Aus dem Zentrum für Neurologie und Psychiatrie der Universität zu Köln
Klinik und Poliklinik für Psychiatrie und Psychotherapie
Direktor: Universitätsprofessor Dr. med. F. Jessen

The role of cognition in the prediction of social functioning in Recent Onset Psychosis

Inaugural-Dissertation zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
Nina Walter
aus Münster

promoviert am 29.04.2025

Gedruckt mit Genehmigung der Medizinischen Fakultät der Universität zu Köln
2025

Dekan: Universitätsprofessor Dr. med. G. R. Fink

1. Gutachter: Universitätsprofessor Dr. med. Dipl.-Psych. J. Kambeitz
2. Gutachter: Professor Dr. med. habil. J. Kuhn

Erklärung

Ich erkläre hiermit, dass ich die vorliegende Dissertationsschrift ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

Bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskriptes habe ich Unterstützungsleistungen von folgenden Personen erhalten:

PD Dr. Lana Kambeitz-Ilankovic
Dr. Julian Wenzel

Weitere Personen waren an der Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die Hilfe einer Promotionsberaterin/eines Promotionsberaters in Anspruch genommen. Dritte haben von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertationsschrift stehen.

Die Dissertationsschrift wurde von mir bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Die dieser Arbeit zugrunde liegenden Datensätze wurden ohne meine Mitarbeit an 10 verschiedenen Studienzentren im Zeitraum von Februar 2014 bis Juli 2019 erhoben und von der Klinik und Poliklinik für Psychiatrie und Psychotherapie der Ludwig-Maximilians-Universität München durch Mitarbeitende des PRONIA Konsortiums zur Verfügung gestellt. Für eine detaillierte Übersicht über die Modalitäten der Datenerhebung verweise ich auf die der Publikation beigefügten zusätzlichen Informationen. Die Auswahl der Probandinnen und Probanden erfolgte nach zuvor festgelegten einheitlichen Ein- und Ausschlusskriterien. Die Erhebung der verwendeten Daten erfolgte mittels standardisierter Testbatterien und Interviews durch geschultes Personal. Die anschließende Datenextraktion und -analyse wurden mit der Hilfe von Frau PD Dr. Lana Kambeitz-Ilankovic sowie Herrn Dr. Julian Wenzel von mir selbst durchgeführt.

Die Datenanalyse erfolgte mit dem Statistikprogramm RStudio (Version 1.3.1056). Die statistischen Messungen wurden von mir selbst durchgeführt. Mithilfe des maschinellen Lernprogramms NeuroMiner (Version 1.05) wurde das für diese Arbeit verwendete Prädiktionsmodell von mir verstellt. Für die Visualisierung der Ergebnisse war ich selbst verantwortlich.

Das Erstellen des Manuskripts und des ergänzenden Materials sowie der darin enthaltenen Grafiken und Tabellen erfolgte durch Frau PD Dr. Lana Kambeitz-Ilankovic und mich.

Erklärung zur guten wissenschaftlichen Praxis:

Ich erkläre hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten (Amtliche Mitteilung der Universität zu Köln AM 132/2020) der Universität zu Köln gelesen habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Köln, den 30.08.2024

Danksagung

An dieser Stelle möchte ich allen danken, die mir mein Studium und das Schreiben dieser Promotion ermöglichten:

Prof. Dr. med. Frank Jessen danke ich für die Möglichkeit, die Doktorarbeit in seiner Klinik anzufertigen.

Meinem Doktorvater, Prof. Dr. Joseph Kambeitz, danke ich für die herzliche Aufnahme in seine Arbeitsgruppe und die stetige Unterstützung während des Projektes.

Meiner Betreuerin, Priv.-Doz. Dr. Lana Kambeitz-Ilankovic, danke ich für die Einarbeitung in das Projekt, für ihre Geduld und ihr offenes Ohr bei all meinen Fragen. Zudem danke ich ihr für die stetige Hilfsbereitschaft und Motivation während der letzten 4 Jahre.

Dr. Julian Wenzel danke ich für die Einführung in die verwendeten Softwares und die technische Unterstützung zu jeder Tages- und Nachtzeit.

