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From Snapshots to Stable Outcomes: Resting-State Functional Magnetic Resonance Imaging–Based Prognosis of Functioning in Patients With Psychosis Risk or Recent-Onset Depression

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ABSTRACT

BACKGROUND: Early recovery of functioning is critical for favorable outcomes in psychotic and affective disorders. Transdiagnostic brain activity patterns may capture pathways for poor outcomes before clinical manifestation, thereby supporting timely prevention and intervention.

METHODS: Using machine learning, we evaluated the transdiagnostic prognostic value of resting-state functional magnetic resonance imaging fractional amplitude of low-frequency fluctuations (fALFF) (slow-5 and slow-4 sub-bands) for functional outcomes in patients at clinical high risk for psychosis (n = 217) or with recent-onset depression (n = 198) from the multisite PRONIA (Prognostic Tools for Early Psychosis Management) study. Leave-site-out cross-validation assessed the geographic generalizability of models across disability and symptom domains, with outcomes defined as snapshots at 9- or 18-month follow-up or across both time points. We examined diagnosis-specific performance, generalization to recent-onset psychosis (n = 140), and negative symptoms and the added value of fALFF over clinical prognostication.

RESULTS: Transdiagnostic models predicting stable good functioning across follow-ups showed up to 10% higher balanced accuracy (BAC) than snapshot models. Decreased slow-5 fALFFs in the default mode network, executive control network (ECN), and dorsal attentional network (DAN) and increased fALFF in the salience network, ECN, and DAN predicted impairment with BAC = 67% (sensitivity = 65%, specificity = 70%, $p < .001$). This model generalized to recent-onset psychosis (BAC = 62%, sensitivity = 64%, specificity = 59%, $p < .001$) and predicted (BAC = 65%, sensitivity = 66%, specificity = 65%, $p < .001$) and was mediated by negative symptoms. Slow-5–based models improved prognostic accuracy over expert ratings in disability (BAC_{raters} = 66%, $BAC_{raters+slow\text{-}5}$ = 75%, W = 1680, $p < .001$) and symptom (BAC_{raters} = 61%, $BAC_{raters+slow\text{-}5}$ = 71%, W = 1444, $p < .001$) domains.

CONCLUSIONS: We highlighted the prognostic value of fALFF for functional impairment in psychosis risk and early depression. Leveraging trajectorial information, we identified candidate imaging biomarkers to improve prognostication, thereby supporting personalized prevention and recovery strategies.

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Daily functioning, the ability to carry out everyday tasks and meet personal milestones, is essential for quality of life (1,2). Functioning deficits drive disease burden across many illnesses and are a hallmark of psychotic and affective disorders (3). Such impairments emerge in states of clinical high risk for psychosis (CHR-P) (4,5), and early functional recovery is associated with better long-term outcomes (4,6–8). Thus, early detection of functional impairments is critical for guiding timely preventive and recovery-oriented strategies that intercept or mitigate disease chronicity. However, early psychosis and depression are characterized by heterogeneous trajectories of psychosocial functioning (4,9) difficult to predict in routine clinical care.

The limited performance of existing functional prognostic models may stem from their reliance on snapshot outcomes and the variability of follow-up intervals. This approach is associated with the risk that models are trapped by transient fluctuations of disease phenomena obscuring meaningful

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associations between outcomes and predictors. Previous studies have identified subgroups of patients who exhibit distinct longitudinal outcome trajectories in psychosis and depression (10–14). Approximately 30% of individuals at CHR-P exhibit sustained functional improvements over multiple follow-ups within 2 years, while the remaining individuals display unstable or persistent impairment (15). Leveraging the temporal information offered by multiple outcome measurements may delineate homogeneous functioning courses that map saliently to the underlying predictive patterns and enhance the robustness of prognostic tools.

Moreover, the variable clinical profiles of individuals in early stages of psychosis and depression offer health care professionals limited prognostic insight into longitudinal functional courses. Previous studies highlighted the clinicians' difficulties in forecasting outcomes in psychosis (16,17), depression (8,18), and CHR-P (19,20). Neuroimaging data may augment clinical decision making by capturing transdiagnostic factors with potential cascade effects on functioning courses and highlight prognostic biomarkers that could inform the development of novel recovery-oriented interventions (21–23). While structural neuroimaging has contributed to predictive models of social and role functioning for CHR-P and recent-onset depression (ROD), with accuracies around 70% to 75% (8,24–26), these models have poor interdiagnostic generalizability (8), which suggests that the respective structural brain signatures differ substantially.

Functional brain alterations shared by psychosis and depression (27,28) may provide a closer proxy for the evolving pathophysiology that underlies functional outcomes. Resting-state fMRI (rs-fMRI) is particularly well suited for clinical contexts compared with task-based fMRI and is adequately reliable (29–31). rs-fMRI measures have been linked to functioning in group-level studies (32,33), and were predictive of transition to psychosis (34,35), treatment response (36,37), and 1-year improvement in functioning in recent-onset psychosis (ROP) (38). Among these, the fractional amplitude of low-frequency fluctuations (fALFF) captures the regional intensity of spontaneous neuronal activity during rest, providing a rich feature dimensionality in the spatial (voxel-level resolution) and temporal domain [frequency sub-bands capturing different neural oscillators (39,40)]. fALFF abnormalities in subcortical regions and the default mode network (DMN), salience network (SN), and frontotemporal network have been reported in CHR-P (41,42) and ROD (43), pointing toward transdiagnostic alterations in these populations. Moreover, fALFF relates to persistent negative symptoms in schizophrenia (44) and treatment response in psychosis (45) and depression (46) and mediates the effects of cognition on functional outcomes (21,47). However, the prognostic value of rs-fMRI measures such as fALFF for functioning outcomes in CHR-P and ROD remains to be elucidated.

In the current study, we aimed to advance individualized predictions of functional outcomes by investigating the prognostic value of multiband fALFF in a transdiagnostic sample of patients at CHR-P or with ROD (and CHR-P criteria not met) from the multisite PRONIA (Prognostic Tools for Early Psychosis Management) study (http://proniapredictors.eu). We hypothesized that fALFF-based machine learning models predicting impairment across the entire 9- to 18-month follow-up period (i.e., impairment at either the 9- or 18-month follow-ups vs. sustained good functioning across follow-ups) would achieve greater accuracy than snapshot models predicting impairment at individual follow-ups (9 or 18 months). Functional outcomes were measured using the Global Assessment of Functioning: Disability (GAF-DI) (psychosocial impairment) and Symptoms (GAF-S) (psychopathology-related distress) subscales. We assessed models' diagnostic specificity and their generalization to later disease stages (ROP). Moreover, we evaluated generalization to sustained negative symptoms—proposed mediators between brain function and functional impairment (21,47,48)—and specificity relative to other symptom domains, to support the mechanistic validity of our prognostic signatures. Additionally, we tested models' potential for augmenting clinical prognostication by integrating clinical raters' predictions with fALFF-based models. Lastly, we examined models' performance across patient subgroups with distinct functional trajectories from study inclusion to the 18-month follow-up, identified using longitudinal clustering.

METHODS AND MATERIALS

Participants

The study adhered to the TRIPOD+AI (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis + Artificial Intelligence) reporting guidelines (49) (Supplement).

