UNIVERSITÀ DEGLI STUDI DI MILANO

DEPARTMENT OF BIOMEDICAL SCIENCES FOR HEALTH

PHD SCHOOL IN TRANSLATIONAL MEDICINE

CYCLE XXXVI

PhD Thesis

Predicting antipsychotic treatment outcomes using brain connectivity and neurocognition in early phases of psychosis

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Academic Year: 2022/23

ABSTRACT

Background: Prognostic biomarkers of clinical remission in individuals with psychotic disorders treated with antipsychotic drugs have been lacking. The development of biomarkers for prediction of clinical improvement may be helpful to guide treatment strategies. The aim of this study was to develop and validate machine learning models based on brain functional connectivity and neurocognition to predict clinical remissions in individuals at Recent Onset of Psychosis (ROP) treated with antipsychotics.

Methods: ROP patients treated with antipsychotics were classified as *remitters* or as *non-remitters* based on the adapted remission criteria of the Positive and Negative Syndrome (PANSS) Scale after a follow-up period of 3, 6 and 9 months. Baseline resting-state fMRI measures of brain connectivity and a neuropsychological test battery were evaluated on their ability to predict symptom remission using machine learning algorithms.

Results: Machine learning models using resting-state fMRI connectivity data predicted clinical remission in 51 ROP individuals treated with antipsychotics after 3 months with the best overall performances (**BAC: 71.2%**, AUC: 0.77). In order to evaluate the generalizability of our methods, we applied machine learning models to an independent replication sample of 41 ROP patients (**BAC: 66.7%,** AUC 0.77).

Conclusions: These results suggest that functional brain connectivity data at baseline could represent potential biomarkers of symptomatic improvement prediction in ROP individuals treated with antipsychotics. The methods and findings in this study could provide a critical step toward fMRI-based personalized patient treatment in early psychosis. Future work is needed to improve prediction performance to be clinically useful.

1. INTRODUCTION AND LITERATURE REVIEW

1.1 BACKGROUND

Schizophrenia is a severe psychiatric disorder that represents one of the top ten causes of disability worldwide[1]. It is characterized by psychotic symptoms, negative symptoms such as apathy and social withdrawal, and cognitive impairment resulting in long-term disability[2]. It is associated with low recovery rates, increased mortality and high personal and societal costs. It can emerge early in life and its progression could be associated with a potential lifetime burden and irreversible neural alterations for many patients across episodes. The mean lifetime prevalence of the disorder is about 1%, with similar rates across different countries, cultural groups, and sexes.

The etiology of schizophrenia is still poorly understood, but is hypothesized to reflect a complex interplay between genetic and environmental risk factors that could influence and alter early brain development[3]. Increasing evidences support the neurodevelopmental model of the disorder; emerging genetic and neuroimaging technology have improved the understanding of early brain precursors to illness[4]. Indeed, it is evident that once psychosis is present in patients with schizophrenia, the underlying biological process of the illness has already been ongoing for many years; a prodromal phase generally begins in the early adolescent years and precedes the onset of first psychotic episode[3,5].

Antipsychotic pharmacotherapy is the primary treatment for schizophrenia, with major effects on the reduction of psychotic symptoms and prevention of relapses[6]. The goals in treating schizophrenia include targeting symptoms, preventing relapse, and increasing adaptive functioning so that the patient can be integrated back into the community[7]. Treatment during the acute phase of schizophrenia is followed by maintenance therapy, which is necessary to help prevent relapse[7]. Schizophrenia requires long-term treatment that is commonly based on antipsychotic medications, which are primarily indicated for the treatment of schizophrenia and psychotic disorders[8]. The

efficacy of this pharmacological class depends on its ability to reduce dopamine function by blocking the dopamine D_2 family of postsynaptic receptors[9]. However, the occurrence of adverse effects associated, led to the introduction of second-generation antipsychotics which are potent 5-HT_{2a} receptor antagonists and relatively weaker dopamine D_2 antagonists and are associated with a substantially lower risk of neurologic adverse effects[10].

Given the generally low recovery rates for the disorder, in recent years there has been an increasing interest on early identification and intervention measures. Indeed, subjects with recent onset schizophrenia spectrum disorders have not endured many years of illness and functional decline and generally respond better to treatment[11]. Therefore, current primary lines of research are represented by the development of new methodologies and their application to better understand, predict and prevent the onset and evolution of psychotic disorders. In recent years, machine learning has been a promising approach in the research of treatment outcome prediction in psychosis. Importantly, recent studies used different neuroimaging, neurophysiological, genetic, and clinical features to predict antipsychotic treatment outcomes in patients at different stages of schizophrenia[12].

1.1.1 Neurobiological basis of Schizophrenia

Diagnosis of schizophrenia is operationally defined by symptoms and characteristic impairments of the disorder. The two major diagnostic systems for schizophrenia in common use are the Diagnostic and Statistical Manual, fifth edition (DSM-5)[13], and the International Classification of Diseases (ICD-10)[14]. The diagnostic criteria take into account characteristic positive, negative and cognitive symptoms along with symptom duration, and their effect on social and occupational functioning.

Schizophrenia is characterized by three broad categories of symptoms, including positive symptoms, negative symptoms, and cognitive impairment. Positive psychotic symptoms are represented by alterations in behaviors and thoughts, consisting of delusions, hallucinations and disorganized speech and behavior. Negative symptoms include social withdrawal, affective flattening, anhedonia and

diminished initiative and energy. Finally, cognitive symptoms are expressed as a broad set of cognitive dysfunctions. Schizophrenia is frequently characterized by a fluctuating course with enduring residual symptoms alternated by acute exacerbations of positive symptoms[6].

Development of schizophrenia is influenced by various modifiable and non-modifiable risk factors, such as prenatal and perinatal complications, paternal age, urban environment, migration status, drug abuse and social adversities. Indeed, genetic and environmental factors are hypothesized to contribute in evolution of schizophrenia influencing brain development[3]. Interestingly, increasing evidence supports the hypothesis that dopaminergic, neurodevelopmental and cognitive alterations are highly interconnected and have a broad role in underling onset and evolution of the disorder. These abnormalities are commonly present before the onset of frank psychosis episode; also clinically, schizophrenia is frequently preceded by a prodromal phase of sub-clinical psychotic symptoms[15].

Abnormalities in neurotransmission have provided the basis for theories on the pathophysiology of schizophrenia. Most of these theories center on the neurochemical imbalance of neurotransmitters, such as dopamine[16].The most frequently confirmed neurobiological correlates of schizophrenia come from the application of neuroimaging techniques. Structural and functional neuroimaging finding highlights neural alterations typical of the disorder. Reduction of brain volumes, enlargement of the ventricular system, alterations in cortical thickness and gyrification, alterations in brain activity and connectivity are characteristic aspects found in patients with schizophrenia[3],[6].

1.1.2 Model of psychosis onset from Clinical High Risk

In approximately 80–90% of patients with schizophrenia the onset of psychotic symptoms is preceded by the emergence of a prodromal syndrome characterized by subtle changes in belief, thought and perception such as attenuated forms of delusions, formal thought disorder and hallucinations, respectively[3]. In the last decades, the construct of a clinical high-risk (CHR) state for psychosis has evolved to capture this pre-psychotic phase, describing people presenting prodromal symptoms. First

investigations of early detection and intervention in subjects with prodromal symptoms began in the 1990s, with the development of validated operational CHR criteria and psychometric instruments of detection[17]. In recent years, there has been increased focus of research on subthreshold stages of psychotic disorders, attempting to predict and prevent progress to fully psychosis[18].

The Comprehensive Assessment of At-Risk Mental State (CAARMS)[19] and the Structured Interview for Prodromal Symptoms (SIPS)[20] are the most commonly interview measures used to diagnose the CHR in help-seeking individuals aged 8 to 40 years based on similar criteria. According to CHR diagnostic criteria, inclusion requires the presence of 1 or more of the following: attenuated psychotic symptoms (APS), brief limited intermittent psychotic episode (BLIP), and genetic risk and deterioration syndrome. Therefore, these subgroups are not considered psychotic and do not receive a diagnosis of full-blown psychosis. Different diagnostic criteria relate to complementary sets of clinical features, identifying different and subsequent phases of prodromal state; they have distinct clinical profiles, with different risk to develop psychosis[17,21].

Criteria of transition to psychosis require the occurrence of at least 1 fully positive psychotic symptom several times a week for more than 1 week[22]. Although subjects with potentially prodromal features are at increased risk to develop a psychotic disorder, it was shown that less than 40% will actually develop one some years later[23]. However, subjects who don't develop a psychotic disorder frequently remain at a lower level of functioning and have comorbid clinically debilitating diagnoses, such as anxiety, depression, and substance use disorders, suggesting that initial prodromal categorization is associated with persistent disability for a significant proportion[17].

Research indicates that the progression of disease from subthreshold states to chronic schizophrenia tends to present a degree of etiological and clinical continuity. Indeed, evidence suggests that early stages of schizophrenia are critical in forming and predicting the course and outcome of the disorder[5]. Therefore, dynamic models of the onset of mental disorders were recently proposed to explain the

continuous progression to subsequent stages of the illness and develop more accurate prediction studies[18].

