Tor Wager: Understanding the placebo effect

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Dr. Wager is a Professor of Psychology and Neuroscience and a faculty member in the Institute for Cognitive Science at the University of Colorado, Boulder. He received his Ph.D. from the University of Michigan in cognitive psychology in 2003, and served as an Assistant and Associate Professor at Columbia University from 2004-2009. Since 2010, he has directed Boulder's Cognitive and Affective Neuroscience laboratory. He has a deep interest in how thinking influences affective experiences, affective learning, and brain-body communication. His laboratory also focuses on the development and deployment of analytic methods, and has developed several publicly available software toolboxes for fMRI analysis.

Serge Prengel, LMHC is the editor the *Relational Implicit* project (http://relationalimplicit.com).

For better or worse, this transcript retains the spontaneous, spoken-language quality of the podcast conversation.

Serge Prengel: This is a conversation with Tor Wager. Hi Tor.

Tor Wager: Hello.

Serge: So the focus of your career has been to study the placebo effect.

Tor: Right. I've been interested for a long time in what we can do with our minds to promote healing and well being. And it relates to the idea that health is not just the absence of disease but its an active process that's constructed in large part by our brains, by what's happening in us and around us all the time. And so, I think, I see mental health and a lot of neurological health as being about what's happening endogenously, or inside your brain, and how your brain and you adapt to your presence circumstances. I think it's been really fruitful and interesting for me because I'm finding that a number of the processes that are likely involved in showing a therapeutic progress response are really processes that are about how a person responds to the context or to the situation, so they are essentially self healing processes.

Serge: So, what we're talking about is what makes all of this possible is actually… we're not talking about something that is purely unfiltered stimulus response, something happens and creates pain… but it's a filtered, a constructed process, and we're not just talking about pain, but we're talking about health in general, where the constructed process means there is some filtering from the brain, and this is what makes all of this possible.

Tor: Right. If you think about what the mechanisms underlying placebo effects are, there are many. There are relatively simple stimulus responses, stimulation processes, or stimulus association processes, so things are triggered unconsciously. There are placebo or therapeutic contexts that can trigger changes in emotional state, which are based on how you appraise the situation. And there

are also roles for cognitive contributions, for things like expectations, which are really thoughts about the future, but future implications and consequences. There are also other kinds of cognitive effects that relate to how we remember past experience, given the treatment context. And how we think about the social world, how we feel connected to other people. So I think all of these, there are many mechanisms underlying placebo effects, and they range from these very low level ones to very conscious, cognitive, elaborate ones. And part of our job as researchers is to understand how to unpack those mechanisms and understand what their relative contributions are.

Serge: So…

Tor: In my view, a lot of what creates mental health, and some of it physical health, not all of it, is constructed. So I see emotion as a constructed phenomenon, it emerges from the interaction of many systems working together. And your emotional response in life, in health, in turn contributes in certain ways to physical health. So, I think there's nothing magical here. It's not as though you can always think yourself better and into physical health in all circumstances, but that there are some defined pathways by which emotional responses happening in your brain can influence your body, can influence your state of well being in ways that can really have an impact on your long term health.

Serge: Yeah. So as you talk about it this way, then, in a way it's changing perspective on the way in everyday language we talk about placebo, because in every day language we talk about placebo we focus on the 'this is a harmless pill, this is a sham, this is bullshit,' and in fact what you're talking about is that what makes it possible is actually a very complex view of what is healing and what is health that takes into consideration this constructed… the interaction of many processes influencing health, including brain processes.

Tor: Right. The word placebo has always been a very tricky word, because it's used to identify something that by definition has no direct pharmacological or physiological action, but rather works by the context, by changing what a person thinks about the treatment itself. And so, for many people in medicine, a placebo effect by definition is a null effect. It doesn't work. And this has been additionally sort of confused because where the person in a clinical trial takes a placebo and gets better, that's a placebo response, but it's not clear whether there was an active mechanism there, it's not clear that it was caused by something happening in the person's brain. For various reasons. They might have gotten better anyway. There's a certain sort of very… fluctuating up and down and they [indiscernible] sort of symptoms at a high point. There are other kinds of statistical artifacts as well that all go to a placebo response. And so that doesn't prove that the placebo is actually having an active effect, however a number of other experimental studies done, really over the last sixty or seventy years now, starting in the fifties with Beecher, really demonstrate that placebo…. taking a placebo can have active effects in how you interpret the treatment, what you think about the treatment. It can effect how much pain you feel, how much distress you feel, depression, Parkinson's disease symptoms, movement and reward learning, and probably other types of outcomes as well. So in that sense that's a placebo with a real effect, but the effect is mediated through the brain itself.

