Brain age prediction for post-traumatic stress disorder patients with convolutional neural networks: a multi-modal neuroimaging study

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Abstract:

Brain imaging shed lights on brain development which is closely related to various cognitive abilities. Immaturity and accelerated aging of the brain are typical consequence of developmental brain disorders. We developed a deep learning method to use convolutional neural networks (CNNs) to predict age of patients with post-traumatic stress disorders (PTSD) and healthy controls based on multi-modal brain imaging. N-fold cross validation was conducted to evaluate the prediction accuracy of age on healthy controls. Then the CNNs were trained with data of healthy controls and tested with PTSD group and another healthy control group with traumatic experiences, but no long-lasting PTSD symptoms. Our result showed that CNNs can be used to predict age with accuracy comparable to state-of-the-art machine learning methods such as ridge regression. Importantly, we found that the predicted age for PTSD patients are older than that of the control group, indicating an accelerated aging process of the brain in PTSD patients relative to healthy population.

Keywords: machine learning; DNN; brain imaging; PTSD

Introduction

Magnetic resonance imaging (MRI) and functional MRI (fMRI) provide researchers with a powerful tool to examine the structural and functional characteristics of human brain. Recently, machine learning methods are widely applied in brain imaging analysis of patients with a variety of mental disorders such as Alzheimer disease (AD) (Kloppel et al., 2008), schizophrenia (Sun et al., 2009) and PTSD (Niehaus et al., 2014). These studies aimed to explore the neural signature of mental disorders, as well as to build mathematical models to differentiate patients from healthy control. One popular application of machine learning methods is to predict biological age with brain imaging. It has been found that gray matter volume (GMV) combined with fractional anisotropy (FA) can predict age with high degree of accuracy (Erus et al., 2015). Multi-model brain imaging can further improve age prediction accuracy (Liem et al., 2017). It is important to note that brain age could be used as an aging biomarker of an individual's brain health, which allows ones to assess cognitive precocity and delay. The difference between predicted age and chronological age is not merely due to noise, but reflects the brain maturity. Thus, the predicted age with brain imaging features serves as a brain developmental index. Other studies have found that the brain ages were estimated to be older than the chronological ages in patients with traumatic brain injury (Cole, Leech, & Sharp, 2015) and schizophrenia (Schnack et al., 2016). The results suggest the accelerated aging effects of brain in patients with brain injuries and mental disorders.

With the growing size of brain imaging data, deep neural network (DNN) has become a promising tool to explore more complex patterns of brain imaging. It is attractive to train the model with raw imaging data without standard pre-processing procedures. Recent study showed that convolutional neural network with raw brain images can achieve age prediction accuracy comparable to traditional regression models (Cole et al., 2017). In that work, however, only T_1-weighted

structural MRI were used. With the availability of different brain imaging modalities, likely representing different characteristics of the brain tissue, it is conceivable to combine multimodal neuroimaging data for brain age prediction. In the current study, we proposed a deep learning method to predict the brain age of PTSD patients and healthy controls using multimodal neuroimaging. Specifically, CNNs were trained with brain imaging features extracted from T_1-weighted structural MRI, diffusion tensor imaging (DTI) and resting state fMRI. We also compared our results with ridge regression.

Methods

Brain imaging data.

We obtained multimodal brain imaging data including T1-weighted imaging, diffusion tenser imaging (DTI), and resting state functional brain imaging (rsfMRI) from the Philadelphia Neurodevelopmental Cohort (PNC) data base (Satterthwaite et al., 2014). We selected 165 subjects, among which 70 (50 females) were PTSD patients (PTSD group), 35 (9 females) were healthy controls who experienced traumatic events without long-lasting PTSD symptoms (trauma group) and 60 (29 females) were healthy control without traumatic experiences or PTSD.

Brain imaging processing

Gray matter volume (GMV) were extracted from T1 image. Fractional anisotropy (FA) was extracted from the DTI data. FA is a summary measure of microstructural integrity. Amplitude of low-frequency fluctuation (ALFF) was extracted from the rsfMRI data. ALFF measures the brain signal variability of a given voxel in the frequency domain. GMV and resting state features were averaged based on the brain regions in the Harvard-Oxford probabilistic atlases. DTI features were averaged based on the John Hopkins white matter atlas.