1.1.3 Early intervention in psychosis

Treatment with antipsychotics is the primary therapy for people with psychotic disorders. Antipsychotics have been commonly classified into 'typical' or first-generation antipsychotics (FGAs) and 'atypical' or second-generation antipsychotics (SGAs) based on their pharmacological characteristics and extra-pyramidal adverse factors[3]. The best-known mechanism of action of antipsychotics is reduction of dopaminergic tone, that represents a common property of effective medication in treatment of psychotic symptoms[24].

In early-phase schizophrenia spectrum disorders, symptoms and functional decline have not endured many years; response rates to treatment are generally higher than in patients who have experienced multiple episodes. Additionally, evidence suggests that lower doses of antipsychotics are effective in patients at first episode[3]. Indeed, interventions in earlier stages of the illness may be more effective and less harmful than treatments delivered later in the illness course. For these reasons, there has been an increasing focus of research on identification and treatment optimization of earlier stages of the illness, such as CHR and recent onset of psychosis. Therefore, a key goal of specific intervention is develop early detection and effective treatments in early stages of psychosis that can mitigate or prevent further episodes and the progression of illness to more advanced stages and deterioration[25].

Preventive and early interventions in psychosis are feasible and can be effective. In recent years, several research programs yielded promising results for early intervention services that provide multimodal treatment, including different psychosocial and psychopharmacological interventions, in decreasing psychosis symptoms, improving functional outcomes, and reducing long-term disability[11]. Prospectively, further research is necessary to develop reliable and broadly accessible treatment

algorithms and prognostic tools to optimize and individualize targeted treatment in patients at early phases of psychosis[5].

1.2 FUNCTIONAL CONNECTIVITY AND EARLY PSYCHOSIS

1.2.1 Neuroimaging and psychosis

Over the last decades, brain imaging greatly contributed to better understand brain structural and functional organization, providing advances in understanding of the biological and etiological basis of mental functions in psychiatric disorders. Indeed, neuroimaging techniques have been employed to explore also neurobiological correlates of psychosis. Brian imaging data can elucidate symptom-related brain regions or can measure brain correlates underlying pathophysiology[26]. Moreover, they may reveal changes in information processing that precede the onset of the clinical disorder and thus provide markers of risk or prognosis. Therefore, neuroimaging findings can be used as biomarkers to provide a universal, predictable model for diagnosis, treatment and follow-up of the illness[27].

Brain imaging techniques commonly used in psychiatry include and structural and functional approaches. Structural techniques are computerized tomography (CT) and magnetic resonance imaging (MRI), while functional techniques are mainly represented by functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)[26]. Among functional neuroimaging techniques, fMRI is a non-invasive technique that has been widely employed to investigate functional connectivity, Functional magnetic resonance imaging (fMRI) is a non-invasive technique that utilizes changes in blood oxygen level-dependent (BOLD) signal to identify areas of increased or decreased neuronal activity[28]. This technique has proven extremely valuable, allowing researchers to identify brain areas associated with the performance of different tasks or during resting-state condition, identifying temporal interactions of increases or decreases in neuronal activity[29].

Indeed, neuroimaging studies have shown structural and functional abnormalities in patients with chronic schizophrenia compared with healthy individuals[3]. It is evident that total grey and white brain

volumes are generally reduced and ventricular volumes are increased inpatients with schizophrenia[30]. Moreover, changes in cortical thickness and gyrification were reported[31]. Interestingly, functioning neuroimaging studies have shown altered patterns of activation in cortical and subcortical brain regions associated with positive, negative or cognitive symptoms in patients with schizophrenia during specific tasks or in resting-state condition[3].

Additionally, individuals with a first episode of schizophrenia or CHR also present abnormalities in brain structure and functional activity[32]. Structural neuroimaging studies from first episode schizophrenia subjects reported small reductions in global and regional gray and white matter volumes at initial presentation, with progressive deterioration during illness progression[33],[34],[35]. Interestingly, significant differences have been seen also in subjects with CHR compared to healthy samples, although these seem to be smaller than those evident in people with frank psychosis[36]. Moreover, functional imaging studies indicate that the abnormalities during cognitive tasks are qualitatively similar but less severe in CHR subjects in comparison to patients with recent onset psychosis[37].

1.2.2 Functional connectivity and fMRI methods

In the last years, there has been an increasing use of resting-state fMRI to examine functional connectivity in the brain via the temporal correlation of low-frequency fluctuations in the MRI signal that reflect synchronized variations in neuronal and mental activity[38],[39]. Specifically, the measures of functional connectivity are not influenced by differences in task demand or performance making resting-state fMRI scans relatively easy to acquire and particularly suitable for investigation of abnormalities in functional connectivity of clinical populations[38]. Resting-state fMRI studies revealed coherent signal fluctuations of distinct regions organized in mutually correlated and functionally balanced networks[40].

Different techniques are commonly used to perform resting-state fMRI investigations, such as seed-based correlations and independent components analysis (ICA)[41,42,43]. In the seed-based correlation technique signal is extracted from a specific a priori region of interest, and a functional connectivity map is created by computing the correlation between the extracted time-varying resting state signals and signal in all other brain voxels[39,44]. After constructing functional connectivity maps from the data collected at rest and calculating group level statistics, inferential tests are applied to examine the existence of functional connections between different brain areas[45].

In contrast, ICA is a statistical technique that considers all voxels at once and uses a mathematical algorithm to separate a set of signals into independent components[46]. Graph method is an alternative approach where brain activity is represented as a network (a graph) of elements and their pairwise interconnections, called nodes and edges[47]. Finally, another method used to analyze resting-state data is clustering, where algorithms attempt to group samples that are alike, based on a set of relevant characteristics in such a way that samples in a cluster are more similar to each other than those in other clusters[45].

The seed-based correlation approach is the most straight forward method for resting-state fMRI analysis data analysis. Interestingly, seed-based correlation analysis approach was the first method adopted to identify the resting state networks[44]. Additionally, the contents of functional connectivity maps are starting to be used as biomarkers and features to train supervised machine learning algorithms[45].

1.2.3 Functional connectivity networks

Resting-state fMRI studies revealed coherent signal fluctuations of distinct regions organized in mutually correlated and functionally balanced networks[48]. Brain networks can be defined based on structural connectivity or functional interdependence of interconnected brain areas that interact to perform circumscribed function[49]. The whole-brain network parcellation in the human cortical and

subcortical structures was explored using resting-state functional connectivity MRI in 1000 healthy participants; the results revealed at several major networks associated with distinct neural functions [50,51,52]. In normal conditions, there is abundant evidence of integration between brain regions in these neural networks[49].

Interestingly, functional connectivity magnetic resonance imaging studies have been used to detect resting-state cortical networks presumed to underlie fundamental aspects of human brain organization and functions[53]. Three main mutually interacting large-scale networks have consistently been identified: the default mode network (DMN), involved in internal modes of cognition, the control executive network (CEN), involved in higher cognitive and executive functions, and the salience network (SN), involved in the selection of relevant internal and external stimuli[54,55,56].

The DMN is a specific, interconnected, anatomically defined functional network preferentially active at rest when individuals are not focused on the external environment. Interestingly, DMN is active during mental explorations referenced to oneself, including autobiographical memory, considering hypothetical social interactions, and envisioning of the future. DMN is organized around a set of interacting subsystems that comprise distributed association areas of the brain including medial prefrontal cortex, medial temporal lobe and posterior cingulate cortex[54,57.]

The CEN or dorsal frontoparietal network is an important system for maintaining and manipulating information in working memory and is involved in higher level cognitive functions, attention, and external task performance[58]. It links dorsolateral frontal and parietal neocortices[55].

Finally, the SN is involved in the integration of internal and external stimuli, such as sensory, emotional and cognitive information, and the appropriate assignment of salience to these informations. The SN, together with its interconnected brain networks, contributes to a variety of complex brain functions, including communication, social behavior, and self-awareness through the integration of sensory, emotional, and cognitive information[59]. The SN is intrinsically anchored in

the anterior insula and dorsal anterior cingulate cortex. It also includes three subcortical structures: the amygdala, the ventral striatum, and the substantia nigra and ventral tegmental area[56].

In physiological conditions, normal functioning of these networks is thought to depend on the appropriate switching between the anti-correlated CEN and DMN processes. During the performance of many cognitively demanding tasks, the CEN typically shows increase in activation, whereas the DMN shows consistent decrease in activation below the resting baseline. Emerging evidence suggests that the SN plays a crucial role in switching between reciprocal activation and deactivation of DMN and CEN involved in and internally oriented mental processes and externally oriented attention respectively[56,60,61].

Network models are now being widely used to characterize brain deficit and dysfunctions in a wide range of psychiatric and neurological disorders[62]. Indeed, increasing evidence suggests a major role of dysfunctional organization of the major functional networks in many psychopathologies, including schizophrenia. The model proposes that altered salience detection and mapping from the SN gives rise to aberrant engagement of the CEN, compromising cognition and goal-relevant adaptive behavior. Aberrant DMN organization and weak engagement or disengagement of the DMN by salient events are then associated with altered self-referential mental activity[56].

1.2.4 Functional connectivity and psychosis

The dys-connection hypothesis of schizophrenia suggests that abnormal synaptic neuromodulation and subsequent altered functional integration of neural networks play a key role in pathophysiology of the illness[63,64,65]. In the last decades, several resting-state fMRI studies have focused on dysfunctional brain organization and abnormalities of functional connectivity in psychosis. Neuroimaging studies provided a wealth of results supporting the hypothesis by showing that schizophrenia is characterized by widespread abnormalities in functional connectivity[66].