CHR-P individuals and individuals with ROD were recruited within the PRONIA study, spanning 10 different European sites (see Table S1 for inclusion/exclusion criteria). In addition to the consortium procedure (Figure S1), we excluded the Bari and Düsseldorf sites from the current analyses, due to an insufficient number of healthy control individuals (HCs) available for estimating site effects. Participants were also excluded if they 1) had no examinations available after the 3-month time point, 2) did not have a baseline fMRI scan, or 3) had scans of insufficient quality (Figure S1). A total of 125 CHR-P participants and 121 patients with ROD had functioning data available for both follow-up time points (median 9 and 18 months) (see Functional Outcome Labels). Sociodemographic and clinical characteristics of the CHR-P and ROD samples are detailed in Table S2. An additional 92 CHR-P individuals and 77 patients with ROD with 9-month but no 18-month follow-up data were included for building snapshot models of 9-month outcomes and for validation and generalization analyses together with 140 patients with ROP. A total of 416 HCs were used to correct fALFF images for nuisance covariates while retaining clinically relevant effects. Figure S2 presents diagnostic comorbidities of the CHR individuals and patients with ROD. Table S3 compares the transdiagnostic model discovery sample with the 2 model application samples.

Adult participants provided written informed consent, and participants younger than 18 years and their guardians provided written informed assent and consent, respectively. The study was registered at the German Clinical Trials Register (DRKS00005042) and approved by local research ethics committees.

Functional Outcome Labels

Functional impairment was assessed separately for the GAF-DI (psychosocial functioning) and GAF-S (symptoms distress)

subscales (50) by trained clinical raters. A score of ≤79 indicated the presence of functional impairment, while scores of ≥80 were considered minimal or no impairment, indicating good functioning (50). Machine learning models were trained to predict the following time point–specific outcome labels: 1) first follow-up time point (median 9 months), computed using the GAF scores at the 9-month postbaseline measurement (n = 381) or, if not available, the 12-month (n = 1) or 6-month (n = 33) measurements; 2) second follow-up time point (median 18 months), computed using the GAF score at the 18-month postbaseline measurement (n = 210) or, if not available, the 27-month (n = 12) or 36-month (n = 24) follow-up measurements; and 3) functional impairment within the entire 9- to 18-month follow-up period (i.e., impairment at either the first or second follow-up vs. sustained good functioning across both time points). The distribution of outcomes across baseline and follow-ups is presented in Figure S3. Resulting functioning outcome groups were compared on sociodemographic and clinical dimensions.

rs-fMRI Data Acquisition and Processing

Details on data acquisition and processing are provided in Supplemental Methods. Briefly, the PRONIA Consortium utilized minimal harmonization of MRI acquisition parameters across sites to facilitate real-world translation (Tables S4 and S5). Structural T1-weighted images required for the preprocessing of functional images were processed using the CAT12 toolbox (version r1207; http://dbm.neuro.uni-jena.de/cat12/) (Supplemental Methods).

The rs-fMRI data preprocessing was conducted using the SPM software (version 12-6685; http://www.fil.ion.ucl.ac.uk/spm) and the REST toolkit [version 1.8 (51); http://www.restfmri.net/], adapted from a previously developed pipeline (52). Preprocessing steps included discarding the first 8 volumes, slice-time correction, realignment, T1 coregistration, reslicing, Montreal Neurological Institute (MNI) space normalization, nuisance covariate regression (white matter, cerebrospinal fluid, and Friston 24 motion parameters), smoothing (6 mm full width at half maximum Gaussian filter), despiking-based motion correction, and detrending (Supplemental Methods). fALFF was computed using the REST toolbox by transforming the voxelwise preprocessed time series to the frequency domain using the fast Fourier transform. Then, fALFF was calculated as the ratio of the integrated power spectrum of the interest frequency range to that of the entire frequency range for 2 sub-bands shown to contain functionally meaningful signal (53), slow-5 (0.01–0.027 Hz) and slow-4 (0.027–0.073 Hz). We discarded higher frequencies known to primarily contain noise (54), but we report exploratory results for the slow-3 sub-band (0.073–0.0198 Hz) in the Supplement. Voxelwise z score standardization was applied to fALFF maps (55).

Machine Learning Approach

The open-source toolbox NeuroMiner (version 1.3; https://github.com/neurominer-git) was used to train machine learning models to predict the 3 time point–dependent outcome labels in the transdiagnostic CHR-P and ROD sample utilizing a leave-site-out repeated nested cross-validation approach (56) with 10 permutations in both layers. We corrected the fALFF data for site effects using a mean offset adjustment based on a matched sample of HCs (Supplemental Methods). Further preprocessing steps were wrapped within the inner cross-validation layer and involved nuisance covariate regression (age, sex, mean framewise displacement of the fMRI volumes), upweighting features based on F scores relative to outcome labels, dimensionality reduction using principal component analysis, and median-based standardization and winsorization of outliers over ±4 SDs (Supplemental Methods).

We used a maximum relevance minimum redundancy filter (57) for feature selection in combination with L2-regularized support vector machine (SVM) classifiers (LIBLINEAR; https://www.csie.ntu.edu.tw/∼cjlin/liblinear/) for training fALFF sub-band–specific models for the GAF-DI and GAF-S subscales. The SVM slack parameter was optimized in geometric progression between 2^{-6} and 2^{4}. A stacked multiband model was trained on the decision scores coming from the 2 sub-band–specific models. We evaluated the statistical significance of the models using a permutation-based approach (1000 permutations) and visualized the predictive patters of significant models using feature importance and feature stability metrics [sign-based consistency (58) and cross-validation ratio (59)] (Supplemental Methods).

The best-performing transdiagnostic models were applied to 2 independent samples: 1) left-out CHR-P individuals and individuals with ROD with first follow-up but no second follow-up time point data to assess transferability across time points; 2) ROP patients with data from both follow-ups. To explore the clinical validity of the predictive signatures, models were applied to predict sustained absence of negative symptoms across follow-ups (score of 0 on the Scale for the Assessment of Negative Symptoms, corresponding to the 25th percentile per time point) in the transdiagnostic model discovery sample. Follow-up analyses explored the mediating role of negative symptoms between our models' predictions and functioning outcome labels and the specificity of model generalization to negative symptoms relative to other symptom domains (see Supplemental Methods).

Furthermore, we explored the predictive gains offered by our best-performing transdiagnostic models to the performance of trained clinical raters (average 30 months of rating experience), who were asked to predict patients' good versus poor outcomes during the baseline assessment. Specifically, we trained stacked models combining the decision scores of the fALFF models that performed above chance level with those of the raters and evaluated significant differences between the raters' performance alone and that of combined cybernetic models using Quade tests (60). Similarly, we compared the cybernetic models with models based on baseline sociodemographic and clinical data.

Finally, we assessed the performance of the transdiagnostic models for the CHR-P and ROD groups, for CHR-P patients with and without affective comorbidities, and we trained SVM models for the prediction of functioning separately in the CHR-P and ROD samples to evaluate diagnostic specificity. Models that performed above chance level were applied to the other clinical group to assess interdiagnostic transferability.

