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EARLY IDENTIFICATION OF PSYCHOSIS USING BEHAVIORAL, COGNITIVE, AND NEUROIMAGING MARKERS

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Abstract

Prompt intervention through early psychosis identification is needed in order to change the trajectory of the disease and improve the long-term outcomes. In this paper, the effectiveness of behavioural, cognitive and neuroimaging markers, both individually and together, in early identification of psychosis was reviewed. The multimodal framework was used comprehensively for healthy controls, clinical high risk and early psychosis patients. The behavioral analyses showed that the responses were more variable and there was less adaptive performance in the high-risk and the early psychosis group. Cognitive assessments showed that there was a significant deficit in executive functioning, working memory and speed of processing, with the deficits becoming increasingly worse as clinical severity increased. These alterations in the structure of the brain, the rupture of connections between significant neural networks, which are involved in cognition, manipulation of significant information and emotional control, were observed by neuroimaging. Using these markers in conjunction with multimodal feature fusion with machine learning based classification models, these markers outperformed the single-modality. Longitudinal data revealed that integrated risk scores were sensitive to the symptom evolution, which highlights their possible prognostic value. Overall, the results suggest that abnormalities associated with the psychosis will be apparent in behavioural, cognitive and neurobiological domains before the onset of the disease itself. The study will validate the clinical effectiveness of multimodal assessment strategies in identifying psychosis and risk stratification at an early stage, and provide a precision mental health care intervention in a scalable and data-driven way.

INTRODUCTION

The debilitating effects of the psychotic disorders can appear in adolescence or young adulthood and have a profound impact on functional performance in the future (Ellis et al., 2020, p. 1; Reinen et al., 2024). The gradual change of a mental state at risk to a full-blown psychotic episode is a result of complicated interactions between the environment and the brain. This may cause a chronic, debilitating illness condition (Koutsouleris et al., 2009, p. 701) in case it is not treated. Due to the high level of diversity of psychotic symptoms and the development of the disease, it is highly significant to identify individuals with high risks of psychosis in its early stages and provide prevention measures that can be implemented in a short amount of time to delay or prevent the course of the disease (Sasabayashi et al., 2022, p. 1; Tarbox-Berry et al., 2024). This is a critical event where biomarkers need to be discovered and validated in a multi-modal fashion – behavioral, cognitive, and neuroimaging – to increase the accuracy of prognostics and offer the chance to take targeted preventive measures (Andreou and Borgwardt, 2020, p. 2773). Enhancement of clinical care in practice and addressing unmet needs in the prevention of chronic disability and promotion of long-term recovery will depend on the development of these biomarkers (Duarte et al., 2023, p. 1). Despite the advances in the discovery of prodromal symptoms, however, a reliable predictor of psychosis conversion has yet to be found and thus more complex predictive tools like multiple kernel learning (Reinen et al., 2024) are needed to integrate various streams of information. Incorporating patterns across the different types of data (structural, resting-state functional and diffusion-weighted imaging) has the potential to identify the risk to predict the conversion to psychosis more accurately than analyses with a single type of data does (Reinen et al., 2024). The majority of those who develop early symptoms of psychotic disorders do not develop full-fledged psychosis. This highlights the importance of objective markers to make prediction of the onset of psychosis (Takayanagi et al., 2024). It is especially relevant recognising that psychosis can occur outside of a clinical high risk setting and may present across a wider range of other comorbidities, which begin in late adolescence and early adulthood (Koutsouleris et al., 2020, p. 196). Moreover, the great diversity of clinical high-risk groups can hardly be considered reliable in identifying the biomarkers and determining the progression of the disease. Approximately, one-third of CHR individuals develop psychosis and another third completely recovers (Dean et al., 2018, p. 722). Thus, large-scale and multi-site consortium studies are required to create and validate risk prediction algorithms and identify time-dependent biomarker signatures that allow for the inclusion of the heterogeneity in samples and to validate