Serge: Mhmm.

Tor: Now, another part of this that you alluded to earlier is, what happens when a person takes… goes to a doctor or a hospital, and takes an active drug, takes a painkiller? Now, they get the drug,

but they also know they're getting the drug, so they get the social context of the caring physician, the y get the hospital or the actors environment so they get the physical cues that have been associated with healing and treatment in therapeutic responses in the past. They, hopefully, have an enhanced sense of trust and belief that they will get better. Their emotional state might well improve, and they have, perhaps, more specific lower level associations between the act of taking a treatment, being treated, and even the physical characteristics of the treatment in itself. And therapeutic responses in the past. So, depending on the situation, all of those things could be active ingredients of the placebo. So, now go back to the situation where the person is taking a painkiller, standard painkiller, they have all these potential mechanisms at play and not just the pharmacological actions of the drug. So in several studies, what has been shown is that in some cases about half of that drug effect, or in one case at least, all of that drug effect is actually due to that context, is due to the social and contextual mechanisms rather than the pharmacological actions of the drug.

Serge: Mhmm. and what you're… so it's half due to the drug itself, if you want, and half is due to the social or emotional context, but what your studies show is that it's not just that people report it, but they actually experience it that way as far as can be traced by observing what is happening in their brain.

Tor: Right, we started doing brain imaging studies, fMRI, and less frequently PET studies, positron emission tomography studies. Well, about… almost fifteen years ago, now, and really the point of this was many studies have demonstrated that placebos can change what people reported about their pain, they can cause reported pain relief. And that's actually our best guess about what people are really feeling. Right? There's no better way to tell how someone's really feeling than to ask them. But, we also know that people's self reports of pain are very complex. Their judgments are based on very complicated social and cultural context. And we know we can influence people's reports in ways that are sometimes trivial. If you take a rating scale and you change the anchor point of the scale it will change people's rating sometimes dramatically, if you give them reference frames that are differ it will change their rating dramatically. So we don't think these things are rally meaningful in the same way as an active pharmacological effect produces a meaningful change. So, that's why we started using these brain imaging studies from years ago. And what we've been able to find over a series of studies is that the regions in terms of pain, the regions most commonly associated with the processing of that pain in the cerebrum show reduced activity show reduced activity when taking a placebo relative to a matched control condition. So in these studies, each person serves as their own control, they get a placebo treatment in one case, and they a control treatment which is often an identical cream, or sometimes a nasal spray, or sometimes an injection. And then they're tested under the placebo condition and the control conditions. And we usually do this by applying a thermal stimulus to the arm, so it's a hot probe, it heats up to a specific temperature so it's painful but not damaging to the skin. It's like holding a hot cup of coffee, essentially. So when we do this task we apply the same temperature on the skin with the placebo and without, and what we can see is a drop in the pain people report with the placebo, and a drop in activity in the brain areas that are most closely associated with pain processing, and increases in some areas of the brain that are associated with the use of context and the use of ignition to change goals and physiological outcomes. Also to ascribe meaning to events and value, and to create and resolve stress. So a number of these circuits that are probably involved in the mechanisms of creating that pain relief. And one other important finding, I think, for me, that we've been able to show, is that we know a lot about pain control systems in the brain, although we have much more to learn, and one of the main systems is the endogenous opioid system, so your brain will release

opioids in different behavioral circumstances. It's adaptive, evolutionarily sort of adaptive to block pain, and opioids are involved in many of those forms of pain relief. So what happens when we give people pain with a placebo treatment, placebo cream, is we see increases in the release of endogenous opioids in much of the circuitry that's thought to be associated with pain control. So those are some the ways in which some of the main arguments which we really think that placebo effects can really change how your brain responds to pain in a relatively fundamental way in certain circumstances.

Serge: So I want to go back to what you said. And so, two points. One is that to the extent that reality is measured by activity in the brain in the centers where pain naturally occurs, there's something that can be observed in reduction of the pain, so it's not just a reporting mechanism. And the other thing you were mentioning is something about the involvement of the areas or the circuitry of the brain involved in context and meaning making. And so we're talking about context and meaning making at a level that is pre-verbal. There's nothing about reasoning and cognitive therapy or philosophy about it but it's something that happens very quickly in a way that' we're not aware of, and these functions influence the meaning and experience of pain.