Post Hoc Associations of Prognostic Models' Signatures

To further understand the effects of different baseline-to-follow-up outcome trajectories on model performance, we compared the best-performing models between subgroups of patients with distinct functional trajectories spanning from baseline to follow-ups. Trajectory types were identified using k-means longitudinal clustering (Supplemental Methods).

Lastly, we investigated associations of the models' decision scores with average scan displacement and cumulative dosages of antipsychotic and selective serotonin reuptake inhibitor (SSRI) medication to exclude potential confounding effects.

RESULTS

Sociodemographic and Clinical Group-Level Comparisons

Baseline comparisons between patients with and without snapshot functional impairment at the 9- and 18-month follow-ups are presented in Tables S6 and S7, respectively.

Patients with functional impairment present within the follow-up period were compared with patients with sustained good functioning (Table S8). Transdiagnostically, participants with follow-up functional disability had fewer education years ($t_{241} = 2.2$, $p = .03$) (see Table 1 for group means) and higher baseline levels of negative ($t_{244} = -3.0$, $p = .003$) and disorganized ($t_{243} = -3.4$, $p < .001$) symptoms, measured by the Structured Interview for Prodromal Syndromes (61). Moreover, the impaired group had lower levels of functioning in the month prior to baseline (GAF-DI: $t_{242} = 5.1$, $p < .001$; GAF-S: $t_{242} = 5.1$, $p < .001$) and lifetime (GAF-DI: $t_{242} = 4.04$, $p < .001$; GAF-S: $t_{242} = 3.57$, $p < .001$).

A lower proportion of patients achieved sustained good functioning across the 2 follow-ups in the GAF-S domain ($n = 19$, 8% of the sample) compared with the GAF-DI domain ($n = 43$, 18% of the sample). We found a higher proportion of male individuals ($\chi^2_4 = 5.3$, $p = .02$), lower levels of functioning on the baseline GAF-S scale ($t_{242} = 2.6$, $p = .001$), and lower lifetime functioning (GAF-DI: $t_{242} = 3.30$, $p = .001$; GAF-S: $t_{242} = 3.57$, $p < .001$) in the GAF-S impaired group (Table S8).

Table 1. Performance Metrics of the Functioning Outcome Classifiers in the Transdiagnostic Sample (Clinical High Risk for Psychosis and Recent-Onset Depression) Across GAF Subscales and Time Point Classification Tasks

	Sensitivity	Specificity	BAC	TP	TN	FP	FN	PPV	NPV	PSI	AUC (95% CI)	p_{FDR} Value
Snapshot Functioning Outcome Prediction at the 9-Month Follow-Up, $n = 415$												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	63.5%	55.0%	59.2%	66	171	140	38	32.0%	81.8%	13.9	0.62 (0.55–0.68)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	67.3%	40.5%	53.9%	70	126	185	34	27.5%	78.8%	6.2	0.54 (0.47–0.60)	>.05
Multiband model	66.3%	49.5%	57.9%	69	154	157	35	30.5%	81.5%	12.0	0.61 (0.54–0.67)	.006*
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	54.5%	55.3%	54.9%	36	193	156	30	18.8%	86.5%	5.3	0.57 (0.50–0.65)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	62.1%	42.7%	52.4%	41	149	200	25	17.0%	85.6%	2.6	0.56 (0.48–0.63)	>.05
Multiband model	60.6%	50.4%	55.5%	40	176	173	26	18.8%	87.1%	5.9	0.55 (0.48–0.63)	>.05
Snapshot Functioning Outcome Prediction at the 18-Month Follow-Up, $n = 246$												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	56.8%	52.3%	54.6%	46	90	82	35	35.9%	72.0%	7.9	0.57 (0.49–0.64)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	65.4%	48.8%	57.1%	53	84	88	28	37.6%	75.0%	12.6	0.56 (0.48–0.64)	<.001*
Multiband model	60.5%	51.7%	56.1%	49	89	83	32	37.1%	73.6%	10.7	0.58 (0.50–0.66)	>.05
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	54.4%	44.9%	49.6%	31	88	108	26	22.3%	77.2%	−0.5	0.51 (0.42–0.59)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	50.9%	44.9%	47.9%	29	88	108	28	21.2%	75.9%	−3.0	0.49 (0.41–0.58)	>.05
Multiband model	49.1%	45.9%	47.5%	28	90	106	29	20.9%	75.6%	−3.5	0.48 (0.40–0.56)	>.05
Functioning Outcome Prediction Across the 9- to 18-Month Follow-Ups, $n = 246$												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	65.0%	69.8%	67.4%	132	30	13	71	91.0%	29.7%	20.7	0.70 (0.62–0.78)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	41.9%	55.8%	48.8%	85	24	19	118	81.7%	16.9%	−1.4	0.48 (0.39–0.58)	>.05
Multiband model	48.3%	79.1%	63.7%	98	34	9	105	91.6%	24.5%	16.0	0.68 (0.60–0.76)	<.001*
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	58.1%	57.9%	58.0%	132	11	8	95	94.3%	10.4%	4.7	0.67 (0.55–0.78)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	37.9%	52.6%	45.3%	86	10	9	141	90.5%	6.6%	−2.9	0.46 (0.32–0.60)	>.05
Multiband model	65.2%	36.8%	51.0%	148	7	12	79	92.5%	8.1%	0.6	0.57 (0.44–0.70)	>.05

Snapshot models were trained for separately predicting functional outcomes at the 9- and 18-month follow-ups. Additionally, models were trained to predict the presence of functional impairment within the entire 9- to 18-month follow-up period relative to sustained good functioning across follow-ups. p Values were adjusted using FDR correction for multiple comparisons ($\alpha = 0.05$) within each time point classification task.

*Significant p values.

AUC, area under the curve; BAC, balanced accuracy; FDR, false discovery rate; FN, false negative; FP, false positive; GAF, Global Assessment of Functioning; NPV, negative predictive value; PPV, positive predictive value; PSI, prognostic summary index; TN, true negative; TP, true positive.

When we compared CHR-P and ROD in the discovery sample (Table S2), we found that patients with ROD were older (t_{244} = 3.3, p = .001), had more education years (t_{241} = 2.4, p = .02), were less often working/studying (χ^2_6 = 14.8, $p < .001$), and had a lower likelihood of a family history of psychosis (χ^2_6 = 10.3, p = .001). Comparing the discovery sample to the group without a second follow-up, we found that the former had more education years (t_{406} = 2.26, p = .02), more partnerships (χ^2_{12} = 59.99, $p < .001$), more often working/studying (χ^2_6 = 25.10, $p < .001$), more psychopharmacological treatment (χ^2_4 = 6.47, p = .01), and higher levels of baseline psychotic and depressive symptoms (Table S3). The ROP group had a higher percentage of male patients (χ^2_4 = 4.73, p = .03), a lower employment/studying rate (χ^2_6 = 8.73, p = .01), and more clinical deficits (Table S3).

Prognostic Models' Performance

Transdiagnostic Prognostic Models. Performance metrics of transdiagnostic machine learning models are presented in Table 1 and in Supplemental Results for the slow-3 sub-band (Table S9).