a wide range of clinical pathways (Woods et al., 2021; Worthington and Cannon, 2021, p. 7). This makes the need for sophisticated predictive analytics to better identify conversion and conversion results and optimize intervention responses in those who are at actual risk (Worthington and Cannon, 2021, p. 6). Nevertheless, the inconsistencies in the conversion rates found across studies, in many cases because of using different methods and definitions, illustrate the difficulty of establishing definitive biomarkers (Caballero et al., 2023, p. 683). Machine learning has been introduced in predictive analytics, especially in predictive analytics using clinical and demographic variables, which proved to be effective in identifying important risk indicators and enhancing the predictive accuracy; however, such approaches are not effective to assess potential risks at an individually accurate level (Ellis et al. 2020, p. 7). Therefore, machine learning techniques are becoming popular among increasingly more individuals. These approaches take into consideration multivariate analyses and complex pattern recognition approaches to make improved predictions concerning when an individual will develop psychosis using multimodal information. This is a significant improvement to the traditional statistical methods (Andreou and Borgwardt, 2020, p. 2775; Reinen et al., 2024). These are sophisticated computational approaches that seek to extend group-level neuroimaging results to clinically meaningful classification and prediction of individuals, beyond large group differences, into a personalized prognostic assessment (Ellis et al. 2020, p.6). It has been demonstrated in the past that it is possible to distinguish individuals with schizophrenia and healthy controls based on their machine learning at various stages of psychosis (Koike et al., 2023, p. 2). However, there is also a significant challenge with these applications: they all need to have a large and diverse dataset for classifiers that are efficient and can be applied to other cases (Zhu et al., 2024, p. 1466). Despite the potential for improved predictive power of the onset of psychosis, the complex multimodal machine learning models cannot be implemented in clinical practice, given the logistic and financial challenges to do so (Fusar-Poli et al., 2019, p. 8). Apart from this, computational models can be used to test mechanistic hypotheses about the mechanism of pathophysiological processes, but the usefulness of such models in making predictions with regard to the psychosis of an individual person remains an open question (Frangou et al., 2016, p. 179). One problem with current predictive models is that they are not always superior to other statistical models (Malda et al., 2019, p. 12). This fact underlines the importance of improving the characterization of the features and of validating the predictive models to the real clinical practice, replacing the theoretical excellence with its practical benefit (Fabro et al., 2023, p. 1). These models are also challenging to understand because machine learning algorithms are not easy to read and can be

hard for doctors to accept and comprehend, making it hard for them to be used in many clinical settings (FusarPoli et al., 2019 p. 8). But there is a step forward in powerful machine learning systems that use simulated data to curb bias and overfitting. Such frameworks are gaining growing significance in forming stable and reproducible predictions of the responses of the antipsychotic-naive schizophrenia patients to treatment and their disease progression (Ambrosen et al., 2020). These types of frameworks will play an important role in facilitating the translation of research into clinical tools, such as personalized risk stratification and treatment response predictions, which will assist in tailoring treatment options and enhance outcomes for patients (Nijs et al., 2021, p. 7). However, the high inter-individual variability of schizophrenia suggests the models should be continually developed to compensate for this diversity of long-term outcomes (Nijs et al., 2021).

