Supplementary Materials

Figure S1. Visualization of all CUD-discriminative FCs. Histogram indicated the node strength calculated from the sum of the linked FC importance. VIS, visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; LIM, limbic network; FPC, frontoparietal control network; DMN, default mode network.

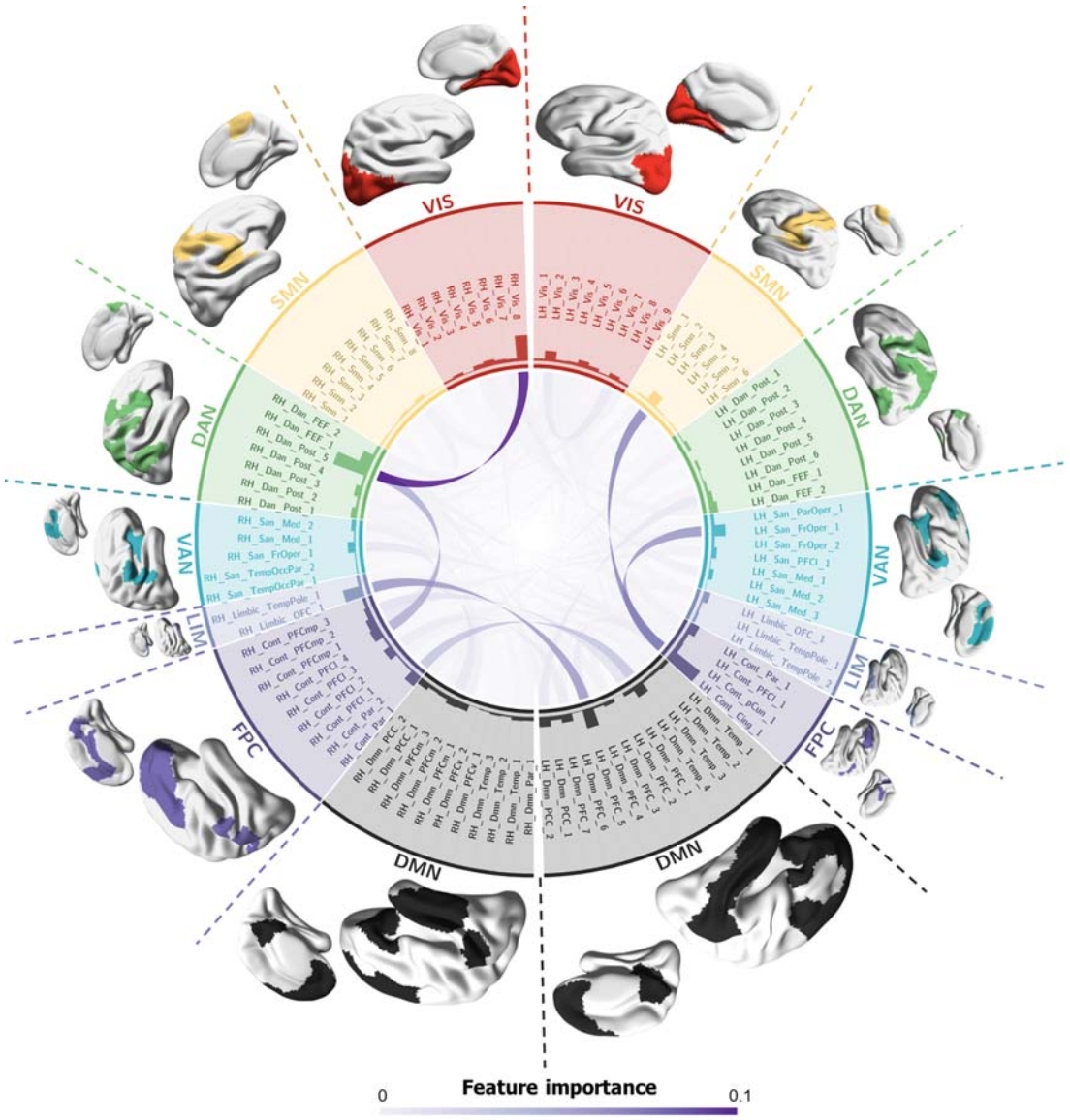
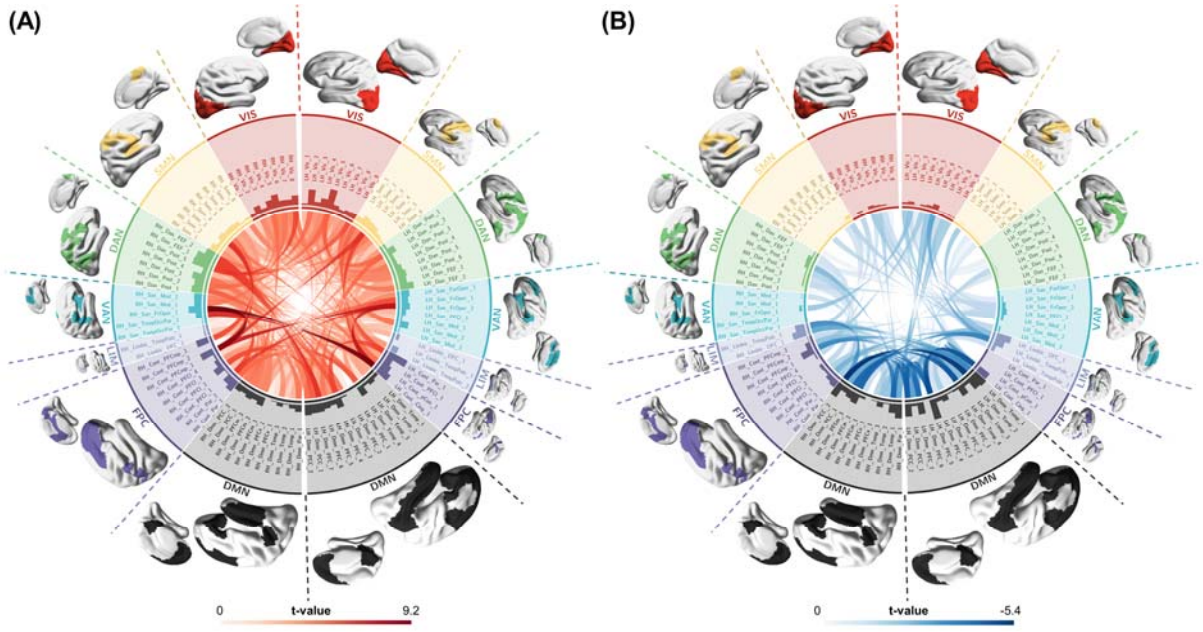


