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Anhedonia as a Potential Transdiagnostic Phenotype With Immune-Related Changes in Recent-Onset Mental Health Disorders

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ABSTRACT

BACKGROUND: Chronic low-grade inflammation is observed across mental disorders and is associated with difficult-to-treat-symptoms of anhedonia and functional brain changes, reflecting a potential transdiagnostic dimension. Previous investigations have focused on distinct illness categories in people with enduring illness, but few have explored inflammatory changes. We sought to identify an inflammatory signal and the associated brain function underlying anhedonia among young people with recent-onset psychosis and recent-onset depression.

METHODS: Resting-state functional magnetic resonance imaging, inflammatory markers, and anhedonia symptoms were collected from 108 (mean [SD] age = 26.2 [6.2] years; female = 50) participants with recent-onset psychosis (n = 53) and recent-onset depression (n = 55) from the European Union/Seventh Framework Programme–funded PRONIA (Personalised Prognostic Tools for Early Psychosis Management) study. Time series were extracted using the Schaefer atlas, defining 100 cortical regions of interest. Using advanced multimodal machine learning, an inflammatory marker model and a functional connectivity model were developed to classify participants into an anhedonic group or a normal hedonic group.

RESULTS: A repeated nested cross-validation model using inflammatory markers classified normal hedonic and anhedonic recent-onset psychosis/recent-onset depression groups with a balanced accuracy of 63.9% and an area under the curve of 0.61. The functional connectivity model produced a balanced accuracy of 55.2% and an area under the curve of 0.57. Anhedonic group assignment was driven by higher levels of interleukin 6, S100B, and interleukin 1 receptor antagonist and lower levels of interferon gamma, in addition to connectivity within the precuneus and posterior cingulate.

CONCLUSIONS: We identified a potential transdiagnostic anhedonic subtype that was accounted for by an inflammatory profile and functional connectivity. Results have implications for anhedonia as an emerging transdiagnostic target across emerging mental disorders.

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The early phases of mental illness are often characterized by heterogeneity in outcomes, with considerable overlap of symptoms across disorders (1). While the prospect of recovery is enhanced with early treatment and intervention, many young people will have an incomplete recovery (1). Only 20% of people with psychosis and 25% of people with depression will experience full remission following pharmacological treatment (2,3). Others will continue to experience residual or difficult-to-treat symptoms including anhedonia—described as an inability to feel pleasure—which is a central symptom across disorders such as depression and psychosis (4–6). The lack of a mechanistic understanding of the underlying pathways that contribute to individual or subgroup differences in the severity of symptoms such as anhedonia has hampered the development of new therapies (7).

There is increasing interest in immune-related subgroups associated with elevated levels of peripheral inflammatory markers. Increased circulating concentrations of inflammatory cytokines, such as interleukin 6 (IL-6) and its acute phase reactant C-reactive protein (CRP), have been robustly reported in meta-analyses in a subgroup of patients with schizophrenia and recent-onset psychosis (ROP), as well as in patients with depression (8–10). This suggests that cytokine changes may reflect a transdiagnostic dimension of mental illness. However,

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most studies reported to date have not used a transdiagnostic approach to explore underlying mechanisms, which has the potential to improve identification of subgroups of patients who experience enduring symptoms (11,12).

Investigating functional network connectivity in the brain offers another dynamic way to explore the underlying inflammatory effects on complex symptoms. In particular, the default mode network (DMN), which exhibits coherent, large-scale neural activation at rest, spans a number of critical regions involved in interoceptive experience (i.e., the ability to feel), as well as complex social, emotional, and cognitive functions (13). Interoceptive signaling within the DMN has been linked to emotion regulation and homeostasis, suggesting a role for bidirectional brain immune signaling within the DMN (14). Interoceptive dysfunction has been linked to blunted emotion and anhedonic states, which may provide mechanistic insight into inflammation-linked depression and psychosis (15). There is a wealth of evidence demonstrating aberrant connectivity in the DMN in individuals with psychosis and depression (16,17), but the association with inflammation remains unclear. In individuals with depression, increased levels of CRP have been associated with decreased connectivity within and between DMN and non-DMN nodes (15,18). When entering the identified multivariate network features into a support vector machine algorithm, the model achieved high prediction accuracies for depressive symptoms, which included anhedonia and motor slowing (19). Two recent studies of schizophrenia have also investigated an association between resting-state connectivity within the DMN and the association with cognition (20). King *et al.* showed that IL-6 plasma levels and decreased connectivity between the parietal cortex and precuneus during resting state mediated the effects of early-life adversity and lower social cognitive function (20). There were similar findings for the precuneus during a social cognitive task in patients with schizophrenia, where IL-6 mediated the relationship between childhood neglect and increased connectivity in the DMN during the task (21).