Der ganzen Arbeitsgruppe danke ich für die herzliche Aufnahme in das Team und die angenehme und familiäre Atmosphäre im Büro.

Für die Durchsicht meiner Arbeit danke ich Priv.-Doz. Dr. Lana Kambeitz-Ilankovic und Jan Hertel.

Ganz besonders danke ich meiner Familie, die mir das Studium ermöglicht hat und mich stets uneingeschränkt unterstützt. Zudem danke ich meinen Freundinnen und Freunden, die immer motivierende Worte für mich gefunden haben.

Inhaltsverzeichnis

Abkürzungsverzeichnis

ARMS	At-risk mental states
BAC	Balanced accuracy
CT	Cognitive training
CHR	Clinical high risk
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Version V
FU	Follow-up
FEP	First-episode psychosis
GF	Patients with good social functioning
GF-S	Global Functioning: Social-Scale
IA	Introspective accuracy
ICD-11	International Statistical Classification of Diseases and Related Health Problems – Version 11
IQ	Intelligence quotient
ML	Machine Learning
MRI	Magnetic resonance imaging
MVPA	Multivariate pattern analysis
OOCV	Out-of-sample-cross-validation
PF	Patients with poor social functioning
PoC	Proof-of-concept
PRONIA	Personalized Prognostic Tools for Early Psychosis Management
RCT	Randomized controlled trial
ROD	Recent Onset Depression
ROP	Recent Onset Psychosis
rsFC	Resting-state Functional Connectivity
SCT	Social cognitive training
SHG	Supplementary human guidance
SVM	Support Vector Machine
SV	Support Vector
SSD	Schizophrenia spectrum disorder
TAU	Treatment as usual

1. Zusammenfassung

Kognitive Beeinträchtigungen gehören zu den primären Symptomen bei der klinischen Präsentation psychotischer Störungen [1]. Insbesondere bei einer neu auftretenden Psychose (Recent Onset Psychosis, ROP) treten kognitive Defizite schon früh im Krankheitsverlauf auf und können verschiedene Aspekte des alltäglichen Lebens beeinträchtigen [2]. Trotz zahlreicher Jahre klinischer Forschung ist es nach wie vor eine Herausforderung, kognitive Defizite effektiv zu behandeln [3,4].

In den letzten Jahren konnte ein klarer Zusammenhang zwischen Kognition und sozialem Funktionieren bei ROP festgestellt werden. Kognitive Beeinträchtigungen sind mit einem schlechten langfristigen sozialen Funktionsniveau assoziiert [5–7], während Beeinträchtigungen der sozialen Kognition als guter prognostischer Indikator für ein schlechtes funktionelles Outcome nach einer Krankheitsepisode dienen [8].

Kognitives Training (CT) wird in klinischen Studien als eine der wichtigsten ergänzenden Therapien zur Verbesserung kognitiver Beeinträchtigungen in den Bereichen Aufmerksamkeit, Arbeitsgedächtnis, exekutive Funktion und soziale Kognition empfohlen [9–11]. Obwohl mehrere Meta-Analysen über geringe bis mäßige Auswirkungen von CT auf die Kognition berichten [9,12,13], bleibt das Therapieansprechen auf CT heterogen, was eine gezielte Behandlung anspruchsvoll macht [12,14,15].

Verfahren des maschinellen Lernens (ML) werden in der psychiatrischen Forschung zunehmend eingesetzt, um klinische Ergebnisse auf individueller Ebene vorherzusagen und zu stratifizieren [16]. Während es mehrere ML-Strategien basierend auf neuronaler Bildgebung zur Vorhersage klinischer Ergebnisse gibt, ist die Evidenz für kognitionsbasierte ML-Vorhersagen bei Psychosen begrenzt. Wir haben eine multivariate Musteranalyse (multivariate pattern analysis, MVPA) verwendet, um zu untersuchen, ob Veränderungen der sozialen Funktionsfähigkeit nach 10 Stunden CT innerhalb von 4-6 Wochen bei ROP-Patientinnen und -Patienten basierend auf kognitiven Daten vorhergesagt werden können.