Interestingly, conceptualization of psychosis as aberrant signaling of salient events has led researchers to propose that abnormalities in interaction between major brain functional networks may explain the genesis of psychotic symptoms such as delusions and hallucinations[67,56]. In patients, positive and negative symptom severity and lower cognitive performance have been associated with reduction of global network efficiency and lower functional connectivity[66]. Abnormalities in functional and structural interactions within and between DMN, CEN and SN that may underlie symptoms and cognitive impairments have been found in patients with schizophrenia[68,69,70.]

Abnormal resting-state functional connectivity in psychosis has been widely investigated by using a seed-based fMRI approach, comparing patients with healthy controls. The majority of these studies reported a trend of widespread altered connectivity within and between large-scale brain networks in patients, highlighting the contributory role of dys-connectivity underlying the psychopathology of schizophrenia[71,72,73].

A recently published meta-analysis explored functional connectivity alterations in schizophrenia. Results showed that schizophrenia is characterized by hypo-connectivity within the DMN; additionally, hypo-connectivity between the SN and DMN and CEN were found in schizophrenia, motivating an empirical foundation for a disconnected large-scale brain networks model of schizophrenia in which the SN plays the core role in altered communication between functional networks[73].

Nonetheless, such functional connectivity abnormalities seem to vary considerably during the course of illness[74]. Regarding recent onset of psychosis, an overall trend toward hypo-connectivity with the rest of the brain was identified for the DMN, while the SN and CEN displayed specific hyper- and hypo-connectivity patterns in patients with first-episode of psychosis. Additionally, negative symptoms positively correlated with DMN abnormalities. These results suggest that widespread functional dys-connectivity of the DMN and SN represents the core pathophysiology mechanism from the early illness stages[72].

Moreover, some studies reported hypo-connectivity or hyper-connectivity in different high-risk for psychosis samples[71]. Interestingly, these findings and the evidence of a dys-connectivity gradient in subjects at risk of developing psychotic disorders support the hypothesis of a progressive increase of functional connectivity abnormalities from the psychosis risk, to recent onset of psychosis, to chronic schizophrenia[75,76].

1.2.5 Functional connectivity and antipsychotic treatment

Over the past years, there has been a growing interest in neuroimaging measures associated with effect of treatment on brain structure and function. Moreover, neural correlates of medication efficacy and outcome have a potential role as prognostic biomarkers of treatment response. Findings from fMRI studies may represent promising basis for tracking and predicting treatment outcomes at different stages of schizophrenia using a noninvasive and widely accessible method[77].

The effects of antipsychotic treatment on brain activity have been established in several fMRI studies; a general consensus of the normalizing effects of antipsychotic treatment on brain function in schizophrenia has been reached[78,79,80]. Functional alterations during different treatment modalities in schizophrenia were observed in diverse brain regions, including prefrontal cortex, anterior cingulate, and inferior frontal cortex[80]. Additionally, considering results for different antipsychotics, there is evidence that pharmacological properties may influence brain functional activity coupled with regulation of dopamine release[81,82].

Considering resting-state functional connectivity and large-scale brain networks, an increasing number of published studies have explicitly investigated systems-level effects of antipsychotic treatment. Evidence suggests that functional dys-connectivity brain networks in patients with schizophrenia is modulated by treatment with antipsychotic medication[83,84,85,86]. Additionally, effects on functional connectivity in certain key brain regions after antipsychotic therapy were reported in studies focusing on first episode of schizophrenia[87,88,72]. Interestingly, in a recent meta-analysis hypo-

connectivity between both the DMN/SN seeds and prefrontal regions was displayed in antipsychotic treated patients[72].

In recent years, different fMRI studies have examined changes in functional circuitry that correlated with response to antipsychotic medications, contributing to the evolving field of biomarkers for prediction of treatment efficacy in psychotic disorders[77]. A role for connectivity changes involving the striatum, hippocampus, and the prefrontal and anterior cingulate cortices in the mechanism of response is suggested by several treatment-based studies[89,90,91,92,93].

Interestingly, an increase in functional connectivity of the striatum with critical limbic and prefrontal regions was associated with greater efficacy of antipsychotic treatment in first-episode patients with schizophrenia[89]. Indeed, striatal connectivity also demonstrated success as a prognostic marker of response to treatment and its role could be useful for understanding of the neural pathophysiology underlying therapeutic effects of antipsychotic medications[94,95,96].

More recently, few studies have focused on functional connectivity of the hippocampus in treated first-episode and chronic patients with schizophrenia, suggesting that hippocampal connectivity may predict treatment response, and hence could be a useful biomarker for treatment development[90,91]

In studies that have examined assessments of large-scale functional connectivity networks in the context of therapeutic efficacy, response to treatment with antipsychotics was associated with differences in connectivity within and between the DMN, SN and CEN[87,97,98.] Indeed, good clinical response to treatment in first-episode or chronic patients with schizophrenia was associated with normalization of functional connectivity, while connectivity deficits were found in patients who failed antipsychotic treatment, suggesting that baseline connectivity changes can be used to predict response or resistance to antipsychotic treatment[87,97,98.]

1.3 PREDICTIVE MODELS OF TREATMENT OUTCOME IN PSYCHOSIS

Psychiatric disorders are complex phenomena that depend on and interact with a large number of variables. Computational psychiatry combines multiple levels and types of computation with multiple types of genetic, cognitive, clinical and neuroimaging data. Computational psychiatry provides data-driven machine learning approaches that can improve classification of disease, predict treatment outcomes or improve treatment[99,100]. Machine learning, through the extraction of meaningful patterns from inference, has the potential to advance a biologically grounded redefinition of major psychiatric disorders allowing early disease detection, individualized treatment selection, and dosage adjustment to reduce the burden of disease[101].

Although in medical research there has been a progress on identification of multiple prognostic factors, at present machine learning investigations using neurobiological markers to predict progression or response to treatment in patients with recent onset of psychosis have been scarce. In recent years, there has been an increasing interest on machine learning techniques and several studies have used support vector machines (SVM) to classify groups in a binary manner in order to predict progression of the psychiatric illness considering clinical or functional outcomes[102].

A tool using baseline neuroimaging and neurocognitive data to make predictions of future treatment responses would be of great value for individualized clinical decision-making before the commencement of treatment at the early course of the illness. The search for biomarkers that can predict clinical response to the treatment of early phases of psychosis could be a task of clinical importance in order to identify patients who likely would respond to a specific treatment and to improve remission rates, reducing progression of chronic symptoms and functional impairment. Thus far, improved prediction of treatment response could optimize treatment, with many benefits for patients and reduction of health care costs[103].

1.3.1 Machine learning methods in psychiatry

Machine learning is considered a subfield of artificial intelligence and is broadly defined as a computational strategy that automatically determines methods and parameters to reach an optimal solution to a problem rather than being programmed a priori to deliver a fixed solution. Machine learning algorithms are contributing greatly to psychiatry by addressing multidimensional clinical and biological data and making generalizable predictions at the single-subject level. Importantly, the aim of using machine learning approaches is to produce models that are sufficiently meaningful, accurate, and generalizable to be integrated into clinical care. Commonly, in machine learning classification models, predictor variables (features) are used to predict separated groups based on outcome variables (labels). In machine learning procedures, multiple models are trained and tested to automatically determine analysis parameters with optimal accuracy and generalizability[104].

Generalizability can be defined as the extent to which a statistical model generated in one group performs accurately in other groups. Performance metrics commonly used to interpret results and optimize predictions are sensitivity, specificity, accuracy, and balanced accuracy, used to optimize models with unbalanced sample sizes. Although external validation by directly applying the model to a new sample represents the gold-standard, it is possible to estimate and optimize generalizability using machine learning techniques such as simulations that resample data[104,105]. Generalizability can be assessed and optimized using Cross Validation (CV), a resampling technique consisting of training and test sets where the sample is separated into folds in which the models are learnt and those in which the models are then tested. In nested CV, which includes a CV cycle within another, accuracy of statistical models is maximized in the inner CV1 cycle before the models are ultimately applied to the left-out subjects of the outer CV2 cycle[106,107]. In multicenter studies, is also possible to assess the degree to which models generalize across sites using the leave-site-out CV[108].

To avoid unintentional information leakage that can invalidate generalizability by transferring the test data information into the training data, preprocessing steps such as scaling, imputation, filtering, and dimensionality reduction are needed to be performed on the data prior to classification or regression.

These steps are embedded into a CV pipeline wherein parameters of the preprocessing steps can be optimized during training based on performance criteria and applied to test sets[104]. Preprocessing techniques can maximize accuracy during training with the ability of the models to generalize to the test sample. However, it is important to note that the possibility of overfitting to training and test data increases with the number of tested parameter combinations[109].

Importantly, the choice of machine learning algorithms is generally associated with their ability to learn hyperparameters that can be modified to determine a model with optimized accuracy and generalizability[110]. Many machine learning algorithms have been developed in order to reduce overfitting and increase generalizability. Indeed, Support Vector Machine (SVM) has been widely used in psychiatry and neuroscience[111]. SVM allows categorization of an individual data into a predefined group using a classification algorithm, developed on a training data set. In recent years, SVM has been successfully applied in the context of disease diagnosis, transition prediction and treatment prognosis, commonly using neuroimaging data[112]. The SVM algorithm works by identifying cases on the closest external borders of group distributions to construct a margin that maximally separates cases with different labels from a linear boundary called hyperplane. The hyperplane classifies current cases and is used to optimally and generalize to future cases by regulating the margins. The margin and classification prediction ability are controlled via the C hyperparameter, which can be optimized during the CV process[104].