Age prediction with Neural networks

We built a CNN to predict brain age with neuroimaging data with TensorFlow and Keras. For each layer, Rectified Linear Unit (ReLU) activation function was used, together with L_2-norm regularization with parameter set to .01. The network was trained with brain imaging features on the healthy controls and tested on the PTSD and trauma group. Prediction accuracy was defined as Pearson correlation between the chronological age and the predicted brain age. To evaluate prediction performance on the healthy control group, 3-fold cross validation (CV) was run on the healthy control data. In each CV, 2 folds of data were selected to train the model and the remaining fold was tested with the neural network. The model was run for each modality of GMV, FA and ALFF separately and for all three modalities combined.

Age prediction with ridge regression

We also run ridge regression with L_2-norm regularization. The parameter of regularization was optimized with a 5-fold cross validation on the healthy control group. Then the model was applied on the PTSD and trauma group. To evaluate prediction accuracy on the healthy control group, a nested 5-fold CV was run on the healthy control data. The inner CV was run to optimize the regularization parameter and the outer CV was run to test the performance of the model. Prediction accuracy was defined same as above in the neural network session. The model was run with GMV, FA and ALFF separately and with all three modalities combined.

Results

Prediction with CNNs

The prediction performance on age of CNNs for the healthy control (HC), PTSD and trauma group are shown in Table 1. Among the three modalities, the prediction accuracy of age with GMV are highest on all three groups. When multi-modal combined, the prediction accuracies are higher for the healthy control and trauma group, but not for PTSD. As shown in Figure 1, the predicted brain age of PTSD group is older than that of the trauma group. And the difference between predicted brain age and chronological age is smaller in the trauma group than that in the PTSD group (p=.04) (Figure 2).

Table 1: Prediction accuracy of neural networks.

Modality	HC	PTSD	Trauma
GMV	.34 (6.77)	.54 (7.47)	.43 (6.30)
FA	.01 (7.48)	.07 (7.85)	.10 (6.50)
ALFF	.05 (6.31)	.17 (7.18)	.32 (7.11)
Multi-modal	.44 (6.38)	.43 (6.39)	.62 (6.49)

Prediction accuracies are defined as Pearson' correlation between the model predicted age and the biological age. The values in brackets are mean square error.

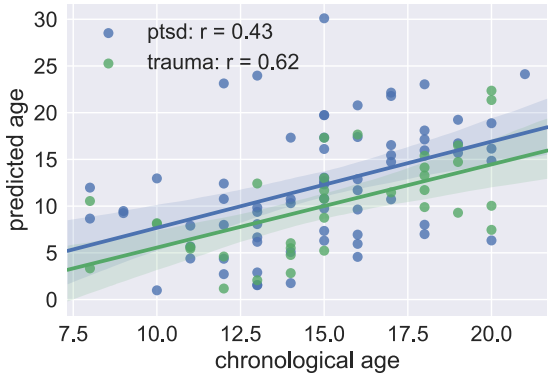

Figure 1: Scatter plot of age and predicted age by neural network with multi-modal imaging for the PTSD and trauma group.

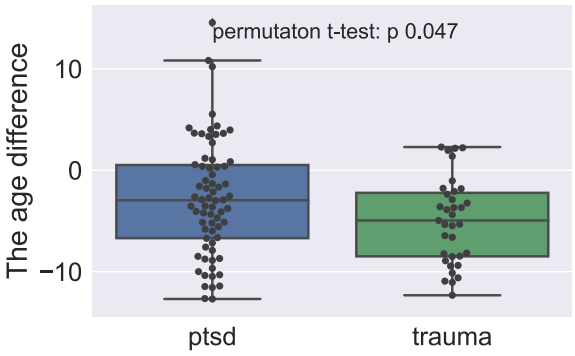

Figure 2: Difference between predicted age and chronological age by neural network with multi-modal features for the PTSD and trauma group. The age difference denotes the difference between predicted brain age and chronological age.