Figure S2. Statistical difference in the classifier-identified discriminative FCs between CUD patients and healthy controls, examined by two-sample t-tests. (A) All significant hyperconnections (CUD > healthy controls). **(B)** All significant hypoconnections (CUD < healthy controls). Histogram indicated the node strength calculated from the sum of the linked FC importance. VIS, visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; LIM, limbic network; FPC, frontoparietal control network; DMN, default mode network. Only the significant t values that survived FDR were



shown.

Figure S3. The importance of network-level functional connectivity. (A) We grouped the importance of FC features defined from the frequency of the feature occurrence in XGBoost models based on Yeo's 7 networks. Then the network-level importance sorted in descending order, was shown in light grey. The difference between sorted and adjacent importance was calculated and visualized in deep grey. The network importance is dramatically decreased with the largest adjacent difference when it comes to the VIS-DAN connectivity. **(B)** To further assess the significance of important FCs for further analyses, we randomly permuted FCs in each pairwise network 1000 times and calculated the difference between the average permute performance and the raw performance as feature importance. The sorted importance was plotted. The top 5 important network FCs, which were significantly ($p_{fdr} < 0.05$) larger than the permuted results, were on the left of the vertical line. Only 4 network-level FCs with significant importance were observed in both calculation strategies (VIS-DAN, LIM-DMN, SMN-FPC, VAN-FPA). Therefore, we only analyzed the association between the top 4 discriminative network-level FCs with cognitive behavioral assessments.

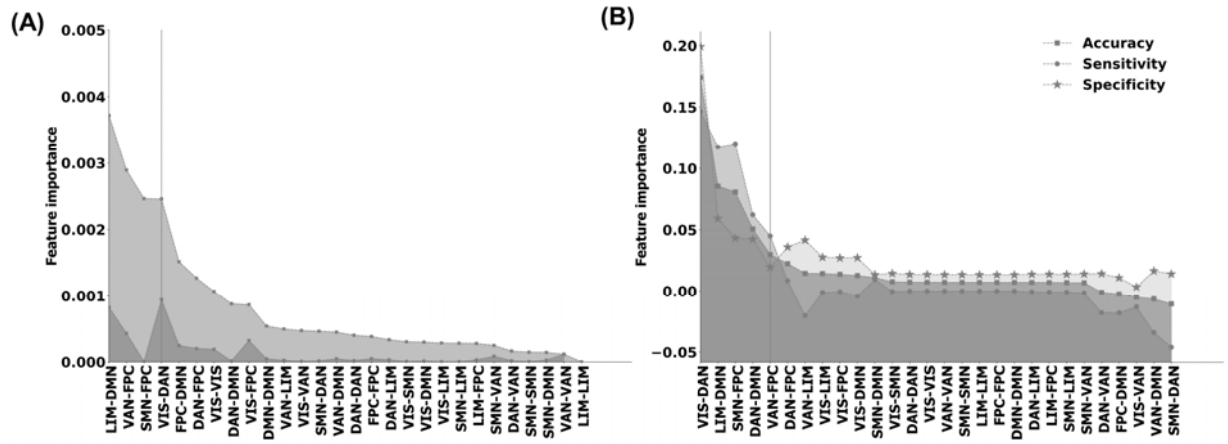


Figure S4. Classification of the CUD and HC in discovery cohort with comorbid confounder control. We regressed out the comorbid variables for each FC, using the simple linear regression models and then trained the models with same hyperparameters in 10-fold cross validations. **(A)** Averaged classification performance: the accuracy, sensitivity, and specificity are 0.71 ± 0.14, 0.67 ± 0.20, and 0.74 ± 0.14, respectively. **(B)** The CUD-discriminative signature.

