FROM CHRISTIAN SCIENCE TO THE PLACEBO EFFECT: A CHAT WITH TOR WAGER

Tor Wager, PhD, is a Professor of psychology and neuroscience and the Director of the Cognitive and Affective Neuroscience Laboratory at the University of Colorado, Bolder. Together with his lab, Wager investigates the pain pathways underlying the generation and regulation of pain and emotion. Wager sat down with Lincoln Tracy, a research fellow from Monash University, Australia, at the 2019 Australian Pain Society Annual Scientific Meeting, which took place April 7-10, 2019, on the Gold Coast, Australia. Wager discussed how his Christian Science upbringing contributed to his interest in the placebo effect, how clinical trials need to place greater emphasis on psychosocial context, and the importance of taking an anti-competitive stance in research. Below is an edited transcript of their conversation.

What was your path to pain research?

I started studying pain because I was interested in placebo effects—and pain was the most prominent area for studying placebo effects. I think I've always had an interest in what we can do with our thoughts, wondering what kind of processes or outcomes can our conceptual thoughts influence? Does it matter what you think? I feel that the placebo effect was one way of studying the relationship between our mind and body.

At first, I was nervous because I wasn't originally trained in pain research, in a pain lab—I was trained in cognitive neuroscience. It seemed scary, like it was a whole different world, which it is! But the more I studied pain, the more I found out how important it is—and that it is a rich area for science. You can do psychophysics on pain because you can control the input to the body very carefully, and fit curves and models to really understand a lot about how it works. Yet pain is also still a process that is heavily influenced by emotion, cognition, and social context—it's quite interesting.

If you weren't working in pain research, what do you think you would be doing?

When I was little I was raised in Christian Science, which is a religion that believes in a very strong version of mind over matter and the power of thought to heal.

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I think I was always interested in that from a scientific perspective—wanting to understand if that matters. I was curious about the power of thought—in what ways is it powerful, and what are its limitations? Are there benefits if you have a strong belief in self-healing? When I think back to why I got into the field of psychology and neuroscience, that was always something that was there.

Then later when I was doing my PhD, I studied the control of attention, which in a way is another aspect of the power of thought. Thinking about self-control and self-regulation—how can you use goals and

instructions, things that you tell yourself to shape your attention? It's a very powerful process. After I finished my PhD I had a choice whether to give my job talk on my dissertation or the placebo effect—and I chose the placebo effect because it just seemed so interesting. I had my doubts about it, but I realised that was where my heart was and went for it. And I think it was a good decision.

What has been the most interesting study you have been involved with?

There are a few studies that have been real turning points for me. One is our first study on the placebo effect in Science, which was two studies in brain imaging showing both reductions in pain-related areas during pain and increases during pain anticipation in frontal striatal systems. This study provided evidence that something important was going on from a physiological perspective. There was also a follow up study in PNAS that looked at opioid release associated with placebo effects. Those two papers really launched me into placebo research.

Another major turning point would be more recently, when we published our pain signature paper in the New England Journal of Medicine. That paper marked a real change and consolidation in how we started thinking about—and analysing—brain data. We've started using these things more as defined measures that we could characterise across studies. This has really been the paradigm that has dominated my research program over the last few years.

Looking forward over the next five to 10 years, what's the next big thing for pain research?

I think there are several big things. One important thing is that the pendulum is really swinging back towards appreciation of the power of the psychosocial context to influence pain long term, both clinically and in terms of the brain processes that mediate them. We are always learning from our experiences and our brains are changing all the time—there is neuroplasticity as we understand our experiences. But this isn't passive. The environment doesn't just make our brains learn. What we learn about and what we take away from our experiences depends on what we bring to the table—it depends on our assessment of what those things mean.

I like to use a headache as a simple example. When you have a headache, you take an aspirin and you lie down for half an hour, and eventually you feel better, right? But what caused you to get better? And what did you learn from that? Do you learn that aspirin is great? Do you learn that resting is great? Would you have gotten better anyway? What you take away from that situation is anybody's guess—but we make these decisions and causal attributions all the time, and that guides what we learn about. I'm interested in thinking about these things, how suggestions and context impact and shape what we learn from experiences over time and how these influence the rest of our lives.