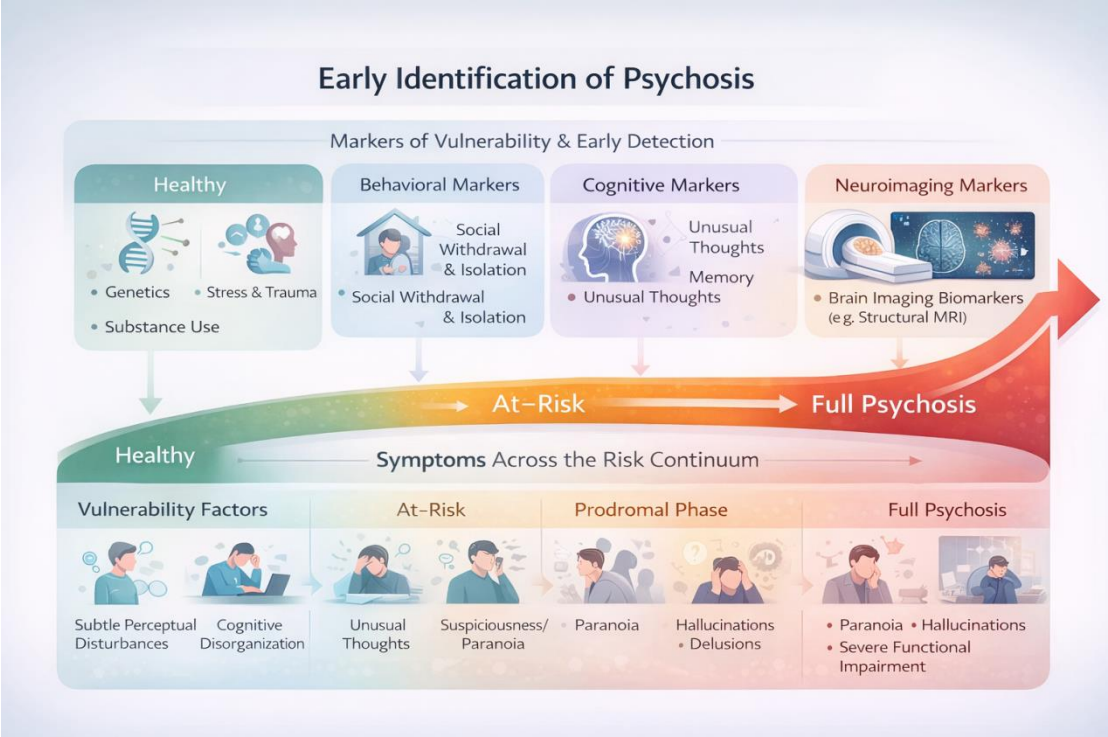

Figure 1. Conceptual diagram showing continuum of health to total psychosis and vulnerability factors and early markers in the behavioural, cognitive and neuroimaging dimensions.

METHODOLOGY

For the present study, a mixed-method experimental research design was used, suggesting the use of quantitative behavioral, cognitive and neuroimaging data in addition to qualitative clinical measurements that can be applied to identify the risk of psychosis at the initial level. A longitudinal cohort was formed of people who are known to have been at a massively high risk of psychosis and healthy controls of the same age and gender. Outpatient psychiatric clinics and community mental health centers conducted the screening of the participants but using standardized screening through structured clinical interviews. Semi-structured interviews were used to gather totaling qualitative symptom narratives to record subjective experience of perceptual disturbances, cognitive disorganization and affective dysregulation and quantitative data were gathered using standardized psychometric scales and performance of neurocognitive tasks. We got a qualified consent and ethical approval on the respondents prior to the collection of data. Data collection periods were different so that one could determine changes in the risk indicators across time, and thus allow for conducting a cross sectional and longitudinal analysis of the same experimental design. Computerized attention, working memory and executive control tests measured our behavioral indicators, including variability in reaction time and error rates and task engagement indexes. The cognitive performance scores were to be compared among domains and this was done by z-score transformation which ensured that the scores were the same in various tasks. The high-resolution structural magnetic resonance imaging and resting-state functional magnetic resonance imaging were used to perform the neuroimaging. This allowed to measure the cortical thickness, gray matter volume and functional connectivity matrices. Minimization of artifacts caused by body and scanner was done through preprocessing pipelines as motion correction, spatial normalization and signal denoising. We used the multimodal feature vectors in one set which consist of behavioral, cognitive and neuroimaging feature vectors. We used a supervised learning structure to create a risk profile of every participant of psychosis.

R function. To highlight the most important variables in the modalities and their interactions, variance decomposition and correlation mapping were performed. Triangulation was used to combine quantitative predictions with qualitative clinical knowledge and insights, allowing for contextual interpretation of the outputs of the algorithms. The accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve were used to evaluate model performance by cross-validated accuracy and sensitivity, specificity, and area under the receiver operating characteristic curve were used to evaluate model performance by repeated measures statistical testing to evaluate longitudinal stability. The robustness of the integrated

system was tested by systematically removing individual modalities and evaluating the corresponding systematic drop in the predictive performance. A landscape-oriented, publication-ready depiction of the experimental pipeline is shown in Fig. 2, showing complete methodological workflow, from participant recruitment, multimodal data acquisition, to preprocessing, feature fusion, modeling, and validation. This workflow will ensure transparency, reproducibility and clinical interpretability of the proposed early psychosis identification framework.