Ein Support Vector Machine (SVM)-Klassifikator wurde auf den kognitiven Daten von 70 ROP-Patientinnen und -Patienten der PRONIA-Studienstichprobe (Personalized Prognostic Tools for Early Psychosis Management) trainiert, um das soziale Funktionieren in einer unabhängigen Stichprobe vorherzusagen. Die soziale Funktionsfähigkeit konnte dabei von unserem Klassifikationsmodell mit einer ausgewogenen Genauigkeit (balanced accuracy, BAC) von 66,4% vorhergesagt werden. Anschließend wurde der ursprüngliche SVM-Klassifikator auf eine Interventionsstichprobe angewendet, die 54 ROP-Patientinnen und -Patienten umfasste. Die Teilnehmerinnen und Teilnehmer der Interventionsstichprobe wurden nach dem Zufallsprinzip einer Gruppe für soziales kognitives Training (SCT) oder einer Gruppe für die übliche Behandlung (treatment as usual, TAU) zugewiesen und anhand ihres Global

Functioning-Social (GF-S) -Scores zum Zeitpunkt der Nachuntersuchung (follow-up, FU) in gut (GF-S ≥7) und schlecht (GF-S <7) funktionierende Patientinnen und Patienten eingeteilt. Mittels out-of-sample-cross-validation (OOCV) wurde das soziale Funktionsniveau in der Interventionsstichprobe mit einer BAC von 59,3% zum Zeitpunkt des Studieneinschlusses (T0) und mit einer BAC von 64,8% zum Zeitpunkt des FU 6 Wochen nach der Intervention vorhergesagt. Nach der SCT-Intervention wurde eine signifikante Verbesserung der vorhergesagten Werte für die soziale Funktionsfähigkeit in der SCT-Gruppe im Vergleich zur TAU-Gruppe beobachtet (*P* = <0,05; ES[Cohens'd] = 0,18).

Diese Ergebnisse deuten darauf hin, dass die Verwendung von kognitiven Ausgangsdaten eine robuste individuelle Schätzung der künftigen sozialen Funktionsfähigkeit und des Therapieansprechens auf CT liefern könnte. Aufgrund des geringen Stichprobenumfangs sowie geringer kognitiver und funktioneller Gewinne durch CT innerhalb der Interventionsstichprobe war es in der aktuellen Studie nicht möglich, Charakteristika für ein positives individuelles Ansprechen auf die SCT-Intervention vorherzusagen. Größer angelegte Studien sind notwendig, um unsere Ergebnisse in einer Stichprobe mit höherer kognitiver und funktioneller Variabilität zu replizieren und das kognitive Muster, welches prädiktiv für ein positives Therapieansprechen auf CT ist, näher zu untersuchen.

2. Summary

Cognitive impairments are among the primary symptoms in the clinical presentation of psychotic disorders [1]. Especially in Recent Onset Psychosis (ROP), cognitive deficits emerge early in the course of the disease and adversely affect several aspects of everyday life [2]. Despite numerous years of clinical research, addressing them effectively remains challenging [3,4].

In recent years, a clear link has been established between cognition and social functioning in ROP. Cognitive impairments are associated with poor long-term social functioning [5–7], while impairments in social cognition serve as a good prognostic indicator of poor functional outcome post-episodic [8].

Cognitive training (CT) is recommended in clinical guidelines as one of the most significant complementary therapies for enhancing cognitive impairments in the domains of attention, working memory, executive functioning, and social cognition [9–11]. Although several meta-analyses reported small to moderate effects of CT on cognition [9,12,13], the therapy response to CT remains heterogeneous, making targeted treatment demanding [12,14,15].

Machine learning (ML) techniques are increasingly used in psychiatric research to predict and stratify clinical outcomes at an individual level [16]. While there are several neuroimaging-based ML studies for predicting clinical outcomes, the evidence regarding cognition-based ML predictions in psychosis is limited. We used multivariate pattern analysis (MVPA) to examine whether cognitive data can predict the enhancement of social functioning following 10 hours of CT in ROP patients.

