J Neurophysiol 114: 2558–2560, 2015.
First published March 18, 2015; doi:10.1152/jn.00075.2015.

Discriminating neural representations of physical and social pains: how multivariate statistics challenge the "shared representation" theory of pain

A. Rogachov,[1,2] J. C. Cheng,[1,2] and D. D. DeSouza[1,2]

[1]*Division of Brain, Imaging and Behaviour-Systems Neuroscience, Toronto Western Research Institute, University Health Network, Toronto, Ontario, Canada; and* [2]*Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada*

Submitted 23 January 2015; accepted in final form 16 March 2015

Rogachov A, Cheng JC, DeSouza DD. Discriminating neural representations of physical and social pains: how multivariate statistics challenge the "shared representation" theory of pain. *J Neurophysiol* 114: 2558–2560, 2015. First published March 18, 2015; doi:10.1152/jn.00075.2015.—Overlapping functional magnetic resonance imaging (fMRI) activity elicited by physical pain and social rejection has posited a common neural representation between the two experiences. However, Woo and colleagues (*Nat Commun* 5: 5380, 2014) recently used multivariate statistics to challenge the "shared representation" theory of pain. This study has implications in the way results from fMRI studies are interpreted and has the potential of broadening our understanding of different pain states and future development of personalized medicine.

pain; fMRI; multivariate statistics; social rejection

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI) techniques have been broadly used to study the neural correlates of various behaviors. Activations based on the blood oxygenation level-dependent (BOLD) signal are interpreted as evidence for the neural involvement of a brain region in the task or experience at hand. The significance of these BOLD response changes under different conditions are determined using univariate or multivariate statistical approaches, with univariate techniques implemented within the general linear model (GLM) being the most common. Whereas univariate fMRI approaches examine voxels independently to determine where brain activity is elicited by the experimental condition, multivariate analyses use the combined signals across voxels to cancel noise, optimizing the extraction of the brain signals of interest (Haufe et al. 2014). A machine learning classifier such as a support vector machine (SVM) can then be trained on this multivariate data to accurately categorize novel observations.

There are several lines of evidence to suggest that physical pain and social pain/rejection share common neural underpinnings (Eisenberger 2012; Eisenberger et al. 2003; Macdonald and Leary 2005). As such, a shared representation theory has emerged, with shared brain activations between the two experiences, as detected by fMRI, providing some rationale to support this theory (Eisenberger 2012). In these previous studies, univariate fMRI techniques were used to investigate brain activity in response to both physical and social pain, with the results indicating overlapping patterns of brain activation, particularly in brain regions implicated in the affective dimensions of pain [e.g., dorsal anterior cingulate (dACC), anterior insula (aINS)] (Eisenberger 2012; Eisenberger et al. 2003; Macdonald and Leary 2005). For example, fMRI data acquired from subjects playing Cyberball, a virtual ball-tossing game intended to induce social rejection, elicited activations of the dACC and aINS, with dACC activity being positively correlated with self-reported distress (Eisenberger et al. 2003). Other support for the shared representation theory comes from the literature examining the effectiveness of opiates in providing both physical pain relief and counter distress related to social separation and the phenomenon of using physical pain words to describe experiences of social pain (e.g., broken heart), which transcends many languages, positing a potential universal overlap between the two experiences (Eisenberger 2012).

Despite this body of interdisciplinary evidence, the shared representation theory may not fully encompass the true nature of the physical-social pain overlap. In fact, Woo et al. (2014) recently used the multivariate approach, multivoxel pattern analysis (MVPA), to demonstrate that physical and social rejection pain show distinct multivariate fMRI patterns and suggested that different neural populations within similar gross anatomical regions may mediate these perceptions. These multivariate patterns of activation are represented by a classifier weight in each voxel, generated by training a SVM on the imaging data. The classifier weights are consequently used by the SVM model to accurately classify new observations or to distinguish groups based on different experiences (e.g., physical pain vs. social pain).

