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What is the proper control group for a fibromyalgia study? Comment on the article by Loggia et al

To the Editor:

The recent study by Loggia et al (1) has design problems that may negate the authors' conclusions. First, they chose a control group composed of healthy pain-free individuals rather than a group with chronic pain of peripheral tissue origin. As in several other studies of pain processing (2–5), use of a normal control group eliminates, at the design level, the possibility of determining whether brain circuitry alterations in patients labeled as having fibromyalgia differ from those in patients with pain-causing disorders known to be peripheral and nociceptive.

Second, the pain-free control group differed from the study group not only in the presence or absence of chronic pain but also (and markedly so) in indices of depression and fatigue, as shown in Table 1 (1). These differences may add important confounders to cerebral imaging (6,7). Unless such variables are matched in the control group, they may introduce indeterminacy into the interpretation of imaging and psychophysical findings. The proper controls thus should be patients with chronic peripheral pain accompanied by depression.

Furthermore, the authors could have extracted a modicum of information, even in the absence of a relevant control group, by displaying a severity-related gradation in the results. The large standard deviations shown in Table 1 suggest that some patients had 6-fold higher scores than others for pain intensity and the number of pain sites. The decision by the Loggia group not to sort the study group results according to pain level may mask discovery of relevant findings such as whether or not there was an ascending response to increased baseline pain or a threshold below which differences were not present.

In summary, the authors' finding of differences from normal controls cannot demonstrate anything unique or aberrant about the study group's pain-processing brain circuitry, nor can the findings be seen as supportive of "augmented central processing," the primary axiom of the fibromyalgia hypothesis. Without the discovery of distinct differences between patients and carefully matched control subjects with underlying nociceptive peripheral chronic pain, speculative claims of brain circuitry disruption that is unique to the group with fibromyalgia cannot be substantiated.

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Reply

To the Editor:

We very much appreciate the perspective of Dr. Lampman regarding our recent study. In biomedicine, and indeed in most experimental sciences, the choice of a proper control group (or condition) is a fundamental step to ensure that the conclusions drawn from an experiment have validity and are meaningful.

What is a proper control in a fibromyalgia study? The answer is, of course, "it depends on what question is being investigated." In our recent study, we used functional magnetic resonance imaging to test the hypothesis that patients with fibromyalgia demonstrate altered brain activity during anticipation of both pain and pain relief. For this experiment, we elected to compare patients with fibromyalgia with pain-free healthy volunteers rather than a disease control group (such as a group with a different pain disorder). Dr. Lampman criticized this choice, suggesting that our approach prevented us from assessing whether the observed alterations in brain activity are unique to fibromyalgia (or could be observed in other pain conditions, such as "pain-causing disorders known to be peripheral and nociceptive").

We would like to point out that the purpose of our study was never to identify brain alterations specific to fibromyalgia, and we never made such a claim in our report. Instead, our aim was to demonstrate the presence of alterations in brain activity in patients with fibromyalgia compared with healthy, pain-free individuals (which may or may not be unique to this particular chronic pain disorder). For this purpose, we believe that the choice of a demographically matched control group of healthy volunteers was entirely appropriate. Future experiments will need to assess whether a similar paradigm applied to the study of other chronic pain disorders, with greater or lesser peripheral or nociceptive pain components, does or does not yield similar results. Indeed, a newly proposed pain taxonomy (1) provides several categories

of chronic pain conditions, and it would certainly be instructive to compare patients with fibromyalgia and samples of patients with, for instance, localized peripheral or central neuropathic pain conditions, visceral pain syndromes, cancer-related pain, or regional musculoskeletal pain disorders.

We certainly agree that our fibromyalgia and control groups differed not only in the presence or absence of widespread pain but also in terms of other factors (e.g., negative affect, fatigue). These differences, however, are truly reflective of the multisymptom nature of fibromyalgia, and we do not believe that they are confounders in our experimental design. Symptoms such as fatigue, anxiety, depression, and sleep or cognitive deficits are highly comorbid with, and therefore an integral part of, fibromyalgia (2,3). Attempting to identify a control group that is perfectly matched to the fibromyalgia group, except for the presence of pain, would be extremely difficult and would also generate results that are not reflective of the full spectrum of the fibromyalgia disorder. Nonetheless, we agree that it is important to try to determine whether any specific symptoms reported by patients with fibromyalgia contribute more than others to explain any differences in the observed brain processing. Such an analysis requires a multivariate statistical approach in a large patient sample, and we hope that future analyses will in fact be able to tease out the distinct contributions of different variables to the neuroimaging alterations observed in previous studies.

Finally, regarding the wide range in the scoring of clinical pain intensity and unpleasantness reported by our patients, we believe that this is endemic to the fibromyalgia population and may be advantageous for dynamic range in further statistical analyses, something we will take full advantage of in future analyses exploring the relationship between pain levels and brain activity.

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Standardized incidence ratios for gout: comment on the article by Krishnan

To the Editor:

I read with great interest the recent article by Krishnan on the incidence of gout (1). Dr. Krishnan reports that, compared with the rate of incidence of gout in the Rochester Epidemiology Project (2), the age-standardized incidence ratio (SIR) was 745 (95% confidence interval [95% CI] 714–778) among participants in the Multiple Risk Factor Intervention Trial (MRFIT). Additionally, the SIRs were 581 (95% CI 540–623), 792 (95% CI 788–796), and 1,759 (95% CI 1,479–2,122) among participants in the MRFIT with estimated glomerular filtration rates (GFRs) of $\geq$90 ml/minute/1.73 m^2, 60–89 ml/minute/1.73 m^2, and $<$60 ml/minute/1.73 m^2, respectively. Since participants in the MRFIT are at increased risk of gout (overweight/obese, hypertension, etc.), one would expect that the incidence of gout in this population should be higher than that among the participants in the Rochester Epidemiology Project; however, these SIRs, which refer to a 581–1,759 times higher risk between the 2 cohorts, seem too large.

To illustrate this point, I have calculated the highest possible SIR of incident gout between the 2 cohorts using the formula described by Breslow and Day (3). First, I estimated the lowest possible expected number of gout cases in the MRFIT study by multiplying the incidence rate among subjects in the youngest overlapping age group (30–39 years) from the Rochester Epidemiology Project by the total number of person-years from the MRFIT study (i.e., 0.6/1,000 person-years $\times$ 76,602 person-years = 46 cases). Then I divided the 46 expected gout cases by the total number of observed gout cases in the MRFIT study (i.e., 722 cases). In this way I calculated the highest possible value of the SIR as 15.7. I found that even this maximum possible SIR value is substantially smaller than the rates reported in the article. By the same approach, the SIRs were 11.2, 17.6, and 45.3 among the participants with estimated GFRs of $\geq$90 ml/minute/1.73 m^2, 60–89 ml/minute/1.73 m^2, and $<$60 ml/minute/1.73 m^2, respectively–also smaller, by similar magnitudes, than the corresponding estimates reported by Dr. Krishnan (i.e., 581, 792, and 1,759).

In conclusion, while my results also show that incidence rates of gout among participants in the MRFIT are higher than those in the Rochester Epidemiology Project and that those with severe kidney disease are at increased risk of gout, my analysis indicates that the magnitude of the SIR estimates should be substantially smaller than the findings reported by Dr. Krishnan.

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