ratings actually measure. The authors' statements such as "Reliability: More is not always better" and "The value of brain markers, whether reliable or not, is in measuring neurophysiological processes that are closely and consistently aligned with particular 'ingredients' of pain…" are misleading. If not reliable, neuroimaging-based markers, no matter how computationally sophisticated, cannot be "closely and consistently" aligned with anything.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Reply

Letter To Editor:

Letzen et al.[5] have thoughtfully responded to our comment on the limitations of reliability measures in brain imaging and beyond. We find much to agree with and a few points that require additional clarification. We agree that interindividual reliability is a cornerstone of measurement theory, and there has been too little emphasis in neuroimaging studies on measurement properties.

We also agree that there are many valid and reliable pain-related assessments that go far beyond intensity ratings, including measures associated with diverse aspects and consequences of pain.[3,7,10] These assessments are valuable, and neuroimaging studies would do well to identify predictive signatures for biological component processes underlying these diverse aspects of pain.

Despite these points of agreement, we would like to emphasize several additional points related to reliability and neuroimaging. First, it does not make sense to talk about the reliability of neuroimaging as a whole, any more than it does to talk about the reliability of behavior as a whole. Brain imaging provides myriad measures, some reliable, others not. Most are irrelevant for pain. When assessing the reliability of brain measures related to pain, we must carefully select measures that are maximally pain related. This is true even when considering a priori regions of interest. For example, the anterior mid-cingulate cortex is pain related in general, but it contains on the order of 550 million neurons, and there are literally hundreds of ways to define a summary measure of activity across the region as a whole. Some will yield signals that are pain related, and others signals that are completely unrelated.[13] Thus, before assessing reliability, we should define measures that are as closely related to the construct of interest as possible. That is why it is particularly relevant to assess the reliability of brain signatures such as the

Neurologic Pain Signature[12]—which appears to be approximately as reliable as pain self-reports.[15]

Second, most pain neuroimaging studies have not focused on individual differences. Reliability places a cap on the validity of assessing interindividual variability—for example who feels more or less pain—but not on the validity of measures assessing why pain exists at all, or what brain and behavioral processes might be driving it. Most pain imaging studies have been designed to identify brain processes that are consistent across individuals, and so have striven to maximize homogeneity. The net result, as Letzen et al.[5] point out, is reduced reliability—but these studies are still valuable for their contribution to understanding the nature of pain processing. Neuroimaging studies should examine both consistent effects and interindividual variability in more diverse community and patient samples.

Third, we disagree with Letzen et al. that "if neuroimaging markers are truly representative of the symptom in question (pain), then they should be similarly influenced by the same factors that influence self-report." As Letzen et al.[5] point out, pain is a multidimensional experience,[3,8] and diverse aspects of functionality and well-being are also important.[10] In addition, people are diverse in the ways they reflect on and describe pain. Thus, it is unlikely that one brain marker can, even in principle, capture pain reports in all contexts. It is more likely that pain is supported by a family of brain states, and shades and hues in pain are emergent properties that arise from a family of basic neurophysiological "ingredient" processes (cf. Ref.6). It is also unlikely that one brain marker will ever be able to capture effects of every treatment or variable that affects pain report—as our earlier work has shown.[12,14] Some "factors that influence self-report" influence nociception, whereas others affect emotion, decision making about experience, or social self-presentation, instead of nociception.

Furthermore, neuroimaging and behavioral measures are likely to have *complementary* sources of bias and noise. All kinds of decisions (not just those about pain) are subject to cognitive biases, including anchor-and-adjust decision biases,[11] self-consistency biases,[9] social conformity effects,[16] and others. Some pain-related neuroimaging measures (including the Neurologic Pain Signature[12]) may be less subject to these forms of decision bias. They are, however, subject to their own sources of error, including sensitivity to factors such as caffeine intake,[4] vascular aging,[2] and "off-target" activity that is not pain related. To the extent that they have complementary sources of error but load on the same construct "pain," measuring brain responses and behavior will be superior to either alone.[1] Thus, using converging measures to "triangulate" on pain and its consequences may prove advantageous.

In sum, rather than looking for one brain measure that tracks all aspects of self-reported pain in all contexts, neuroimaging measures can be acknowledged for what they are: a source of information about the *component neurophysiological ingredients* that give rise to pain. These *component processes* may combine in various ways to contribute to what is reported as pain, as letters combine to form words (cf. Ref.17). The presence or absence of individual neurophysiological components may prove to be informative about the *nature* of a person's pain, beyond its mere presence or intensity. They may have implications for health independent of a person's subjective pain experience and may ultimately be considered as end points in their own right.

Conflict of interest statement

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