Schizophrenia Bulletin vol. 48 no. 2 pp. 505–513, 2022
https://doi.org/10.1093/schbul/sbab112
Advance Access publication September 15, 2021

Cerebello-Thalamo-Cortical Hyperconnectivity Classifies Patients and Predicts Long-Term Treatment Outcome in First-Episode Schizophrenia

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It has previously been shown that cerebello-thalamo-cortical (CTC) hyperconnectivity is likely a state-independent neural signature for psychosis. However, the potential clinical utility of this change has not yet been evaluated. Here, using fMRI and clinical data acquired from 214 untreated first-episode patients with schizophrenia (62 of whom were clinically followed-up at least once at the 12th and 24th months after treatment initiation) and 179 healthy controls, we investigated whether CTC hyperconnectivity would serve as an individualized biomarker for diagnostic classification and prediction of long-term treatment outcome. Cross-validated LASSO regression was conducted to estimate the accuracy of baseline CTC connectivity for patient-control classification, with the generalizability of classification performance tested in an independent sample including 42 untreated first-episode patients and 65 controls. Associations between baseline CTC connectivity and clinical outcomes were evaluated using linear mixed model and leave-one-out cross validation. We found significantly increased baseline CTC connectivity in patients (P = .01), which remained stable after treatment. Measures of CTC connectivity discriminated patients from controls with moderate classification accuracy (AUC = 0.68, P < .001), and the classification model had good generalizability in the independent sample (AUC = 0.70, P < .001). Higher CTC connectivity at baseline significantly predicted poorer long-term symptom reduction in negative symptoms (R = 0.31, P = .01) but not positive or general symptoms. These findings provide initial evidence for the putative "CTC hyperconnectivity" anomaly as an individualized diagnostic and prognostic biomarker for schizophrenia, and highlight the potential of this measure in precision psychiatry.

Key words: cerebellum/thalamus/functional connectivity/diagnostic biomarker/prognostic biomarker/schizophrenia

Introduction

Recent studies have provided converging evidence that increased functional connectivity in the cerebello-thalamo-cortical (CTC) circuitry is likely an inherent and state-independent neural trait for schizophrenia.[1–4] Specifically, this abnormality is significantly predictive of onset of psychosis among individuals at clinical high risk,[1,3] present in diagnosed patients with schizophrenia,[1,4] and manifest in monozygotic cotwins discordant for schizophrenia,[2] suggesting a heritable and disease-state-independent neuropathology. Moreover, CTC hyperconnectivity in these populations can be robustly detected using a broad range of functional imaging paradigms,[1,2] suggesting that this abnormality is not limited to a particular neurocognitive domain and thus is independent of the brain's functional state.

These observations render the CTC hyperconnectivity a promising biomarker candidate for precision psychiatry.[5] Importantly, while prior studies were chiefly performed on comparisons of CTC connectivity strength between different populations, little is known about the value of this identified biomarker in individualized clinical practice. Therefore, the current study aimed to address two questions: (1) How accurately would CTC connectivity distinguish first-episode patients with schizophrenia from healthy controls at the individual level? and (2) Whether measures of CTC connectivity would predict long-term treatment outcome in first-episode patients? The answers

to these questions are of translational significance since they extend the previously population-based discoveries to the scale of single patients and therefore inform clinical utility of CTC changes in individualized characterization and treatment of the disorder. In addition, compared to other individual-level imaging biomarkers identified with a data-driven approach in the literature,[6–10] the examination of a priori CTC network may be particularly meaningful given its established validity in relation to the pathogenesis of psychosis.