These findings suggest that DMN functional connectivity may serve as a replicable neural imaging marker of immune-brain processing that is potentially associated with a transdiagnostic phenotype. However, most studies to date have been limited to those with enduring illness that transcends distinct illness categories and is therefore potentially confounded by duration of illness and medication history. In the current study, we sought to identify mechanisms underlying anhedonia among young people with ROP and recent-onset depression (ROD). Given the challenge of complex, multimodal heterogeneous data, we developed a prediction model using a machine learning approach to determine the independent contribution of a blood-based inflammatory model and a functional connectivity model in classifying individuals into a transdiagnostic anhedonic subgroup or a normal hedonic subgroup in young people with recent-onset disorders (psychosis and depression).

METHODS AND MATERIALS

Study Design

We analyzed data from the European Union/Seventh Framework Programme–funded PRONIA (Personalised Prognostic Tools for Early Psychosis Management) study, which is a European-wide study of 7 centers aimed at identifying prognostic markers and staging of early mental disorders that ran between October 2013 and March 2019. The details of the dataset can be found in Table 1. A comprehensive clinical battery was used to record sociodemographic, physical, clinical, and psychometric variables; blood sampling; and resting-state functional magnetic resonance imaging (rsfMRI). Informed consent was obtained from all adult participants, and assent forms were provided by a legal guardian of participants under the age of 16 years. The study was registered at the German Clinical Trials Register (DRKS00005042) and approved by the local research ethics committees in each location. Details of the PRONIA study sites, recruitment protocol, and quality control procedures were described in a previous publication (22). In brief, participants with ROP had to meet the following criteria: 1) DSM-IV-TR affective or nonaffective psychotic episode (lifetime), 2) DSM-IV-TR affective or nonaffective psychotic episode criteria fulfilled within the past 3 months, and 3) onset of psychosis within the past 24 months. Patients with ROD had to meet the following criteria: 1) DSM-IV-TR major depressive episode (lifetime), 2) major depressive disorder criteria fulfilled within the past 3 months, and 3) duration of first depressive episode no longer than 24 months.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: 1) age between 15 and 40 years, 2) sufficient language skills for participation, and 3) capacity to provide informed consent/assent. Exclusion criteria consisted of 1) an IQ <70, 2) current or past head trauma with loss of consciousness (>5 minutes), 3) current or past known neurological or somatic disorders potentially affecting the structure or functioning of the brain, 4) current or past alcohol dependence, 5) polysubstance dependence within the past 6 months, and 6) any MRI contraindications. Participants who met criteria for ROD or ROP were included in this study. Diagnoses were ascertained using the Structured Clinical Interview for DSM.

Outcome Data

The Scale for the Assessment of Negative Symptoms (SANS) (23) is a structured and validated scale designed to evaluate the severity and characteristics of negative symptoms in individuals with psychiatric disorders, particularly schizophrenia. It consists of subscales that measure the various dimensions of negative symptoms: affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attention. We used the SANS anhedonia-asociality subscale as our outcome variable and dichotomized the scale scores into anhedonic and normal hedonic subgroups (total score of 20; 6-point Likert scale rated 0–5 from absent to severe). A normal hedonic subgroup was defined by subscale scores in the range of 0 to 8 (capturing absent to mild item ratings). The anhedonic subgroup was categorized by subscale scores in the range of 12 to 20 (reflecting item scores rated as moderate-marked-severe). Participants who scored in the middle range (i.e., 9–11) were removed from the analysis ($n = 6$) to distinguish a true anhedonic state from participants with mild state–like features,