A Support Vector Machine (SVM) classifier was trained on cognitive baseline data of 70 ROP patients of the naturalistic Personalized Prognostic Tools for Early Psychosis Management (PRONIA) study sample to predict social functioning in an independent sample. Within this original classification model, social functioning was predicted with a balanced accuracy (BAC) of 66.4%. Next, the SVM classifier was applied to an intervention sample that obtained 54 ROP patients. Participants of the intervention sample were randomly assigned to a social cognitive training (SCT) or treatment as usual (TAU) group and dichotomized into good (GF-S ≥7) and poor (GF-S <7) functioning patients based on their level of Global Functioning-Social (GF-S) score at follow-up (FU). By using out-of-sample cross-validation (OOCV), social functioning in the intervention sample was predicted with a BAC of 59.3% at baseline (T0) and with a BAC of 64.8% at FU 6 weeks after the intervention. After SCT intervention, a significant improvement in predicted social functioning values was observed in the SCT compared to TAU group (P = <0.05; ES[Cohens'd] = 0.18).

These findings suggest that the use of baseline cognitive data could provide a robust individual estimate of future social functioning and therapy response to CT. Due to a small

sample size and modest cognitive and functional variability in response to CT within the intervention sample, it was not feasible to analyze individual characteristics predictive of a good therapy response in the current study. Large-scale studies with participants showing greater cognitive and functional variability in response to CT are needed to replicate our results and to further analyze the cognitive pattern predictive of a good therapy response to CT.

3. Introduction

Over the past few decades, psychotic disorders have come under increasing social and medical scrutiny. During this time, not only the understanding of psychotic illnesses but also their therapy approaches have constantly changed. While psychotic syndromes were diagnosed based on the presence of positive and negative symptoms for many years, the presence of cognitive and functional impairments in psychotic illnesses is now widely acknowledged [1]. Some authors even suggest that psychosis is in fact a cognitive illness [17]. The most recent versions of current classification systems, such as the Diagnostic and Statistical Manual of Mental Disorders – Version V (DSM-V) or the International Statistical Classification of Diseases and Related Health Problems – Version 11 (ICD-11), have expanded the diagnostic criteria for psychotic disorders to include the dimension of cognitive impairment [18].

Recognizing cognitive deficits as an unavoidable component of psychotic illnesses also meant that therapeutic approaches have to be adapted. While positive and negative symptoms usually respond well to antipsychotic medication, cognitive and functional impairments remain almost untapped by it [19,20]. In turn, cognitive impairment is associated with poor functional outcomes, which can include daily, social, and role functioning [21]. For this reason, cognitive training (CT) has been recommended in a recent review on remediation in first-episode psychosis (FEP) [22] as a promising complementary therapy, as it leads to improvements in multiple cognitive domains [9–11]. Despite good evidence, the therapeutic response to CT in Recent Onset Psychosis (ROP) is heterogeneous and it remains unclear which factors positively influence a good therapeutic response.

Machine learning (ML) approaches are increasingly used in psychiatric research as they are particularly well suited to predict and stratify clinical outcomes [23,24]. Therefore, they promise future clinical applicability at the single subject level in order to disentangle the treatment response to CT in ROP.

3.1. Recent Onset Psychosis

ROP refers to first episodes or early stages of psychosis in which symptoms typical of psychotic illnesses occur [25]. Although the manifestation of psychosis can occur at any age, it mostly affects people in late adolescence or young adulthood, with a mean age in the early twenties [26]. Symptoms of psychosis, including ROP, consist of positive symptoms such as hallucinations, delusions, and disordered thinking, and negative symptoms such as social withdrawal, blunted affect, poverty of speech, and cognitive impairment [18,27]. Rapid initiation of antipsychotic pharmacological treatment in FEP is indicated as early initiation of treatment is associated with a better prognosis and possibly lower antipsychotic dose required to treat as compared to a long duration of untreated psychosis [28]. Further, early antipsychotic treatment can shorten psychotic episodes, reduce the frequency of recurrences, and limit the progressive decline of cognitive and functional capacity [29].