Harnessing this powerful tool, one of the experimental aims of Woo et al. (2014) was to determine whether separate multivariate fMRI patterns could be identified from brain activity elicited by physical and social rejection pain. Toward this aim, the researchers first identified a priori voxels associated with the terms "pain," "emotion," and "social," generated from a meta-analytic database of previously published neuroimaging studies. These voxels were then used as masks for the subsequent analyses of two tasks: *1*) a social rejection task, whereby participants saw a head shot of their ex-partner (ex-partner condition) or a close friend (friend condition), and *2*) a physical pain task, where participants received either hot (painful) or warm (nonpainful) thermal stimuli. They then trained an SVM to distinguish between brain activity within these voxels elicited from heat-pain and all other conditions, and ex-partner vs. all other conditions. The goal was to determine if distinct multivariate patterns could be obtained for physical and social rejection pain by determining if each multivariate pattern was separately modulated by their respective conditions. The results indicated that the SVM-generated

Address for reprint requests and other correspondence: A. Rogachov, Division of Brain, Imaging and Behaviour-Systems Neuroscience, Toronto Western Research Institute, Univ. Health Network, Toronto, ON, Canada M5T 2S8 (e-mail: anton.rogachov@mail.utoronto.ca).

multivariate pattern for physical pain distinguished between physical and social pain with 100% accuracy, and between heat-pain and warmth with 92% accuracy, but performed at chance level when distinguishing between the social rejection conditions (ex-partner vs. friend), demonstrating its responsivity only to physical pain. In contrast, the social rejection SVM-generated multivariate pattern classified physical pain and social pain with 88% accuracy, and ex-partner vs. friend with 80% accuracy, but performed at chance level when distinguishing heat pain from warmth (physical pain conditions), demonstrating its responsivity to only social pain. Using these whole brain fMRI multivariate patterns, Woo et al. (2014) cited this result as the first evidence of separate modifiability between pain and rejection, suggesting the existence of functionally independent neural representations between the two conditions. To confirm that the multivariate patterns between physical pain and social rejection were indeed separate, a correlational analysis between pattern classifier weights was conducted and revealed that the two pattern maps were uncorrelated ($r = -0.04$, $P = 0.28$). Higher voxel weights from certain regions were found to be more predictive of physical pain, particularly in brain regions associated with nociception and modulation (e.g., ventral and dorsal posterior insula, periaqueductal gray). In contrast, voxel weights in brain areas involved with understanding mental states of others and negative emotions (e.g., dorsomedial prefrontal cortex and perigenual anterior cingulate cortex) were more predictive of social rejection (Woo et al. 2014).

Although these analyses demonstrated that the physical pain- and social rejection-related multivariate fMRI patterns were uncorrelated in the brain regions involved in pain processing, Woo et al. (2014) conducted further tests to determine if there were shared representations in other areas of the brain. The results indicated that similar multivariate fMRI patterns existed for pain and rejection in areas described as being located outside of the core pain-processing regions in the brain (e.g., left parahippocampal gyrus, fusiform gyrus, and right temporoparietal junction). The authors discussed that these regions are more likely associated with general processes related to context or memory, among other functions, but not nociception.

This important study has several implications for the field of pain. First, it suggests that the current shared representation theory may need to be appended. Social exclusion and physical pain have been previously shown to recruit similar brain regions involved with the affective dimension of pain based on univariate analyses. However, shared representation theory does not provide evidence for how the two experiences may be differentiated by activity in shared brain regions. In this theory, physical pain has been proposed to be differentiated from social rejection by the recruitment of brain regions involved with the sensory components of pain, a system not necessarily required for the perception of social exclusion (Eisenberger 2012). However, the work by Woo et al. (2014) appends the shared representation theory by demonstrating that the perception of physical pain and social rejection may be differentiated on the basis of different multivariate patterns of activity within shared brain regions. These authors further suggest that these experiences are possibly mediated by different neuronal populations within similar brain regions, subserving our ability to distinguish between the two perceptions. In line with this hypothesis, recent neurophysiological evidence suggests functionally distinct subpopulations of neurons within the dACC (Sheth et al. 2012). In this context, Woo et al. imply that the interpretation of previous studies that used univariate statistics to interpret fMRI data are limited in detecting activations from anatomically distinct neurons within a localized region.