Table 1. Sociodemographic Characteristics of the Study Sample, *n* = 108

Characteristic	Diagnostic Groups		Classified Groups		Statistic	*p* Value
	Patients With ROP, *n* = 53	Patients With ROD, *n* = 55	Normal Hedonic Group, *n* = 59	Anhedonic Group, *n* = 49		
ROP/ROD	–	–	25/34	28/21	$\chi^2 = 2.3$	.126
Age, Years	26.1 (5.9)	26.3 (6.6)	25.9 (6.4)	26.6 (6.1)	$t = -0.588$	.588
Sex, Female/Male	24/29	26/29	29/30	21/28	$\chi^2 = 0.427$	.514
IFN-γ, pg/mL	2.6 (3.1)	4.9 (17.1)	5.0 (16.5)	2.2 (3.1)	$t = 1.14$	.128
IL-1ra, pg/mL	644.3 (605.9)	796.2 (1551.4)	720.9 (1482.5)	722.4 (680.1)	$t = -0.006$	.497
IL-4, pg/mL	8.3 (4.8)	11.9 (11.9)	11.2 (11.2)	8.8 (6.2)	$t = 1.29$	.98
S100B, pg/mL	35.2 (43.6)	41.8 (60.8)	34.3 (43.7)	43.7 (62.6)	$t = -0.907$	.183
IL-1β, pg/mL	0.7 (0.6)	5.2 (32.8)	4.9 (31.7)	0.7 (0.7)	$t = 0.933$	.176
IL-2, pg/mL	0.7 (1.1)	1.0 (1.7)	1.0 (1.6)	0.7 (1.1)	$t = 1.27$	.103
IL-6, pg/mL	0.8 (0.7)	0.8 (0.8)	0.7 (0.7)	0.9 (0.8)	$t = -0.789$	.216
TNF-α, pg/mL	1.6 (1.1)	1.6 (1.1)	1.6 (1.1)	1.6 (1.1)	$t = -0.529$	.299
CRP, pg/mL	863,299.6 (1,207,808.6)	1,656,398.2 (2,527,325)	1,361,378.6 (2,150,799.9)	1,153,784.6 (1,872,471.5)	$t = 0.529$	.299
TGF-β, pg/mL	362,519.5 (385,495.5)	411,289.5 (399,938.1)	481,092.7 (422,816.1)	274,489.6 (320,078.3)	$t = 2.81$	.003
BDNF, pg/mL	19,627.5 (9731.8)	22,461.3 (9130.8)	22,220.7 (19,685.9)	19,685.9 (11,223.7)	$t = 1.38$	.84

Values are presented as *n* or mean (SD).

BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; IFN-γ, interferon gamma; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; ROD, recent-onset depression; ROP, recent-onset psychosis; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

consistent with previous literature that established meaningful anhedonic cutoff scores using the SANS (24,25).

Neuroimaging

Acquisition and Harmonization. All participants across the consortium underwent the same multimodel MRI protocol; structural MRI and rsfMRI were both acquired (26). Sites were compliant with a minimal harmonization protocol that ensured standardization of the MR sequence across the different scanners. The harmonization protocol is available in the Supplement. T1 reference images utilized a multiecho magnetization-prepared rapid acquisition gradient-echo sequence, while whole-brain blood oxygen level–dependent images employed an echoplanar imaging sequence. One brain volume consisted of 52 slices; each slice was 3 mm in thickness with no gap between slices. The repetition time was 3 seconds, and the echo time was 34.5 ms. Voxel size was 3 × 3 × 3 mm, with a field of view of 224 × 224 × 210 and a 90° flip angle. For the duration of the resting-state scans (192 volumes), participants were instructed to keep their eyes open (26).

Neuroimaging Preprocessing. For rsfMRI, preprocessing included core steps (slice-time correction, unwarping, realignment) and denoising steps (motion correction with time series despiking, confound signal regression, background filtering, and temporal bandpass filtering) using the BrainWavelet Toolbox (http://www.brainwavelet.org/) (27). To remove any cases with excess motion from the analysis to improve the accuracy of our effects, we calculated an average framewise displacement (FD) and excluded participants with an average FD >0.5 mm (28,29). The FD was calculated as the sum of the absolute values of the 6 realignment parameters converted from degrees to millimeters by calculating displacement on the surface of a sphere with a radius of 50 mm (28).