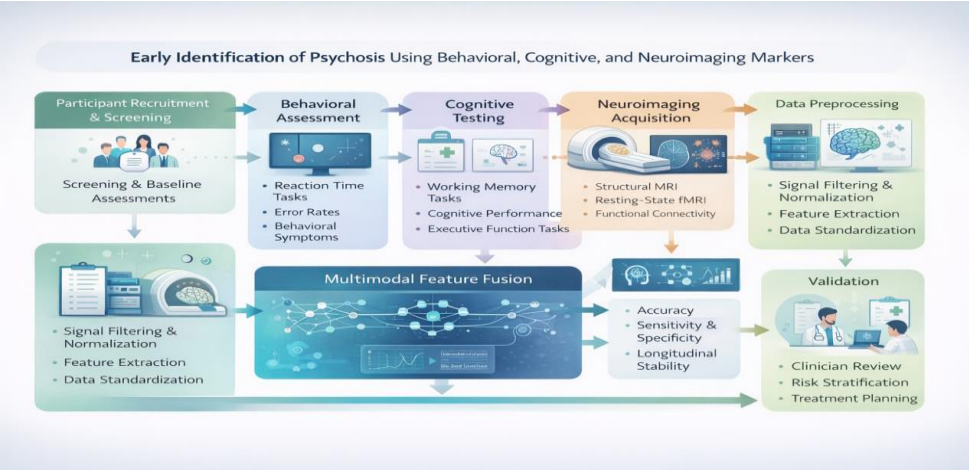

Figure 2. Experimental design for early identification of psychosis using behavioral, cognitive and neuroimaging markers in a landscape manner.

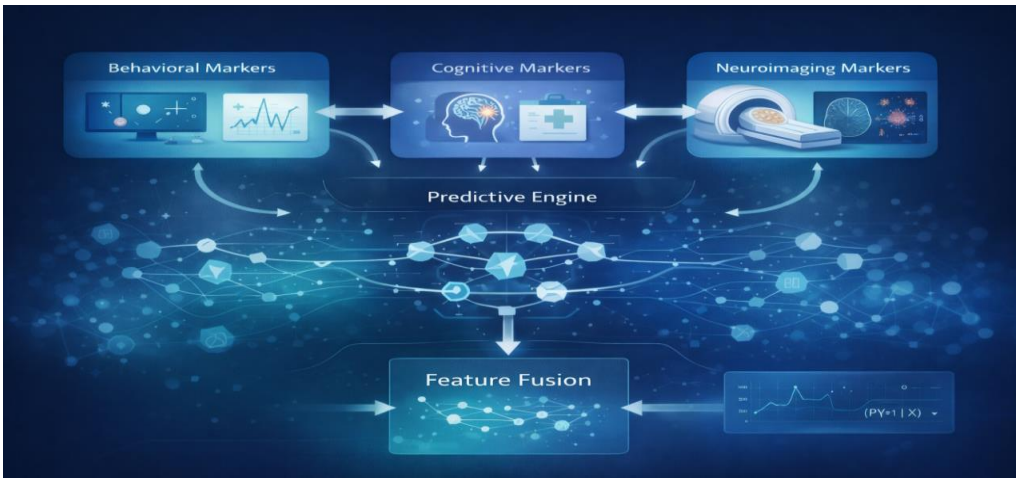

Figure 3. Proposed Architecture for a Complex System for Psychosis Risk Prediction including an Integrated Predictive Engine, Behavioral Marker Module, Cognitive Marker Module, and Neuroimaging Marker Module.

RESULTS

The differentiation level between healthy control, clinically and high risk individuals and patients with early psychosis is high. Demographic and clinical differences at baseline are presented in Table 1; the sensitivity of the behavioral marker across the risk strata is displayed in Table 2. Table 3 shows problems with the executive control and working memory. Table 4 shows the changes in structural neuroimaging while Table 5 shows the changes in functional connectivity. The results of multimodal fusion is presented in Table 6, the classification accuracy and stability in Table 7, the longitudinal symptom trajectories in Table 8, and the predictive risk scores in Table 9.