In this study, we investigated the above questions using resting-state functional magnetic resonance imaging (rs-fMRI) data acquired from two independent datasets of untreated patients with schizophrenia. In the main dataset that included a large sample of 214 untreated first-episode patients (62 of whom with longitudinal data after medication) and 179 healthy subjects, we trained a supervised machine learning model on measures of CTC connectivity to test diagnostic classification accuracy, and examined whether baseline connectivity strength of the predefined CTC network was predictive of symptom severities after long-term antipsychotic treatment. The generalizability of the trained model was then assessed in an independent dataset including 42 untreated first-episode patients and 65 controls. It was hypothesized that the studied CTC abnormality would show potential as an individualized diagnostic and prognostic biomarker.

Methods

Subjects

Two clinical datasets were used in this study. The main dataset included baseline clinical and neuroimaging data acquired from 214 first-episode patients with schizophrenia who had not received any treatment (age 24.2 ± 9.1 years, 98 males) and 179 demographically matched healthy controls (age 25.6 ± 7.8 years, 88 males). Patients were recruited from the psychiatric department of the West China Hospital, and controls were recruited from the local communities via advertisement. All participants provided written informed consent for the study protocol approved by the Ethics Committee of West China Hospital. Diagnosis was based on the Structured Clinical Interview for DSM-IV. Duration of illness was determined by the Nottingham Onset Schedule (NOS[11]) according to information provided by patients, family members, and medical records. Clinical symptoms were evaluated by the Positive and Negative Syndrome Scale (PANSS[12]). General exclusion criteria for all participants included a prior history of neurological illness, alcohol/drug abuse or dependence, significant medical conditions, and gross brain abnormalities in the T1- or T2-weighted images. Healthy subjects were excluded if they had a first-degree relative with known major psychiatric disorders. Demographic and clinical characteristics of the baseline sample are provided in table 1.

Patients in the main dataset underwent baseline MRI scans and clinical assessments, and then began treatment with second-generation antipsychotics, with drug and dose choice made independently by treating physicians. A subsample of these patients (N = 62, age 24.2 ± 8.1 years, 27 males) was clinically followed up at least once at the 12th and 24th months. During each follow-up point, symptom severities were assessed by PANSS, and rs-fMRI scans were reacquired. The patients were instructed to take medication regularly based on their prescriptions, and chlorpromazine-equivalent dosages of antipsychotics were calculated.[13] Except for medication, none of the patients received other types of treatment across the entire follow-up period. Details on this follow-up sample are presented in supplementary table S1.

In addition to the main dataset, a second dataset was included to examine the generalizability of results and to estimate an unbiased classification accuracy of CTC connectivity. This generalization dataset consisted of similar baseline clinical and neuroimaging data from 42 untreated first-episode patients (age 29.3 ± 11.2 years, 12 males) and 65 healthy participants (age 25.2 ± 4.3 years, 17 males) as part of the study on neurobiological mechanisms of early schizophrenia jointly supported by National Natural Science Foundation of China (NSFC) and National Institute of Health (NIH). The patients were recruited from the West China Hospital and the 4th People's Hospital of Chengdu City. The diagnosis criteria, inclusion and exclusion criteria, and clinical assessments

Table 1. Demographic and Clinical Details of the Baseline Sample in the Main Dataset

	Untreated First-Episode Patients (N = 214)	Controls(N = 179)	P value
Age (years)	24.2 ± 9.1	25.6 ± 7.8	0.11
Sex (M/F)	98/116	88/91	0.51
Age of onset (years)	22.3 ± 7.8	–	–
Duration of untreated psychosis (months)	11.9 ± 19.7	–	–
PANSS total	89.0 ± 17.5	–	–
PANSS positive	24.5 ± 6.5	–	–
PANSS negative	18.6 ± 8.0	–	–
PANSS general	45.9 ± 10.0	–	–
Head motion (FD, mm)	0.13 ± 0.3	0.11±0.1	0.32

were the same as the main dataset. All subjects provided written informed consent following procedures approved by the Ethics Committee of West China Hospital. Details of this generalization dataset are presented in supplementary table S2.