When predicting snapshot functional impairment at individual follow-up time points, we found relatively low performances across frequency sub-bands and GAF subscales. The slow-5–based model (balanced accuracy [BAC] = 59.2%, sensitivity = 63.5%, specificity = 55.0%) and multiband model (BAC = 57.9%, sensitivity = 66.3%, specificity = 49.5%) performed above chance level for the prediction of the GAF-DI score at the first follow-up (Table 1). The slow-4–based model (BAC = 57.1%, sensitivity = 65.4%, specificity = 48.8%) and multiband model (BAC = 56.1%, sensitivity = 60.5%, specificity = 51.7%) predicted GAF-DI outcomes at the second follow-up time point. None of the models predicted functional impairment on the GAF-S at the first or second follow-up.

The prognosis of sustained good functioning across the follow-up period performed significantly better (Table 1), with the slow-5–based models showing the best prediction accuracy for both GAF-DI (BAC = 67.4%, sensitivity = 65.0%, specificity = 69.8%) and GAF-S (BAC = 58.0%, sensitivity = 58.1%, specificity = 57.9%). Lower fALFF in the DMN, executive control network (ECN), limbic network (LN), and dorsal attentional network (DAN); increases and decreases in the cerebellum; and higher fALFF in the SN and ventral regions of the ECN and DAN were predictive of functional impairment in the disability and symptom domains (Figures 1 and 2).

Comparatively, multiband models performed above chance level for GAF-DI, but not GAF-S, while none of the slow-4–based models performed above chance level (Table 1). Nonetheless, we included these models in follow-up analyses for exploratory completeness. Moreover, given the higher performances of models predicting functioning within the entire follow-up period in comparison to snapshot outcomes at individual time points (independent of sample composition) (Table S10), we focused on these models for further analyses.

Model Application. Generalizability metrics of the transdiagnostic models in the application samples are presented in Table 2. Models predicting follow-up functional impairment performed similarly to the discovery sample and above chance level when applied to the prediction of functional impairment at the first follow-up time point for patients with no available second follow-up data (Table 2). The highest application performance was found for the slow-5–based prediction of GAF-DI outcomes (BAC = 64.7%, sensitivity = 61.9%, specificity = 67.4%), also best performing in the discovery sample. All sub-band and multiband models generalized to patients with ROP for GAF-DI outcomes, with the multiband stacked model performing the best (BAC = 65.9%, sensitivity = 55.3%, specificity = 76.5%) (Table 2). Only the slow-4–based model generalized to patients with ROP for GAF-S outcomes (BAC = 58.5%, sensitivity = 66.9%, specificity = 50.0%).

Moreover, the slow-5– and slow-4–based GAF-DI models and the slow-4–based GAF-S models generalized to the prediction of absent negative symptoms across follow-ups (GAF-DI: slow-5: BAC = 65%, sensitivity = 65.6%, specificity = 64.5%; slow-4: BAC = 61.3%, sensitivity = 58.1%, specificity = 64.5%; GAF-S: slow-4: BAC = 60%, sensitivity = 81%, specificity = 39.1%) (Table 3). Model generalization was specific for negative and, to a lesser extent, disorganized symptoms, but not positive or general symptoms (Table S11). Negative symptoms mediated the relationship between slow-5 models' signatures and functioning outcomes (Table S12).

Prognostic Gains Compared With Trained Raters. The trained clinical raters' ratings of patients' outcomes mapped to follow-up functional impairment with BAC = 65.9% (sensitivity = 36.5%, specificity = 95.2%) for GAF-DI scores and BAC = 61.1% (sensitivity = 32.7%, specificity = 89.5%) for GAF-S scores. Raters' performance was independent of their experience level. Combining the trained rater–based models with the slow-5–based models significantly increased performance both for GAF-DI (BAC = 74.7%, sensitivity = 68.0%, specificity = 81.4%; W = 1680, $p < .001$) and GAF-S (BAC = 70.8%, sensitivity = 62.6%, specificity = 78.9%; W = 1444, $p < .001$) compared with clinical judgment alone. The cybernetic model performed better than a combined sociodemographic and clinical model for GAF-DI (W = 878, p = .007) but not GAF-S (W = 859, p = .016) (Table S13).

Diagnostic Specificity and Interdiagnostic Transferability. The transdiagnostic models had comparable performances for the CHR-P individuals and individuals with ROD (Table S14) and slightly higher performance for CHR-P individuals without affective comorbidities (Table S15). Additionally, we trained classifiers individually on the CHR-P or ROD groups for the prediction of functional impairment and applied them to the other group. For GAF-DI, the slow-5 sub-band was most predictive of outcomes in both groups. The predictive patterns of group-specific models were highly similar to the transdiagnostic signature ($R^2_{\text{CHR-P–Transdiagnostic pattern}}$ = 0.36, $p < .001$; $R^2_{\text{ROD–Transdiagnostic pattern}}$ = 0.37, $p < .001$) (Figures 2 and 3) and moderately similar to each other ($R^2_{\text{CHR-P–ROD pattern}}$ = 0.10, $p < .001$), with opposite effects in the LN and cerebellum (Figures 2 and 3). CHR-P slow-5 models showed interdiagnostic generalizability to patients with ROD, but the ROD model did not generalize to CHR-P (Table 4). For GAF-S, the slow-5 model performed best in the ROD group, while the slow-4 model