Typical high dimensionality of features relative to cases can results in lower accuracy and generalizability by overfitting. Therefore, feature selection is the selection of specific variables from a larger set to enhance accuracy and generalizability as part of preprocessing or combined with the machine learning algorithm[104]. Filter techniques assess the relevance of features independent of the classification algorithm and remove low-scoring features. Afterwards, the subset of relevant features is presented as input to the classification algorithm. On the other hand, wrapper methods embed the model hypothesis search within the feature subset search. Various subsets of features are generated;

the evaluation of a specific subset of highest performing features is obtained by training and testing a specific classification model[113]. Moreover, another possibility to reduce dimensionality is by using Principal Component Analysis (PCA), a technique based on projection that constructs relevant features by linearly transforming highly-dimensional correlated variables into a smaller number of uncorrelated variables also known as principal components which are later used for machine learning analyses. PCA has been successful in extracting relevant features in neuroimaging classification studies[114].

Finally, fusion and stacking approaches represent ensemble methods that use multiple learning algorithms to obtain better predictive performance. In late fusion, pipelines for different algorithms can be optimized and are then fused together to produce an average score that is used to make a final decision[104]. Stacked generalization is a technique that combines decision scores from different training models, training then a meta-model using another learning algorithm from these base level decision scores to obtain a final prediction[115]. Combined, these fusion and stacking methods are useful because they allow specialized learning of multivariate patterns[104].

1.3.2 Machine learning to predict outcomes of antipsychotic treatment in psychosis.

Treatment choices for psychiatric disorders are currently based on treatment guidelines broadly depending on clinical conditions and symptom classification. Therefore, identification of advanced biological markers that can predict response to pharmacotherapy is a task of substantial practical importance. Especially when beginning treatment, a reliable biomarker of early response could potentially help in finding a correct treatment and improving remission rates[116]. Despite the increasing number of studies published in this area over recent years, the impact of machine learning for treatment response prediction in patients with psychosis is still unclear. In this context, in a recent study we performed a comprehensive literature review of current knowledge about machine learning methodologies applied for prediction of antipsychotic treatment response in individuals with early and chronic course of schizophrenia[12].

Overall, several studies were identified, among them many using a single-modality approach and some combining data from multiple modalities. The majority of included studies considered structural and functional neuroimaging biomarkers as predictive features used in machine learning models. Specifically, fMRI features contributed to antipsychotic treatment response prediction of psychosis with higher accuracies, when compared to studies that used machine learning models based on clinical features. Importantly, examining the additive effects of combining features, the predictive value might be improved applying multimodal approaches. However, most of included studies presented several limitations, such as small sample sizes and a lack of replication tests. Moreover, considerable clinical and analytical heterogeneity among included studies posed a challenge in synthesizing findings and generating robust overall conclusions[12].

Importantly, the broad majority of included studies used features extracted from a single modality as input to the machine learning algorithms. Many of them used neuroimaging measures to predict treatment outcomes in patients with psychosis, while the others used clinical features.

-*sMRI features:* Only few studies used structural neuroimaging features as input to the machine learning algorithms[117],[118],[119]. These studies demonstrate structural radiomics approaches to predict clinical response of antipsychotic treatment with significant accuracies. Specifically, gray matter volume and thickness measures of specific brain regions, such as thalamic, temporal, and frontal areas, may represent important features that could play a role in the development of prognostic tools for individualized early treatment of schizophrenia.

-*fMRI features:* Among the included fMRI studies, most of them considered resting-state activity and functional connectivity measures as predictive features[120],[121],[122],[123],[124],[125]. These studies showed substantial heterogeneity in the brain functional biomarkers that were found as meaningful predictors of antipsychotic treatment outcomes. Despite a wide degree of methodological heterogeneity between the included studies, these findings suggest that fMRI features may contribute to prediction of clinical outcome in early onset of psychosis with high accuracies. Specifically, several functional connectivity

studies revealed that brain areas implicated in functional networks that play a key role in emotion and cognitive regulation were the most predictive features of treatment outcome and may be targets of antipsychotic treatment. Moreover, it was found that also specific patterns of brain activation in cortical and subcortical brain regions may be useful for predicting treatment outcomes in recent onset of psychosis. However, it is important to note that included studies presented several limitations, such as small sample sizes and lack of replication samples. Specifically, Li et al.[120] recruited samples of FEP patients treated with olanzapine for 8 weeks: one sample of 32 subjects as a train set and another sample with 44 subjects as a test set. Fractional amplitude of low frequency fluctuation (fALFF) and SVR analysis were used to predict treatment response, showing a positive relationship between baseline fALFF levels in the left ventromedial putamen and improvement in positive symptoms. Also, Sarpal et al.[121] divided the cohort into a training set of 41 FEP subjects and a test set of 40 patients with chronic schizophrenia to develop a prognostic index based on rs-fMRI. A Cox regression analysis was performed in subjects classified as responders and non-responders. A striatal connectivity index was built from functional connectivity values between the striatum and 91 brain regions. The index significantly predicted the treatment response, and this result was validated in the independent cohort. Shan et al.[122] explored whether the brain voxel-mirrored homotopic connectivity might predict individual treatment response in 21 patients with schizophrenia treated with olanzapine. A SVR analysis revealed that FC in the superior/middle prefrontal cortex at baseline could predict the symptomatic improvement of PANSS total, positive, and negative symptom subscale scores after eight weeks of treatment. Cao et al.[123] enrolled a small dataset of 43 fisrt-episode of psychosis subjects for 10 weeks of risperidone treatment. By using SVR analysis and the FC of superior temporal cortex with dorsal-lateral prefrontal, cingulate, temporal and parietal cortices, this study predicted response to antipsychotic treatment at an individual level with an accuracy of 82.5%. Finally, Smucny et al.[124] evaluated the ability of different algorithms to predict symptomatic improvement in 65 patients with SCZ treated with SGAs by using fMRI frontoparietal activations during a continuous performance task as features, showing good accuracies (accuracy of 70%).

-*Socio-demographical and clinical features:* noteworthy, several studies used different socio-demographic and clinical measures as features for ML analysis. Many of them found that important predictors of antipsychotic treatment outcome were baseline severity of psychotic symptoms[126],[127],[128],[129],[130] and comorbidities[105],[131], suggesting that ML models developed by including routinely available, patient-reportable information might present adequate predictive ability to be applied in clinical settings.

-*Multi-modality studies:* In recent years, advances have been made towards combining data from multiple modalities, in order to improve treatment response prediction[132],[133],[134],[135],[136]. These studies have utilized features from a variety of modalities, including structural and functional neuroimaging, socio-demographical, and cognitive data. These studies that compared different features found that functional neuroimaging contributed the most to predictions of clinical outcome of psychosis relative to specific structural neuroimaging and genetic features. Nevertheless, most of models that combined multiple features showed a higher accuracy than single-modality models, suggesting that, due to the complexity and heterogeneity of psychotic disorders, multimodal approaches may be able to predict more accurately outcomes of antipsychotic treatment. However, these findings must be interpreted with caution due to inconclusive results reported in some of the included studies.

2. EXPERIMENTAL PROJECT

2.1 INTRODUCTION

In the present study a machine learning approach was used to predict remission versus non-remission to antipsychotic treatment in patients with recent onset of psychosis using data from a multi-center study called Personalised Prognostic Tools for Early Psychosis Management (PRONIA)[137].

Patients with recent onset psychosis were classified as remitters or non-remitters after antipsychotic treatment using an adaptation of the remission criteria of the Schizophrenia Working Group Consensus[138] at 3, 6, and 9 months from baseline assessment. Baseline resting-state fMRI and neurocognitive features were evaluated on their ability to predict treatment response by using a machine learning approach.

2.1.1 The PRONIA Project Overview

The PRONIA research project (http://www.proniapredictors.eu) is a prospective, multi-center, observational study aiming to implement reliable and accessible prognostic tools facilitating the prediction and prevention of psychosis. It is based on baseline and follow-up examinations in recruited healthy controls and subjects defined by recent onset of psychosis, recent onset of depression, and at-risk mental state. Comprehensive clinical assessment is performed at baseline and after 9 months, with condense examinations at months 3 and 6. Multi-modal MRI, neuropsychological testing and blood sampling are performed at baseline and after 9 months, with the objective to identify biological markers of prediction diagnosis and treatment response in, early psychosis, early depression and clinical high risk. International centers participating in the project include Ludwig-Maximilian University of Munich (LMU), University of Basel (UniBas), University of Cologne (UKK), University of Birmingham (UoB), University of Turku (UTU), University of Udine (UniUd), and University of Milan (UniMi). Each Local Research Ethics Committee declared

their ethical approval for the study. Recruitment of subjects started from February 1, 2014, to May 31, 2017.