Although antipsychotic drugs have proven to be highly effective, they are associated with a wide number of side effects that can cause significant distress for those affected [30]. Patients with ROP are marginally affected by antipsychotic medication and their side effects due to the short duration of treatment. In contrast, a prolonged course of antipsychotic medication may result in distortions [31,32]. By using a sample of ROP patients in this study, we minimized the possible bias that can be caused by these distortions.

3.1.1. Role of cognition and social functioning in Recent Onset Psychosis

Upon the initial diagnosis of psychosis, the cognitive function is already significantly impaired in the majority of those affected [33–35]. Studies even suggest that mild cognitive impairment in individuals who develop schizophrenia or related disorders is already present during early childhood [36]. Impairments have been reported in the cognitive domains of attention, verbal memory, processing speed, working memory, and executive functioning [35]. They are associated with worsening of negative symptoms [37] and poor social functioning [5–7], whereas impairments in the cognitive domains of working memory [38] and social cognition [39] are particularly associated with poor future social functioning. Vice versa, preserved cognitive function is strongly associated with clinical improvements in FEP [40].

Within ROP patients, two neurocognitive subtypes presenting with disparate levels of cognitive impairment have recently been identified: a cognitively impaired cluster and a cognitively spared cluster [41]. Both subtypes show significant impairments in the cognitive domains of attention and verbal memory when compared to healthy controls (HC), underlining the impact of psychotic illnesses on cognition even at the early stages of the disease. With regard to functional outcomes, impairments in social-, occupational- and role functioning have

been shown to be more severe in the cognitively impaired cluster than in the cognitively spared cluster.

The evidence regarding the course of cognitive impairments in ROP is inconsistent across studies, rendering a definitive conclusion challenging. While some research findings indicate no cognitive decline in patients who show a clinically high risk (CHR) for psychosis [35], others suggest that cognitive decline occurs primarily between the prodromal phase and the first psychotic episode [36]. Findings regarding the trajectory of cognition during the first decade after the initial psychotic episode are likewise conflicting, with some studies reporting cognitive stability [42,43] or improvement [44], while others observe declines in specific cognitive domains [45]. Evidence across studies suggests a correlation between deficits in cognitive domains and the presence and severity of psychotic symptoms [42,46]. Further, the extent and timing of cognitive impairments and declines seem to differ between the cognitive domains [36].

Social functioning deficits at the onset of psychosis include strained relationships, social isolation, homelessness, and substance use, among others [7,47–49]. Just like cognitive deficits, deficits in social functioning are associated with a worsening of psychotic symptoms. [8,50]. There are several factors predictive of future social functioning: while a poor premorbid outcome is predictive of a poor outcome after illness onset [7], better premorbid functioning is predictive of a better outcome post-psychosis [51]. Further, a young age of illness onset and a high socioeconomic status also favor better social functional outcomes [52]. With regard to cognition, impairments in the cognitive domain of social cognition have been identified as a good prognostic indicator of poor social functional outcome [8].

In comparison to cognitive trajectories, social functioning trajectories in ROP are relatively stable, with four distinct trajectories identified over periods ranging from one year [53] to two decades [7] after psychosis onset.

Although beneficial effects of antipsychotic medication on cognitive domains have been described [27,32], drug treatment alone is not a viable option for significantly improving cognition in individuals with ROP [2,20]. Moreover, cognitive impairment can persist beyond the presence of positive and negative symptoms [41]. Therefore, preserving and improving cognition through the implementation of supplementary therapies in ROP is crucial in order to alleviate the burden of psychotic symptoms and functional impairments caused by cognitive deficits.

3.2. Cognitive Training

CT has been used increasingly in recent years as one of the main supplementary therapies to ameliorate cognitive deficits in psychotic disorders [10,11]. The primary focus of cognitive remediation is enhancing cognitive function to facilitate improvements in daily functioning [21]. According to the Cognitive Remediation Experts Workshop held in Florence, Italy, in April 2010, cognitive remediation is defined as a "behavioral training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization" [9]. To achieve this, specifically designed and behaviorally constrained cognitive or socio-affective learning events that improve neural system operations are delivered to the patients [52]. The training modalities differ between paper-and-pencil, computerized, or human-guided training and can be tailored to the individual patient [12,52].