Data Acquisition

All subjects' imaging data in this study were acquired from the West China Hospital, Sichuan University. Specifically, rs-fMRI images in the main dataset were acquired on a 3T GE Signa EXCITE scanner equipped with an 8-chanel head coil, and rs-fMRI images in the generalization dataset were acquired on a 3T SIEMENS TrioTim scanner equipped with a 32-chanel head coil. See supplementary materials for details on data acquisition.

Imaging Processing

Imaging data in both datasets were analyzed using the Statistical Parametric Mapping software (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and Data Processing and Analysis for Resting-State Brain Imaging[14] toolbox running under Matlab R2018a using the same preprocessing pipeline. Preprocessing of rs-fMRI data included the following steps: removal of first five volumes to discard saturation effects, slice time correction, realignment, segmentation, normalization to the MNI space, and spatial smoothing at 4-mm FWHM. The images were further corrected for white matter and cerebrospinal fluid signals, and 24 head-motion parameters (6 translation and rotation parameters, their first derivatives, and the square of these 12 parameters), and temporally filtered at 0.01–0.1 Hz.

We calculated volume-to-volume frame-wise displacements (FD) for each individual based on the previous definition.[15] Volumes with an FD >0.5 mm and their two subsequent volumes were "scrubbed" before further analysis. In addition, subjects with an average FD >0.3 mm in the main dataset were excluded to mitigate head motion effects on functional connectivity measures. This led to rejection of 12 patients and 6 controls, leaving 202 patients and 173 controls for further data analysis.

The calculation of CTC connectivity followed previous publications .[1,2] Specifically, the mean preprocessed time series were extracted from each of the 270 nodes defined in the expanded Power atlas.[1,16–18] A 270 × 270 pairwise whole-brain connectivity matrix was subsequently generated for each subject by computing Pearson correlation coefficients between the extracted time series. From these connectivity matrices we extracted the connectivity strength of the previously reported CTC network ,[1,2] which encompassed a total of 84 links predominantly centered at the thalamus and posterior cerebellum. A detailed list of these links was given in the prior publication .[1]

Group Comparison and Clinical Associations

To confirm the presence of CTC hyperconnectivity in untreated first-episode patients, an analysis of covariance (ANCOVA) was first conducted in the baseline sample of the main dataset, where mean CTC connectivity across the 84 links was included as the dependent variable and group was included as the independent variable, covarying for age, sex, and global mean of the whole-brain connectivity matrix. Pearson correlations were further performed to examine relations between mean CTC connectivity at baseline and PANSS scores of each domain (positive, negative, general).

Estimation of Classification Accuracy

We next sought to investigate whether connectivity measures in the CTC network would be capable of distinguishing patients from healthy controls at the individual level. For this purpose, we trained a LASSO regression model on the 84 extracted connectivity measures in the baseline sample of the main dataset. The LASSO regression is a L1-norm regularization method that incorporates a shrinkage penalty term λ to avoid model overfitting, which coerces the coefficients of some predictors to be shrunken to zero .[19] Specifically, all 84 predictors included in the model were first adjusted for age, sex, and global mean of the whole-brain connectivity matrix using a linear model. A repeated nested cross-validation (CV) method (10 outer folds, each with 5 inner folds) was used in which the tuning parameter λ was optimized within the inner cycles and subsequently utilized to predict remaining subjects in the outer cycles. This procedure eventually yielded predicted probabilities of illness for each individual in the main dataset, based on which the classification accuracy was calculated. The generalizability of the classification performance was examined in the generalization dataset. Here, the final model was trained using the entire main dataset with features whose coefficients were not shrunken to zero during all outer cycles, and the model parameters were subsequently applied to the generalization dataset without modification. The classification accuracy was determined by the receiver operating characteristic (ROC) curve, and the significance of the derived accuracy was determined by 1000 permutations.