The Section for Neurodiagnostic Applications headed by Prof. Nikolaos Koutsouleris at the LMU developed since 2009 Neurominer (http://proniapredictors.eu/neurominer/), a text-based free software that provide machine learning methods for the analysis of heterogeneous data such as clinical and neurocognitive read-outs, structural and functional neuroimaging data, and genetic information. The software works on MATLAB command line. The program is an interface to a large variety of unsupervised and supervised pattern recognition algorithms that have been developed in the machine learning field over the last decades. Furthermore, the application implements different strategies for preprocessing, filtering and fusion of heterogeneous data, training ensembles of predictors, and for the visualization and testing of the significance of the computed predictive patterns. Using this tool, it is possible employ various Cross Validation (CV) schemes, implement preprocessing, choose a machine learning algorithm, and interpret the models with a graphical interface.

2.2 PROJECT OBJECTIVES

The primary aim of the present project was to evaluate the ability of resting-state fMRI measures and neurocognitive features, collected at baseline, to predict symptomatic remission in patients with recent onset of psychosis during continuous treatment with antipsychotic medications. To achieve this, we employed a machine learning approach to compare and possibly enhance the accuracy of outcome predictions within the current research framework. Hence, we applied a machine learning approach using whole brain, resting-state functional connectivity measures and neurocognitive features to predict remission versus non-remission of psychotic symptoms at different time points following the commencement of treatment with antipsychotics. Additionally, we explored the effects of combining these features, investigating whether the predictive value might be improved applying a multimodal machine learning approach.

2.3 PROJECT PROTOCOL

The present project adhered to a protocol, encompassing the recruitment, assessment, and data acquisition procedures. Project participants were recruited within the framework of the multi-centered observational study PRONIA. Subjects with a recent-onset psychosis were recruited in order to generate a large and representative database across different populations and healthcare systems. These patients were uniformly characterized by neurobiological and behavioral measures, structural and functional neuroimaging data, as well as clinical information.

Subjects were recruited across 7 sites in Finland (UTU), Germany (LMU, UKK), Italy (UniMI, UniUd), Switzerland (UniBas), and the United Kingdom (UoB) from February 1, 2014, to May 31, 2017. Follow-up for included patients continued for 9 moths, with visits every 3 months. Adult participants gave informed consent before study inclusion. Participants younger than 18 years and their guardians provided their written informed assent and consent. The PRONIA observational study was approved by all local research ethics committees.

Included subjects with recent onset of psychosis treated with antipsychotics were assessed at baseline and during a follow-up at 3, 6, and 9 months to perform machine learning analyses. An additional sample with the same inclusion criteria were recruited to replicate the analyses and test reproducibility of machine learning models.

2.3.1 Baseline inclusion and exclusion criteria

Patients were recruited if they had first episode of psychosis defined by transition criteria or ICD-10, duration of psychosis less than 12 months, and duration of antipsychotic treatment less than 3 months at baseline[139,140]. General inclusion criteria were age between 15 and 40 years, sufficient language skills for participation as well as capacity to provide informed consent/assent. General exclusion criteria were an IQ below 70, current or past head trauma with loss of consciousness (> 5 minutes), current or past known neurological or somatic disorders potentially affecting the structure or

functioning of the brain, current or past alcohol dependence, or polysubstance dependence within the past six months, and any medical indication against MRI.

Only patients that were receiving a treatment with antipsychotic medication at baseline were selected for the analysis of the present project. Medication regimen (type and dosage) was assessed by clinical records at baseline and follow-up. Medication adherence was based on self-report.

2.3.3 Follow-up and outcome selection

Recruited patients with recent onset of psychosis were tested at baseline with a comprehensive clinical assessment, including serial multi-modal fMRI scanning and a neuropsychological test battery. Recruited patients treated with antipsychotics were then tested with a clinical assessment after 3, 6 and 9 months from baseline evaluation, to assess clinical outcome at different time points.

Symptoms were assessed at baseline and during follow-up using the Positive and Negative Syndrome Scale (PANSS)[141]. The PANSS was used to evaluate clinical remission at follow-up, using an adaptation of the remission criteria of the Schizophrenia Working Group Consensus[138]. These operational criteria for symptomatic remission are based on an absolute severity threshold. Patients were defined as "remitters" if they achieved a final score of mild or less (PANSS items scores of ≤ 3) simultaneously on eight core symptoms of the PANSS (P1, P2, P3, N1, N4, N6, G5, and G9). At baseline, all patients had at least a moderate or higher score (PANSS items scores of ≥4) on one of the core symptoms. At follow-up, included subjects were considered "remitters" at different time points (T3, T6, and T9) following antipsychotic treatment if they met remission criteria at 3, 6, and 9 months, respectively. Conversely, those with a moderate or higher score (PANSS items scores of ≥4) on at least one of the core symptoms at these time points were classified as "non-remitters".

2.3.2 Baseline assessments and feature selection

At baseline, recruited patients were assessed with a comprehensive clinical assessment, including serial multi-modal MRI scanning, a neuropsychological test battery and psychometric scales, to generate a multi-modal profile of each participant.

-***Clinical battery*:**

Socio-demographic variables, consisting of age and sex.

Interview-based psychopathological symptom assessments: The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia[141], The Scale for the Assessment of Negative Symptoms (SANS)[142].

Functional variables: Global Assessment of Functioning (GAF)[143], Global Functioning: Social (GF-S), and Role (GF-R) scale[144].

-***Neuropsychological battery*:** computerized cognitive tests assessing different functional domains.

Neurocognitive performance in the general intelligence (Wechsler Adult Intelligence Scale - WAIS)[145].

Processing speed (Digit-Symbol Substitution Test - DSST)[146].

Trail Making Test A, (TMT-A)[147].

Visual working memory (Self-Ordered Pointing Task - SOPT[148]; Rey-Osterreith Figure - ROCF[149]; digits forward and backward tests[145]).

Verbal fluency (Semantic and Phonetic Verbal Fluency - SVF/PVF)[150].

Cognitive flexibility, sustained attention and inhibitory control (Trail-Making Test B - TMT-B)[151].

Facial emotion recognition as a measure of the social cognitive domain (Diagnostic Analysis of Non-Verbal Accuracy - DANVA)[152].

-***Neuroimaging*:** resting-state fMRI (rsfMRI) brain scans were acquired from all participants using a 3 Tesla MRI scanner. While acquiring brain resting-state activity, subjects were instructed to keep their eyes open and not to think about anything. To facilitate the evaluation of real-world generalizability, a minimal MRI harmonization protocol was implemented across all study sites[153]. rsfMRI preprocessing was divided into two main processes: core preprocessing consisted on realignment, coregistration, warping to Montreal Neurological Imaging (MNI) space and smoothing, whereas denoising methods consisted of motion correction using time series despiking, background filtering, and temporal band-pass filtering[154]. Following preprocessing, the brain was parcellated into 160 regions of interest (ROIs) according to the Dosenbach functional atlas[155]. Individual ROIxROI connectivity matrices were generated, resulting in 12720 rsFC features for each participant.

At follow-up, clinical examinations at months 3, 6, and 9 were performed. The PANSS scale was used to identify the clinical outcome of included individuals, classified as *remitters* or *non-remitters* at different time points.

2.5 MACHINE LEARNING

Collected rsfMRI and neuropsychological data were used as predictors of treatment response after pharmacological treatment with antipsychotics. Clinical well-established criteria of response to treatment after 3, 6, and 9 months from baseline were used as labels for the machine learning analysis. Support vector machines (SVM) were used to predict binarized treatment remission as outcome from brain connectivity measures and neurocognitive data in recent onset of psychosis patients. Models were trained using baseline rsfMRI data and neuropsychological tests as features separately and combined using a multimodal approach. Finally, in order to replicate the prediction models, machine learning models were applied to an independent replication sample.

The NeuroMiner software Version 1.1.0-BEORN was used to train machine learning models to predict *remission* versus *non-remission* to antipsychotic treatment. Several exploratory analyses were

performed to train models with various CV schemes, preprocessing steps, and machine learning algorithms to find optimal accuracy and predictive power. Trained models used baseline fMRI data, consisting of 12720 ROIxROI connectivity features, and neuropsychological data, consisting of 47 features, as predictors of clinical outcome. These features were used individually for each model, or in combination when a multimodal approach was performed. The Early Fusion option of Neurominer software was used when both rsfMRI and neuropsychological features were utilized in combination. Symptomatic remission criteria were used as outcome to be predicted, assigning ROP subjects to two groups: *remitters* and *non-remitters* after antipsychotic treatment at 3, 6, and 9 months. Age and gender were used as covariates. Balanced Accuracy (BAC) was defined as the optimization criterion for all trained models; BAC is defined according to the following formula: BAC = (Sensitivity+Specificity)/2.

-*Cross-validation settings*: as commonly recommended, repeated, nested, 5-fold CV was firstly used with 5 permutations in both the inner and outer loops respectively[156].

-*Preprocessing pipeline*: all models were trained pruning non-informative features, regressing out age and sex covariates attenuating covariate effects, and finally scaling each feature independently to the interval [-1, 1].

-*Machine learning algorithms*: parameter setups in SVM were selected to identify optimal accuracy and reduce overfitting. To assess performance of commonly used classifiers, L2-regularized logistic regression (L2LR) SVM algorithms were trained using neuroimaging and neurocpsychological features. Additionally, to effectively handle problems with unbalanced samples, the separating hyperplane was weighted.

-*Multimodal approach*: to integrate multiple data from neuroimaging and neuropsychological modalities, the early fusion process was performed as additional step of machine learning analyses[157].

-*Model validation*: in the final step of the analysis strategy, machine learning models were externally validated with an independent replication sample.

