Neurosci. Bull. October, 2019, 35(5):955–957
https://doi.org/10.1007/s12264-019-00409-1

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

RESEARCH HIGHLIGHT

# Cardiopulmonary Comorbidity, Radiomics and Machine Learning, and Therapeutic Regimens for a Cerebral fMRI Predictor Study in Psychotic Disorders

**Xiao-Hui Wang[1] · Angela Yu[2] · Xia Zhu[3] · Hong Yin[4] · Long-Biao Cui[5]**

Received: 21 November 2018 / Accepted: 16 April 2019 / Published online: 10 July 2019


Recently, two researches by Doucet *et al*. and Collin *et al*. used functional neuroimaging as a tool to improve the management of schizophrenia and other psychotic disorders [1, 2]. We would like to highlight several issues in relation to cardiopulmonary comorbidity, radiomics and machine learning, and therapeutic regimens, along with their clinical implications.

Gaelle E. Doucet and colleagues assessed the predictive potential of baseline brain functional magnetic resonance imaging (fMRI) and structural MRI (before treatment with antipsychotics for 24 weeks) in patients with schizophrenia [1]. Intriguingly, this study indicated the cohesiveness of the default mode and central executive networks and their integration with the salience, somatosensory, and visual networks as key predictors of symptomatic change in early schizophrenia. Gussje Collin and colleagues assessed the predictive potential of the baseline functional connectome based on MRI that precedes conversion to psychosis (before 1-year follow-up) in individuals at high risk for psychosis [2].

Notably, medical comorbidity plays a major role in the death of patients with schizophrenia. Given that schizophrenia is associated with higher rates of cardiovascular disease and metabolic syndrome, cardiometabolic health was considered in the investigation [1]. They collected and compared body mass index (BMI) before and after treatment as an important characteristic of cardiometabolic health. However, many more medical comorbid factors occur in patients with schizophrenia. Such patients who also suffer from lung cancer and other respiratory diseases (chronic obstructive pulmonary disease, influenza, or pneumonia) have higher mortality rates than the general population [3], while chronic kidney disease is more common in patients with schizophrenia [4]. In addition to BMI, evidence for other medical comorbidities as significant confounders in neuroimaging studies is scarce and not yet fully understood. For instance, smoking is a risk factor for cardiovascular and pulmonary diseases. Smoking status in patients with schizophrenia has been shown to correlate with their psychotic symptoms [5]. Consequently, both BMI and cigarette consumption could be recorded as general measures for a cerebral fMRI predictor study of psychotic disorders.

The key default mode, central executive, and salience networks noted above are also involved in other mental disorders. Given that some genetics and symptoms are shared with other psychiatric illnesses, could these network features be used to predict the treatment response in schizophrenia rather than other mental disorders? Machine learning is currently gaining importance in psychiatric research. As a valid approach that examines functional connectivity to diagnose schizophrenia with an accuracy of

✉ Xia Zhu
zhuxia_285459079@qq.com

✉ Long-Biao Cui
lbcui@fmmu.edu.cn

1 Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

2 Department of Medicine, Eastern Health, Box Hill, VIC 3128, Australia

3 Department of Military Psychology, School of Medical Psychology, Fourth Military Medical University, Xi'an 710032, China

4 Department of Radiology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China

5 Department of Clinical Psychology, School of Medical Psychology, Fourth Military Medical University, Xi'an 710032, China

87% with radiomics [6], which enables imaging data to be extracted for improving the predictive accuracy within clinical decision support, machine learning has been used to identify the endophenotypes that discriminate schizophrenia from depression [7]. The term 'machine learning' was coined in 1959 by Arthur Samuel. The science of artificial intelligence shows an evident capacity to reveal relationships between the different variables used for classification. When used across illnesses, it enables identification of the determinants of network features used for differentiating response predictors for schizophrenia, depressive disorder, or bipolar disorder. Doucet *et al.* and Collin *et al*. carried out integrated multivariate analyses and psychosis-free survival analysis, respectively [1, 2]. Currently, radiomics is a method for obtaining more high-dimensional features that might be options used for machine learning analysis. Efforts to develop radiomics/machine learning-based objective means for psychotic disorders have intensified. Future research needs to integrate and optimize them, resulting in accurate prediction for individualized clinical management of schizophrenia and other psychotic disorders.

In addition, sample characteristics in the study of Doucet *et al.* show that the majority of patients received second-generation antipsychotics (most commonly risperidone/paliperidone and olanzapine) and the minority received first-generation antipsychotics (most commonly haloperidol and fluphenazine) in approximate recommended doses (olanzapine equivalents, 8.5–9.3 mg/day, based on the chlorpromazine equivalents) [1]. Patients in this study underwent heterogeneous antipsychotic treatments, and it appears that the finding is predictive regardless of the type of antipsychotic drug. The clinical heterogeneity of the disorder should be explained, as well as the effect of medication on the brain imaging features for treated patients. In other words, it is of paramount importance to demonstrate whether neuroimaging-based signatures are informative in identifying patients with schizophrenia who will respond to a single antipsychotic drug. In addition, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and electroconvulsive therapy could be effective alternatives for some patients. Cerebral fMRI has provided insights into the neural mechanisms underlying psychotic disorders, especially schizophrenia [8]. However, fMRI signatures that can predict the clinical response are yet to be defined. These therapeutic regimens are important factors in the study design.