Estimation of Long-Term Outcome

To estimate long-term treatment outcome, a linear mixed model was employed in which time point (baseline, 12th month and 24th month) was considered as fixed variable, with random slope estimated for each individual. This model was applied to quantify subject-specific slope coefficients for PANSS scores, a continuous measure indexing individualized average symptom reduction rate across the follow-up period. A larger negative slope coefficient indicates a larger degree of symptom reduction over time and

thereby better treatment outcome. Similarly, to examine whether CTC connectivity per se would be modulated by treatment over time, the same mixed model was conducted to extract individual slope coefficients for mean CTC connectivity.

To examine whether baseline CTC connectivity would predict treatment outcome, Pearson correlations were performed to associate the connectivity of the CTC network at baseline with slope coefficients of PANSS scores. The individual predictability was evaluated by leave-one-out cross validation (LOOCV), where each subject was treated as the test sample once and the model fitting was performed on the left 61 subjects.

Results

CTC Connectivity in Untreated Patients at Baseline

As expected, untreated first-episode patients with schizophrenia demonstrated significantly increased mean connectivity in the CTC network compared with healthy controls (P = .01, figure 1A). No correlations were observed between CTC connectivity and severity of clinical symptoms at baseline (R < 0.10, P > .15), supporting the previous finding that CTC hyperconnectivity is a robust biomarker for schizophrenia, irrespective of state measures such as symptom severity.

Classification Accuracy of CTC Connectivity at Baseline

In the main dataset, a total of 15 edges in the CTC network had non-zero coefficients during all CV cycles and were therefore selected as final features (figure 2A). These edges were centered at the cerebellum and thalamus, and included connections between these two structures and the sensorimotor cortex, visual cortex, and default-mode areas (eg, medial prefrontal cortex, angular gyrus, medial temporal cortex). Details on these 15 connections are shown in supplementary table S3. In the main dataset, the area under curve (AUC) for the classification ROC was 0.68, which was higher than any derived AUCs during permutations (P < .001, figure 2B). The trained classification model showed good generalizability in the independent generalization dataset, with an AUC of 0.70 (P < .001, sensitivity = 0.67 and specificity = 0.73).

Prediction of Treatment Outcome Using Baseline CTC Connectivity

The mixed model demonstrated significant reductions of symptom severities from baseline to follow-up (positive symptoms: β = −8.2, negative symptoms: β = −3.5, general symptoms: β = −13.9, all P < .001, figure 3A), suggesting that each year after treatment, the positive, negative, and general symptom scores decrease 8.2, 3.5, and 13.9, respectively. In contrast, the change of mean CTC connectivity was not significant at follow-up compared with baseline (β = −0.006, P = .37, figure 1B), supporting the notion that CTC hyperconnectivity is trait-like that stays stable after long-term treatment, even clinical symptoms have ameliorated.

The baseline CTC connectivity significantly predicted slope coefficients of negative symptoms during follow-up (R = 0.31, P = .01, figure 3B), where patients with higher CTC connectivity at baseline had poorer treatment outcome in terms of negative symptoms. The result remained stable when focusing on the 15 edges identified from the classification analysis (R = 0.26, P = .04), or when controlling for duration of untreated psychosis (DUP) and medication dosage (R = 0.28, P = .03). In contrast, no significant associations were found between baseline CTC connectivity and slope coefficients for positive and general symptoms (R < 0.14, P > .27).

Using mean CTC connectivity as the single predictor, the LOOCV revealed a significant correlation between predicted slope coefficients of negative symptoms and actual slope coefficients (R = 0.21, P = .04 with 1000 permutations, figure 3C), suggest that baseline CTC connectivity has potential as a predictor for negative symptom changes at the individual level. The correlation slightly increased when adding DUP as a second predictor in the model (R = 0.22, P = .04).