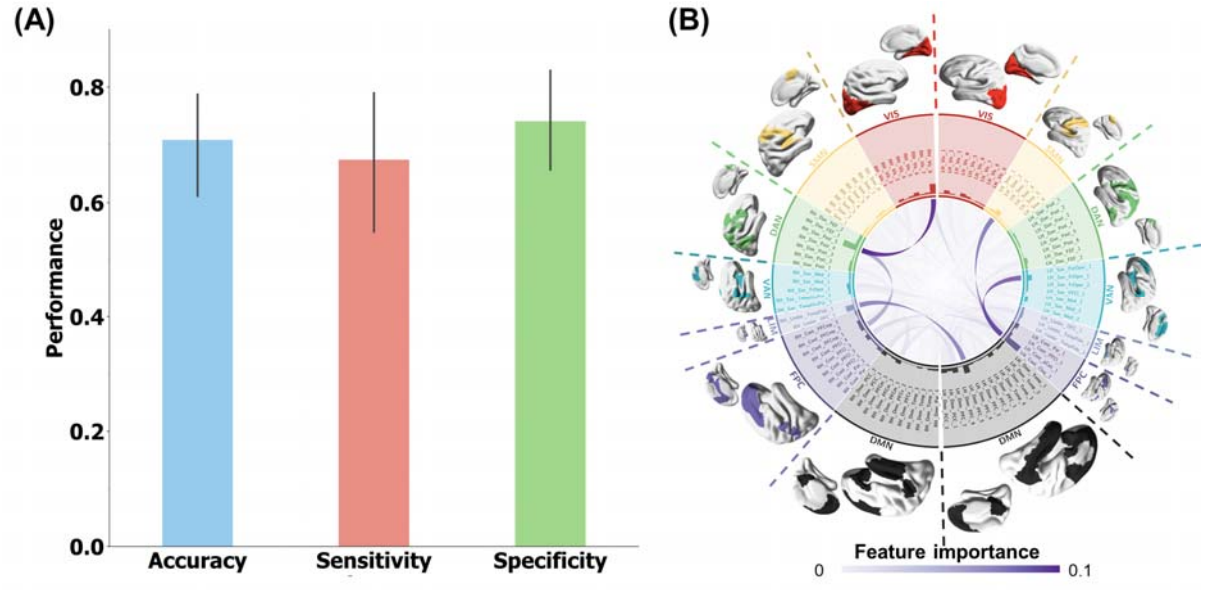


Figure S5. Site classification. All subjects (including 145 patients with multiple mental disorders such as attention-deficit/hyperactivity disorder, bipolar disorder) from UCLA-CNP were used for classification. **(A)** The performance of classifying all subjects from UCLA-CNP or the combination of NYU and SUDMEX-TMS datasets (accuracy = 0.58; sensitivity = 0.53; specificity = 0.70). The performance of distribution was from 1000 random permutations, $accuracy_{mean}$ = 0.48; $sensitivity_{mean}$ = 0.47; $specificity_{mean}$ = 0.54 **(B)** To fairly objectively compare the site classification performance with the reproduced diagnosis classification performance and avoid the size effect of different sample sizes, we randomly subsampling all subjects from UCLA-CNP to the size of healthy controls from UCLA-CNP 1000 times. The average performance randomly subsampling subjects from UCLA-CNP or the combination of NYU and SUDMEX-TMS datasets (accuracy = 0.61 ± 0.03; sensitivity = 0.53 ± 0.06; specificity = 0.70 ± 0) was plotted.

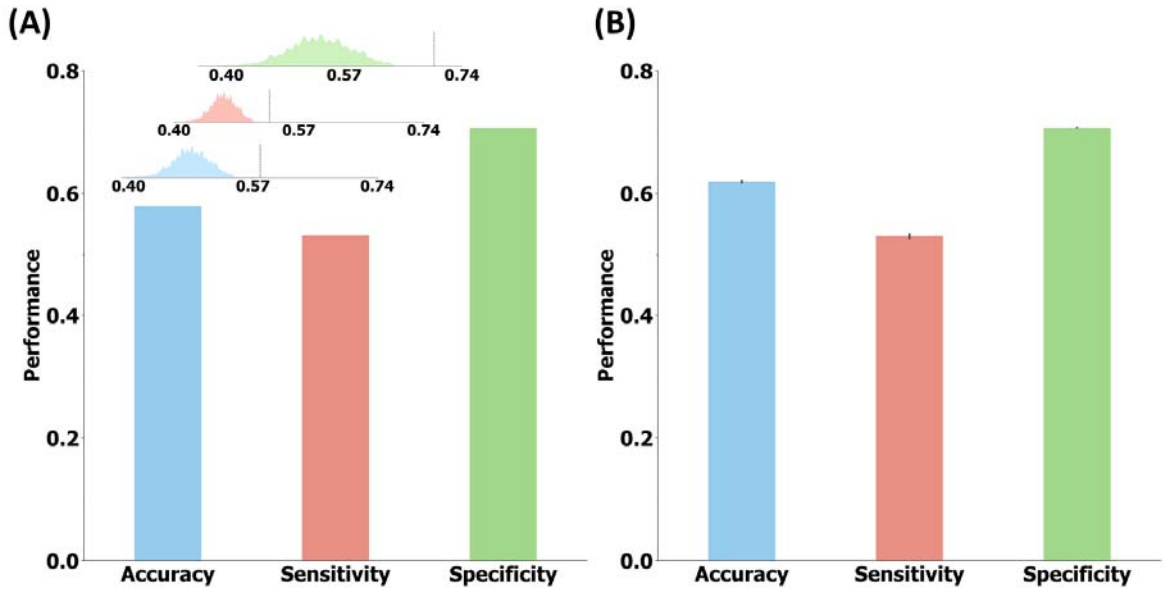


Figure S6. CUD classification reversely. To further verify that the generalizability of our CUD discriminative FC signatures in independent cohort was not primarily dominant by the site effect, we trained the classification models in the independent cohort with same strategy in Figure S5B first. The performance was evaluated with ten-fold cross validation. Then, the obtained discriminative signatures were tested using the discovery cohort. **(A)** The accuracy, sensitivity, and specificity of models in independent cohort are 0.77 ± 0.10, 0.78 ± 0.12, and 0.75 ± 0.13, respectively. **(B)** The accuracy, sensitivity, and specificity of models applied in the discovery cohort are 0.63, 0.63, 0.63, respectively.