2.5 RESULTS

2.5.1 Demographic and Clinical Information

Baseline data were available for 159 recruited patients with recent onset of psychosis across 7 sites in the discovery sample (Table 1). Of this sample, 51 subjects met the inclusion criteria at 3 months of follow-up (T3 subgroup), 49 subjects met the inclusion criteria at 6 months of follow-up (T6 subgroup), and 61 subjects met the inclusion criteria at 9 months (T9 subgroup). At follow-up, 21 patients were classified as *remitters* and 30 patients were classified as *non-remitters* based on the adaptation of Schizophrenia Working Group Consensus remission criteria[138] in T3 subgroup. At follow-up, 27 patients were classified ad *remitters* and 22 patients were classified as *non-remitters* in T6 subgroup. At follow-up, 33 patients were classified as *remitters* and 28 patients were classified as *non-remitters* in T9 subgroup.

Table 1: sociodemographic characteristics of discovery sample

	T3	T6	T9
F/M	*22/29*	*21/28*	*24/37*
Remitters/non-remitters	*21/30*	*27/22*	*33/28*
Age	*26.1 (5.3)*	*26.6 (5.1)*	*26.0 (5.4)*

In the replication sample (Table 2), at 3 months follow-up (27 subjects), 12 patients were classified as *remitters* and 15 patients were classified as *non-remitters* (R-T3 subgroup). At 6 months follow-up (25 subjects), 13 patients were classified ad *remitters* and 12 patients were classified as *non-remitters* (R-T6 subgroup). At 9 months follow-up (44 subjects), 23 patients were classified ad *remitters* and 21 patients were classified as *non-remitters* (R-T9 subgroup).

Table 2: sociodemographic characteristics of replication sample

	3 months: 27	6 months: 25	9 months: 44
F/M	11/16	*10/15*	
Remitters/non-remitters	12/15	*13/12*	*23/21*
Age	27.1 (5.9)	*27.8 (6.6)*	*29.0 (6.7)*

At baseline, all patients completed clinical and fMRI assessment and reported moderate or higher score on one or more core PANSS symptoms selected by the Schizophrenia Working Group Consensus. The mean total PANSS score at baseline for all patients was 74.1 (SD 19,9) for subgroup T3, while the after 3 months of antipsychotic treatment, there was a general improvement with a mean PANSS score of 53.3 (DS 19.3). The mean total PANSS score at baseline for all patients was 77.9 (SD 19,2) for subgroup T6, while the after 6 months of antipsychotic treatment, there was a general improvement with a mean PANSS score of 51.4 (DS 20.5). The mean total PANSS score at baseline for all patients was 75.5 (SD 20.8) for subgroup T9, while the after 9 months of antipsychotic treatment, there was a general improvement with a mean PANSS score of 49.8 (DS 20.3).

2.4.2 Trained machine learning models

BAC and Area Under the Curve (AUC) of models trained using different modalities in different groups are reported and described (Table 3). The most robust predictive performances were observed when machine learning models were applied to rs-fMRI connectivity data to forecast clinical remission in treated ROP individuals after 3 months from baseline (**BAC: 71.2%**, AUC: 0.77). Conversely, when the investigation expanded the analysis to include additional time points, specifically at 6 months and 9 months, and incorporated a set of features derived from neuropsychological data, the developed models did not exhibit significant predictive performances. Moreover, when rs-fMRI and neuropsychological features were used as combined inputs for multimodal approach, the resultant predictive performances did not exhibit an improvement over the performance achieved with one selected modality. The comprehensive results of our analysis are presented in the following sections.

Table 3: Summary of machine learning models performances from training set

	3 months (n=51)		6 months (n=49)		9 months (n=61)	
	BAC	AUC	BAC	AUC	BAC	AUC
FC	**71.2**	**0.77**	59.8	0.68	50.2	0.47
NP	53.3	0.56	51.6	0.55	43.9	0.41
Early Fusion	71.2	0.77	61.6	0.68	49.9	0.46

Abbreviations: AUC: area under the curve; BAC: balanced accuracy; FC: functional connectivity features; NP: neuropsychological features

-*rs-fMRI features*: in the patients with recent onset of psychosis treated with antipsychotic medications, trained models predicting clinical response to antipsychotic treatment using fMRI connectivity features were significant and performed a balanced accuracy higher than 50%. The best model correctly classified of patients as being early improvers at 3 months of follow-up with a BAC of 71.2% (Table 4, 5, 6).

Table 4. Performance metrics of model using fMRI features of T3 subgroup.

Performance metrics	
TP/TN	*11/27*
FP/FN	*3/10*
Accuracy (%)	*74.5*
Sensitivity (%)	*52.4*
Specificity (%)	*90*
Balanced Accuracy (%)	***71.2***
Area Under the Curve	*0.77*
Matthews Coorelation Coefficient	*0.5*
Positive Predictive Value (%)	*78.6*
Negative Predictive Value (%)	*73.0*
False Positive Rate	*10*
Positive Likelihood Ratio	*5.2*
Negative Likelihood Ratio	*0.5*
Prognostic Summary Index	*51.5*

Youden's J statistic	*0.4*
DOR	*27.4*

Table 5. Performance metrics of model using fMRI features of T6 subgroup.

Performance metrics	
TP/TN	*20/10*
FP/FN	*12/7*
Accuracy (%)	*61.2*
Sensitivity (%)	*74.1*
Specificity (%)	*45.5*
Balanced Accuracy (%)	***59.8***
Area Under the Curve	*0.68*
Matthews Coorelation Coefficient	*0.2*
Positive Predictive Value (%)	*62.5*
Negative Predictive Value (%)	*58.8*
False Positive Rate	*54.5*
Positive Likelihood Ratio	*1.4*
Negative Likelihood Ratio	*0.6*
Prognostic Summary Index	*21.3*
Youden's J statistic	*0.2*
DOR	*1.8*

Table 6. Performance metrics of model using fMRI features of T9 subgroup.

Performance metrics	
TP/TN	*19/12*

FP/FN	*16/14*
Accuracy (%)	*50.8*
Sensitivity (%)	*57.6*
Specificity (%)	*42.9*
Balanced Accuracy (%)	***50.2***
Area Under the Curve	*0.47*
Matthews Coorelation Coefficient	*0.1*
Positive Predictive Value (%)	*54.3*
Negative Predictive Value (%)	*46.2*
False Positive Rate	*57.1*
Positive Likelihood Ratio	*1.0*
Negative Likelihood Ratio	*1.0*
Prognostic Summary Index	*0.3*
Youden's J statistic	*0.1*
DOR	-

-*Neuropsychological features*: overall predictive performances of trained models predicting clinical remission in treated ROP patients using neuropsychological features are reported (Tables 7, 8, 9). The best model correctly classified of patients as being early improvers at 3 months of follow-up with a BAC of 53.3%.

Table 7. Performance metrics of model using neuropsychological features of T3 subgroup.

Performance metrics	
TP/TN	*8/20*

FP/FN	*10/12*
Accuracy (%)	*56.0*
Sensitivity (%)	*40.0*
Specificity (%)	*66.7*
Balanced Accuracy (%)	***53.3***
Area Under the Curve	*0.56*
Matthews Coorelation Coefficient	*0.1*
Positive Predictive Value (%)	*44.4*
Negative Predictive Value (%)	*62.5*
False Positive Rate	*33.3*
Positive Likelihood Ratio	*1.2*
Negative Likelihood Ratio	*0.9*
Prognostic Summary Index	*6.9*
Youden's J statistic	*0.1*
DOR	*1.4*

Table 8. Performance metrics of model using neuropsychological features of T6 subgroup.

Performance metrics	
TP/TN	*15/10*
FP/FN	*12/11*
Accuracy (%)	*52.1*
Sensitivity (%)	*57.7*
Specificity (%)	*45.5*
Balanced Accuracy (%)	***51.6***
Area Under the Curve	*0.55*
Matthews Coorelation Coefficient	*0.1*
Positive Predictive Value (%)	*55.6*
Negative Predictive Value (%)	*47.6*

False Positive Rate	*54.5*
Positive Likelihood Ratio	*1.1*
Negative Likelihood Ratio	*1.0*
Prognostic Summary Index	*3.2*
Youden's J statistic	*0.1*
DOR	*1.1*

Table 9. Performance metrics of model using neuropsychological features of T9 subgroup.

Performance metrics	
TP/TN	*18/9*
FP/FN	*18/15*
Accuracy (%)	*45*
Sensitivity (%)	*54.5*
Specificity (%)	*33.3*
Balanced Accuracy (%)	***43.9***
Area Under the Curve	*0.41*
Matthews Coorelation Coefficient	*-0.1*
Positive Predictive Value (%)	*50*
Negative Predictive Value (%)	*37.5*
False Positive Rate	*66.7*
Positive Likelihood Ratio	*0.8*
Negative Likelihood Ratio	*1.4*
Prognostic Summary Index	*-12.5*
Youden's J statistic	*-0.1*
DOR	*0.7*

-*Multimodal approach*: overall predictive performances of trained models predicting clinical remission in treated ROP patients using rs-fMRI and neuropsychological features in a multimodal approach are reported (Tables 10, 11, 12). The best model correctly classified of patients as being early improvers at 3 months of follow-up with a BAC of 71.2%.

Table 10. Performance metrics of model using Early Fusion for T3 subgroup.

