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Reply to the Letter to the Editor by Dr. Lampman ("What is a proper control group in fibromyalgia study?")

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To the Editor

We very much appreciate the perspective of Dr. Lampman regarding our recent publication in Arthritis and Rheumatology, titled "Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia"(1). In biomedicine, and indeed 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 fibromyalgia patients demonstrate altered brain activity during anticipation of pain and of relief. For this experiment, we elected to compare the fibromyalgia patients to pain-free healthy volunteers, rather than a different "diseased control group" (such as a group with a different pain disorder). In the Letter to the Editor by Lampman, this choice was criticized because our approach, it was argued, 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 the manuscript. Rather, our aim was to demonstrate in fibromyalgia patients the presence of alterations from the healthy brain (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

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peripheral or nociceptive pain components, yields similar results or not. Indeed, a newly-proposed pain taxonomy (2) provides a number of categories of chronic pain conditions, and it would certainly be instructive to compare fibromyalgia patients to samples of patients with localized peripheral or central neuropathic pain conditions, visceral pain syndromes, cancer-related pain, regional musculoskeletal pain disorders, etc.

We certainly agree that our fibromyalgia and control groups did not differ only for the presence or absence of widespread pain, but also in terms of other factors (negative affect, fatigue, etc). These differences, however, are truly reflective of the multisymptom nature of fibromyalgia and we do not believe are ‘confounds’ in our experimental design. Symptoms such as fatigue, anxiety, depression, sleep and cognitive deficits are highly comorbid with, and therefore an integral part of, fibromyalgia (3, 4). Attempting to identify a control group that is perfectly matched to the fibromyalgia group, except for the presence of pain, would not only be extremely difficult, but also would generate results that would not reflect the full spectrum of the fibromyalgia disorder. On the other hand, we agree that it is important to try to determine whether any specific symptoms reported by fibromyalgia patients contribute more than others to explain any differences in brain processing observed. 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 reported in previous studies.

Finally, as for the large range in clinical pain reported by our patients, we feel 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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