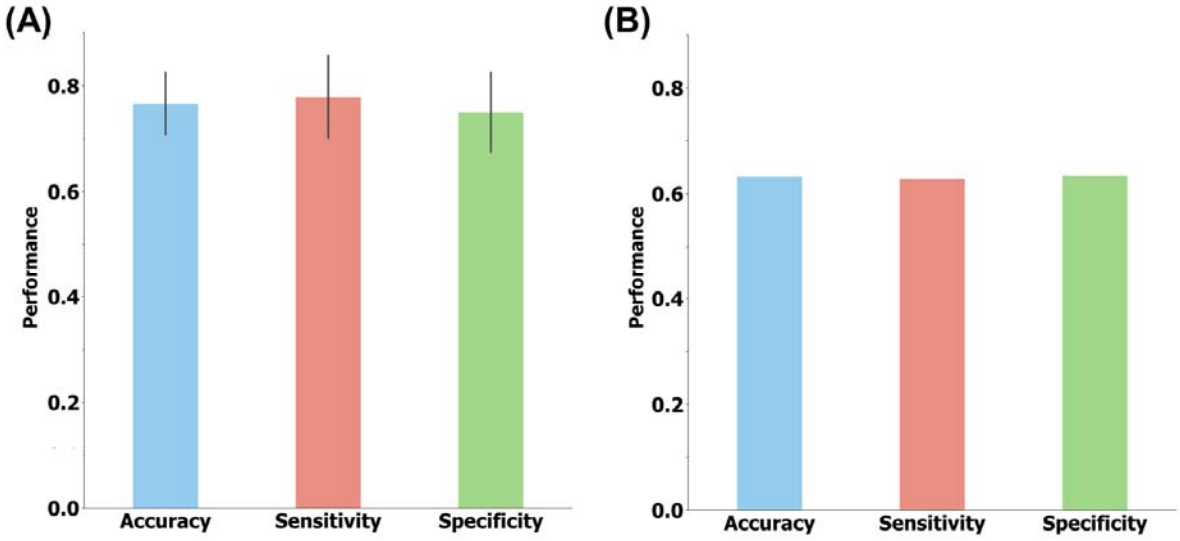


Figure S7. Control study of prediction of the craving visual analog scale (VAS) score changes specific to active rTMS treatment. To verify our hypothesis that the phenotyping FCs own advantage in reflecting the rTMS treatment response, we implement two control studies. **(A)** We used all FCs to predict the active rTMS VAS score change in ten 5-fold cross validations. The predicted scores were averaged from ten models. $R^2 = 0.07$ and Pearson's $r = 0.42$, $P = 0.037$ based on the one-sided test against the alternative hypothesis that $r > 0$. **(B)** The Wilcoxon signed-rank test of the predicted performance from ten models, training with discriminative FC and all FC. The higher R^2 and r in scatterplot than the mean of ten models were due to the ensemble learning effect [1]. **(C)** We randomly subsampled all FC features as equal to the size of phenotyping FCs in differentiating CUD and HC. The distributions of the r and R^2 were shown. The vertical line was the performance from discriminative FC.

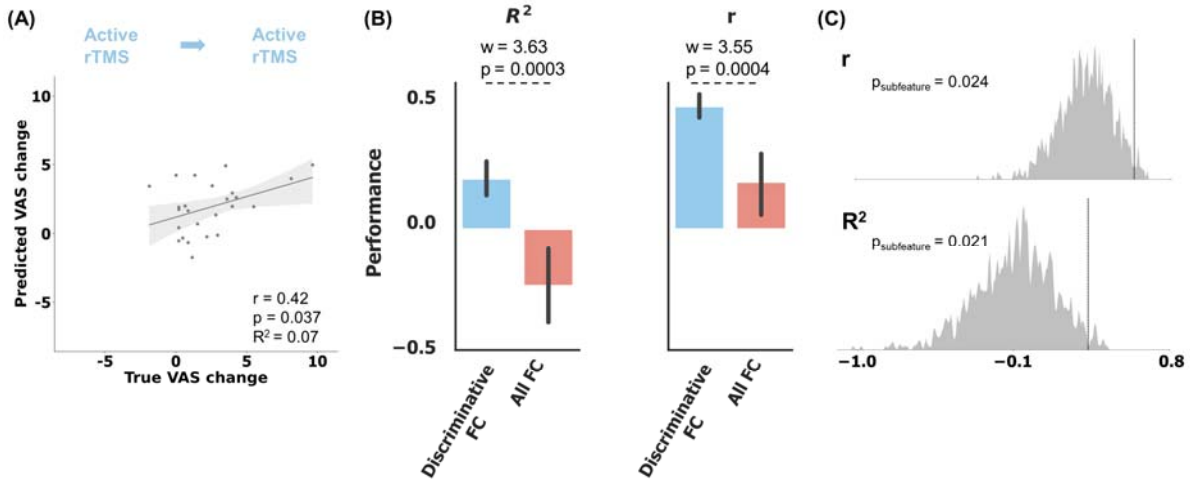


Figure S8. Visualization of the CUD-discriminative FCs involved in repetitive transcranial magnetic stimulation treatment response prediction. (A) The rTMS predictive FC signature. **(B)** We grouped the importance of predictive FCs into the seven typical networks including visual network (VIS), somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LIM), frontoparietal control network (FPC), and default mode network (DMN).

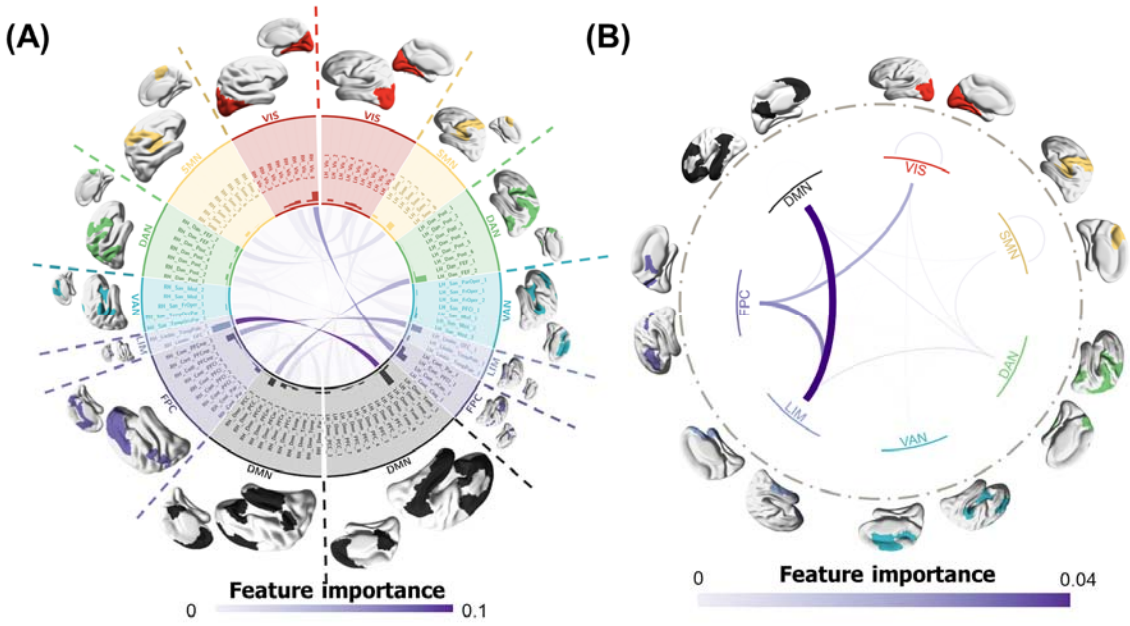
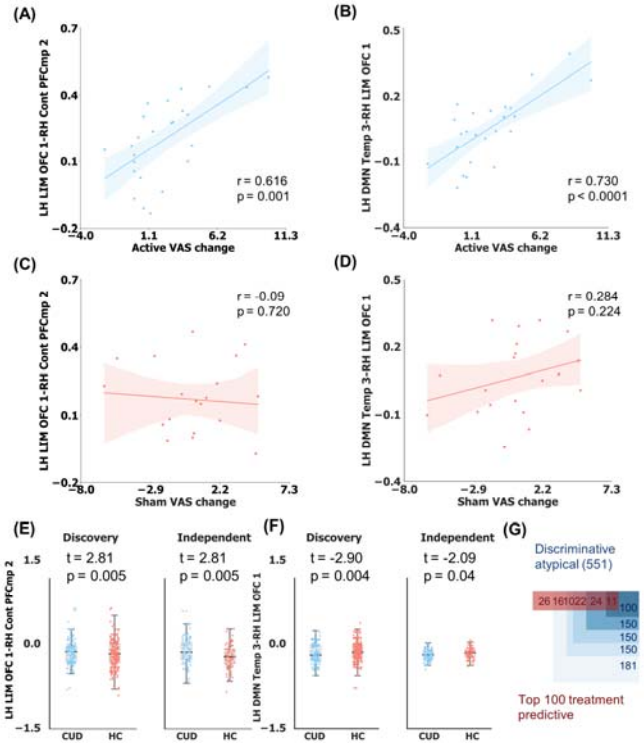