Performance metrics	
TP/TN	*11/27*
FP/FN	*3/10*
Accuracy (%)	*74.5*
Sensitivity (%)	*52.3*
Specificity (%)	*90*
Balanced Accuracy (%)	***71.2***
Area Under the Curve	*0.77*
Matthews Coorelation Coefficient	*0.46*
Positive Predictive Value (%)	*78.6*
Negative Predictive Value (%)	*73.0*
False Positive Rate	*10*
Positive Likelihood Ratio	*5.2*
Negative Likelihood Ratio	*0.6*
Prognostic Summary Index	*51.5*
Youden's J statistic	*0.4*
DOR	*27.4*

Table 11. Performance metrics of model using Early Fusion for T6 subgroup.

Performance metrics	
TP/TN	*21/10*

FP/FN	*12/6*
Accuracy (%)	*63.2*
Sensitivity (%)	*77.8*
Specificity (%)	*45.5*
Balanced Accuracy (%)	***61.7***
Area Under the Curve	*0.68*
Matthews Coorelation Coefficient	*0.2*
Positive Predictive Value (%)	*63.3*
Negative Predictive Value (%)	*62.5*
False Positive Rate	*54.5*
Positive Likelihood Ratio	*1.4*
Negative Likelihood Ratio	*0.5*
Prognostic Summary Index	*26.1*
Youden's J statistic	*0.2*
DOR	*2.0*

Table 12. Performance metrics of model using Early Fusion for T9 subgroup.

Performance metrics	
TP/TN	*20/11*
FP/FN	*17/13*
Accuracy (%)	*50.8*
Sensitivity (%)	*60.6*
Specificity (%)	*39.3*
Balanced Accuracy (%)	***49.9***
Area Under the Curve	*0.46*
Matthews Coorelation Coefficient	*-0.1*
Positive Predictive Value (%)	*54.1*
Negative Predictive Value (%)	*45.8*

False Positive Rate	*60.7*
Positive Likelihood Ratio	*1.0*
Negative Likelihood Ratio	*1.0*
Prognostic Summary Index	*-0.1*
Youden's J statistic	*0.1*
DOR	*1.0*

2.4.2 Validated machine learning models

In order to evaluate the generalizability of our methods, we applied machine learning models to an independent replication sample of ROP patients (Table 13). Importantly, predictive performances of machine learning models employing rs-fMRI connectivity features to predict clinical remission of treated ROP individuals after 3 months from baseline, continued to demonstrate significant predictive performances (**BAC: 66.7%,** AUC 0.77). The comprehensive results of replication analyses are presented in the following sections.

Table 13: Replication set

	3 months (n=27)		6 months (n=25)		9 months (n=44)	
	BAC	AUC	BAC	AUC	BAC	AUC
FC	**66.7**	**0.77**	45.7	0.49	50	0.63
NP	56.7	0.77	48.6	0.51	45	0.45
Early Fusion	66.7	0.77	50.0	0.63	50	0.63

Abbreviations: AUC: area under the curve; BAC: balanced accuracy; FC: functional connectivity features; NP: neuropsychological features

-rs-fMRI features: overall performance of replication analyses of trained machine learning models using rs-fMRI connectivity features are reported (Tables 14, 15, 16).

Table 14. Performance metrics of replication analyses when fMRI features were used for T3 subgroup.

Performance metrics	
TP/TN	*1/10*
FP/FN	*0/2*
Accuracy (%)	*84.6*
Sensitivity (%)	*33.3*
Specificity (%)	*100*
Balanced Accuracy (%)	***66.7***
Area Under the Curve	*0.77*
Matthews Coorelation Coefficient	*0.5*
Positive Predictive Value (%)	*100*
Negative Predictive Value (%)	*83.3*
False Positive Rate	*0*
Positive Likelihood Ratio	*3.3*
Negative Likelihood Ratio	*0.7*
Prognostic Summary Index	*83.3*
Youden's J statistic	*0.3*
DOR	-

Table 15. Performance metrics of replication analyses when fMRI features were used for T6 subgroup.

Performance metrics	
TP/TN	*1/5*
FP/FN	*2/4*
Accuracy (%)	*50.0*
Sensitivity (%)	*20.0*
Specificity (%)	*71.4*
Balanced Accuracy (%)	***45.7***

Area Under the Curve	*0.48*
Matthews Coorelation Coefficient	*-0.1*
Positive Predictive Value (%)	*33.3*
Negative Predictive Value (%)	*55.6*
False Positive Rate	*28.6*
Positive Likelihood Ratio	*0.7*
Negative Likelihood Ratio	*1.1*
Prognostic Summary Index	*-11.1*
Youden's J statistic	*-0.1*
DOR	*0.5*

Table 16. Performance metrics of replication analyses when fMRI features were used for T9 subgroup.

Performance metrics	
TP/TN	*5/2*
FP/FN	*2/5*
Accuracy (%)	*50*
Sensitivity (%)	*50*
Specificity (%)	*50*
Balanced Accuracy (%)	***50***
Area Under the Curve	*0.63*
Matthews Coorelation Coefficient	*0*
Positive Predictive Value (%)	*71.4*
Negative Predictive Value (%)	*28.6*
False Positive Rate	*50*
Positive Likelihood Ratio	*1*
Negative Likelihood Ratio	*1*

Prognostic Summary Index	*0*
Youden's J statistic	*0*
DOR	*0*

-*neuropsychological features*: overall performance of replication analyses of trained machine learning models using neuropsychological features are reported (Tables 17, 18, 19).

Table 17. Performance metrics of replication analyses when neuropsychological features were used for T3 subgroup.

Performance metrics	
TP/TN	*1/8*
FP/FN	*2/2*
Accuracy (%)	*69.2*
Sensitivity (%)	*33.3*
Specificity (%)	*80*
Balanced Accuracy (%)	***56.6***
Area Under the Curve	*0.77*
Matthews Coorelation Coefficient	*0.2*
Positive Predictive Value (%)	*33.3*
Negative Predictive Value (%)	*80*
False Positive Rate	*20*
Positive Likelihood Ratio	*1.7*
Negative Likelihood Ratio	*0.8*
Prognostic Summary Index	*13.3*
Youden's J statistic	*0.1*
DOR	*2.8*

Table 18. Performance metrics of replication analyses when neuropsychological features were used for T6 subgroup.

Performance metrics	
TP/TN	*2/4*
FP/FN	*3/3*
Accuracy (%)	*50.0*
Sensitivity (%)	*40.0*
Specificity (%)	*57.1*
Balanced Accuracy (%)	***48.6***
Area Under the Curve	*0.51*
Matthews Coorelation Coefficient	*-0.1*
Positive Predictive Value (%)	*40*
Negative Predictive Value (%)	*57.1*
False Positive Rate	*42.9*
Positive Likelihood Ratio	*0.9*
Negative Likelihood Ratio	*1.1*
Prognostic Summary Index	*-2.9*
Youden's J statistic	*-0.1*
DOR	*0.*

Table 19. Performance metrics of replication analyses when neuropsychological features were used for T9 subgroup.

Performance metrics	
TP/TN	*4/2*
FP/FN	*2/6*
Accuracy (%)	*42.9*
Sensitivity (%)	*40*

Specificity (%)	*50*
Balanced Accuracy (%)	***45***
Area Under the Curve	*0.45*
Matthews Coorelation Coefficient	*-0.1*
Positive Predictive Value (%)	*66.7*
Negative Predictive Value (%)	*25*
False Positive Rate	*50*
Positive Likelihood Ratio	*0.8*
Negative Likelihood Ratio	*1.2*
Prognostic Summary Index	*-8.3*
Youden's J statistic	*-0.1*
DOR	*0.6*

-*multimodality approach:*: overall performance of replication analyses of trained machine learning models using combination of rs-fMRI and neuropsychological features are reported (Tables 20, 21, 22).

Table 20. Performance metrics of replication analyses when Early Fusion were used for T3 subgroup.

Performance metrics	
TP/TN	*1/10*
FP/FN	*0/2*
Accuracy (%)	*84.6*
Sensitivity (%)	*33.3*
Specificity (%)	*100*
Balanced Accuracy (%)	***66.7***
Area Under the Curve	*0.77*
Matthews Coorelation Coefficient	*0.5*
Positive Predictive Value (%)	*100*

Negative Predictive Value (%)	*83.3*
False Positive Rate	*0*
Positive Likelihood Ratio	*3.3*
Negative Likelihood Ratio	*0.7*
Prognostic Summary Index	*83.3*
Youden's J statistic	*0.3*
DOR	*-*

Table 21. Performance metrics of replication analyses when Early Fusion were used for T6 subgroup.

Performance metrics	
TP/TN	*1/4*
FP/FN	*3/4*
Accuracy (%)	*41.7*
Sensitivity (%)	*20*
Specificity (%)	*57.1*
Balanced Accuracy (%)	***38.6***
Area Under the Curve	*0.49*
Matthews Coorelation Coefficient	*-0.24*
Positive Predictive Value (%)	*25*
Negative Predictive Value (%)	*50*
False Positive Rate	*42.9*
Positive Likelihood Ratio	*0.47*
Negative Likelihood Ratio	*1.4*
Prognostic Summary Index	*-25*
Youden's J statistic	*-0.2*
DOR	*0.2*

Table 22. Performance metrics of replication analyses when Early Fusion were used for T9 subgroup.