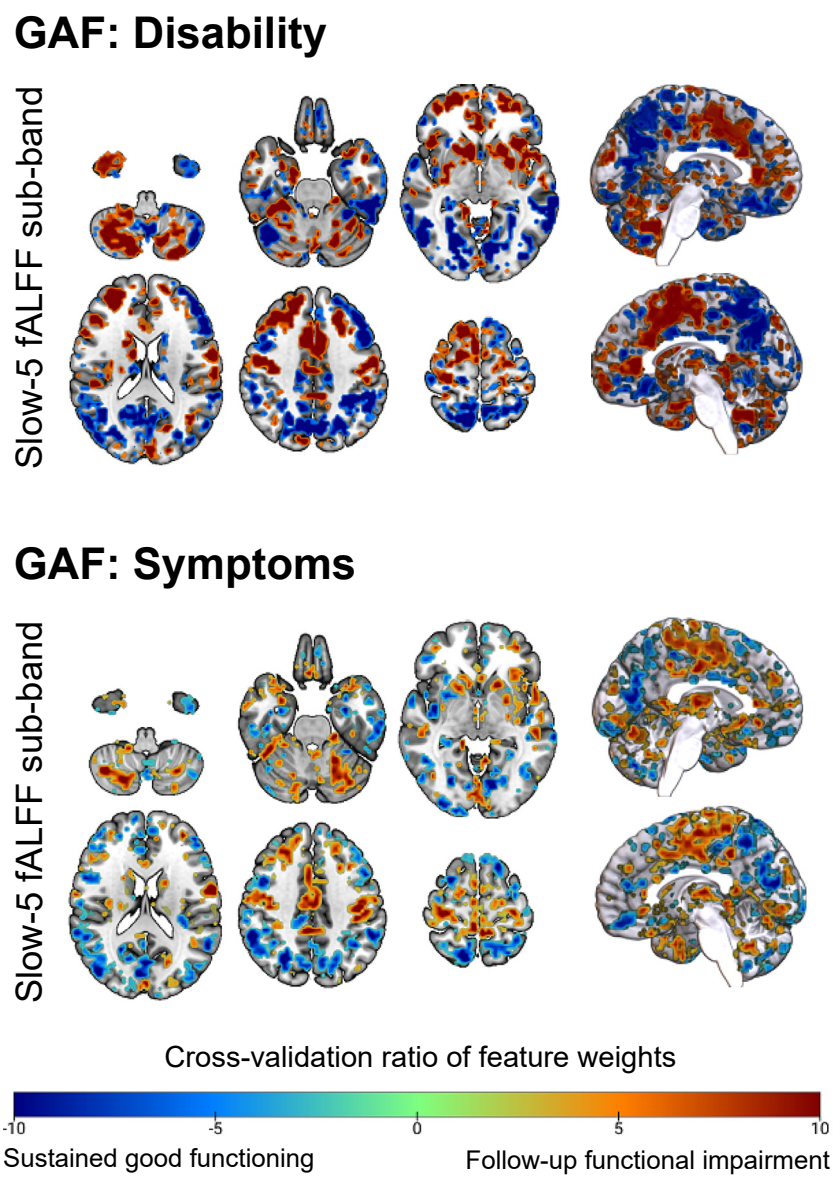


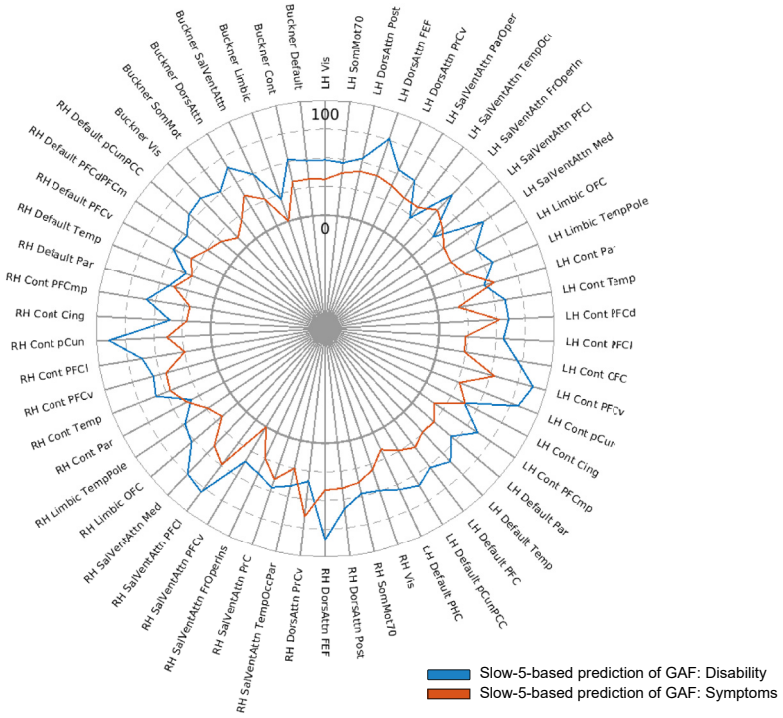
Figure 1. Visualization of predictive features for the sub-band–specific transdiagnostic prognostic models of follow-up functional impairment for (the Global Assessment of Functioning (GAF) disability subscale and the GAF symptoms subscale. Only models that performed above chance level (based on permutation testing) were visualized. Feature stability across the cross-validation structure was quantified using the cross-validation ratio measure (Supplemental Methods). Only features (voxels) that were statistically significant at $\alpha = 0.05$ (false discovery rate corrected) based on a sign-based consistency measure (48) of feature significance are displayed. fALFF, fractional amplitude of low-frequency fluctuation.

performed best in the CHR-P group (Table 4). The slow-5–based ROD model generalized to CHR-P individuals, but the slow-4–based CHR-P model did not generalize to patients with ROD (Table 4).

Post Hoc Analyses

For GAF-DI, supplementary longitudinal clustering analyses revealed 4 trajectories across baseline and follow-ups: 1) stable good functioning at baseline and follow-ups, 2) stable medium functioning at baseline and follow-ups, 3) improvers (low baseline but good follow-up functioning), and 4) stable poor functioning at baseline and follow-ups (Supplemental Methods and Figure S4A). The slow-5–based models of follow-up functional disability performed the best for the improvers subgroup (BAC = 75%, sensitivity = 70%, specificity = 80%) (Table S16), particularly in comparison to clinical raters (BAC = 57%, sensitivity = 34%, specificity = 80%) (Table S16). For GAF-S, a 2-trajectory clustering solution explained the data best: 1) improvers (low baseline but good follow-up functioning) and 2) stable poor functioning at baseline and follow-ups (Figure S4B). The slow-5–based prognostic models performed with the highest sensitivity (70%) in the stable poor functioning group.

Lastly, the decision scores of the transdiagnostic models were not associated with the cumulative dosage of antipsychotic or SSRI medication or the mean scan framewise displacement (Table S17).