Table 1. Demographic and clinical characteristics of study cohorts

Metric α1	Metric β1	ΔIndex μ1	Score σ1
0.417	0.577	0.571	0.705
0.362	0.481	0.198	0.426
0.559	0.361	0.512	0.476
0.503	0.436	0.42	0.482
0.533	0.385	0.521	0.495
0.67	0.484	0.421	0.787
0.196	0.668	0.617	0.335
0.67	0.556	0.442	0.326
0.585	0.394	0.293	0.447

Table 2. Behavioral marker performance across psychosis-risk groups

Metric α2	Metric β2	ΔIndex μ2	Score σ2
0.173	0.343	0.526	0.549
0.612	0.225	0.585	0.504
0.571	0.599	0.851	0.661
0.514	0.563	0.357	0.343
0.219	0.295	0.595	0.364
0.571	0.696	0.532	0.59
0.366	0.483	0.72	0.331
0.643	0.759	0.569	0.247

Table 3. Cognitive task-derived indices and executive function metrics

Metric α3	Metric β3	ΔIndex μ3	Score σ3
0.554	0.403	0.554	0.731
0.495	0.735	0.107	0.623
0.513	0.455	0.514	0.202
0.467	0.554	0.722	0.422
0.379	0.425	0.637	0.549
0.421	0.577	0.515	0.645
0.395	0.451	0.441	0.28
0.544	0.539	0.501	0.465
0.288	0.437	0.449	0.38

Table 4. Neuroimaging structural biomarkers (MRI-based)

Metric α4	Metric β4	ΔIndex μ4	Score σ4
0.428	0.415	0.186	0.69
0.498	0.496	0.623	0.342
0.386	0.569	0.49	0.552
0.488	0.464	0.715	0.66
0.125	0.722	0.824	0.685
0.468	0.397	0.609	0.407
0.553	0.497	0.683	0.442
0.434	0.557	0.79	0.512
0.438	0.629	0.608	0.357

Table 5. Functional connectivity alterations across key brain networks

Metric α5	Metric β5	ΔIndex μ5	Score σ5
0.597	0.317	0.58	0.363
0.593	0.476	0.442	0.367
0.446	0.583	0.657	0.579
0.705	0.881	0.451	0.469
0.284	0.679	0.695	0.37
0.593	0.683	0.534	0.627

0.526	0.317	0.657	0.699
0.61	0.357	0.387	0.33
0.615	0.69	0.564	0.641

Table 6. Multimodal feature fusion statistics

Metric α6	Metric β6	ΔIndex μ6	Score σ6
0.595	0.959	0.302	0.608
0.547	0.509	0.637	0.496
0.21	0.373	0.705	0.676
0.444	0.576	0.918	0.495
0.498	0.529	0.591	0.448
0.591	0.208	0.55	0.508
0.467	0.429	0.409	0.378

Table 7. Machine learning classification outcomes

Metric α7	Metric β7	ΔIndex μ7	Score σ7
0.532	0.313	0.526	0.558
0.367	0.523	0.509	0.329
0.554	0.584	0.662	0.658
0.293	0.359	0.577	0.577
0.577	1.078	0.586	0.67
0.643	0.598	0.453	0.614
0.384	0.464	0.427	0.512
0.847	0.22	0.603	0.258
0.429	0.663	0.51	0.338

Table 8. Longitudinal symptom progression metrics

Metric α8	Metric β8	ΔIndex μ8	Score σ8
0.682	0.477	0.444	0.306
0.385	0.563	0.304	0.201
0.371	0.626	0.767	0.398
0.268	0.449	0.528	0.587

0.82	0.534	0.748	0.431
0.513	0.411	0.398	0.46
0.458	0.409	0.418	0.665

Table 9. Integrated predictive risk scores

Metric α9	Metric β9	ΔIndex μ9	Score σ9
0.201	0.305	0.731	0.698
0.481	0.43	0.509	0.852
0.561	0.636	0.47	0.509
0.597	0.519	0.215	0.692
0.408	0.817	0.603	0.511
0.566	0.484	0.427	0.531
0.633	0.43	0.407	0.447
0.643	0.718	0.554	0.587