Tor: That's right, and you know I can elaborate on that a little bit by saying that these meaning making systems, I think we have evidence now that they can function unconsciously. That's possible, but they also are influenced by one's reasoning processes and one's explicit conscious expectations. So if I can give you a sort of thumbnail sketch of this system, our working hypotheses now are that, well it's not one system but several, and it's these systems that connect the prefrontal cortex to the brain stem to the body are the ones that are designed to provide control over lower level physiological responses, including pain and your heart rate and your blood pressure and innate motivational responses perhaps thirst and insulin in your body and release of hormones by control of these processes, by the higher level context, by the overall appraisal of the situation that you're in. And so a thumbnail sketch would be that we maintain our conscious expectations and goals in the lateral and anterior parts of our lateral and prefrontal cortex. And this really proves a kind of context that we need to understand where we are and what's happening to us, and to generate emotional appraisals. So we go from the lateral prefrontal cortex to the ventral medial prefrontal cortex, which is an area that is capable of and directly projects to the centers that control various aspects of physiological responses in the body. So it connects to areas that control cortisol release in the hypothalamus and autonomic responses in the brainstem, and pain control systems in the brainstem. And it responds both to cues that influence value and essentially context in a way that is unconscious, and it also responds to information that is very much unconscious, that has to do with goals and what you explicitly value, if that makes…

Serge: Mhmm.

Tor: And so we see this whole process in the prefrontal cortex as being a mix of unconscious priming and unconscious process and conscious goals and expectations coming together to form, really, a picture of the self in context, who you are in context. And that picture of the self in context, in turn, influences pain. It influences other types of emotional and physiological responses.

Serge: Mhmm.

Tor: And also in my view-

Serge: So… go ahead, go ahead.

Tor: So, that's in my view… that process of constructing this situation and then using that to guide pain and other kinds of responses in something that's partly of voluntary control, but not completely. Because its influenced by both conscious and unconscious processes.

Serge: Yeah. Okay so that was the question I wanted to ask. So this is not something that is thought out. There are some conscious processes, but it's a mixture of conscious and unconscious processes. And to try and simplify this is it's some kind of context, not just a context of putting but essentially a context of orienting… this is who I am and where I am. So essentially within that context, the information maybe of the placebo is to say you're not alone with it, there's society as we know it, science, medicine, people who believe in science, the nice person, doctor, whoever, behind you, so there's this message that you're not alone in fighting it. Is this a simple way of putting what you said?

Tor: I think so. I think that some… that kind of social or interpersonal effect can be a big part of the… it can tap into the mechanisms that also create placebo effects. So for example, we find that this area, the ventral medial prefrontal cortex, is an area in your brain, its the third eye in the middle of your forehead, and that area projects very strongly to the hypothalamus, that regulates hormones, it projects to the brain stem, which is involved in pain control and other kinds of basic physiological functions, and it's also connected to the prefrontal cortex, and we think it's essentially involved in the central meaning making process in a variety of situations. Something as simple as deciding what you're going to have for lunch or your value of meaning for now, that s essentially the self in context task. Or you then, deciding what you want to have for lunch, given your dieting goal, that's a part of the meaning making process. So it turns out this same area of the brain is involved in very strongly in placebo responses, so it's activated consistently what you get a placebo treatment.

Serge: So that's meaning making?

Tor: And… and…

Serge: Go ahead. Mhmm… so that meaning making production, that-

Tor: Oh, right. So yeah just-

Serge: That meaning making function is essentially self in situation, which could be given all I know about myself and consciously and unconsciously what am I going to have for lunch, so its an appraisal of where you are and a decision that's made from that. So, in that context when you're describing the placebo its in a way the organism based on all this information in a way saying the odds of fighting the disease are in my favor and something happening as a rule of that.