However, a potential limitation of this interpretation by Woo et al. (2014), and more generally a concern with multivariate pattern analysis, is that the amplitude of multivariate classifier weights assigned to different brain regions does not represent the strength of their neurophysiological involvement with the experimental condition (Haufe et al. 2014). In their article, Woo et al. discuss that the different fMRI patterns obtained via the multivariate analyses imply that the neuron-level population codes are different between physical and social pains. However, Haufe et al. have demonstrated scenarios where voxels that do not contain the signal of interest evoked by the experimental condition are assigned larger positive classifier weights than voxels that do (Haufe et al. 2014). In relation to this study, one can draw the conclusion that a separate multivariate pattern exists for physical and social rejection pain, but to interpret the different patterns of classifier weights as evidence that they are mediated by different neuronal populations would be a form of reverse inference. However, by generating a forward model based on these classifier weights, this would allow for proper interpretation of the neurophysiological processes underlying these pattern differences (Haufe et al. 2014).

Future studies may be able to use multivariate statistical approaches to expand our understanding of both acute and chronic pain states. For example, it is known that pain can be characterized by different qualities (e.g., burning, prickling, aching), which may be generated by different underlying pathophysiological mechanisms in chronic pain states (Truini et al. 2013). Through the use of multivariate analyses coupled with forward modeling, it may be possible to determine if these different pain qualities are encoded by different neuronal populations within the brain. Additionally, these techniques have implications for the future development of personalized pain management. For example, there may be a separate multivariate pattern for different types of chronic pain, which may be useful as a diagnostic tool. Moreover, specific multivariate patterns may be used to determine which patients, within a specific chronic pain group, may respond better to one treatment over another. Taken together, coupling multivariate analyses with forward modeling would offer a powerful window into discovering whether specific neuronal populations are responsible for mediating different pathological pain states, as well as determining drug efficacy, information that cannot be resolved using traditional univariate fMRI approaches.

In summary, this elegant study by Woo et al. (2014) demonstrates that in addition to previous fMRI studies showing physical and social rejection pains being shared by common gross anatomic brain regions, there may actually be distinct neural representations for these experiences that can be detected using multivariate statistical approaches. This study advances our understanding of how different painful experiences are processed and additionally raises caution with regard to how we interpret fMRI studies implementing univariate statistical approaches. Future studies aimed at determining the precise neural populations underlying different painful experiences are warranted.

ACKNOWLEDGMENTS

We thank Paul Dufort for thoughtful feedback and review of this manuscript.

GRANTS

J. C. Cheng was supported by a University of Toronto Centre for the Study of Pain (UTCSP) Pain Scientist Scholarship. D. D. DeSouza was supported by an Ontario Graduate Scholarship.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.R., J.C.C., and D.D.D. interpreted results of experiments; A.R., J.C.C., and D.D.D. drafted manuscript; A.R., J.C.C., and D.D.D. edited and revised manuscript; A.R., J.C.C., and D.D.D. approved final version of manuscript.

REFERENCES

Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nat Rev Neurosci* 13: 421–434, 2012.

Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An FMRI study of social exclusion. *Science* 302: 290–292, 2003.

Haufe S, Meinecke F, Gorgen K, Dahne S, Haynes JD, Blankertz B, Biessmann F. On the interpretation of weight vectors of linear models in multivariate neuroimaging. *Neuroimage* 87: 96–110, 2014.

Macdonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull* 131: 202–223, 2005.

Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, Bush G, Eskandar EN. Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. *Nature* 488: 218–221, 2012.

Truini A, Garcia-Larrea L, Cruccu G. Reappraising neuropathic pain in humans–how symptoms help disclose mechanisms. *Nat Rev Neurol* 9: 572–582, 2013.

Woo CW, Koban L, Kross E, Lindquist MA, Banich MT, Ruzic L, Andrews-Hanna JR, Wager TD. Separate neural representations for physical pain and social rejection. *Nat Commun* 5: 5380, 2014.