During the past 3 years, fMRI findings in other studies have established links between the clinical response to antipsychotic treatment and distinctive functional connectivity of the striatum [9] and superior temporal cortex [10] in patients with schizophrenia. Striatal connectivity is a reasonable predictor of the response to risperidone/aripiprazole for 12 weeks (80% sensitivity and 75% specificity), showing an association with lower connectivity with the anterior cingulate and medial prefrontal cortex and higher connectivity with the posterior cerebral areas [9]. In addition, functional connectivity of the superior temporal cortex has been found to predict the response to risperidone for 10 weeks (82.5% accuracy, 88.0% sensitivity, and 76.9% specificity) [10]. In spite of clinically meaningful accuracy, the model needs an even greater level of predictive performance than that found in these studies. As suggested previously, the alterations on functional imaging are more like state markers rather than trait markers for schizophrenia [11]. Cognitive impairments are frequently observed in patients with schizophrenia. The interpretation of multimodal imaging data sets together with other biomarkers and cognitive assessments would have allowed for a more comprehensive understanding of the treatment response. Nevertheless, fMRI holds great promise for improving the prediction of illness development and prognosis in psychiatric domains, leading to more personalized medicine.

Therefore, current efforts are intended to enhance the integration of functional neuroimaging predictors and personalized psychiatric medicine, and improve psychiatric care by recognizing medical illnesses, radiomics and machine learning, and therapeutic regimens. Cerebral fMRI researchers should further investigate the generalizability of findings across psychotic disorders and ultimately improve clinical decision-making by considering the complete patient profile.

**Acknowledgements** This highlight was supported by grants from the National Natural Science Foundation of China (81801675) and the Military Medical Major Program during the Thirteenth Five-Year Plan Period of China (AWS17J012).

**Conflict of interest** We declare that we have no conflict of interest.

## References

1. Doucet GE, Moser DA, Luber MJ, Leibu E, Frangou S. Baseline brain structural and functional predictors of clinical outcome in the early course of schizophrenia. Mol Psychiatry 2018. https://doi.org/10.1038/s41380-018-0269-0.
2. Collin G, Seidman LJ, Keshavan MS, Stone WS, Qi Z, Zhang T, *et al.* Functional connectome organization predicts conversion to psychosis in clinical high-risk youth from the SHARP program. Mol Psychiatry 2018. https://doi.org/10.1038/s41380-018-0288-x.
3. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015, 72: 1172–1181.
4. Iwagami M, Mansfield KE, Hayes JF, Walters K, Osborn DP, Smeeth L, *et al.* Severe mental illness and chronic kidney disease:

a cross-sectional study in the United Kingdom. Clin Epidemiol 2018, 10: 421–429.

5. An HM, Tan YL, Tan SP, Shi J, Wang ZR, Yang FD, *et al.* Smoking and serum lipid profiles in Schizophrenia. Neurosci Bull 2016, 32: 383–388.
6. Cui LB, Liu L, Wang HN, Wang LX, Guo F, Xi YB, *et al.* Disease definition for schizophrenia by functional connectivity using radiomics strategy. Schizophr Bull 2018, 44: 1053–1059.
7. Liang S, Vega R, Kong X, Deng W, Wang Q, Ma X, *et al.* Neurocognitive graphs of first-episode schizophrenia and major depression based on cognitive features. Neurosci Bull 2018, 34: 312–320.
8. Li B, Cui LB, Xi YB, Friston KJ, Guo F, Wang HN, *et al.* Abnormal effective connectivity in the brain is involved in auditory verbal hallucinations in schizophrenia. Neurosci Bull 2017, 33: 281–291.
9. Sarpal DK, Argyelan M, Robinson DG, Szeszko PR, Karlsgodt KH, John M, *et al.* Baseline striatal functional connectivity as a predictor of response to antipsychotic drug treatment. Am J Psychiatry 2016, 173: 69–77.
10. Cao B, Cho RY, Chen D, Xiu M, Wang L, Soares JC, *et al.* Treatment response prediction and individualized identification of first-episode drug-naive schizophrenia using brain functional connectivity. Mol Psychiatry 2018. https://doi.org/10.1038/s41380-018-0106-5.
11. Ren W, Lui S, Deng W, Li F, Li M, Huang X, *et al.* Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. Am J Psychiatry 2013, 170: 1308–1316.