Tor: Yes. I think that's right. I think that this area of the brain, the ventral medial prefrontal cortex, is the meaning making center in our view, and it has a special relationship with stress, with pain, with control of the body, and so to give you a few examples… we can change activity in this are when we induce a psychosocial stress. So, we can ask a pupil to give a speech in front of an audience. And the one area in the brain that changes the most is part of the medial prefrontal cortex. And the more it goes up, the more the brain stem increases in the midbrain, and the more than happens the more the heart goes up, the heart rate increases. So I really think there's this direct pathway there, and it

really is about a reflection on how the environmental context bears on you, your sense of self. So that's the relationship with placebo that's about the relationship with stress, his last example, and then in terms of pain, you know what we find is that normally if you get a painful stimulus applied to your arm, this area decreases with pain, but, so its the more active it is, essentially, the more pain goes off in many circumstances.

Serge: So the mechanism you describe has similarity with emotional regulation… with affect regulation, with self regulation in general?

Tor: Yeah, it does and there is evidence that this area is quite important for generating and regulating affect for all kinds of appraisals that give rise to emotional experiences, and when a person self regulates and they think pain up or down and they imagine it as horrible and damaging, activity in this are goes down. and when they appraise it as better, you know not so bad, its going to end soon, is a warm blanket on a cold day, its spread around the body, all these helpful kinds of imagery and cognition, then activity in this area goes up. And the more it goes up the less pain people feel. So in healthy people this area seems to be heavily involved in pain regulation. And what's interesting is in people with some kinds of chronic pain disorders that we've seen including [indiscernible] and chronic low back pain, which are both complex disorders that affect people throughout their lives for years and are hard to understand medically in some cases, that the relationship between pain and activity in this area changes. so now, normally when this area is activity, this sort of meaning making center, pain goes down, and in those patients, activations seems to be associated with increasing pain, so one interpretation of that is that they're using these mechanisms in the brain for constructing sense of self in context, for meaning making in the service of enhancing those pain signals.

Serge: Hmm.

Tor: So usually it is potentially something that's happening in their brain that is exacerbating the pain. And given the same level of input from the body it might well feel much worse, because their brain is saying this is significant, this is bad, this means bad things in my future.

Serge: So is this something that could be related to the mechanism by which something is traumatic, the PTSD type thing, in a way we learn, 'I've been burned,' and the negative experience is stored and we have some sort of priority and we go back to it, and in a way go through the intensity of the past experience instead of the present experience?

Tor: So you know, one thing that we've found in looking at studies of PTSD in the brain is that this area that is attributed to the prefrontal cortex again is consistently reduced in activity in people with PTSD. So it's often associated with the regulation of or contextual association of events. In many ways, one of things about PTSD is that there's a failure to contextualize.

Serge: Mhmm.

Tor: So I think the classic case of the bomb on the sides of the road is only one feature of PTSD. After you've been exposed to the bomb on the side of the road and it blows up then any movement on the side of the road can trigger that immediate kind of response. So its a high amount of arousal. One of the main idea underlying some kinds of PTSD symptoms, anyway is that there is a failure

then to contextualize, that that is then and this is now, I'm home safe back in Colorado and there are no bombs or snipers. But the brain still doesn't have context.

Serge: So the context and the ability to realize this was then and this is now and this is safe now. So, I'm just wondering, connecting to that third eye activity that allows to do that, the extent to which this hypothesis, this ability to that makes us susceptible to good effects and to the placebo effect might be related to how we from attachment. And in the same way how we say attachments might have developed our capacity for self-regulation. Is this connected, has this from your experience and studies, is there something that might make sense in that area.

Tor: Yeah, that's a really interesting question. Our working hypothesis now in working in some of our new studies is that how we perceive the social world, so if you have the support from an attachment figure in one of our recent studies, people report less pain and they show changes in the brain that respond to that production of less pain. So having a partner hold your hand, or one that provides support, can be extremely beneficial. This is also true clinically, you know in child birth for example, it's been demonstrated in a number of studies. So we think that the mechanisms that underlie that kind of interpersonal attachment that likely works though the same types of pathways. So essentially they work by changing the appraisals of safety and those appraisals of safety might in some cases even let your body or your brain go into a different mode of processing. Instead of being in threat mode, to put it simply, where in, recover best in recover mode, or play best in play mode, and that shift, right, so that shift in the context and the interpersonal environment, you know, and one's social attachments are an important part of that interpersonal context that then is a main ingredient for putting our own brain into a different state of being, including different perception of pain, including thoughts of whether the future will get better or worse, and other types of emotional responses as well.

Serge: So just to summarize to see that I hear you correctly, then the interpersonal relationship, this interaction, creates… in a restoring that allows the brain to go into a different mode, and a mode from which it can have the resources to integrate the difficult experience by putting it into a larger context.