Figure S9. Association between the discriminative FCs and treatment-outcome-predictive FCs. (A), (B) We visualized the correlation between the top 2 active rTMS treatment response predictive FCs and active rTMS VAS score change in scatter plot as illustrative examples. These two FCs were between the oribitofrontal cortex (LH LIM OFC 1) and anterior cingulate cortex (RH Cont PFCmp 2), and between middle temporal cortex (LH DMN Temp 3) and superior oribitofrontal cortex (RH LIM OFC 1). **(C), (D)** The correlation between these two FCs and sham rTMS VAS score change. **(E), (F)** These two FCs distribution between CUD and HC in the discovery and independent cohorts. The data in discovery cohort was augmented twice. These two FCs were significantly and specifically correlated to the VAS score change and significantly different between CUD and HC. **(G)** Venn diagram indicating the association between discriminative and abnormal FCs (551) with active rTMS treatment outcome. Discriminative atypical FCs were defined as the discriminative FCs identified by our classification models and the significantly atypical FCs detected by two-sample t-tests comparing CUD and HC subjects, with those surviving FDR correction ($p_{fdr} < 0.05$). The number of discriminative atypical FCs was equal to the sum of hyperconnections and hypoconnections. Deeper bluer shading indicates larger treatment predictive weights. The red numbers in the red rectangle represents the overlapping numbers between the top 100 treatment predictive FCs and all discriminative



atypical FCs in descending order.

Figure S10. Illustration of our proposed analytical framework. (A) Region of interests (ROIs) level time series were extracted from fMRI BOLD signals based on the Schaefer atlas. Functional connectivity was calculated by Pearson's correlation in time series between any pair of ROIs. **(B)** The functional connectivity features were used to train the XGBoost model to classify the subjects into CUD patients or healthy controls. **(C)** Utilized phenotyping functional connectivity (FC) features, a relevance vector machine (RVM) model was employed to predict changes in visual analog scale (VAS) scores for patients undergoing repetitive transcranial magnetic stimulation (rTMS) treatment.

