just basically luck, essentially.

An idea that I thought about for a long time is how sound might be able to modulate synaptic transmission. In fact, I came up with the idea when I was a graduate student, because I used to play the music really loud when I was doing my experiments. And apparently, it was obnoxious to some people, and they would ask, "So why do you have to play your music so loud?" I was like, "The neurons are healthier if I play the music loud."

I was just kind of joking, just to see if I could get a response out of them. But then I had this idea that sound vibrations or mechanical energy could cause a disruption in membranes and, through the disruption in the membranes, could mimic natural processes for releasing a neurotransmitter.

So, what Mike and I are doing with sound now, ultrasound transducers, is we're basically using those transducers and positioning them away from various types of tissue, both in intact animals as well as in brain slices. And we're projecting various waveforms of hypersonic energy into the tissues and finding that we can control synaptic transmission. But we're using a stimulus, a sound frequency that's in the kilohertz range.

And what's interesting about kilohertz sound--like hundreds of kilohertz, right? This is way above what we're capable of hearing. What's interesting about hundreds of kilohertz is that we can actually penetrate bone, muscle, and tissue with very little power loss, whereas most of the sound-based therapies or sound-based techniques that people use for imaging rely on megahertz sound.

In the megahertz frequency, there's a lot of energy that's needed and it doesn't readily penetrate bone. So what we think we are going to be able to do is to be able use triangulation techniques, or constructive interference techniques, different types of constructing waveforms, to be able to penetrate, localize, and target sounds to regions within the brain to control neural activity.

Peggy: And so the hypersonic sound causes release of vesicles?

Jamie: Imagine a jar full of marbles. The jar would represent a synaptic terminal. This is a pre-synaptic compartment where neurotransmitter-containing synaptic vesicles are located. So if you go to your jar and you look at your jar, you have a series of marbles in your jar. And if you look at the bottom of the jar, the marbles at the bottom of the jar represent vesicles that we refer to these as "docked-and-primed". These are vesicles which are capable of being released. They're also constructed of a lipid bi-layer, like all the cell membranes of our body.

In the pre-synaptic active zone, the place where they actually fuse and there's a pore that's formed and they release their neurotransmitter contents is also a lipid bi-layer. So one of the processes we think may be happening (and we're testing these hypotheses now), is basically the sound will cause a resonance of the pre-synaptic membrane or the vesicle, and through this resonant interaction, it will drive the synaptic vesicle into the pre-synaptic membrane and cause the release of neurotransmitter.

To look at this, we're using a genetically-encoded opti-physiological probe known as synaptopHluorin. When I was at Harvard, there was a graduate student Jean Lee who made some mice using this probe synaptopHluorin. The interior of a synaptic vesicle (the inside of a synaptic vesicle) has an acidic pH. For synaptic vesicles to repackage themselves with neurotransmitters, so after a synaptic vesicle bonds and releases its neurotransmitter, and to get neurotransmitter back in, it uses an ATP-dependent proton pump. So this is a pump that pumps protons into the synaptic vesicle and then there's another pump that will pump neurotransmitter in and a proton out. But the interior of a synaptic vesicle has an acidic pH.

So this guy, Gero Miesenbock, constructed this probe synaptopHluorin which is basically a synaptic vesicle protein that forms a fusion within the pH sensitive GFP. At rest, with an acidic environment, the fluorescence of the GFP is quenched. But when a synaptic

vesicle bonds to the pre-synaptic membrane, you lose the proton concentration in the synaptic vesicle, the pH shifts towards neutral, and we see that there's an increase in the fluorescence intensity of the synaptophysin. So we're basically using tissues from these mice, or these mice in certain in vivo applications, to be able to say pretty definitively that we are controlling synaptic vesicle exocytosis or controlling synaptic vesicle fusion using hypersonic sound.

Peggy: It seems like something like hypersonic neuromodulation could revolutionize medicine in multiple ways. Are there any examples where it's already being used in treatment?

