Neurosci. Bull.
https://doi.org/10.1007/s12264-021-00722-8

www.neurosci.cn
www.springer.com/12264

RESEARCH HIGHLIGHT

Developing Neuroimaging Biomarker for Brain Diseases with a Machine Learning Framework and the Brainnetome Atlas

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Received: 1 February 2021 / Accepted: 25 March 2021

Neuroimaging made it possible to quantify brain structure and function. However, there are few neuroimaging biomarkers for the early diagnosis, prognosis, and evaluation of therapy for brain diseases. The development of neuroimaging biomarkers for brain diseases faces two major bottleneck problems. First, the neuroimaging datasets of brain diseases are always characterized by small sample size, high dimension, and large heterogeneity. Second, a fine-grained individualized human brain atlas for effective dimensionality reduction has always been lacking. Due to the inherent high-dimensional nature of neuroimaging, collecting a large amount of data on specific brain diseases of interest is essential to avoid model overfitting, obtain meaningful biological insights, and enhance statistical power. However, limited by real-world clinical scenarios, it is often difficult for a single center to obtain massive samples of specific diseases. So multi-center data analysis has gradually become a research trend. Besides, on the one hand, a reliable brain atlas can be used as prior knowledge to effectively reduce the dimensionality of neuroimaging to reduce the possibility of overfitting. On the other hand, it also helps us to integrate research conclusions, to further reveal the mechanism of the disease. Therefore, a systematic framework to accurately locate brain regions and networks, and then investigate how to effectively aggregate multi-center neuroimaging datasets and robustly search imaging features for the comparison of different individuals is needed. This will help to clarify the imaging biomarkers of brain diseases and push neuroimaging into clinical applications. Recently, major progress has been achieved in this field [1, 2].

For example, clinical pain, characterized by its sustained nature, keeps the patient in an unhealthy and uncomfortable state, and imposes a heavy economic burden to society [3]. However, pain is difficult to assess objectively as it is a complex process affected by multiple factors. To get a better understanding of clinical pain, tonic experimental pain (TEP), rather than experimental phasic pain (EPP), is usually used as the experimental model of clinical pain. However, the neurobiological relationship between TEP, EEP, and clinical pain remains unclear. Recently, Lee *et al*. [2] addressed this question by extracting a brain-based neuroimaging biomarker of tonic pain intensity from the whole-brain functional connectivity with a promising machine-learning framework. Besides, they believe that this neuroimaging biomarker has potential application value in real-world clinical setting.

Broadly speaking, Lee *et al*. addressed three research questions in this study. First, they trained and compared the functional connectivity-based predictive models of taste-induced tonic pain with two independent fMRI studies (Studies 1 and 2). To obtain an unbiased performance

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Published online: 14 June 2021

estimate of the selected optimal model named the tonic pain signature (ToPS), the authors tested it with the fMRI data of Study 3, which led to the first conclusion that the neuroimaging-based signature for tonic pain could be identified based on the whole-brain functional connectivity and had good generalizability across independent datasets. Next, the authors applied the ToPS directly to two clinical back pain datasets (Studies 4 and 5) and came to the second research conclusion that the ToPS can serve as a model explaining the severity of two types of clinical pain (subacute back pain and chronic back pain) and accurately discriminating patients with chronic back pain from the control group. What is even more exciting is that the model trained on the tonic pain dataset was even better than the model trained directly on the corresponding clinical dataset to predict clinical pain scores. Finally, the researchers conducted an in-depth analysis of the weights of the ToPS to explain the potential role of different brain regions, functional connections, and functional networks in tonic pain. At the same time, by comparing ToPS with the model of subacute back pain (trained with the subacute back pain dataset, Study 5) and the experimental phasic pain model (trained with the experimental heat pain dataset, Study 6), the researchers found the relationship across tonic, clinical, and phasic pain: they found that the network-level representations of tonic experimental and clinical pain were similar, particularly in the somatomotor, frontoparietal, and dorsal attention networks. However, they differ from the representations of experimental phasic pain.

It is worth noting that the two-step machine-learning framework adopted by Lee *et al*. is worthy of in-depth consideration and promotion: developing thousands of candidate models based on the training dataset and selecting the optimal model based on the validation dataset. Specifically, the authors first trained 5,916 candidate models with multiple combinations of hyperparameters (including four different types of parcellation and two different types of functional connectivity measurement, as well as three different types of algorithm and their corresponding multiple hyperparameter settings) using the training data, and then selected the best model with the validation data according to its comprehensive performance on 7 criteria. Importantly, the authors went on to test the selected optimal model with a completely independent dataset. This two-step model development framework together with the independent testing is critical to ensure the robustness, generalization, and credibility of the selected model especially in a field where data heterogeneity has a wide range of sources.