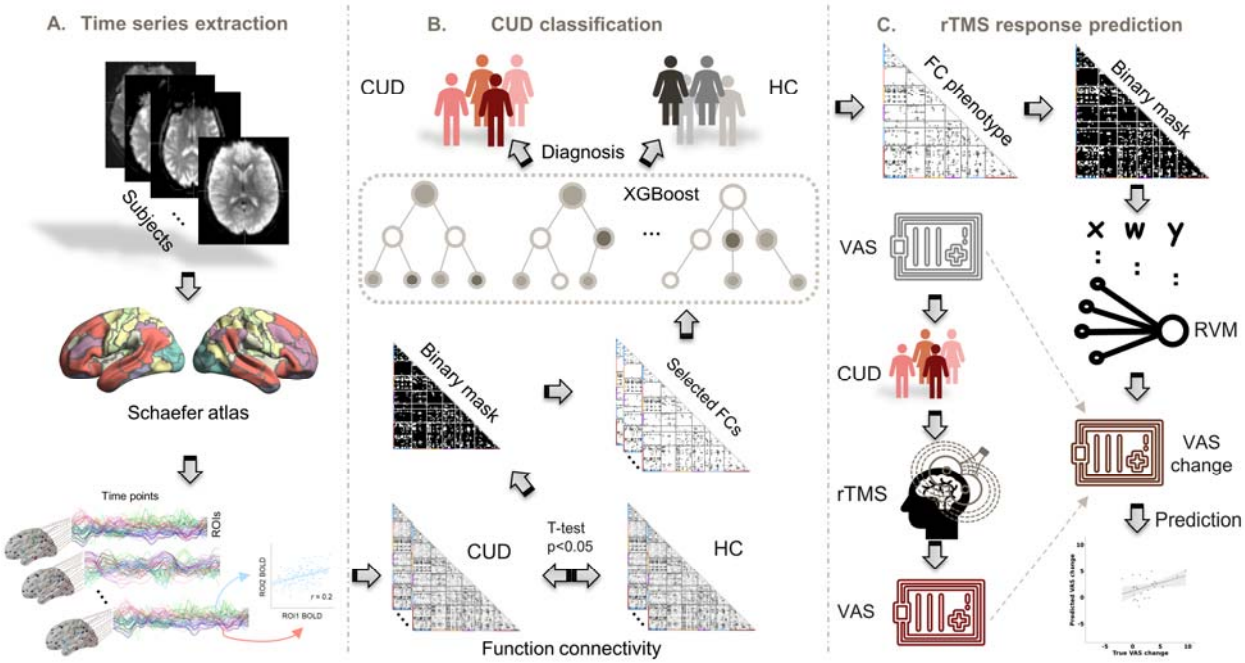


Figure S11. The significant ($p_{fdr} < 0.05$) Pearson's correlation between each FC and mean of framewise displacements after FDR correction for each dataset. **(A)** Correlation matrix of the SUDMEX-CONN dataset. **(B)** Correlation matrix of the UCLA-CNP dataset. **(C)** Correlation matrix of the SUDMEX-TMS dataset. Correlation matrix of the NYU dataset is not visualized here since only two FCs significantly correlated to FCs.

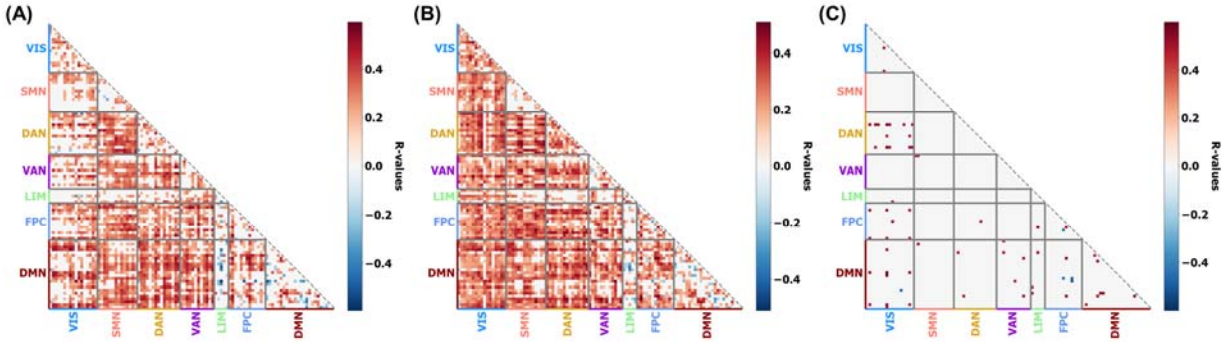


Figure S12. Effects of data augmentation on classification performance. When the augmentation time was equal to 0, the models were trained with FCs extracted from all-sequence time series. When the augmentation time was equal to 1, the models were trained with the FCs extracted from all-sequence time series and from the first semi-sequence time series. When the augmentation time was equal to 2, the models were trained with the FCs extracted from all-sequence time series, from the first semi-sequence time series (the first 150 volumes) and from the second semi-sequence time series (the last 150 volumes). When the augmentation time was equal to 3 or 4, one or two more FC features were extracted from randomly segmented time series with a length of 150 volumes. Without augmentation, the accuracy was 0.70 ± 0.07, sensitivity was 0.66 ± 0.21, and specificity was 0.74 ± 0.16. Applying augmentation once, accuracy was 0.76 ± 0.09, sensitivity was 0.74 ± 0.15, and specificity was 0.78 ± 0.10. Applying augmentation twice, the accuracy was 0.83 ± 0.10, sensitivity was 0.80 ± 0.18, and specificity was 0.85 ± 0.10. Applying augmentation three times, the accuracy was 0.82 ± 0.11, sensitivity was 0.84 ± 0.13, and specificity was 0.82 ± 0.15. Applying augmentation four times, the accuracy was 0.84 ± 0.07, sensitivity was 0.83 ± 0.16, and specificity was 0.85 ± 0.14. Finally, we augmented the FC twice to pursue exhaustive analysis since the performance was no longer further increased.

