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| **From:** | Llew Mills |
| **To:** | Scientias nl |
| **Subject:** | RE: A few questions about your study - from The Netherlands |
| **Date:** | Wednesday, 15 February 2023 7:48:56 AM |
| **Attachments:** | image001.png<br>image002.png |

Hoe Gaat Het Caroline!

Thank you for your interest in my research. I would be honoured to appear on your website and more than happy to answer your questions. Please see my responses below. Let me know if you have any more questions.

All the best

Llew

- Can you explain what kind of withdrawal symptoms people can experience when they quit drinking coffee?

Headache and fatigue are the most common in the short term. But once the acute withdrawal phase is over the symptoms are the same as for any drug of dependence: irritability, tension, anxiety, depression, trouble sleeping, and cravings. Most people addicted to caffeine don't know they are because they never go without it long enough to experience these symptoms. Among our participants the model number of past attempts to quit caffeine was zero. Caffeine is cheap, socially-encouraged, and available absolutely everywhere. There is little reason to quit.

- Did the fact that decaf coffee could reduce the withdrawal symptoms surprise you in any way? Why (not)?

Yes and no. No because we had observed the effect in two previous studies with a very similar design. Yes because usually placebo effects are driven by expectancy: when people expect a drug will have an effect and they think they have taken the drug they experience the effect even if they have been given no drug. The people in the group we gave the decaf to who knew they were getting it had no expectancy that the decaf would reduce their withdrawal (we know, we asked them) yet their withdrawal still went down. That is surprising.

- People expected water to reduce their withdrawal more than decaf. Isn't it surprising that the placebo effect isn't happening there?

It is now that you mention this. I hadn't actually asked myself why this happened till you asked just now. My guess, based on the theory, is that (a) the expectancy of withdrawal reduction for water, while greater than for decaf, was still not that great, certainly nowhere near as high as the expectancy for caffeinated coffee (b) there was no conditioning effect with water.

- Can you explain - in layman's terms - how decaf is reducing the withdrawal symptoms?

I'll try! We believe decaf can reduce withdrawal symptoms because of *conditioning*. Daily coffee drinkers drink thousands of cups of coffee over the course of their life. Every cup (especially the first one in the morning) reduces their withdrawal, so over time they come to associate coffee

and all the stimuli surrounding it – the taste, the smell, the warmth of the cup, the heat of the liquid – both consciously and unconsciously, with caffeine withdrawal reduction. Over time that association means that those stimuli acquire the power to evoke the withdrawal reduction effect *without* the caffeine. Decaf, especially a really good one, has many of the same properties as caffeinated coffee, it tastes, looks and feels the same. So when you drink a cup of decaf you are evoking a conditioned withdrawal-reduction response.

- Why do you expect this placebo effect to be temporary?

Conditioned responses fade. The placebo response is competing with all the signals from your body telling you 'I need caffeine!'. It can overcome those for a little while but not indefinitely. Also all withdrawal reduction is temporary. Even if you drink a cup of real, caffeinated coffee the withdrawal reduction effect fades and withdrawal comes back. That's how addictions work.

- An 'addiction' to coffee is quite innocent. But in the paper you suggest the study could help in the development of treatments for other (maybe more serious) addictions. How could the study help with that exactly?

I don't know why you put the word addiction in quotes  Caffeine is most certainly addictive (see Laura Juliano and Roland Griffith's excellent 2004 review in *Psychopharmacology*) and if it suddenly became expensive, illegal, and difficult to obtain it would quickly become less innocent. But you are right that its effects and withdrawal symptoms are milder than for more serious drugs. This is why it is a good drug with which to study addiction processes, and you never have a problem recruiting subjects!

The study helps generally because it provides yet more evidence that cognitive factors like conditioning and expectancy – which drive the placebo effect – play a big role in withdrawal. Clinical addiction specialists have been saying this for years but it has mostly been based on observation rather than empirical evidence. Most innovations in drug treatment have been pharmacological, but our study suggests there may be benefits in developing treatments that take into account human cognition.  More specifically we suggest in the paper that, for example, when people are tapering off an agonist medication (e.g. methadone) their active doses could be interspersed with open-label placebo pills during the reduction phase, then, as they approach and pass 0 mg they are given the open-label placebo. Much more careful research is required of course. People with dependence on alcohol, amphetamine, heroin etc are among the most vulnerable and stigmatised people in our society. You cannot take researching their problems lightly.

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**From:** Scientias nl <info@scientias.nl>
**Sent:** Wednesday, February 15, 2023 2:16 AM
**To:** Llew Mills <llew.mills@sydney.edu.au>
**Subject:** A few questions about your study - from The Netherlands

Dear Llewellyn,

We would love to write an article about your study that was published in the Journal of Psychopharmacology. This article will be published on the Dutch scientific website www.scientias.nl. In order to write the article, I would like to ask you a few additional questions. Would you be willing to answer the questions? You can find them below!

- Can you explain what kind of withdrawal symptoms people can experience when they quit drinking coffee?
- Did the fact that decaf coffee could reduce the withdrawal symptoms surprise you in any way? Why (not)?
- People expected water to reduce their withdrawal more than decaf. Isn't it surprising that the placebo effect isn't happening there?
- Can you explain - in layman's terms - how decaf is reducing the withdrawal symptoms?
- Why do you expect this placebo effect to be temporary?
- An 'addiction' to coffee is quite innocent. But in the paper you suggest the study could help in the development of treatments for other (maybe more serious) addictions. How could the study help with that exactly?

I'm looking forward to hearing from you and writing about your study! Thank you in advance for your help!

Best,
Caroline Kraaijvanger
Scientias.nl