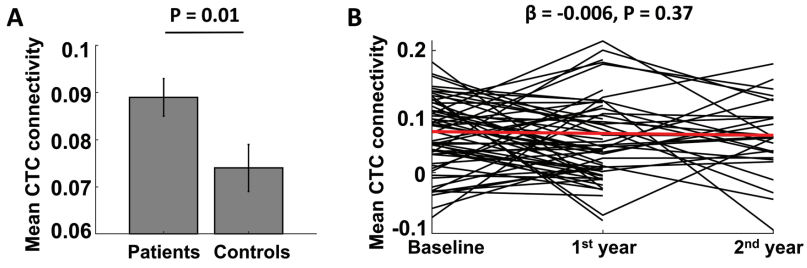

Fig. 1. Mean CTC connectivity at baseline and follow-ups in the main sample. (A) Significantly higher connectivity was observed in untreated first-episode patients with schizophrenia compared with healthy controls at baseline. The error bars indicate standard error. (B) Individual trajectories and group trajectory for CTC connectivity during follow-ups. No significant change was found for CTC connectivity after treatment.

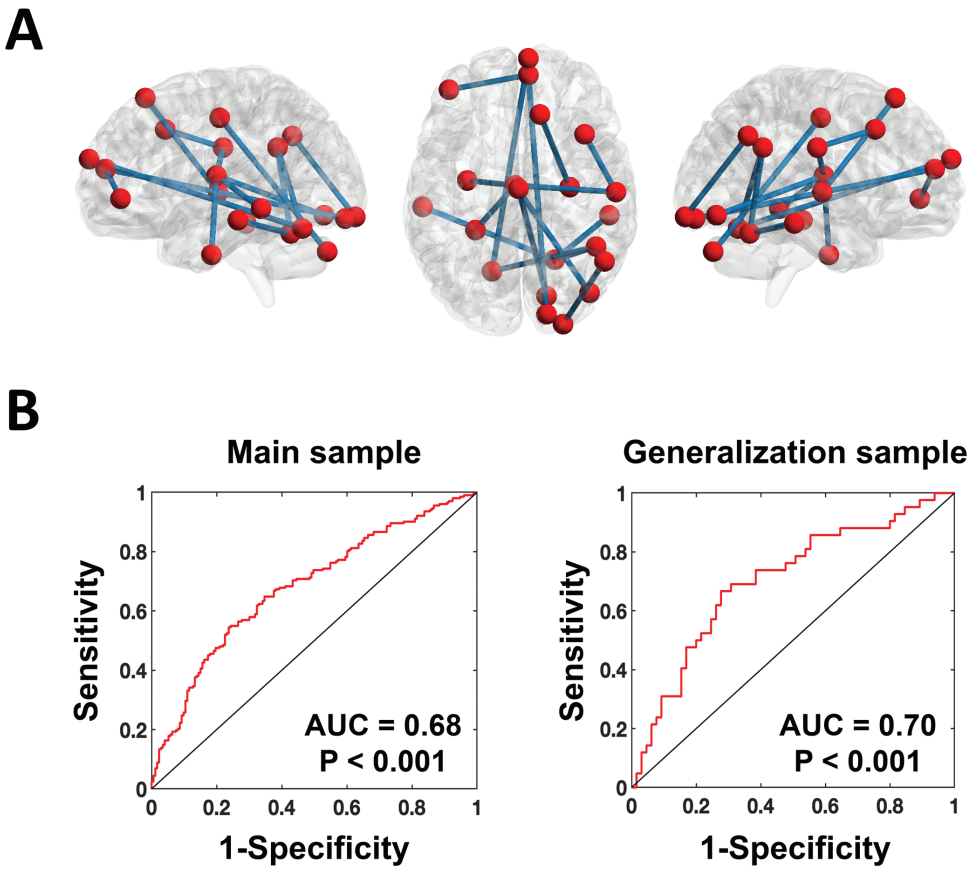

Fig. 2. Classification accuracy of CTC connectivity in discriminating untreated first-episode patients from controls. (A) The selected CTC connections showing highest predictability for patients from cross-validated LASSO regression in the main dataset. See supplementary table S3 for details of these connections. (B) The receiver operating characteristic (ROC) curves for the main and generalization datasets.

