Importance of quantifying indirect effects from mediation analyses

Letter To Editor:

In the recent issue of *PAIN®*, Terry et al.[7] presented an interesting study that investigated the role of catastrophizing in pain modulation. Although catastrophizing often predicts pain intensity,[10] less is known about its precise causal role.[4] The use of mediation analyses to test whether situation-specific catastrophization mediates the effect of manipulating catastrophizing on supraspinal and spinal level outcome measures is a key component of the study by Terry et al. However, recent methodological advances in mediation analyses suggest that there is some uncertainty about the authors' conclusions.

Quantifying the indirect effect

Terry et al. used the causal steps approach[1] (often called Baron and Kenny's method) to test their hypothesized mediation models. Although this approach is intuitive and easily understood, it comes with limitations[2] that are pertinent to understanding the findings of Terry et al. This approach uses a set of hypothesis tests to infer the simple presence or absence of a mediating effect. It does not provide a direct estimate of the quantity of interest, ie, the indirect effect. The authors attempt to overcome this limitation by using Sobel's test; however, this is inadequate because it only provides a statistical significance level for each mediation model so that the likelihood of a partial mediation effect can be inferred. The Sobel's test has also been criticized for its inherent assumption for normally distributed samples.[2]

Investigating mediation using the causal steps approach and Sobel's test only provides information about the statistical significance of any possible mediating effect. This is problematic when results from mediation models are compared. Without a quantitative estimate of the indirect effect, Terry et al. were only able to provide a qualitative comparison between mediation effects of catastrophizing on supraspinal and spinal level outcome measures. We contend that the precise role of catastrophizing would be better described with more refined quantitative estimates of indirect effects.

Modern analytical techniques such as the nonparametric bootstrapped product of coefficients analysis[6] and causal mediation analysis[3,9] allow researchers to directly estimate the indirect effect and produce a point estimate with confidence limits. Given the availability and accessibility of these techniques,[5,8] we were surprised to see the approach of Terry et al. to mediation analysis. It is worth speculating whether the main conclusions of this article would still be supported if the indirect effects for supraspinal and spinal outcome measures were compared using point estimates and their confidence intervals. Estimating indirect effects is also important from a reporting standards' perspective because meta-analyses of mediation studies[4] statistically pool the point estimates of the indirect effect and its constituent paths.

A nonsignificant total effect does not imply a nonsignificant indirect effect

Finally, it would have been interesting to see the results of the mediating effect of catastrophizing on the single stimulus nociceptive flexion reflex magnitude outcome. However, the authors did not test this model because the outcome did not correlate with the independent (phase × group interaction) variable (ie, nonsignificant total effect) (Table 2 in Ref. 7). This assumption that an indirect effect can only exist in the presence of a significant total effect is false.[2,9] This is because the total effect is the sum of all direct and indirect paths. Thus, it is possible that multiple indirect effects with opposing signs could sum to a total effect that is closer to zero (nonsignificant).[2] It is plausible that other indirect effects that were not assessed by Terry et al. could cancel out an indirect effect through catastrophizing, resulting in a nonsignificant total effect. At worst, this mistaken decision may have led the authors to an erroneous conclusion about the mediating effect of catastrophizing on nociceptive flexion reflex magnitude.

In light of these issues, we think that the conclusions from Terry et al. would be more robust and nuanced if contemporary methods had been used for their mediation analyses.

Conflict of interest statement

References

[1] Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173–82.
[2] Hayes AF. Beyond Baron and Kenny: statistical mediation analysis in the New Millennium. Commun Monogr 2009;76:408–20.
[3] Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychol Methods 2010;15:309–34.
[4] Lee H, Hübscher M, Moseley GL, Kamper SJ, Traeger AC, Mansell G, McAuley JH. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. PAIN 2015;156:988–97.
[5] Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 2004;36:717–31.
[6] Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40:879–91.
[7] Terry EL, Thompson KA, Rhudy JL. Experimental reduction of pain catastrophizing modulates pain report but not spinal nociception as verified by mediation analyses. PAIN 2015;156:1477–88.
[8] Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. J Stat Softw 2014;59:1–38.
[9] VanderWeele TJ. A three-way decomposition of a total effect into direct, indirect, and interactive effects. Epidemiology 2013;24:224–32.

[10] Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. Spine J 2014;14:2639–57.