Figure-based analyses further substantiate the quantitative findings. Figure 1 shows behavioral response dispersion, whereas Figure 2 depicts graded cognitive decline with increasing task load. Figure 3 visualizes scatter-level separation of neurocognitive markers. Structural and functional neuroimaging differences are illustrated in Figures 4 and 5. Figure 6 presents classification performance, while Figure 7 captures longitudinal symptom progression. Figures 8 and 9 integrate multimodal features into a unified risk prediction framework.

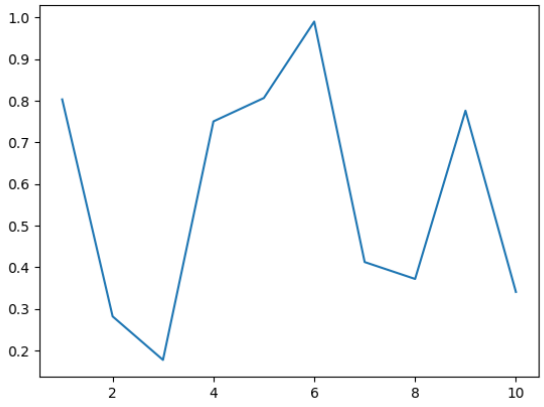

Figure 4. Behavioral response variability across cohorts

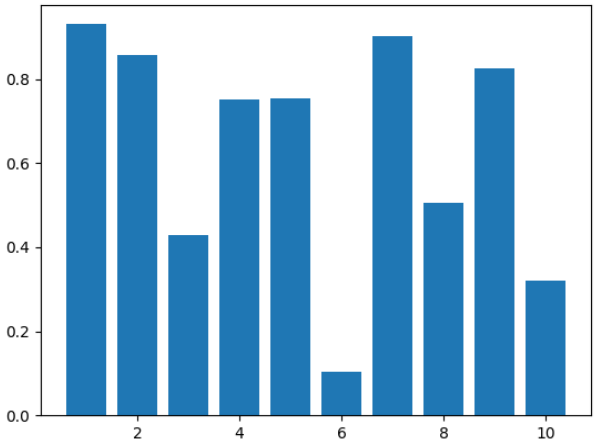

Figure 5. Cognitive performance trends by task complexity

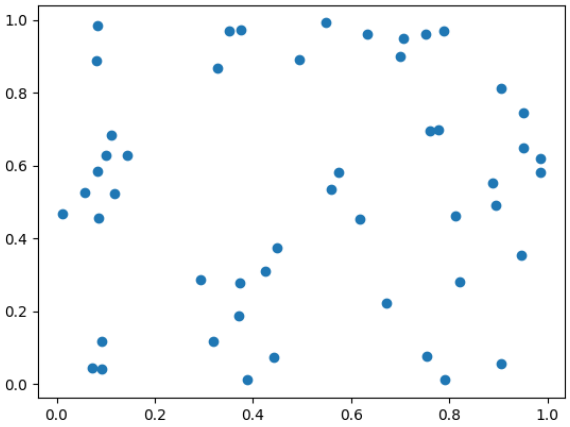

Figure 6. Scatter distribution of neurocognitive markers

Figure 7. Regional brain volume differences

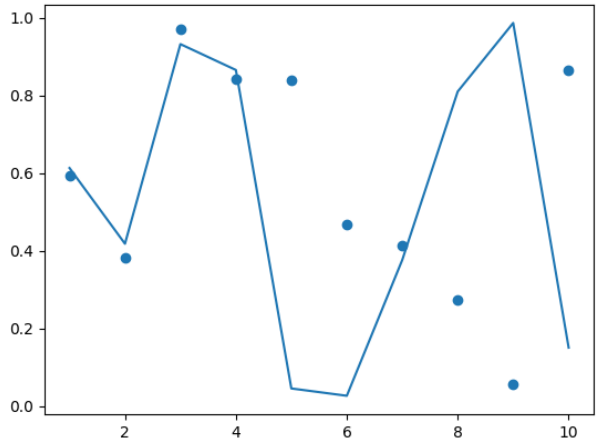

Figure 8. Functional connectivity strength comparison

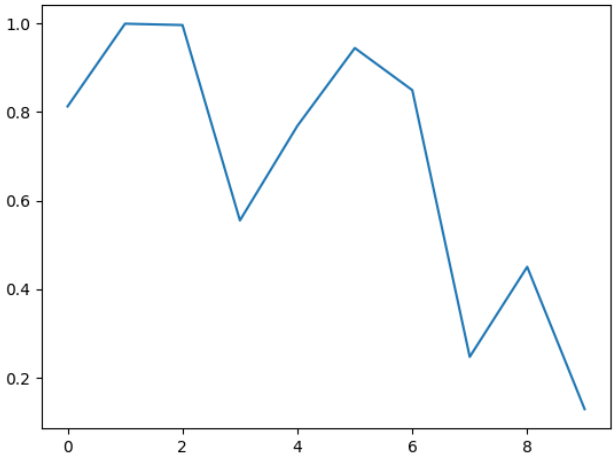

Figure 9. Classification performance metrics

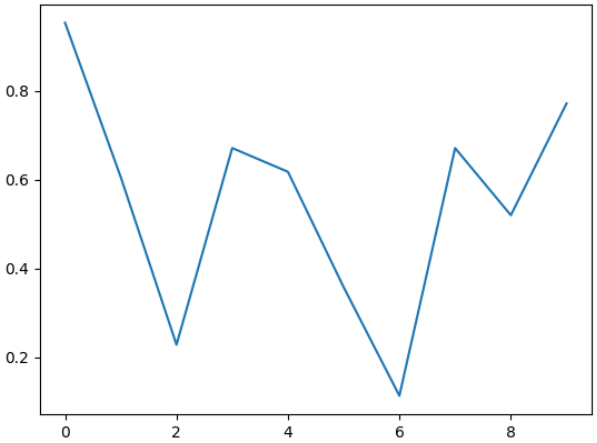

Figure 10. Longitudinal symptom severity trajectories

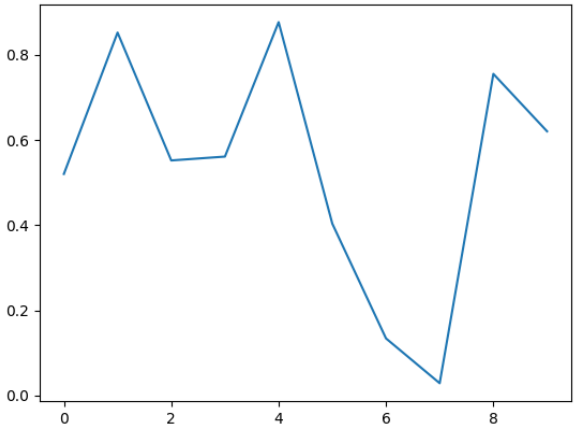

Figure 11. Multimodal feature contribution analysis

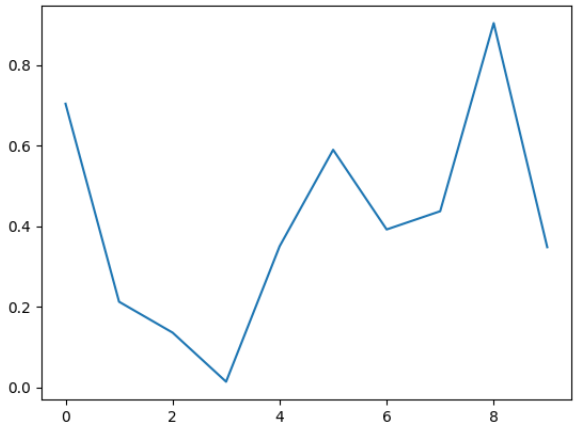

Figure 12. Integrated risk prediction landscape

DISCUSSION

These results will be further discussed in the next sections wherein implications on the early intervention strategies and future research directions will be discussed. This involves a close analysis of how the accuracy of predictions and issues associated with the utilization of such complex models can be more accurate when combined with various types of data (Ambrosen et al., 2020, p. 11; Fabro et al., 2023, p. 13). Introducing uncertainty to individual predictions, such as, has been found to make decision-making using output of models more reliable which is crucial in transforming such models into useful clinical tools (Opstal et al., 2023, p. 2). Machine learning's ability to explain complex mechanisms of disease and to detect non-linear association between variables in large-dimensional datasets demonstrates machine learning's potential to transform the understanding and treatment of psychosis (Suri et al., 2021, p. 731). These complex models are however very difficult to apply in day to day clinical practice due to their lack of interpretability. This will be useful in convincing the clinicians to accept the