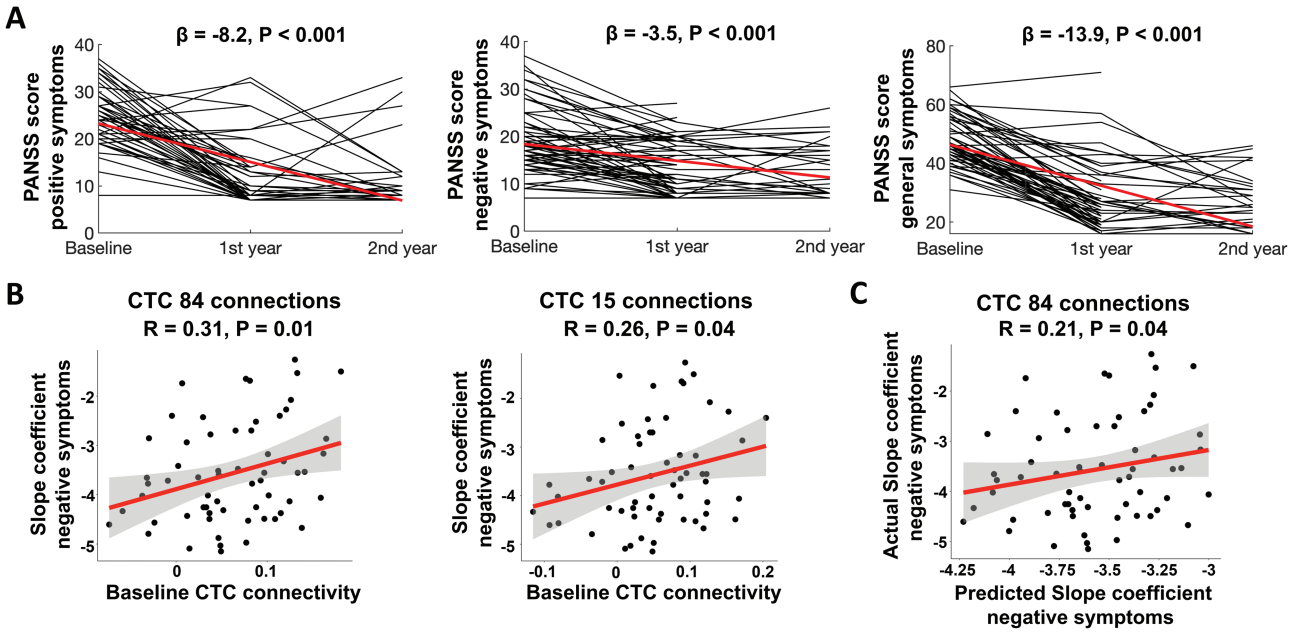

Fig. 3. Long-term clinical outcome after treatment in the follow-up sample of the main dataset. (A) Individual trajectories and group trajectories for positive symptoms, negative symptoms, and general symptoms. The slope coefficients for all symptoms were highly significant. (B) The mean CTC connectivity at baseline significantly predicted changes of negative symptoms during follow-up, where patients with higher baseline CTC connectivity had worse outcome. (C) The predicted slope coefficients of negative symptoms were significantly correlated with the actual coefficients, as revealed by leave-one-out cross validation.

Discussion

This study used two independent untreated first-episode patient samples to extend the previously identified CTC hyperconnectivity in schizophrenia to the individual level. Specifically, increased connectivity in the examined CTC network was robustly present in patients both before and after treatment, able to discern whether an individual was schizophrenic or not with reasonable accuracy and good generalizability, and significantly predictive of long-term treatment outcome in patients. These findings provide initial evidence for the clinical utility of CTC hyperconnectivity in precision medicine.

