

## Summary/Q+A

Okay. So the things I'd like for you to take away today are that:

- Psychological factors including attention and emotions activate endogenous modulatory systems in the brain that can increase or decrease pain.
- Some CAM therapies alter psychological state and may alter pain through these mechanisms.
- Chronic pain and CAM therapies have opposite effects on brain anatomy.
- And acupuncture and brain stimulation have strong placebo effects that may have independent mechanisms.
- And placebo analgesia involves descending modulatory systems, including those using opiates and dopamine.

And I'd like to thank my collaborators. And some of these collaborators have come down here with me, Marta Ceko, Chantal Villemure, Lucie Low, Scott Thompson. And we have others that are not on this list that have joined our group since we've come here. But anyway, I'd like to thank all these people. Thank you.

[applause]

[Dr. Briggs]

Thank you very much, Dr. Bushnell. There is time for a few questions.

Have there been any studies comparing buprenorphine for opium addicts who are in chronic pain versus morphine with naloxone... [unintelligible]

[Dr. Bushnell]

A: The data on the effects of naloxone alone on chronic pain are mixed. So it may have some small effect but not a huge effect.

Q: Are any of the gray matter zones that you've seen have different thickening? Are they affected in Alzheimer's, any of them?

A: Well, yeah, I don't know the Alzheimer's literature, but all the frontal cortexes, in my understanding, is altered with Alzheimer's, and Alzheimer's patients have altered—they actually feel pain less than their matched controls.

Q: So is anybody looking at any of these CAM therapies for persons at Alzheimer's risk?

A: Not that I know of. But it's...it could be interesting.

Q: [Dr. Briggs] Can I ask you to speculate about these changes in size of certain brain regions? In the chronic pain sufferer in which, say, the anterior cingulate cortex is smaller, and yet is often activated. How do you think about why activation would be associated with decreased size and how might one get at them—?

A: Well, this is something that we have a basic lab that we're working on at the same time because this is over the last as I said, by now almost 10 years since 2004, there's been a ton of studies in all different types of pain conditions showing less gray matter. But now there's been three studies including one that we were involved in with David Seminowicz, that in fact shows if somebody had chronic pain for a long time, then they have pain relief, if they have osteoarthritis and have a hip replacement, or they've had back pain and they have successful surgery, that in fact some of these changes can be reversed and in a fairly quick time period—in the matter of a few months. So what we were thinking of this as really cell loss, more and more we're thinking of it as changes in synaptic connectivity and dendritic arborization, and so that's why we're going back to the animal studies and looking. So far we tend to see increase in neuroinflammatory responses that could probably alter some of this neuronal structure more so than actual cell loss. So I mean, it's still there, the areas are still there and they're still going to be activated, and I think that it's just that they're not—you're getting changes in the way neurons are talking to each other.

Q: In your research, have you found ethnic or racial group differences in pain outcomes; and if you have, can you please speculate on what you think is happening there? And if you have not, can you please expound?

A: Okay. We have not studied that at all. In Florida, Roger Filingham in his group, really the only group I know of that has been publishing on racial differences, and I think it's a very important factor. And now that I'm back in the States and not in Canada, where there's—it's a much more homogeneous population in Canada, and it's harder to do these studies that, I think it's important that the whole issue of genetics and pain is something that a lot of people are involved in. And so there's the cultural aspects, there's the genetic aspects, there are chronic pain diseases that are specific for African-Americans. We're actually going to be studying—doing some work with sickle cell pain and as a chronic pain condition, so I think it's an important subject matter that has not been studied the way it should be.

Q: Thanks, that was a great talk. There was a suggestion in your answers about the neuroinflammatory pathways, and I was just wondering, there's evidence to show that cytokines are involved with craving for alcohol or the change in response to your mood or your hostility and that kind of thing. And it seems like when you have a loss of brain matter, gray matter particularly, you'd expect to see changes in the cytokine responses through neuroinflammation. Have you ever thought about looking at CSF cytokines?

A: We actually are going the route of looking—there are some markers for astrocyte and microglia activation and where we can do PET scans and we can look to see these activations in the brain, so that's kind of—but I agree, the CSF is just a little more invasive. But there is evidence clearly a lot of animal evidence now, a lot going on studies at the level of the spinal cord not so much of the brain. But we have—there's some—a few studies that are showing that in the frontal cortex, there is increased inflammation in these areas after long-term pain, so I think this is a very important area of study that we'd like to get into more.

Q: I have a follow-up question on the acupuncture. Trigger point injection is widely used, where you just inject a little bit of lidocaine intra—is that the same principle as acupuncture, or is there...? [inaudible]

A: I think there's a lot of placebo—a lot of acupuncture studies, and maybe Josie probably knows this more than I do even, but I think there's a big placebo effect as I showed you. But there seems to be something over and above that, and it's intriguing, this brain imaging study that shows that the placebo response is actually maybe mediated by a different neural circuitry than the acupuncture response. So there's different types of acupuncture. There is painful acupuncture, electroacupuncture that's actually activating pain circuitry, and then you're engaging what we call diffuse noxious inhibitory control, the NIC where one pain alters another pain. And that's been well worked out, the circuitry of that, like a spinal brainstem loop that's been worked out in animal studies. And then there is the nonpainful needling that creates a tingling sensation and more so at certain spots than others. And there is again animal literature showing how tactile stimulation can alter pain pathways as well. So there's some physiological bases on that independent of the placebo component. But I think there really is a strong placebo component as well that seems to show up in the studies.

Q: [inaudible]

[Dr. Bushnell] Well, I think there's multiple mechanisms that can be happening.

[Dr. Briggs] You know, it's an interesting well-known fact that some of the trigger points that are described in fibromyalgia and other conditions overlap with some of the classic acupuncture points. They don't completely. But it is also, as Catherine is saying, in all the experimental work on acupuncture, there is such a strong placebo effect. This is a very effective way, the rituals of acupuncture are a very effective way to activate expectations and perhaps change the emotional state that alters pain. So that always makes it hard to pull out specific effects. There are some hints of it, but it's not really clear-cut. I think we have another question there.

Q: In the study of cortical thickness in fibromyalgia patients, the older patients had more loss of cortical thickness, was the duration of their illness taken into account?

A: Yes, it was kind of a busy slide. There was a little thing right above it showing the duration. In one area, which was premotor cortex, that was the only part of the brain where we saw a duration effect and the others, the duration—and young patients, some of them had quite a long duration pain, so we were surprised. We thought duration would be the factor, but it doesn't seem to be a factor, seems to be age was coming out and duration wasn't.

[Dr. Briggs] So if there are no more questions, I think it's time to wrap up. We at NCCAM are really excited about being able to bring a scientist of Dr. Bushnell's capabilities to this campus and the capabilities here for an integrated trans-NIH

pain program. Tomorrow, one of the Statman fellows who's a potential person we're interested in recruiting, Alexander Chesler, is giving a talk, so people interested in pain may be interested in that as well.

[Dr. Bushnell] Noon in building 49. He uses natural products as a way to probe and toxins as a way to probe the pain system. It's really fascinating work.

[Dr. Briggs] Thank you all for your attention.