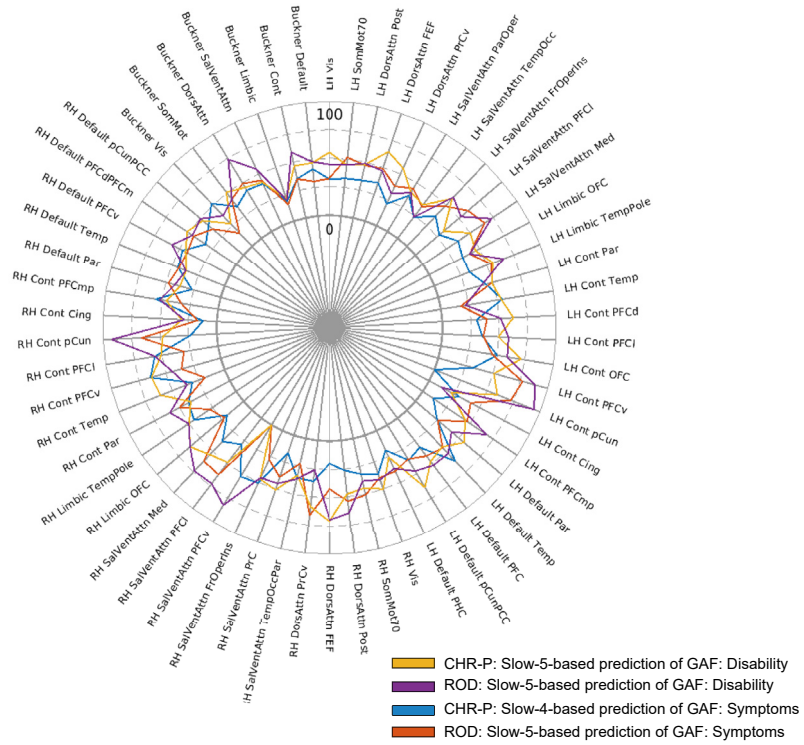


Figure 2. Regional distribution of predictive fractional amplitude of low-frequency fluctuations (fALFF) patterns coming from the sub-band–specific transdiagnostic **(A)** and diagnostic-specific **(B)** models. The percentage of statistically significant voxels was quantified within large-scale brain networks as defined based on the Yeo 7 Networks atlas and the Buckner atlas for cerebellum parcellation. We have only displayed parcellations that had at least 10% of their voxels occupied by the significant fALFF predictive patterns for the models that performed above chance level (based on permutation testing). Predictive patterns were defined as voxels with absolute cross-validation ratios higher than 2 SDs and statistically significant sign-based consistency as detailed in Supplemental Methods. CHR-P, clinical high risk for psychosis; Cont, control network; Default Par, default mode network parietal region; Default Temp, default mode network temporal region; DorsAttn, dorsal attention network; dPFCm, dorsomedial prefrontal cortex; FEF, frontal eye field; GAF, Global Assessment of Functioning; LH, left hemisphere; Limbic, limbic network; Med, medial prefrontal cortex; OFC, orbitofrontal cortex; ParOper, parietal operculum; pCunPCC, precuneus/posterior cingulate cortex; PFCl, lateral prefrontal cortex; PFCv, ventral prefrontal cortex; PHC, parahippocampal cortex; Post, postcentral gyrus; PrCv, precentral gyrus; RH, right hemisphere; ROD, recent-onset depression; SalVenAttn, salience/ventral attention network; SomMOT, somatomotor network; Temp, temporal cortex; TempOccPar, temporo-occipital-parietal junction; VIS, visual network.

Table 2. External Validation Performance of Prognostic Models Predicting Follow-Up Functional Impairment at the 9- and/or 18-Month Follow-Ups

	Sensitivity	Specificity	BAC	TP	TN	FP	FN	PPV	NPV	PSI	AUC (95% CI)	p_{FDR} Value
Functioning Outcome Prediction at the 9-Month Follow-Up in Excluded CHR-P and ROD Individuals, *n* = 169												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	61.9%	67.4%	64.7%	78	29	14	48	84.8%	37.7%	22.4	0.66 (0.57–0.74)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	63.5%	58.1%	60.8%	80	25	18	46	81.6%	35.2%	16.8	0.63 (0.54–0.72)	<.001*
Multiband model	49.2%	79.1%	64.1%	62	34	9	64	87.3%	34.7%	22.0	0.66 (0.57–0.75)	<.001*
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	63.0%	64.5%	63.8%	87	20	11	51	88.8%	28.2%	16.9	0.65 (0.55–0.75)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	66.7%	45.2%	55.9%	92	14	17	46	84.4%	23.3%	7.7	0.60 (0.49–0.70)	>.05
Multiband model	52.9%	77.4%	65.2%	73	24	7	65	91.2%	27.0%	18.2	0.65 (0.55–0.75)	<.001*
Functioning Outcome Prediction Across the 9- to 18-Month Follow-Ups for Patients With ROP, *n* = 140												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	64.2%	58.8%	61.5%	79	10	7	44	91.9%	18.5%	10.4	0.63 (0.50–0.75)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	66.7%	58.8%	62.7%	82	10	7	41	92.1%	19.6%	11.7	0.68 (0.55–0.80)	<.001*
Multiband model	55.3%	76.5%	65.9%	68	13	4	55	94.4%	19.1%	13.6	0.66 (0.53–0.78)	<.001*
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	63.8%	30.0%	46.9%	83	3	7	47	92.2%	6.0%	−1.8	0.48 (0.29–0.67)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	66.9%	50.0%	58.5%	87	5	5	43	94.6%	10.4%	5.0	0.55 (0.38–0.73)	.01
Multiband model	60.0%	50.0%	55.0%	65	6	4	65	94.2%	8.5%	2.7	0.52 (0.33–0.70)	>.05

The sub-band–specific and multiband models were applied: 1) for the prediction of 9-month functional outcomes of left-out CHR-P and ROD individuals with no 18-month follow-up data available in order to assess transferability across time points and 2) to patients with ROP with both 9-month and 18-month follow-up data in order to further evaluate the transdiagnostic generalizability of the models. *p* Values were adjusted using FDR correction for multiple comparisons ($\alpha = 0.05$) within each time point classification task.

*Significant *p* values.

AUC, area under the curve; BAC, balanced accuracy; CHR-P, clinical high risk for psychosis; FDR, false discovery rate; FN, false negative; FP, false positive; GAF, Global Assessment of Functioning; NPV, negative predictive value; PPV, positive predictive value; PSI, prognostic summary index; ROD, recent-onset depression; ROP, recent-onset psychosis; TN, true negative; TP, true positive.

DISCUSSION

Our results demonstrate the transdiagnostic value of fALFF-based machine learning models as precision medicine tools for stratifying functioning courses in CHR-P individuals and individuals with ROD. We observed geographically generalizable BACs of up to 67.4% for the prediction of follow-up functional disability versus sustained good functioning across 9- and 18-month follow-ups, with a 10% performance increase compared with single time point models. Post hoc analyses underscored the utility of our best-performing models for enhancing clinical prognostication and identifying individuals with pronounced disability at screening but prospective functional recovery.

Table 3. Cross-Label Generalizability of Prognostic Models of Follow-Up Functional Impairment to the Prediction of Absent Negative Symptoms Across Both Follow-Up Time Points

	Sensitivity	Specificity	BAC	TP	TN	FP	FN	PPV	NPV	PSI	AUC (95% CI)	p_{FDR} Value
Prognostic Generalizability to Absent Negative Symptoms Across the 9- and 18-Month Follow-Ups												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	65.6%	64.5%	65.0%	141	20	11	74	92.8%	21.3%	14.0	0.69 (0.60–0.78)	.01*
Slow-4 sub-band, 0.027–0.073 Hz	58.1%	64.5%	61.3%	125	20	11	90	91.9%	18.2%	10.1	0.64 (0.54–0.74)	.01*
Multiband model	53.0%	67.7%	60.4%	114	21	10	101	91.9%	17.2%	9.1	0.68 (0.59–0.77)	>.05
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	61.9%	39.6%	50.7%	13	89	136	8	8.7%	91.8%	0.5	0.53 (0.40–0.66)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	81.0%	39.1%	60.0%	17	88	137	4	11.0%	95.7%	6.7	0.56 (0.43–0.70)	.01*
Multiband model	52.4%	47.1%	49.7%	11	106	119	10	8.5%	91.4%	−0.2	0.53 (0.40–0.66)	>.05

Absent negative symptoms were defined as a total score of 0 on the Scale for the Assessment of Negative Symptoms both at the 9- and 18-month follow-up time points, which also corresponded to the 25th percentile of the sample. *p* Values were adjusted using FDR correction for multiple comparisons ($\alpha = 0.05$) within each time point classification task.

*Significant *p* values.

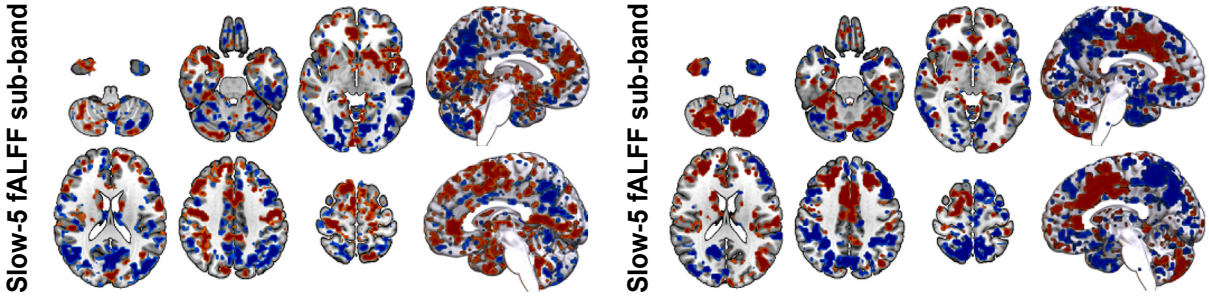
AUC, area under the curve; BAC, balanced accuracy; FDR, false discovery rate; FN, false negative; FP, false positive; GAF, Global Assessment of Functioning; NPV, negative predictive value; PPV, positive predictive value; PSI, prognostic summary index; TN, true negative; TP, true positive.