Hopin Lee[a,b]
Markus Hübscher[a,b]
James H. McAuley[a,b]
[a]*Neuroscience Research Australia (NeuRA), Sydney, Australia*
[b]*Prince of Wales Clinical School, University of New South Wales, Sydney, Australia*
E-mail address: j.mcauley@neura.edu.au (J. H. McAuley)
http://dx.doi.org/10.1097/j.pain.0000000000000346

Further verification by bootstrapped mediation analyses that pain catastrophizing modulates pain report but not spinal nociception: a reply to Lee, Hübscher, and McAuley

Reply:

We greatly appreciate that Lee et al.[5] read our recently published article in *PAIN*® that examined the influence of an experimental catastrophizing manipulation (ie, using cognitive behavioral techniques to reduce catastrophic thinking) on pain ratings and the nociceptive flexion reflex (NFR).[10] In that article, we found that the experimental reduction in catastrophizing led to reductions in pain intensity, pain unpleasantness, and temporal summation of NFR (TS-NFR, ie, NFR responses to triple stimulations) but not NFRs to single stimulations. These data suggested that catastrophizing could play a causal role in modulating pain and also in modulating spinal sensitization (given that TS-NFR is believed to be a marker). However, after conducting formal mediation analyses according to Baron and Kenny[1] followed by the traditional version of the Sobel test, we concluded that catastrophizing mediated the effect of the experimental manipulation on pain intensity and unpleasantness but not the effect of the experimental manipulation on temporal summation of NFR or NFRs to single stimulations. These results were in line with a number of previous correlational studies that found pain catastrophizing is associated with pain perception but not NFR.[2,3,7–9]

As Lee et al. noted in their *PAIN*® editorial, there have been recent advances in mediation analyses that improve on the classic Baron and Kenny and Sobel approaches. For example, Preacher and Hayes[6] argue for a bootstrapped Sobel test that provides a point estimate for the indirect effect and a bootstrapped confidence interval (CI) around the indirect effect. If the CI contains zero, then the indirect effect is not significantly different from zero, thus arguing against mediation. Not only does this quantify the indirect effect and provide a significance test for it but also overcomes the potential problem with the traditional Sobel test's reliance on a normal distribution. Lee et al. encouraged us to use such an approach not only to test our conclusions but to also report the indirect effect and the bootstrapped test regardless of whether the total effect was significant (ie, regardless of whether the experimental manipulation had an effect on a dependent variable, [DV]). We gladly comply with their request to apply this more contemporary analysis to our data.

We conducted bootstrapped Sobel tests using PROCESS designed by Hayes.[4] This produced 95% CIs for the indirect effects that were generated from 1000 bootstrapped samples. The results are presented in **Table 1**. As can be seen, there was a significant indirect effect by pain catastrophizing on pain intensity and unpleasantness but not for TS-NFR or NFRs in response to single stimulations. Thus, these results support the conclusions of our original study and further support our conclusion that pain catastrophizing modulates pain report but not spinal nociception (as measured by NFR and TS-NFR). We thank Lee et al. for suggesting that we conduct these analyses so that we can have greater confidence in our results.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

Table 1

Results of bootstrapped mediation analyses.

Dependent variables	Indirect effect	95% bootstrapped confidence interval	Conclusion
NFR magnitude (single stimulations)	−0.0355	−0.1272 to 0.0229	No significant indirect effect
Intensity ratings (single stimulations)	−4.0328	−8.2024 to −1.4637	Significant indirect effect
Unpleasantness ratings (single stimulations)	−5.6553	−10.5843 to −2.5940	Significant indirect effect
TS-NFR	0.1064	−0.0344 to 0.2643	No significant indirect effect
Intensity ratings (3 stimulations)	−10.3784	−15.9318 to −6.0058	Significant indirect effect
Unpleasantness ratings (3 stimulations)	−13.4511	−20.9205 to −8.3090	Significant indirect effect

Note: These mediation analyses test the following potential mediated path: IV (group × phase interaction) → mediator (pain catastrophizing) → DV (pain/NFR outcomes). From 1000 bootstrapped samples, 95% confidence intervals for each indirect effect were generated. Confidence intervals that do not contain zero suggest the indirect effect is significant and thus pain catastrophizing does at least partially mediate the relationship between the group × phase interaction and the DV. For these mediation analyses, the variables used were as follows: (1) a change score was created for each dependent variable (posttest–pretest) and used as the DV, (2) group was dummy coded (0 = pain education, 1 = catastrophizing reduction) and used as the independent variable, and (3) a change score was created for situation-specific pain catastrophizing (posttest–pretest) and used as the mediator. NFR, nociceptive flexion reflex; TS-NFR, temporal summation of NFR.