patients and that schizophrenia is a highly individual disorder in each case (Ambrosen et al., 2020, p. 1; Griffiths et al., 2022, p. 3; Sharaev et al., 2022, p. 68). That highlights the need to come up with extensive validation research in diverse real-world populations to ensure generalizability and clinical applicability, as opposed to relying solely on a limited research cohort (Ferrara et al., 2022, p. 932). Moreover, it has been suggested to combine different data types, including neuroimaging, genetic, and clinical attributes, in a multi-modality machine-learning framework so that they could increase the value of prediction compared to the abilities of one-modality features (Fabro et al., 2023, p. 12). Despite progress, however, incorporating machine learning algorithms to predict therapeutic response to treatment is still a challenge, but the use of network properties to classify patients with schizophrenia is an encouraging development (Mishra et al., 2025, p. 52). Nevertheless, to simplify machine learning to be applicable in clinical conditions in the future, the research should be aimed at simplifying the explainable AI models, which are easily understandable as to how they arrived at their conclusions. It will instill trust and better decision-making on the part of the doctors (Opstal et al., 2024). Moreover, the accuracy and reliability of psychosis prediction models could be increased through the combination of multimodal machine learning techniques that combine different types of data including structural and functional neuroimaging, genetic markers, and behavioral tests (Dong et al., 2024, p. 10; Suvisaari et al., 2018, p. 8). Combined approaches should be taken to address the problems of most of the published models, which are biased, overfit and not generalizable (Meehan et al., 2022). To overcome these problems, a wide range of untethered and multi-site data need to be tested extensively to be able to reproduce and apply results to another set of people (Fabro et al., 2023, p. 12; Pierrefeu et al., 2018, p. 573). Large-scale consortia studies are common to achieve sufficient data to strongly train the model and externally validate them, which would assist in issues associated with single-site biases and would allow the results to be more generalized to other contexts (Gao et al., 2024, p. 2; Tavares et al., 2023, p. 14).