A Model predictive patterns

GAF: Disability

Clinical high-risk for psychosis

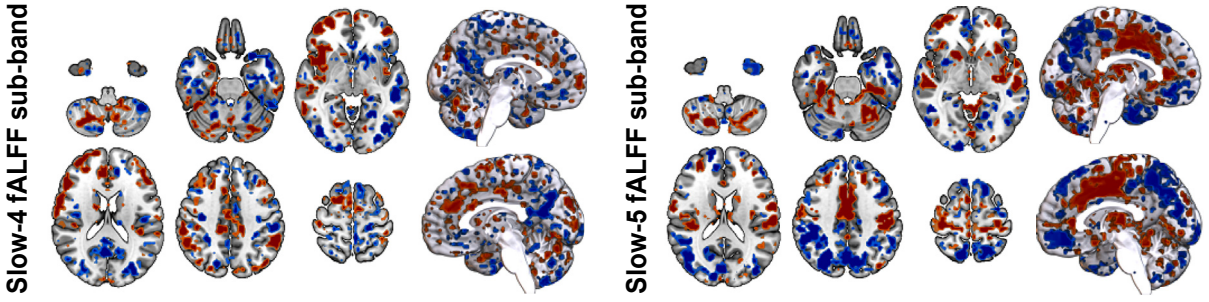
Recent-onset depression

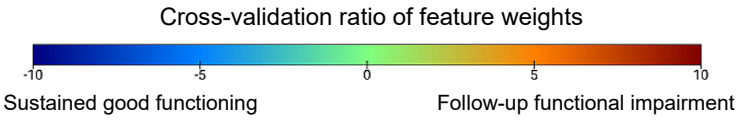


GAF: Symptoms

Clinical high-risk for psychosis

Recent-onset depression

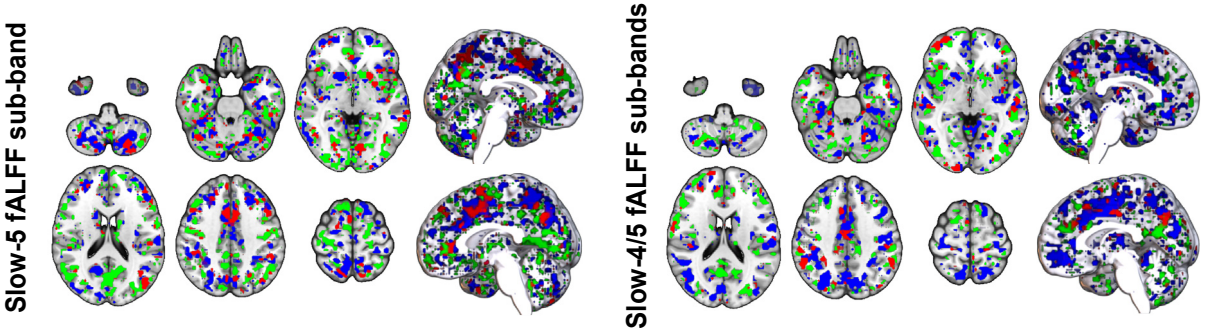




B Shared vs diagnostic-specific predictive patters

GAF: Disability

GAF: Symptoms



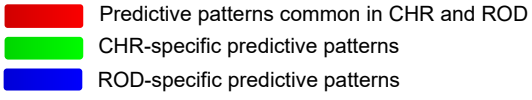


Table 4. Diagnostic-Specific Performance and Interdiagnostic Generalizability of Prognostic Models Predicting Follow-Up Functional Impairment

	Sensitivity	Specificity	BAC	TP	TN	FP	FN	PPV	NPV	PSI	AUC (95% CI)	p_{FDR} Value
CHR-P Model, In-Sample Performance, *n* = 125												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	67.3%	47.6%	57.5%	70	10	11	34	86.4%	22.7%	9.1	0.55 (0.42–0.68)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	58.7%	38.1%	48.4%	61	8	13	43	82.4%	15.7%	−1.9	0.44 (0.31–0.58)	>.05
Multiband model	42.3%	61.9%	52.1%	44	13	8	60	84.6%	17.8%	2.4	0.52 (0.38–0.65)	>.05
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	64.0%	36.4%	50.2%	73	4	7	41	91.2%	8.9%	0.1	0.48 (0.29–0.66)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	51.8%	63.6%	57.7%	59	7	4	55	93.7%	11.3%	4.9	0.57 (0.40–0.74)	<.001*
Multiband model	71.1%	18.2%	44.6%	81	2	9	33	90.0%	5.7%	−4.3	48 (0.29–0.66)	>.05
CHR-P Model→ROD, Out-of-Sample Performance, *n* = 121												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	71.7%	45.5%	58.6%	71	10	12	28	85.5%	26.3%	11.9	0.61 (0.48–0.73)	.001*
Slow-4 sub-band, 0.027–0.073 Hz	75.8%	36.4%	56.1%	75	8	14	24	84.3%	25.0%	9.3	0.52 (0.43–0.68)	.005*
Multiband model	62.6%	45.5%	54.0%	62	10	12	37	83.8%	21.3%	5.1	0.55 (0.42–0.68)	>.05
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	70.8%	37.5%	54.1%	80	3	5	33	94.1%	8.3%	2.5	0.73 (0.57–0.88)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	69.9%	25.0%	47.5%	79	2	6	34	92.9%	5.6%	−1.5	0.50 (0.29–0.71)	>.05
Multiband model	69.0%	62.5%	65.8%	78	5	3	35	96.3%	12.5%	8.8	0.60 (0.41–0.79)	<.001*
ROD Model, In-Sample Performance, *n* = 121												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	65.7%	63.6%	64.6%	65	14	8	34	89.0%	29.1%	18.2	0.66 (0.54–0.78)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	50.5%	45.5%	48.0%	50	10	12	49	80.6%	16.9%	−2.4	0.46 (0.32–0.60)	>.05
Multiband model	46.5%	81.8%	64.1%	46	18	4	53	92.0%	25.4%	17.4	0.65 (0.53–0.76)	<.001*
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	61.9%	50.0%	56.0%	70	4	4	43	94.6%	8.5%	3.1	0.63 (0.45–0.81)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	57.5%	37.5%	47.5%	65	3	5	48	92.9%	5.9%	−1.3	0.47 (0.26–0.68)	>.05
Multiband model	45.1%	62.5%	53.8%	51	5	3	62	94.4%	7.5%	1.9	0.55 (0.34–0.75)	>.05
ROD Model→CHR-P, Out-of-Sample Performance, *n* = 125												
GAF Disability												
Slow-5 sub-band, 0.01–0.027 Hz	57.7%	52.4%	55.0%	60	11	10	44	85.7%	20.0%	5.7	0.63 (0.50–0.75)	>.05
Slow-4 sub-band, 0.027–0.073 Hz	55.8%	57.1%	56.5%	58	12	9	46	86.6%	20.7%	7.3	0.55 (0.41–0.68)	>.05
Multiband model	48.1%	71.4%	59.8%	50	15	6	54	89.3%	21.7%	11.0	0.63 (0.51–0.75)	>.05
GAF Symptoms												
Slow-5 sub-band, 0.01–0.027 Hz	67.5%	63.6%	65.6%	77	7	4	37	95.1%	15.9%	11.0	0.65 (0.50–0.81)	<.001*
Slow-4 sub-band, 0.027–0.073 Hz	59.6%	36.4%	48.0%	68	4	7	46	90.7%	8.0%	−1.3	0.50 (0.32–0.68)	>.05
Multiband model	48.2%	72.7%	60.5%	55	8	3	59	94.8%	11.9%	6.8	0.63 (0.47–0.79)	.01*