Time Series Extraction. In this study, we extracted regional brain activity from denoised rsfMRI images using the Schaefer atlas to define cortical regions of interest (ROIs) and delineated 100 cortical areas across the whole brain (30). This atlas is underpinned by a gradient-weighted Markov random field model, known for integrating local gradient and global similarity approaches to enhance parcellation homogeneity and provide neurobiologically meaningful patterns of brain organization. For the current analysis, we adapted Schaefer's parcellation masks to the dimensions of the denoised images using the software package AFNI (31). Each regional mask was applied to denoised rsfMRI to extract regional activation. By multiplying the mask by an rsfMRI volume, we isolated the signal relevant to a specific ROI in the moment associated with the volume. The signal within the masked area was then averaged to derive a singular activation value for that ROI at that specific time. This procedure was repeated across all volumes to construct a comprehensive time series that reflected the region's activation pattern across the data acquisition period. This process was conducted for every ROI and for all included participants and generated 100 regional activation time series for each participant. These time series represent the fluctuating activity within each cortical area and serve as the foundation for subsequent analyses used to explore functional brain dynamics.

Prediction Modeling: Multivariate Preprocessing Pipeline

An advanced machine learning approach with a repeated nested cross-validation framework was used. The TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) was used for model development and validation (Supplemental Section 1.3) (32). We aimed to classify individuals from the combined group of ROP and ROD participants by normal hedonic versus anhedonic

states based on the SANS anhedonia-asociality subscale. Age and sex were included as covariates because they are known to correlate with levels of inflammation. The dataset consisted of the following cytokines and acute phase proteins: interferon gamma (IFN-γ), IL-1 receptor antagonist, IL-4, IL-1β, IL-2, IL-6, tumor necrosis factor α (TNF-α), CRP, transforming growth factor β (TGF-β), and BDNF (brain-derived neurotrophic factor), together with S100B (a marker of blood-brain barrier permeability) (33). Missing values were imputed using K-nearest neighbors Euclidean distance median replacement using 7 nearest neighbors. For each missing value of a given cross-validation (CV) CV1 or CV2 participant, a subset of cases that had values for the given variable and values on all other variables that were nonempty were identified. Participants in the source subset were sorted according to their similarity to the target participant using the Euclidean distance. Next, the median of the given variable was computed using the 7 nearest neighbors. The original, nonimputed training matrix was used at all times. We employed L2-regularized logistic regression (primal) from the LIBLINEAR library as our primary classification algorithm. For hyperparameter optimization, we systematically tested a range of regularization strengths (0.015625, 0.03125, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16).

We implemented a variable-threshold, cross-parameter ensemble, determining the optimal percentile threshold for optimal cross-node ensemble performance across a search vector of percentiles (75, 80, 85, 90, 95). This ensemble was built using a wrapper approach at all parameter combinations with greedy forward feature selection on the CV1 training and test data, employing early stopping at 50% of the feature pool. All features were evaluated. For feature selection, we optimized across CV1 partitions using a probabilistic feature extraction mode and selecting the top 25% of consistently selected features. Subsequently, cross-CV1 feature agreement data was utilized to retrain all CV1 models using the same selected feature space.

A similar procedure was followed for the rsfMRI model to identify connectivity patterns between the ROIs in a multivariate manner. In this model, site was also controlled for. We employed L2-regularized L2-loss support vector classification (dual) from the LIBLINEAR library as our primary classification algorithm. The dataset consisted of the extracted time series from 100 cortical ROIs. The same parameters that were used in the inflammation model were mostly followed. In this case an ensemble was built with the wrapper approach using a greedy backward feature selection at the parameter optimum only, on the CV1 test data, employing early stopping at 80% of the feature pool and employing a 10% feature stepping approach. For feature selection, we optimized across CV1 partitions using a probabilistic feature extraction mode and selected the top 25% of consistently selected features. Subsequently, cross-CV1 feature agreement data were utilized to retrain all CV1 models using the same selected feature space. The models were developed separately for potential inclusion in a stacked generalization model if they both achieved statistical significance.

RESULTS

Sample

Participant data were included when both cytokine and functional imaging data were available (n = 212). To further remove any residual motion artifacts in the data, participants who had an average FD >0.5 mm were excluded from the imaging analysis (n = 104). This left a sample of 108. Participants were then dichotomized based on their SANS scores into the normal hedonic group (ROP = 25, ROD = 34) or the andehonic group (ROP = 28, ROD = 21). Sample characteristics are provided in Table 1. The mean age of participants was 26.2 (6.2) years, and there were 50 female and 58 male participants.