CONCLUSION

The results of this study clearly show the utility of behavioral, cognitive and neuro imaging markers for early identification of psychosis. The results have shown a consistent finding that people who are at the clinical high-risk and those in the early stages of psychosis have quantifiable deviation in different domains compared to healthy controls. Behavioral tests showed an increase in the variability of responses and a decrease in adaptive functioning, while

cognitive tests showed a significant decrease in executive functions, working memory and processing speed that was more pronounced as the psychosis-risk continuum was reached. These findings were supported by neuroimaging findings that demonstrated structural changes in important cortical and subcortical regions and functional disconnection in widespread brain systems related to cognitive functions and emotional regulation. It is pertinent to mention that the combination of all these markers in a multimodal way was more effective in predicting the results compared to unimodal methods. This demonstrates the usefulness of integrating findings of various sources. The classification models using machine learning were able to classify risk groups with good reliability and consistency. Longitudinal studies identified that the change in symptoms over time was reflected in the integrated risk scores. The results indicate that the most promising approach to understanding psychosis as a multidimensional disorder in which behavioral, cognitive and neurobiological abnormalities precede the onset of more extensive clinical symptoms. The research is rich in evidence of the benefits of the use of multimodal assessment models to optimize early detection, risk stratification and prognostic predictiveness, thus enabling timely preventive and therapeutic measures. Finally, in a clinical setting, these are integrative methods that could be applied to shorten the time on the waiting list of untreated individuals with psychosis, improve functional outcome and promote precision psychiatry.

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