Jamie: For all kinds of treatment, actually. Many of the athletes out there will know that they've had these ultrasound massages, thought that most of that therapy was based on heat. So it's heat generation from energy transfer from the transducer into the tissue. That's just one example. Other examples:

One of the really cool areas is they can actually, using megahertz transducers, ablate cancer cells. So they also do hypersonic-assisted surgeries, people use hypersonic sound to facilitate bone healing, wound management. With wound management, people know now that hypersonic sound can prevent bacterial infections, as well as promote through unknown mechanisms, the healing of tissues. Not to mention ultrasound imaging, everyone's familiar with ultrasound imaging.

Now we can see these 3-D structures of the fetus in vivo, so you can actually see it looks like a little alien. You get this composite picture of this little alien. So there are all kinds of applications and medical applications where people do use ultrasound in medicine. I'm not sure that what we're working on is necessarily going to revolutionize the use of sound in medicine, but it will certainly change things.

Peggy: Where do you hope this work will take you down the line?

Jamie: Oh no! It will give me something to occupy my mind! That's my biggest hope.

That's a really difficult question. If you'd asked me five years ago what I would be working on, I would tell you that I would at least have at least one component. I would be examining the role of environmental experience and sensory experience on the way that information gets into the nervous system, sensory input gating. So this is something I've been after for a while. Now that things are starting to take off and I'm working on more neural engineering approaches. It's very hard to predict what's going to happen.

I think the reason I ended up in this position is because I've realized that we really have a pretty good understanding of what's happening in the nervous system. Like we know -- there's a lot that we don't know -- but we do have a good understanding of how neural activity arises in the nervous system and how changes in neurological activity affect the nervous system.

So in the future, I just want to keep enjoying what I do. I enjoy my science, I enjoy having something to think about, I enjoy having a challenging problem to try to solve. It's

just really nice to have something that you can't figure out. I don't know where I want it to take me, but we'll see.

Peggy: You're glad you're on the ride?

Jamie: Oh, I'm going to enjoy the ride for sure! I'm definitely going to enjoy the ride, because it's just fun. I get to see things and do things that a lot of people have no idea exist. It's a real privilege in academic science and a lot of people don't realize that you're honored to be in this position where you can go in and study these things. It's exciting. It's a complete unknown. So I don't know where it's going to take me, but it's going to be fun.

Peggy: I just have one more question, and it's completely unrelated to your work. I heard that you're into mountain climbing.

Jamie: Yeah, I enjoy being outside. I don't know what to say really.

Peggy: So what attracted you to this sport?

Jamie: Ever since I was a kid, I've always enjoyed being outside and "playing in the woods" as we used to say. I enjoy it because it's kind of like the mental challenge of performing science, conducting academic science, it provides me a kind of physical challenge as well. There's always some element of the unknown. You don't really know what you're going to face. You're putting yourself out there in the environment. And you're just pushing forward.

I think the rewards are great, too, because it gives you a lot of alone time just to think. The people that I do know and that I climb with – I have really good, really trusting relationships with them. I don't know, there's just something about it I just can't really describe. I just enjoy being out on the rocks and going as high as I can. It's just fun.

Peggy: What climbing experience had the greatest impact on you so far?

Jamie: Oh no! I can't say that one on-air!

Peggy: OK! OK! We can't talk about that.

Jamie: Fourth of July one year... yeah, no.

Peggy: OK, so maybe we can ask, so what's next on your list in that regard?

Jamie: What's next on my list? I don't know. There's a lot of things I'd like to climb. I just like being out there. You can get lost. It's a totally different world.

Peggy: Well Jamie, I want to thank you for taking time to sit with me today. I wish you the best of luck in all your research and your mountain climbing.

Jamie: Thank you.

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Peggy: This is Peggy Coulombe and you've been listening to School of Life Sciences Podcast Science Studio. Our theme music comes from the website Magnatunes and was composed by Yongen from the collection "Moonrise". The School of Life Sciences is in the College of Liberal Arts and Sciences on the Tempe campus of Arizona State University.