However, in the practice of particular research problems (such as specific rare diseases), it is not easy to obtain sufficient independent datasets to adopt this framework. Fortunately, the settings of the optimal model selected by Lee *et al*. from the 5,916 candidate models may have certain reference values. The selected models for pain intensity and pain unpleasantness both used dynamic conditional correlation (DCC) [4], a modified Brainnetome Atlas [5] (combined with additional brainstem and cerebellar regions [6, 7]), and principal component regression [8] but with a different number of components. As the selected measurement of functional connectivity, DCC equipped with a certain random noise immunity can effectively estimate the dynamic changes in correlation in fMRI data which may provide more information about the changes in brain activity. And the finally selected atlas in this research, the Brainnetome Atlas, is a tractography-based atlas that is fine-grained and cross-validated, containing information on both anatomical and functional connections. Besides, the Brainnetome Atlas provides mapping between the delineated structures and mental processes, which makes the model developed with this atlas easier to interpret and is conducive to improving the understanding of the neural mechanism of the research problem. Moreover, the methodology of the human Brainnetome atlas has been transferred to a macaque monkey study [9]. When it comes to machine-learning algorithms, they generally have a certain number of data-dependent hyperparameters to be adjusted. And there are two points of consensus: (1) When encountering high-dimensional features, feature selection or dimensionality reduction is generally necessary and (2) interpretable algorithms are preferred.

In summary, Lee *et al.* developed a functional neuroimaging biomarker for tonic pain which has the potential to be used in clinical settings and studied the neurobiological relationship between TEP, EEP, and clinical pain. More importantly, this research provides an inspiring perspective research paradigm for related studies dedicated to mining neuroimaging biomarkers, as well as a machine-learning framework with universal applicability and promotion value. Specifically, researchers found that the tonic pain model trained with data collected from healthy people was able to predict clinical pain scores, and the performance was even better than the model directly trained with clinical data. This may open up new lines of research for disorders such as schizophrenia, which involves cognitive, perceptual, and emotional dimensions. Can we develop biomarkers of the corresponding state from healthy controls or even experimental animals [10], and then transfer them to the patients? On the one hand, as it is relatively easy to obtain large-scale datasets from easily available subjects, this paradigm can reduce the difficulty of data collection. On the other hand, using normal individuals to conduct research can better avoid uncontrollable factors and confounding variables brought about by diseases. Therefore, this is a research paradigm worth trying, and it

is expected to bring new changes to the field. Finally, the promising two-step machine learning framework and the potential optimal model settings they provide for identifying neuroimaging-based biomarkers that can be applied to research in other brain diseases after adaptive modification or even directly. Overall, the research scheme proposed by Lee *et al*. is useful for both neuroscience and clinical practice, to improve the understanding of the neural mechanisms of certain symptoms and promote the development of precision medicine.

References

1. Li A, Zalesky A, Yue W, Howes O, Yan H, Liu Y. A neuroimaging biomarker for striatal dysfunction in schizophrenia. Nat Med 2020, 26: 558–565.
2. Lee JJ, Kim HJ, Čeko M, Park BY, Lee SA, Park H, *et al.* A neuroimaging biomarker for sustained experimental and clinical pain. Nat Med 2021, 27: 174–182.
3. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012, 13: 715–724.
4. Lindquist MA, Xu Y, Nebel MB, Caffo BS. Evaluating dynamic bivariate correlations in resting-state fMRI: A comparison study and a new approach. Neuroimage 2014, 101: 531–546.
5. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, *et al.* The human brainnetome atlas: A new brain atlas based on connectional architecture. Cereb Cortex 2016, 26: 3508–3526.
6. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, *et al.* A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 2005, 25: 1325–1335.
7. Diedrichsen J, Maderwald S, Küper M, Thürling M, Rabe K, Gizewski ER, *et al.* Imaging the deep cerebellar nuclei: A probabilistic atlas and normalization procedure. Neuroimage 2011, 54: 1786–1794.
8. Hastie T, Tibshirani R, Friedman J. The elements of statistical learning: data mining, inference, and prediction. Springer Science & Business Media, 2009.
9. He B, Cao L, Xia XL, Zhang BG, Zhang D, You B, *et al.* Fine-grained topography and modularity of the macaque frontal pole cortex revealed by anatomical connectivity profiles. Neurosci Bull 2020, 36: 1454–1473.
10. Zhan Y, Wei J, Liang J, Xu X, He R, Robbins TW, *et al.* Diagnostic classification for human autism and obsessive-compulsive disorder based on machine learning from a primate genetic model. Am J Psychiatry 2021, 178: 65–76.