Prediction with ridge regression

The prediction performance of ridge regression on the healthy control, PTSD and trauma group are shown in Table 2. The prediction accuracy of GMV and multi-modal are higher than that of the FA and ALFF features. Similar to the results with CNNs, the predicted age for PTSD is also higher than that for the trauma group (Figure 3), but this effect exists only with GMV features. In addition, the difference between predicted brain age and chronological age for the trauma group are also smaller than that of the PTSD group (p=.04) (Figure 4).

Table 2: Prediction accuracy of ridge regression.

Modality	HC	PTSD	Trauma
GMV	.81 (2.67)	.67 (2.25)	.78 (2.52)
FA	.48 (3.65)	.46 (2.85)	.57 (3.23)
ALFF	.54 (3.70)	.56 (2.60)	.58 (3.20)
Multi-modal	.81 (2.60)	.75 (2.01)	.83 (2.10)

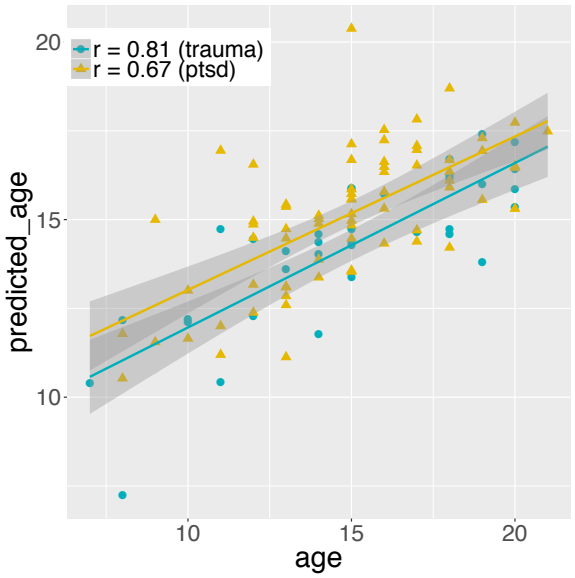

Figure 3: Scatter plot of age and predicted age by ridge regression with GMV features for the PTSD and trauma group.

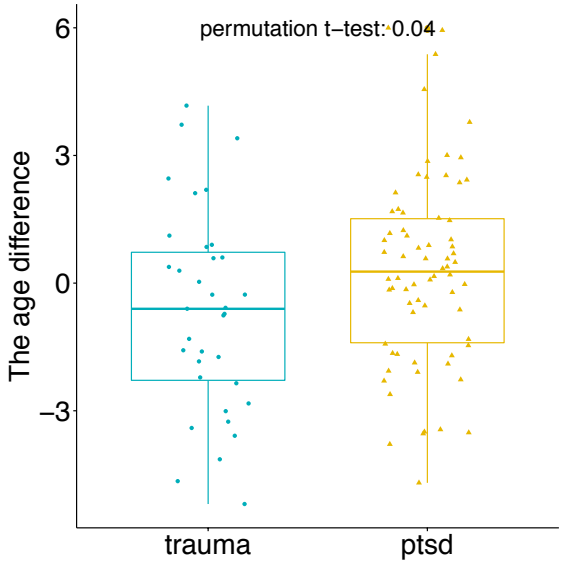

Figure 4: Difference between predicted age and chronological age by ridge regression with GMV features for the PTSD and trauma group.

Discussion

Brain age has been shown to be sensitive in indicating subtle and widespread age-associated brain structural and functional changes. Brain age predicted by neuroimaging data has the potential as a biomarker to characterize the normal brain development and clinical neuropsychiatric disorders. The current study used CNN and ridge regression to predict brain age of the PTSD patients and healthy controls. We found ridge regression can achieve high prediction accuracy on the healthy controls and PTSD patients with each of the three brain imaging modalities, as well as the combined multi-modal imaging. The prediction accuracy for CNNs, albeit low, can also be used for brain age prediction with GMV and multi-modal brain imaging. The predicted age for the PTSD group is larger than that on the trauma group that has traumatic experience but not PTSD symptoms. The differences between the predicted age and chronological age for PTSD patients were larger than that of the trauma group. Our results provide evidence of the accelerated aging process in the brain of PTSD patients, as similar to patients with traumatic brain injury and schizophrenia.

