Title

About the limits of mediation analyses in solving chicken-versus-egg-like type of questions.

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Number of pages: 4

Number of Figures: 0

Number of Tables: 0

Supplemental information: no

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In an interesting study by Mischkowski and colleagues published in PAIN (April 2018, Volume 159, Issue 4, P. 699-711), pain intensity ratings and skin conductance responses (SCR) to a range of noxious and innocuous heat stimuli were recorded. Using mediation analyses, the authors explored the relationship between physical intensity, perceived intensity and the strength of the skin conductance response. They found that the relationship between temperature of the heat stimulus (i.e. physical intensity) and the magnitude of the SCR was associated with the perceived intensity of pain. Based on the inconsistent findings for stimuli perceived as non-painful, the authors suggested that the association between perceived intensity and SCR may be specific to pain perception.

The fact that stimulus salience is associated with the magnitude of the SCR has been well-established, and this observation is not specific to noxious input [1,6,11–13]. Whether salience is a function of physical or perceived stimulus features is an interesting question with implications beyond the pain research field, given the widespread use of SCR as a psychophysiological measure of sympathetic arousal [5]. As such, we appreciate the work of Mischkowski and colleagues to raise and address this important issue. However, we feel that inferences based on the authors' findings require the greatest caution for the following reasons [4]. *First*, the study design and conducted analyses may not really allow one to address the question whether pain perception influences SCR or vice versa. In the study, heat stimuli lasted 8 seconds, and SCRs were recorded from 1s before stimulus onset until 3s after stimulus offset. After stimulus offset, participants rated the stimulus on a pain scale or, during the two-step pain assessment, made a categorical decision (pain vs. no pain) after which intensity ratings were recorded. As such, in the proposed mediation model the outcome/dependent variable (SCR) was measured prior to the mediator (pain intensity ratings). This reversed temporal relationship is critical as this implies that cause and effect relationships cannot be established [7], as reflected in the following quote by Kline (2015) *"without a proper research design—one with time precedence—use of the term "mediation" is unwarranted."* *Second*, even when a clear temporal relationship is absent, inferences regarding mediation analyses can still be valid if the rationale for the assumed directionality is built upon strong theoretical assumptions [7]. In the present case, however, such a strong rationale is lacking, as at least two alternative explanations can be proposed. *First*, the perception of pain is subjected to modulation by various central processes including expectations [14], which have been shown to also affect the strength of the skin conductance response [2]. Hence, it is conceivable that such central processes affect both of them. *Second*, the alternative hypothesis that larger SCRs could bias pain ratings is in line with the Somatic Marker Hypothesis, which states that autonomic responses (including SCR) bias (perceptual) decision-making [3]. In the advent of a study designed to disentangle the temporal relationships between perception and SCR, an alternative option is to switch the order of mediators and outcomes to determine how the outcome relates to the mediator (reversed

mediation), even though this approach has its limitations [8,10]. If the authors would find no mediation of SCR on perception in this reversed mediation model, alternative theoretical interpretations such as the Somatic Marker Hypothesis, become less likely. However, even then, no firm conclusions about the directionality, let alone causality of the relationship between pain perception and SCR can be drawn as model comparison based on the indirect effect can lead to the wrong model selection [8,10]. In sum, conclusions regarding the directionality and causality of the associations between physical and perceived stimulus intensity and the magnitude of the SCR seem premature for the reasons outlined above. Nevertheless, the observation of Mischkowski et al. that both perceived and physical stimulus intensity are associated with psychophysiological responses, suggests that inferences drawn about these measures should be made cautiously when the differences are explained solely in relation to physical stimulus properties.

Acknowledgments: J.Z. is supported by the “Asthenes” long-term structural funding (METH/15/011) – Methusalem grant by the Flemish Government. L.V.O. is an Associate Professor of the KU Leuven Special Research Fund (“Bijzonder Onderzoeksfonds”). The authors have no conflicts of interest to declare.

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