Predictive Modeling

Inflammation Model. The repeated nested pooled cross-validation model using inflammatory markers classified normal hedonic and anhedonic participants transdiagnostically, with a balanced accuracy of 63.9% and an area under the curve of 0.61 (Table 2). Assignment to the anhedonic category by the classifier was driven by elevated levels of IL-6, IL-1 receptor antagonist, and S100B as well as reduced levels of IFN-γ and S100B. Normal hedonic group classification was informed by elevated levels of TGF-β and IL-4 (Figure 1).

Functional Connectivity Model. The repeated nested pooled cross-validation model using the extracted data from 100 cortical resting-state ROIs to classify normal hedonic and anhedonic patients transdiagnostically produced a balanced accuracy of 55.2% and an area under the curve of 0.57 (Table 2). The most heavily weighted mean that classified the anhedonic group included connectivity within the precuneus and the posterior cingulate cortex. Because the functional connectivity model was not significant, we did not stack the models (Table 2).

DISCUSSION

In our European Union–wide study of young people with ROD and ROP, we showed that support vector machine learning was able to identify an anhedonic subgroup based on inflammatory markers, including IL-6, and blood-brain barrier permeability. These findings are consistent with previous literature showing increased inflammation in major depression and psychosis, particularly during early stages and in people with negative symptoms such as anhedonia (8,9,34). We have extended these findings to individuals who were early in their illness course and demonstrate an illness phenotype that extends across diagnoses and that may reflect altered immune function that evokes transdiagnostic symptoms of anhedonia.

Interestingly, proinflammatory cytokines, such as IL-6, were more likely to classify individuals with an anhedonic subtype, while anti-inflammatory cytokines were more likely to distinguish participants in the normal hedonic subgroup. Recent Mendelian randomization studies have pointed to a causal genetic role for IL-6 that underlies the risk of schizophrenia and major depression (35,36). This is consistent with a deficit model of illness, which is typically characterized by greater negative symptoms and poor outcomes (37). In recent work, we identified an impaired phenotype across depression and psychosis, which included a higher load of negative symptoms and gray matter volume loss (5). The impaired phenotype achieved higher precision in predicting poor outcomes in chronic cases than traditional diagnostic groups (5). With the current findings, we have shown that symptoms consistent

Table 2. Classification Performance and Statistical Significance of the Functional Connectivity and Inflammation Models

Model	True Positive	True Negative	False Positive	False Negative	Correct Classification Rate		Balanced Accuracy	Positive Predictive Value	Negative Predictive Value	AUC	Model *p* Value
					Normal Hedonic	Anhedonic					
Functional Connectivity Model	35	25	24	24	59.3%	51.0%	55.2% ± 5.9%	59.3%	51.0%	0.57	.19
Inflammation Model	26	41	8	33	44.1%	83.7%	63.9% ± 0.88%	76.5%	55.4.%	0.61	.04

AUC, area under the curve.

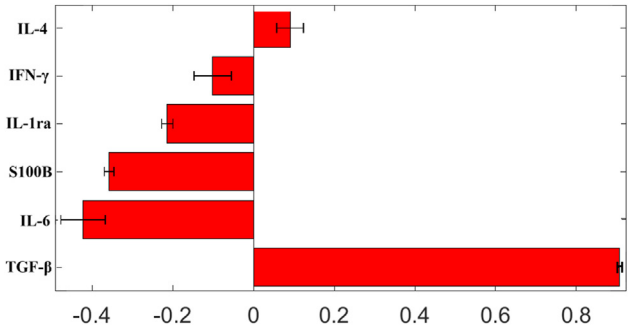

Figure 1. Feature weights of the most significant features in the inflammation model. Derived from 100 random permutations. IFN-γ, interferon gamma; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; TGF-β, transforming growth factor β.

with an impaired phenotype were predicted by proinflammatory markers, a potential transdiagnostic mechanism that warrants further study (38). S100B, which is an astrocytic protein specific to the central nervous system (33), was also predictive of an anhedonic state. There is increasing interest in the role of S100B in mental disorders as a potential marker of increased blood-brain barrier permeability with specific astrocytic inflammatory pathways (33). Our results add to the relevance of peripherally measured markers and the bidirectional relationship of inflammatory signals into and out of the central nervous system.