The results of this study complement the prior work on the high-risk population.[1–4] Specifically, they demonstrated that CTC hyperconnectivity, a previously identified biomarker for the prediction of psychosis onset, is robustly present among patients with first-episode schizophrenia both before and after medication. These observations not only exclude the possibility that the identified CTC changes are related to medication or clinical interventions, but also substantiate the notion that CTC hyperconnectivity is ubiquitously present across different clinical states, thereby corroborating a "trait-like" neural alteration. Such interpretation is further strengthened by the fact that no associations between baseline connectivity and clinical symptoms are detected. This is reasonable since each symptom measure assessed at a single time point is likely to reflect a "state" evaluation of a certain behavioral domain, which may change dynamically over time and is therefore insufficient to represent a behavioral "trait" of the disorder.

Beyond the group level, our study also provided evidence that CTC hyperconnectivity may serve as an individualized predictor for disorder classification. Despite that a plethora of work has previously been performed attempting to identify imaging-based predictors for discriminating schizophrenia from controls,[9,10,20–26] the present result showing the predictability with CTC connectivity is particularly meaningful. Notably, almost all past studies were conducted using a purely data-driven method on samples of patients at a single state. As a result, any state-related variables and clinical confounders would complicate the interpretation of findings, making it difficult to tell whether the derived predictors reflect a real trait underlying the pathogenesis of schizophrenia, a state-dependent neural change, or simply an epiphenomenon. In contrast, this study leveraged an established biomarker independent of clinical and behavioral states, thereby ensuring that the predictors are both biologically meaningful for schizophrenia pathophysiology and clinically useful for disease classification. It is worth noting that, while the classification accuracy was not particularly high in the current work, we consider it to be quite reasonable mainly due to two reasons. First, unlike data-driven studies that selectively picked the features most predictive of disease status across the whole brain,[9,20–26] our predictors were predetermined from completely independent studies,[1,2] which may to certain degree compromise prediction accuracy but meanwhile avoid overfitting and increase interpretability. Second, our study involved a relatively large sample of subjects, which may lead to a relatively high degree of heterogeneity and thus reduce classification accuracy. This is in line with previous studies showing a dramatic drop of prediction accuracy with increase of sample size in clinical studies using machine learning approaches,[27–29] signifying less biased results towards specific sample features. Indeed, our results actually demonstrated quite good generalizability, with classification accuracy in the independent test sample acquired from a different scanner and scan protocol even higher than that in the main sample, suggesting potentially high clinical value.

The LASSO regression model revealed that the most predictive connections within the CTC circuitry were between the cerebellum, thalamus, sensory cortices, and default-mode network. This finding is highly consistent with several studies showing high classification accuracy of these regions using either structural or functional imaging measures.[9,20,22,25] Moreover, dysconnectivity between these regions has repeatedly been reported as robust biomarkers for individuals at CHR,[3,30,31] first-episode patients,[32] and chronic patients,[32–35] suggesting that these connectivity changes are a promising candidate for a reliable and useful trait underlying schizophrenia. As discussed in prior work,[1,2,36] these connections may relate to sensory gating deficits and error/conflict-monitoring-related impairments in cognitive control, leading to perceptual disturbances and "cognitive dysmetria" in patients.[37]

The observation that CTC connectivity at baseline significantly predicted changes of negative symptoms at follow-up is of enormous intrigue. Compared to positive symptoms, negative symptoms such as avolition, anhedonia, and blunted affect are arguably more devastating and detrimental to social functioning and life quality in patients,[38–40] yet the treatment of negative symptoms usually shows limited efficacy.[41,42] As such, there is a pressing need for understanding the pathophysiology of negative symptoms in order to gain a better therapeutic strategy. In our study, while CTC connectivity was not directly associated with baseline negative symptoms, it however, did affect treatment outcome of negative symptoms in the long run, suggesting that this biomarker may serve as an important limiting factor for treatment efficacy and functional outcome. Further, the stable manifestation of this biomarker after treatment may as well contribute to the low efficacy. These findings lead to the speculation that functional modulation of the CTC circuitry may help ameliorate negative symptoms in patients. In line with this speculation, a recent study demonstrated that restoration of normal cerebellar-prefrontal connectivity using

repetitive transcranial magnetic stimulation (rTMS) targeting at the cerebellum would significantly reduce negative symptoms in patients,[43] suggesting that successful modification of cerebellar function is indeed a promising strategy for treatment of negative symptoms.