Even though the CNN did not have better age prediction compared to ridge regression, it had higher prediction accuracy on the multi-modal brain imaging than that on any single modality. In addition, the accelerated aging of PTSD was evident with CNN on multi-modal imaging, whereas for ridge regression, it was found only on GMV features. This result indicates that CNN is capable of integrating multi-modal imaging better than ridge regression. One reason for the higher prediction accuracy for ridge regression may be due to the optimization of the regularization parameters in the nested cross validation. We did not fine tune the parameters in the CNNs but instead used the default values. Furthermore, we should note that our sample size is much smaller than that in the previous work (Cole et al., 2017). We expect that the brain age prediction could be further improved as the sample size is increased and the parameters for CNN are optimized in the future.

References

Cole, J. H., Leech, R., & Sharp, D. J. (2015). Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Annals of Neurology*, *77*(4), 571–581. https://doi.org/10.1002/ana.24367

Cole, J. H., Poudel, R. P. K., Tsagkrasoulis, D., Caan, M. W. A., Steves, C., Spector, T. D., & Montana, G. (2017). Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *NeuroImage*, *163*, 115–124. https://doi.org/10.1016/J.NEUROIMAGE.2017.07.059

Erus, G., Battapady, H., Satterthwaite, T. D., Hakonarson, H., Gur, R. E., Davatzikos, C., & Gur, R. C. (2015). Imaging Patterns of Brain Development and their Relationship to Cognition. *Cerebral Cortex*, *25*(6), 1676–1684. https://doi.org/10.1093/cercor/bht425

Kloppel, S., Stonnington, C. M., Chu, C., Draganski, B., Scahill, R. I., Rohrer, J. D., . . . Frackowiak, R. S. (2008). Automatic classification of MR scans in Alzheimer's disease. Brain, 131(Pt 3), 681-689. doi: 10.1093/brain/awm319

Liem, F., Varoquaux, G., Kynast, J., Beyer, F., Kharabian Masouleh, S., Huntenburg, J. M., … Margulies, D. S. (2017). Predicting brain-age from multimodal imaging data captures cognitive impairment. *NeuroImage*, *148*, 179–188. https://doi.org/10.1016/J.NEUROIMAGE.2016.11.005

Niehaus, K. E., Clark, I. A., Bourne, C., Mackay, C. E., Holmes, E. A., Smith, S. M., . . . Duff, E. P. (2014). MVPA to enhance the study of rare cognitive events: An investigation of experimental PTSD. Paper presented at the Pattern Recognition in Neuroimaging, 2014 International Workshop on.

Satterthwaite, T. D., Elliott, M. A., Ruparel, K., Loughead, J., Prabhakaran, K., Calkins, M. E., . . . Gur, R. E. (2014). Neuroimaging of the Philadelphia Neurodevelopmental Cohort. NeuroImage, 86, 544-553. doi: 10.1016/j.neuroimage.2013.07.064

Schnack, H. G., van Haren, N. E. M., Nieuwenhuis, M., Hulshoff Pol, H. E., Cahn, W., & Kahn, R. S. (2016). Accelerated Brain Aging in Schizophrenia: A Longitudinal Pattern Recognition Study. *American Journal of Psychiatry*, *173*(6), 607–616. https://doi.org/10.1176/appi.ajp.2015.15070922

Sun, D. Q., van Erp, T. G. M., Thompson, P. M., Bearden, C. E., Daley, M., Kushan, L., . . . Cannon, T. D. (2009). Elucidating a Magnetic Resonance Imaging-Based Neuroanatomic Biomarker for Psychosis: Classification Analysis Using Probabilistic Brain Atlas and Machine Learning Algorithms. Biological Psychiatry, 66(11), 1055-1060. doi: 10.1016/j.biopsych.2009.07.019