Performance metrics	
TP/TN	*5/2*
FP/FN	*2/5*
Accuracy (%)	*50*
Sensitivity (%)	*50*
Specificity (%)	*50*
Balanced Accuracy (%)	***50***
Area Under the Curve	*0.63*
Matthews Coorelation Coefficient	*0*
Positive Predictive Value (%)	*71.4*
Negative Predictive Value (%)	*28.6*
False Positive Rate	*50*
Positive Likelihood Ratio	*1*
Negative Likelihood Ratio	*1*
Prognostic Summary Index	*0*
Youden's J statistic	*0*
DOR	*1*

2.5 DISCUSSION

In this study, the main objective was to predict early clinical remission versus non-remission at different time points by using machine learning algorithms with baseline resting-state fMRI connectivity and neuropsychological features in patients with recent onset of psychosis treated with antipsychotics. We tried to predict clinical remission after 3, 6, and 9 months by using differences in baseline functional connectivity or neuropsychological data alone or in combination. Clinical meaningful response was shown by PANSS scores reduction.

The primary and most significant finding of this study pertained to the overall predictive performances of machine learning model that employed functional connectivity features to predict after 3 months clinical remission in a group of 51 individuals diagnosed with recent onset of psychosis who had undergone treatment with antipsychotics. Specifically, the best-performing model achieved a Balanced Accuracy (BAC) of 71.2% and an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.77. These metrics evaluate the predictive performance of classification models, such as employed in this study. Moreover, in this study we also tested the generalizability of these methods. To achieve this, developed machine learning model was applied to a separate, independent group of 41 ROP patients, that confirmed significant overall predictive performances, such as balanced Accuracy (BAC) of 66.7% and an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.77. Therefore, this study demonstrates the efficacy of using machine learning models using resting-state fMRI connectivity data to predict early clinical remission after 3 months from baseline in individuals with recent onset of psychosis treated with antipsychotics. The findings highlight the potential utility of this approach and its consistency when applied to a separate group of patients, underscoring its potential for broader application and clinical relevance.

The findings of the present investigation yield valuable insights into the predictive capabilities of neuroimaging connectivity measures in the context of psychotic symptom remission. Notably, the results underscore the ability of these neuroimaging metrics to prognosticate early remission, as defined by the amelioration of psychotic symptoms, with overall significant performances at 3 months from the baseline assessment. However, findings of the present study show that the overall predictive performances diminished over an extended period of follow-up, particularly at 6 and 9 months from baseline, with accuracies declining to 59.8% of BAC at 6 months and 50.2% of BAC at 9 months from baseline. Consequently, our study indicates that the most robust overall predictive performance occurs in the initial stages of remission, followed by a gradual decline in predictive accuracy over time. Interestingly, previous research focusing on fMRI predictors of treatment response in early

phases of schizophrenia revealed effective predictive capabilities at the 3-month[121] and 7-month[158] intervals, although those studies featured smaller sample sizes and different neuroimaging techniques in comparison to our research project. In another study that used structural neuroimaging features to predict short- (3 months) and long-term (6 months) treatment response in patients with first-episode schizophrenia, predictive performances were not significant[132]. In this context, our study introduces a novel perspective on the identification of factors that can predict outcomes of treatment in recent onset of psychosis individuals. It may contribute to the recognition of functional connectivity patterns and early response as key elements in this prediction. Indeed, it is important to note that recent research suggested that achieving clinical remission at 3 month can serve as a prognostic indicator for long-term recovery in individuals experiencing their first episode of psychosis[159]. Therefore, the identification of neuroimaging predictors for early remission may hold crucial potential biomarkers for clinical progress. These findings pose critical implications for the development of personalized treatment strategies, emphasizing the importance of tailored therapeutic interventions during the early stages of psychosis, when predictive models using neuroimaging features may exhibit greater accuracies.

Another relevant finding in our study is that machine learning models utilizing functional connectivity features consistently demonstrated notably higher overall predictive performances in comparison to models based on neuropsychological features, across all follow-up time points. Additionally, the implementation of a multidimensional approach, which combined both functional connectivity and neuropsychological data as features, failed to outperform the predictive metrics obtained in models based solely on neuroimaging features. This finding suggests that the primary determinant of treatment response prediction may be associated with the functional connectivity predictors. Indeed, the incorporation of neuropsychological features failed to augment the predictive accuracy of the machine learning models, thereby highlighting the distinct and prominent predictive capacity of functional connectivity features in the context of our study. It is noteworthy to highlight that previous

research which employed a multimodal approach, revealed that functional neuroimaging played a predominant role in predicting clinical outcomes of psychosis when compared to different features, such as specific structural neuroimaging[134] and genetic features[136]. Additionally, in a recent study that used combined fMRI and neurocognitive data incorporating an ensemble of machine learning algorithms for the prediction of short- and long-term antipsychotic treatment response, analyses yielded non-significant results[132]. Therefore, as suggested by relevant research[160], our study highlights the crucial role of baseline resting-state functional connectivity in predicting clinical outcome of treated individuals with recent onset of psychosis.

From a neurobiological perspective, it is crucial to note that distinctions in dopaminergic function potentially suggest a neurochemical foundation for stratifying prognosis of early onset of psychosis. Specifically, Dopamine Receptor D2 (DRD2) has been extensively associated with response to antipsychotics and previous imaging studies have focused on the dopaminergic system given its clear implication in antipsychotic pharmacodynamics[82]. Recent molecular imaging studies have begun to clarify a significant heterogeneity of dopamine function in samples of patients diagnosed with non-affective psychosis. While elevated dopamine synthesis and release capacities appear widespread, receptor/transporter availabilities and synaptic levels may only be abnormal in a subgroup of patients, thereby contributing to inter–individual differences in treatment response and side effects[161]. Indeed, it was found that differences in dopaminergic functions between responders and non-responders to antipsychotic treatments potentially suggests a neurochemical foundation for stratifying psychosis at baseline[162]. Additionally, as the relationship between dopamine synthesis capacity and functional connectivity is different between responders and non-responders to treatment, specific mechanisms of pathophysiology could underlie different subgroups of patients with schizophrenia[163].

In summary, results of present research provide evidence that individual differences in functional connectivity predict response to treatment with atypical antipsychotic drugs in patients with recent onset of psychosis. Evidence from literature suggests that abnormalities in functional dysconnectivity

are observable at the earliest stage of illness onset and progression of psychosis in schizophrenia and could be a potential predictable marker for psychosis[164]. Interestingly, functional connectivity could also represent a predictable marker for response to treatment in early psychosis. Indeed, different patterns of connectivity dysfunction may represent significant predictors of treatment response[165,123]. Previous fMRI studies have found that alterations in striatal and temporal connectivity may predict improvement in clinical symptoms in first-episode schizophrenia patients[121,123]. Additionally, a study that considered whole-brain functional connectivity have shown that treatment resistance is associated with large disruptions to network connectivity, in particular cerebellar-frontal networks, in people with schizophrenia[97]. Therefore, individual patterns of alterations in functional connectivity detectable by fMRI may represent a biomarker of specific ability of antipsychotic medications to modulate neurotransmission and attenuate psychotic symptoms. Prospectively, it would be imperative for future analyses to focus on identification of specific functional connectivity patterns or cerebral regions with heightened predictive value. To be clinically useful, a biomarker of treatment response needs to classify *remitters* versus *non-remitters* with reasonable accuracy, helping to make decisions as to whether to continue the same treatment, adjust the dose or switch to a different medication. Therefore, the present work represents an important preliminary step toward clinical utility in treatment of early–course psychosis. Further studies using larger sample and additional predictive markers may found models with higher levels of prediction and applicability in precision psychiatry of early psychosis care.

Our present analyses have several strengths, including the same data acquisition and pre-processing methodology used for all subgroups, and the use of an independent replication sample for validation of machine learning models[166]. However, results do need to be interpreted with clear acknowledgment of limitations. First, large sample sizes are generally important in machine learning to increase prediction accuracy[110]. Other limitations of this study include the heterogeneity of antipsychotic medications used by patients and the variability in the duration of their treatment regimens. These

factors can introduce confounding variables and may impact the generalizability of our findings. Additionally, the potential influence of specific antipsychotic medications on treatment outcomes was not explored in depth within the scope of this research, which is a noteworthy limitation. Future investigations with larger, more homogeneous patient groups and a focus on the effects of different antipsychotic medications could provide a more comprehensive understanding of treatment outcomes in recent onset of psychosis.

2.6 CONCLUSIONS

Results of machine learning models suggest that functional brain connectivity data at baseline could represent potential biomarkers that can help to predict subsequent symptomatic improvement during antipsychotic treatment in individuals with recent onset of psychosis especially for early treatment outcomes. It is important to note that neurocognitive features failed to significantly predict treatment outcome Moreover, in our study multi-modal approach failed to improve accuracies in prediction of treatment outcomes. In conclusions, the methods and findings in this study could provide a critical step toward fMRI-based personalized patient treatment in early psychosis. The proposed model appears to perform well in predicting treatment response, a fundamental unmet need of current clinical interventions in youth with recent–onset mental disorders. Indeed, the possibility of anticipating the effect of prescriptions seems fundamental to guide clinical decisions and limit exposure to side effects of potentially unnecessary drugs. Although the methods and findings in this study could provide some additional data toward fMRI-based personalized patient treatment in early psychosis, additional analyses on a bigger sample size are needed to obtain good predictive accuracies and reproducibility of trained machine learning models. Importantly, future work is needed to improve prediction performance to be clinically useful.

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