We would like to note some limitations of this study. One major limitation, as we clearly acknowledge here, is that unlike randomized clinical trials commonly used for assessment of acute or short-term drug effects, drug choice and medication dosage were not strictly controlled during follow-up in this study. In addition, although patients were instructed to regularly take the prescribed medications, the degree of their compliance to treatment was hard to be evaluated. Since controlling for these factors is extremely difficult during long-term follow-up due to ethical issues, our results cannot be interpreted as an evaluation of treatment response to any specific medication but rather a general assessment of long-term outcome under regular clinical practice. Second, given the relatively small follow-up sample size and limited follow-up points, we used linear models in the study to maximally utilize available data and to boost statistical power. However, it should be noted that symptom reductions may not be linear in practice, and therefore the examined slope coefficients represent average effects of symptom changes across the follow-up period. Intuitively, those who remitted at both follow-up points were likely to have larger negative slope coefficients than those who failed to remit or relapsed at follow-ups. Third, while we have provided initial evidence for the utility of CTC connectivity as an individualized diagnostic and prognostic biomarker for schizophrenia, the predictive accuracies are moderate. Clearly, these findings for now are not sufficient to be used in a real clinical setting, and CTC connectivity is by no means the only possible predictor in the brain. Future studies are encouraged to investigate the predictive power of this biomarker in combination with other imaging biomarkers, molecular measures, and/or cognitive assessments. Fourth, except for medication, other forms of treatment such as psychotherapy were not performed in the studied sample. Therefore, the prognostic predictability of CTC connectivity in coordinated psychosis cares remains to be investigated.

To summarize, using large samples of never-medicated patients with schizophrenia, our study demonstrated the clinical utility of CTC hyperconnectivity, a previously identified neural trait for the pathogenesis of schizophrenia, in the diagnostic classification and prognostic prediction of clinical outcome. These findings highlight the potential of CTC connectivity measures as an individualized biomarker for psychiatric care and encourage the further examination of this biomarker in schizophrenia research and clinical environments.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

Funding

Dr Cao thanks support from the Brain and Behavioral Research Foundation NARSAD Young Investigator Grant (no. 27068). Dr Lui thanks supports from the National Science Foundation of China (grant nos. 82120108014, 81671664 and 81621003), the 1.3.5 Project for Disciplines of Excellence, West China Hospital (grant nos. ZYYC08001 and ZYJC18020), the Humboldt Foundation Friedrich Wilhelm Bessel Research Award, and the Chang Jiang Scholar (grant no. T2019096). Dr Zhang thanks supports from the Fundamental Research Funds for the Central Universities of China (grant no. 2020SCU12053), the Sichuan Science and Technology Program (grant no. 2020YJ0018), the Postdoc Research Project, West China Hospital of Sichuan University (grant no. 2020HXBH005), the Science and Technology Project of the Health Planning Committee of Sichuan Province (grant no. 20PJ010), and the Postdoc Interdisciplinary Research Project of Sichuan University (grant no. 0040204153248). Dr Xiao thanks supports from the National Natural Science Foundation of China (No. 81901705), and grants from the Humboldt Foundation(Ref 3.5-CHN-1207072-HFST-P), China Postdoctoral Science Foundation (2019M663513), Sichuan Science and Technology Program (2020YFS0116), the Postdoctoral Interdisciplinary Research Project of Sichuan University(0040204153082). Dr Sweeney thanks support from the National Natural Science Foundation of China (grant no. 81820108018).

Acknowledgments

Dr Zhang and Dr Sweeney are consultants for VeraSci. The others report no conflicts of interest.

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