Tor: I think that's a good way of saying it. The language is a little bit different from what I'd use but I understand it. Integrating an event is essentially perhaps localizing it to a time and place so you know when it's going to end and what it means, and whether it's likely to continue being a problem or not. If that's what you mean, then that process is really critical for limiting our negative responses to events, you know.

Serge: So, I meant it in a way, maybe to clarify it a little bit, the way you describe what I meant by integrate was a little bit bad, but not totally. I also meant by integrate the way you digest food, so you have a bite of food, and at some point after chewing on it and digesting it becomes part of our organisms. So in a way it's experience that's not sticking out, you have absorbed it, you have digested it, it is a part of you. So it at least partly covers part of what you're saying, but it isn't totally what you're saying.

Tor: I agree, that's right. It sounds like it isn't totally the same, but in any case, this integration process is very interesting, because my friend Richard Lane and I have been talking a number of years, and one of his theories about what creates the essentially conversion disorders and somatoform pain disorders and experiencing what originate as emotional distress as pain in the

body is, you could say its in some sense a failure to integrate the emotional trauma that one has experienced, and that might play out in this sense that I think that what our lower brains do, our brain stems for example, can operate in a way that's relatively independent of what our prior processes are doing, are holding and representing, and if that's the case, it might be that that's important for understanding what creates this, let's say a strong emotional response that a person doesn't have any really contextual framework. They think they shouldn't be feeling it or they know what they feel isn't appropriate, but it's there, or even something that they don't experience consciously, its happening in their brain stem and it may not have any conscious access at all, so there's no way that they can contextualize or integrate it or digest it into their overall narrative into their life and their overall sense of self. So they don't integrate it at all and its very difficult to gain control over it in some sense. One process I know that's part of the therapeutic process in psychotherapy is trying to find those things which are really not consciously accessible, or that we can't elaborate, it's just bad, we don't know why it's bad, and bring them into our, close our connection in our sense of our narrative of our lives, whatever it means. So that is… I don't really think we're there yet in terms of the neuroscience, but I think there's some sort of integration between processes that are happening in the brain stem, and the amygdala, and other parts of the forebrain, and these higher cortical representations in emotion and meaning, so there could literally be some kind of process, cortical or subcortical integration, that parallels this becoming aware of things that you weren't previously aware of, and brining them into consciousness.

Serge: Mhmm. Yeah. So essentially a mindfulness process.

Tor: Yeah, mindfulness is an interesting way of putting it, because for me mindfulness is sort of increasingly kind of coming to refer to specific kinds of meditation related practices.

Serge: Yeah.

Tor: You're right, certainly one of the many goals of such meditative practices is to sit and be aware, become aware for thoughts, of emotions that you're weren't aware of before, give yourself space for those things to emerge. They perhaps become easier to integrate, in your language.

Serge: Thanks, Tor. Is this a good place to end, or would you want to add something?

Tor: I think so. I think just one more thing which might be useful which is sort of going back to this idea of the conscious and unconscious interplay, and one thing that we're finding, I believe that how our pain is shaped and even what we expect to happen next, whether we expect something bad or not, is a process that involves our expectation in a very conscious sense. But it also is not completely under our control, and it's something that's learned over time, so I really believe that as e practice a particular pattern of thinking or a particular kind of expectation in response to a particular situation, those kinds of responses become stamped in over time. And so we start looking at those things in a rudimentary way, and we can see how this third eye ventral-medial prefrontal cortex representation of the anticipated value of something is updated as you gain experience with it, and I think that's important, because it speaks to the idea that we only have a limited influence on any one moment in time over this process, but as we practice mentally as we practice taking the right mental stance and having the right appraisals toward things, we can stamp in those appraisals over time. So essentially they get more and more automatic the more we practice them.

Serge: So in other words, choice between reinforcing the built in default mode and stereotypes, or expanding and learning from experience to be more accurate?

Tor: Yeah, that's a good example. In every domain in terms of stereotypes, in terms of negative vs. positive thoughts of the future, optimism vs. pessimism, I think all of out patterns become stamped in over time, so as we change, as we work to change you previously stamped in patterns if they're maladaptive for us, if they're bad for us, then we can sort of change the tipping point, right? But it doesn't happen all at once, it doesn't happen in one day, but over time, those more productive or positive ways of thinking become more and more stamped in.

Serge: Great. Thanks.

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