The second area that is really understudied—because it's very difficult to study—is how drugs interact with or depend on the psychosocial context. There is still a lot of money being spent on drug trials in pain, and these trials are failing at increasing rates. As I understand it, clinical trials almost never measure expectations or manipulate the context. There is just the assumption that if you want your drug to work better—to see a greater drug versus placebo difference—then you need to eliminate the psychosocial support. But this assumption might not be true at all.

An antidepressant just doesn't make you better magically—there are examples in the literature that some drugs will only work if you have the psychosocial context. Therefore, if you have no hope,

no social support, and are completely alone and isolated in a cell, is getting an antidepressant really going to make you better? If there is one thing I'd like to see changed, it would be a change in the culture and support in the regulatory environment for clinical trials. A change like this would allow drug companies and researchers to study psychological context during drug trials.

Looking back over your career in pain research, is there anything that you've really changed your mind about in terms of placebo effects?

When we started doing these studies in placebo and pain, I initially thought that it wasn't going to work at all. I just couldn't believe that what we were doing was actually going to influence people's reports. It was like, "the stimulus is right there—you can feel it, you can judge it". But with the right paradigms, the placebo effect has been remarkably robust. The psychological influences on pain can be much stronger than I ever thought they could be.

At the same time, when we saw the results of our first placebo effect studies it seemed like the placebo treatments were just turning down the stimulus intensity. We assumed that the default mechanism of action was the descending modulation of spinal cord input—because that's what is in the textbooks. But we found that what is actually happening is more complicated than that. There is probably spinal modulation under certain conditions, but there is very strong psychological context influencing what happens. And importantly, the brain circuits that are involved in placebo effects are those that relate to the value of pain, and the emotional response or effect of pain.

What are the important things you try and teach the students and trainees you work with?

I think you have to love what you do, and do it with love—that's what is going to make you work hard, right? Finding the meaning in what you do and doing it to the best of your ability. I also take an anti-competitive stance to my work—I think that we are all in this together and while you should do as much good work as you can, you should share as much as you can as fast as you can. I'm in research to do some good, and the worst thing that could ever happen is that my data and my ideas would die with me. We get paid to do research, so why not share it?

When you're not doing research, what do you do?

I used to have a lot of hobbies, but now I try and spend a lot of time with my family—my kids are 13, 10, and 5. Both my wife and I work hard, so we really want to give the time we're not working to them. And it's tough to get the balance right sometimes—so I really try and compartmentalise things. So, if I'm at a talk, I'm only at a talk and I'm listening intently. When I'm with my kids, I'm only there doing something with them—I don't have to worry about other things while I'm there. It's an important skill that we try to cultivate in academia but not one that we always get right. There have been times where I have tried putting a kid in front of the TV while I work, but you feel guilty while they are sitting there—and it's just a big mess. At the end of the day it's a choice, and one that we practice, with the goal of being able to do it perfectly.

Do you have a favourite song, or piece of music?

That's a hard question. I have different songs that I associate with different periods of my life. I really like the older albums of U2. But there are certain songs that are somewhat spiritual to me—they move me, make me contemplate. I associate it with the idea of ragas in Indian classical music. There are different keys or scales that are

used at different times and for different occasions. There are ragas that are played in the morning, some that are played in the evening, different ragas for different seasons. Music carries lots of associations, but when you over use a song in a variety of different contexts, it loses its meaning and the ability to evoke specific emotions at a certain place and time. Personally, I really like the idea of different songs for different occasions. For example, occasionally I listen to Zbigniew Preisner's 'Requiem for My Friend' if I'm falling asleep, because it's very calming and meditative. Then there are a different set of songs I play every time I'm walking through an airport.

Thanks very much for your time, Tor.

No problem, that was really fun!

Lincoln Tracy is a postdoctoral research fellow in the School of Public Health and Preventive Medicine at Monash University and freelance writer from Melbourne, Australia. He is a member of the Australian Pain Society and enthusiastic conference attendee. You can follow him on Twitter (@lincolntracy) or check out some of his other writing on his website

Related reading

Placebo-induced changes in FMRI in the anticipation and experience of pain.
Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD.
Science, 2004.
Link to full text.

Placebo effects on human mu-opioid activity during pain.
Wager TD, Scott DJ, Zubieta JK.
Proceedings of the National Academy of Sciences of the United States of America, 2007.
Link to full text.

An fMRI-based neurologic signature of physical pain.
Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E.
New England Journal of Medicine, 2013.
Link to full text.

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