Sub-band–specific and multiband support vector machine models were trained separately in the CHR-P and ROD samples for the GAF disability and GAF symptoms subscales and then applied to the other clinical group. *p* Values were adjusted using FDR correction for multiple comparisons ($\alpha = 0.05$) within each time point classification task.

*Significant *p* values.

AUC, area under the curve; BAC, balanced accuracy; CHR-P, clinical high risk for psychosis; FDR, false discovery rate; FN, false negative; FP, false positive; GAF, Global Assessment of Functioning; NPV, negative predictive value; PPV, positive predictive value; PSI, prognostic summary index; ROD, recent-onset depression; TN, true negative; TP, true positive.

Figure 3. Visualization of predictive fractional amplitude of low-frequency fluctuations (fALFF) features for prognostic models of follow-up functional impairment (at the 9- and/or 18-month follow-up) trained separately in the clinical high risk (CHR) for psychosis and recent-onset depression (ROD) samples. **(A)** Cross-validation ratio of feature weights (see Supplemental Methods) for models trained separately for the Global Assessment of Functioning (GAF) disability and GAF symptoms subscales. Only models that performed above chance level (based on permutation testing) were visualized. Only features that were statistically significant at $\alpha = 0.05$ (false discovery rate–corrected) based on a sign-based consistency measure (46) of feature significance are displayed. **(B)** Visualization of shared and diagnosis-specific prognostic fALFF patterns for each of the disability and symptoms functional domains.

Our findings revealed the importance of leveraging the temporal dynamics of functional outcomes as prediction targets for prognostic modeling. Investigating outcomes that incorporate multiple follow-up measurements may facilitate a more robust identification of brain-level risk signatures by dampening biological and environmental noise present at arbitrary time points. The highest model performance found for improvers (BAC = 75% vs. BAC = 57% of trained raters) suggests that fALFF data may capture prognostically relevant brain patterns of recovery missed by snapshot clinical evaluations. Moreover, the comparable predictive accuracies of fALFF and clinical raters, but superior performances of cybernetic models (59,62) integrating the two, suggests that fALFF and clinical judgment capture complementary, non-overlapping sources of prognostic variance. Therefore, despite the relatively modest performances of standalone rs-fMRI models, this incremental value over clinical prediction highlights the utility of fMRI-based biomarkers as one component within sequential, multimodal prognostic frameworks.

Predictive signatures centered on oscillatory activity in the slow-5 sub-band, i.e., higher activity in the DMN and ECN and lower activity in the SN and LN. Previous studies have reported higher signal-to-noise ratios in these cortical networks in the slow-5 frequency sub-band compared with higher fALFF frequencies (39,63), potentially explaining the superior prognostic performance of slow-5–based models in our sample. Our findings are consistent with research that has linked within-network DMN connectivity to good outcomes in patients with CHR-P (34) or schizophrenia (64) and with functional alterations in the triple-network model (65) of depression (66) and schizophrenia (67,68). Increased low-frequency activity in the DMN and decreased SN and ECN activity may represent a diagnosis-independent predisposition to good outcomes that points toward better SN-based contextual switching between the DMN and ECN (65). The transdiagnostic nature of these features is underscored by the moderate interdiagnostic transferability of the diagnosis-specific models, corroborating higher DMN and lower SN activity as shared predictors among the CHR-P and ROD groups. Nonetheless, follow-up analyses that reveal the presence of diagnosis-specific predictive signatures suggest the need for disentangling transdiagnostic versus diagnosis-specific pathways in larger samples.

In the GAF-D domain, models successfully generalized to patients with ROP, supporting a stage-invariant role of the putative triple-network abnormalities in the development of functional outcomes across the at-risk and early phases of psychosis. We also found that this model generalized to the prediction of follow-up negative symptoms, consistent with the mediating role of these symptoms between brain abnormalities and functioning in CHR-P (67) and established schizophrenia (44–46). These results support the clinical validity of our prognostic signatures and may offer new targets for the development of psychotherapeutic (cognitive remediation) and brain stimulation–based, recovery-enhancing interventions (21,23,69).

For GAF-S, we observed consistently lower prognostic performances. The discrepancy between the GAF-DI and GAF-S models could be explained by the low number of patients with sustained good GAF-S outcomes, which may have impaired the algorithms' ability to detect robust prognostic patterns. Nonetheless, the slow-5–based model performed with a relatively high sensitivity of 70% in detecting persistent poor baseline-to-follow-up outcomes. This suggests that the model might have captured transdiagnostic patterns related to illness severity, while symptom distress, related to symptomatic remission (70), may be predicted better by diagnosis-specific biological pathways and more sensitive to clinical or exposomal factors specific to psychosis versus depression (71).

Our study has several limitations. First, we focused on identifying biomarkers of any follow-up functional impairment, due to the limited sample size, and did not directly investigate patterns predictive of the whole spectrum of possible trajectories. Nonetheless, our post hoc findings showing varying performances for different functional courses suggest that future studies with larger samples and more dynamic, fine-grained outcome definitions could improve the performance of fALFF-based models. Second, we did not externally validate our prognostic models in a comparable transdiagnostic sample. Although the models generalized to patients with ROP and 9-month outcomes, benchmarking them within an identical validation setup is required to provide a robust and fair estimate of generalizability required for clinical translation. Third, our follow-up timeframe provides valuable insights into short-to-medium term prognoses but may not capture the long-term evolution of functional trajectories. Longer-term longitudinal studies are necessary to establish the prognostic stability of rs-fMRI data over time. Lastly, further research is needed to evaluate the added value of rs-fMRI measures to clinical, behavioral, and biological data domains not investigated here.

Conclusions

Our study provides the first evidence that rs-fMRI models could be useful in silico transdiagnostic biomarkers of functional impairment over the course of 18 months in CHR-P individuals and individuals with ROD. These models provided substantial prognostic gains over clinical judgment alone. The models' signatures comprised oscillatory brain patterns that may inform further outcome subtyping and guide the development of personalized preventive and therapeutic approaches. Future work is needed to evaluate the complementary value of rs-fMRI biomarkers within multimodal prognostic workflows and test their utility in the individualized prevention of functional impairment.

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