In contrast, participants in the normal hedonic group were distinguished by anti-inflammatory cytokines, predominantly TGF-β, which has a regulatory role in the immune system. Regulatory T cells and their effector cells—TGF-β—inhibit the development of immunopathology, with growing evidence suggesting that hypoactive or dysregulated regulatory T cells contribute to immune-related psychopathology in schizophrenia (38,39). IFN-γ is also thought to be a protective inflammatory marker (38). Our results showed that lower levels of IFN-γ were predictive of anhedonia, which suggests that IFN-γ dysfunction could potentially lead to symptomatic load (40).

Another key finding was that the functional connectivity model also classified the anhedonic group, although it did not achieve accuracy as high as the inflammatory model. As hypothesized, connectivity within regions encompassed by the DMN, namely the precuneus and posterior cingulate cortex, contributed the most weight to the anhedonic classification from the whole-brain parcellation. This is consistent with previous research on schizophrenia and major depressive disorder in which connectivity within the precuneus/posterior cingulate cortex was correlated with inflammatory markers, suggesting that these may be key regions involved in parsing immune-affective processing (18,20,21). It is also consistent with the notion of the interoceptive nervous system, where peripheral immune states are communicated via the vagus nerve and medulla to the interoceptive brain system, namely the DMN, and anchored in regions such as the cingulate cortex, where information on how one's body feels is essential for emotion regulation and homeostasis (14,15,41). The consequences of disruption to the interoceptive nervous system have been evidenced following an immune challenge in

experimental studies, which resulted in presentations of sickness behavior—that is, nonspecific behavioral changes such as anhedonia—as an adaptive response to pathogens (15,42).

Study Implications

Findings from the current study have several important implications for practice. First, our results highlight the fact that existing diagnostic categories may mask transdiagnostic dimensions, particularly during the early stages of illness. Our findings show that irrespective of diagnosis, for a subgroup of individuals, there is likely a common biological transdiagnostic mechanism that underlies symptoms of anhedonia. Assessing markers of inflammation and functional connectivity may provide a more objective and reliable way to identify individuals at risk of a poorer outcome. This also provides a target for stratified treatment, where novel or repurposed immune therapies can potentially improve prognoses for these individuals. An experimental medicine study is currently underway to test whether tocilizumab—a humanized monoclonal antibody targeting the IL-6 receptor to inhibit signaling—contributes to symptoms of anhedonia in patients with first-episode psychosis (43). Similar trials are also underway in depression, and this will enable the exploration of the mechanisms by which IL-6 contributes to disease pathology (44,45).

Strengths and Limitations

Our study has several strengths. We used data from multiple sites across Europe and applied semisupervised machine learning with robust cross-validation. We integrated multimodal data including blood biomarkers and functional neuroimaging in young people with recent-onset disorders to predict a transdiagnostic poor outcome group based on clinical symptoms while controlling for potential confounding factors such age, site, sex, and excess movement. However, there are limitations of the current study that should be noted. Our conservative controls for excess movement reduced our final sample size. To compensate for this, we applied a robust wrapper feature selection to reduce the dimensionality of the data against the small sample size. It is also important to note that the functional connectivity model only achieved results that were slightly above chance and not statistically significant. Furthermore, we did not control for lifestyle factors and/or other health conditions that could influence an inflammatory response. Nevertheless, the mean CRP in our sample suggests a sample with systemic low-grade inflammation rather than an acute illness. Future studies should aim to assess the clinical utility of our findings and independently replicate and externally validate our models to increase the validity of the findings. Adopting a longitudinal approach is also better suited to prognostication together with a broader inclusion of a wide range of markers to fully elucidate the underlying causal mechanisms.

Conclusions

We presented novel findings showing that differences in markers of inflammation and resting-state connectivity can potentially be used to distinguish a transdiagnostic anhedonic subtype in young people with ROD and ROP, using advanced machine learning. This has promise for improving identification and early targeted immune-related treatments to potentially improve disabling motivational symptoms and functional outcomes for young people.

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