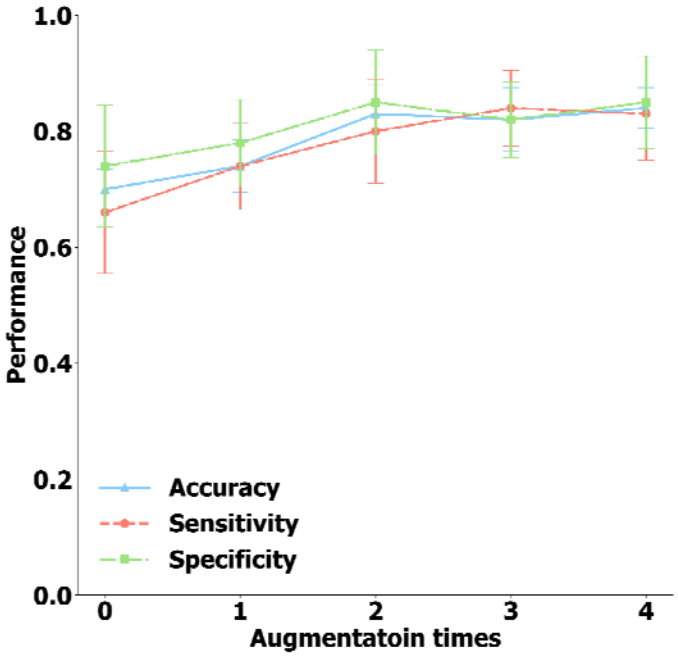
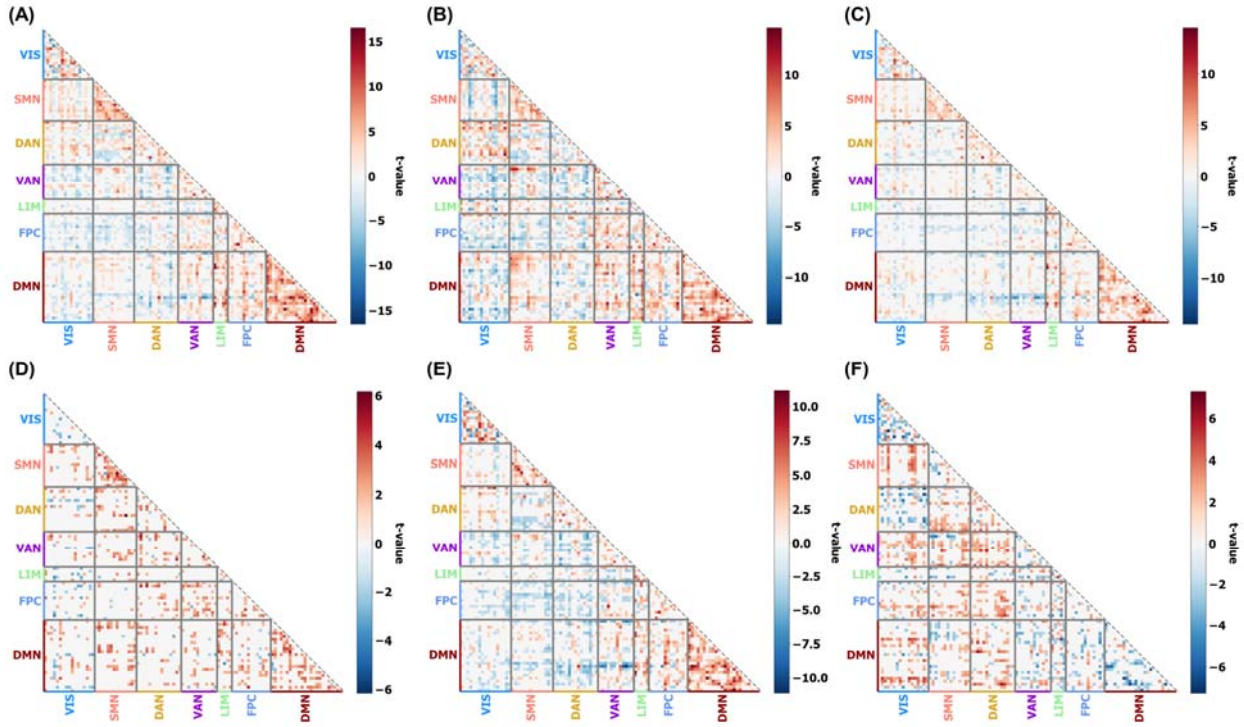


Figure S13. The two-sample t-test comparisons of each FCs across different datasets. (A) Comparisons of FCs in SUDMEX-CONN dataset and NYU dataset (SUDMEX-CONN versus NYU). **(B)** Comparisons of FCs in the SUDMEX-CONN dataset and UCLA-CNP dataset (SUDMEX-CONN versus UCLA-CNP). **(C)** Comparisons of FCs in UCLA-CNP dataset and NYU dataset (UCLA-CNP versus us NYU). **(D)** Comparisons of FCs in SUDMEX-CONN dataset and SUDMEX-TMS dataset (SUDMEX-CONN versus us SUDMEX-TMS). **(E)** Comparisons of FCs in SUDMEX-TMS dataset and NYU dataset (SUDMEX-TMS versus us NYU). **(F)** Comparisons of FCs in UCLA-CNP dataset and SUDMEX-TMS dataset (UCLA-CNP versus us SUDMEX-TMS). All t values shown in the panels survived FDR correction



(p_{fdr}<0.05).

Table S1. Results of two-sample t-test comparison of the top 4 discriminative network-level connections between healthy controls and patients diagnosed with other clinical diagnostic labels in MINI International Neuropsychiatric Interview – Plus Spanish version 5.0 (MINI), including substance abuse and suicide diagnosis. These conditions have been suggested to be highly related to CUD 2. The p-values between each connection and all clinical variables (including MINI and the measurements using in Table S2) were corrected for FDR. Significant results from the t-tests, prior to FDR correction ($p < 0.05$), are displayed in bold and those that passed FDR correction ($p < 0.05$) are highlighted in italic.

	DMN-LIM			VAN-FPC			SMN-FPC			VIS-DAN		
	t	p	p_{fdr}	t	p	p_{fdr}	t	p	p_{fdr}	t	p	p_{fdr}
Suicide risk	**-2.75**	**0.007**	NS	-0.23	0.818	NS	1.20	0.234	NS	0.22	0.828	NS
Alcohol abuse	**-2.80**	**0.006**	NS	1.67	0.098	NS	**2.50**	**0.014**	NS	1.76	0.082	NS
Stimulants used history	0.79	0.431	NS	-0.03	0.978	NS	-0.04	0.965	NS	***-3.36***	***0.001***	***0.011***
Hallucinogens used history	***-3.43***	***0.002***	***0.025***	0.97	0.336	NS	-0.28	0.776	NS	-0.45	0.655	NS
Inhalants used history	***-4.43***	***<0.001***	***0.002***	1.66	0.099	NS	0.85	0.402	NS	2.36	0.020	NS

Table S2. Correlation between the top four discriminative network connections and clinical assessments. The scales using here were summarized as follows: World Health Organization Disability Assessment Schedule 2.0 (WHODAS), Cocaine Craving Questionnaire General (CCQ-G), Barratt Impulsiveness Scale version 11 (BIS), Symptom Checklist-90-revised (SCL). Significant results from the t-tests, prior to FDR correction ($p < 0.05$), are displayed in bold and those that passed FDR correction ($p < 0.05$) are highlighted in italic.

	DMN-LIM			VAN-FPC			SMN-FPC			VIS-DAN		
	r	p	p_{fdr}	r	p	p_{fdr}	r	p	p_{fdr}	r	p	p_{fdr}
WHODAS total	**-0.19**	**0.026**	NS	**0.18**	**0.034**	NS	0.08	0.364	NS	**0.18**	**0.035**	NS
WHODAS cognition	**-0.17**	**0.046**	NS	**0.20**	**0.016**	NS	0.07	0.394	NS	**0.17**	**0.045**	NS
WHODAS mobility	-0.10	0.259	NS	0.11	0.201	NS	0.10	0.229	NS	0.07	0.414	NS
WHODAS self-care	-0.03	0.740	NS	0.15	0.075	NS	0.12	0.175	NS	0.04	0.674	NS
WHODAS getting along	-0.16	0.064	NS	0.12	0.156	NS	0.11	0.201	NS	0.08	0.356	NS
WHODAS life activities	-0.11	0.216	NS	0.15	0.081	NS	0.06	0.475	NS	0.06	0.481	NS
WHODAS participation	-0.15	0.084	NS	0.14	0.112	NS	0.02	0.838	NS	0.15	0.074	NS
CCQ-G	-0.21	0.082	NS	-0.04	0.737	NS	**-0.26**	**0.031**	NS	0.06	0.593	NS
BIS cognitive	-0.03	0.760	NS	0.09	0.369	NS	0.15	0.111	NS	0.13	0.162	NS
BIS motor	-0.07	0.462	NS	0.13	0.168	NS	0.14	0.143	NS	0.14	0.145	NS
BIS non-planning	-0.17	0.071	NS	0.17	0.080	NS	0.11	0.247	NS	***0.27***	***0.004***	***0.026***
BIS total	-0.12	0.230	NS	0.15	0.108	NS	0.16	0.093	NS	**0.22**	**0.021**	NS
SCL somatization	-0.04	0.635	NS	0.11	0.249	NS	**0.21**	**0.023**	NS	0.17	0.06	NS
SCL obsessive compulsive	-0.08	0.366	NS	**0.20**	**0.031**	NS	0.17	0.055	NS	0.14	0.136	NS
SCL interpersonal sensitivity	-0.10	0.294	NS	0.17	0.065	NS	**0.18**	**0.041**	NS	<0.01	0.98	NS
SCL depression	-0.16	0.085	NS	**0.24**	**0.007**	NS	***0.25***	***0.006***	***0.046***	0.10	0.296	NS
SCL anxiety	**-0.19**	**0.041**	NS	**0.23**	**0.011**	NS	***0.26***	***0.004***	***0.038***	0.03	0.706	NS
SCL hostility	-0.08	0.399	NS	**0.21**	**0.021**	NS	**0.21**	**0.018**	NS	0.13	0.158	NS
SCL phobic anxiety	-0.17	0.064	NS	**0.18**	**0.046**	NS	**0.22**	**0.016**	NS	0.10	0.269	NS
SCL paranoid ideation	-0.03	0.776	NS	0.14	0.122	NS	0.18	0.052	NS	<0.01	0.975	NS

SCL psychoticism	-0.17	0.060	NS	**0.20**	**0.027**	NS	**0.18**	**0.045**	NS	0.03	0.775	NS
SCL total	-0.14	0.113	NS	**0.21**	**0.019**	NS	**0.22**	**0.013**	NS	0.11	0.211	NS

Table S3. Correlation between the top four discriminative network connections and tobacco use history.

	DMN-LIM			VAN-FPC			SMN-FPC			VIS-DAN		
	t/r	p	p_{fdr}	t/r	p	p_{fdr}	t/r	p	p_{fdr}	t/r	p	p_{fdr}
Tobacco use in the last year	**2.08**	**0.040**	NS	**-2.04**	**0.044**	NS	-0.64	0.521	NS	***-2.71***	***0.008***	***0.031***
Amount of cigarettes per day	2.83	0.063	NS	2.46	0.09	NS	0.58	0.562	NS	2.81	0.064	NS
Years of tobacco use	***-0.25***	***0.008***	***0.033***	**0.21**	**0.027**	NS	<0.01	0.99	NS	**0.19**	**0.045**	NS
Tobacco age of onset	-0.17	0.087	NS	0.06	0.578	NS	<0.01	0.98	NS	0.122	0.231	NS

Table S4. Demographic information of the discovery cohort (SUDMEX-CONN dataset).

Demographic variables	HC		CUD		Statistic values	
	n	%	n	%	$\chi 2$	p
Gender						
Male	47	84	62	87	0	1
Female	9	16	9	13		
unknown	2		0			
	mean	std	mean	std	t	p
Age	31.4	± 8.2	31.2	± 7.3	0.15	0.88

Table S5. Demographic information of New York University datasets.

Demographic variables	CUD
Gender	
Male, No. (%)	26 (90)
Female, No. (%)	3 (10)
Age, mean ± sd	34.2 ± 9.1

Table S6. Demographic information of SUDMEX-TMS datasets. The statistical comparison was only applied for the patients with rTMS treatments in two weeks.

	CUD						
Demographic variables	**Active rTMS**		**Sham rTMS**		**Statistic values**		**No treatment**
	n	%	n	%	$\chi 2$	p	n
Gender							
Male	21	84	18	90			8
Female	4	16	2	10	0.02	0.88	0
	mean	std	mean	std	t	p	mean ± std
Age	35.9	± 6.8	33.3	± 8.4	1.13	0.27	39.9 ± 4.86

Table S7. Demographic information of UCLA-CNP datasets.

Demographic variables	**HC**		**Other disorders**		**Statistic values**	
	n	%	n	%	$\chi 2$	p
Gender						
Male	65	80	87	58		
Female	16	20	58	42	8.78	0.003
	mean	std	mean	std	t	p
Age	34.2	± 9.1	34.8	± 9.5	0.47	0.64

Table S8. Demographic information of the replication cohort.

Demographic variables	HC		CUD		Statistic values	
	n	%	n	%	$\chi 2$	p
Gender						
Male	65	80	71	87	0.77	0.38
Female	16	20	11	13		
	mean	std	mean	std	t	p
Age	34.2	± 9.1	35.7	± 8.2	-1.12	0.26

sReferences

1. Dong, X., Yu, Z., Cao, W., Shi, Y. & Ma, Q. A survey on ensemble learning. *Front. Comput. Sci* **14**, 241-258 (2019).
2. Zou, Z. et al. Definition of Substance and Non-substance Addiction. *Adv Exp Med Biol* **1010**, 21-41 (2017).