The average duration of CT was shown to amount to 34.9 hours over the period of 13.2 weeks [54] and to target an average of 2.9 cognitive domains [55]. Although training modalities, duration, and targets may vary significantly, the overall evidence supporting the positive effects of CT on cognition and social functioning is well established.

3.2.1. Effects of cognitive training on cognition and social functioning

Several meta-analyses report small to moderate effects of CT in the cognitive domains of attention, working memory, executive functioning, and social cognition: in a meta-analysis examining 26 randomized controlled trials (RCTs) on CT in schizophrenia, the largest effects were observed in the cognitive domains of verbal working memory and social cognition [55]. A more recent meta-analysis comparing 40 RCTs on CT in schizophrenia yielded very similar results: significant improvements were evident in all cognitive domains except in the domain of visual learning and memory. The largest effects were observed in the domains of problem-solving and social cognition [9]. In a 2019 meta-analysis comprising 67 RCTs, the overall effect sizes reflecting the training effects of CT on cognitive domains in schizophrenia were smaller, but significant improvements were observed in all cognitive domains except in the domain of visual memory. The largest effects were observed in the domain of working memory [12]. In all three meta-analyses, the effects of CT on cognition were more pronounced when combined with psychiatric rehabilitation or supplementary human guidance (SHG).

In terms of the durability of cognitive improvements, evidence suggests that CT is able to reduce cognitive deficits with long-term benefits in schizophrenia [10]. In a 1-year follow-up (FU) study, long-term improvements were found in 8 out of 10 cognitive domains. No overtime improvements were observed in the cognitive domains of verbal memory and executive

functioning [56]. However, the evidence for longer-term effects beyond one year remains insufficient.

Just as with the effects of CT on cognition, the evidence surrounding the effects of CT on functional outcomes is extensive, although it is more abstract in nature. The positive impact of CT on functional outcomes can be explained by two different hypotheses: it is possible that improved cognition directly leads to better functional outcomes [8,57–59]. Alternatively, the reduction of negative symptoms in response to CT may mediate this relationship [60,61].

Nevertheless, there is evidence to suggest that this approach is effective. In a meta-analysis from 2021 based on 75 RCTs examining the effects of CT on cognitive and functional outcomes, small effects on functional outcomes were observed [54]. In line with these results, another 2021 meta-analysis comparing 130 studies showed small effects of CT on global functioning [62]. Further, the authors observed bigger effect sizes when CT interventions included active, trained therapists. For the specific outcome of social functioning, a meta-analysis of 67 RCTs indicated small effects of CT on social functioning in schizophrenia [12]. While the impact of CT on functional outcomes is less pronounced than on cognitive outcomes, the existing evidence is nevertheless substantial and robust.

The administration of therapeutic intervention, particularly with antipsychotic medication and CT, has been demonstrated to improve functional outcomes at a short--, medium-, and long course [10]. With regard to social functioning, a RCT from 2019 demonstrated that the intervention group receiving CT exhibited improvements in social and daily functioning that were sustained for up to one year following the intervention [63]. The efficacy of the treatment was greatest when initiated in the early stages of the disease [64].

3.2.2. Therapy response to cognitive training

Despite the broad evidence of the beneficial effects of CT interventions on cognitive and functional outcomes on a group-based level, the therapy response to CT at an individual level is heterogeneous.

The authors of a recent review discovered that approximately 44% of participants who undergo CT fail to achieve cognitive benefits [15]. Such variability in therapy response could potentially weaken the efficacy of CT interventions in real-world settings. Understanding the positive and negative factors that impact the response to CT at an individual level would be of great help in developing individualized therapy approaches.

Markers for successful treatment response to CT have been proposed previously on a group-based level. They include age, pretreatment cognitive function, motivation, therapeutic alliance, and measures of brain reserve [65–68]. It has recently been observed that cognitive impairment can serve as well as a prognostic marker in FEP predicting clinical outcomes [69].

Unfortunately, knowledge of these predictive markers alone does not facilitate the identification of those who will respond to CT at the individual patient level. Standardized assessments of predictive markers that are easy to acquire in everyday clinical practice could help identify those who may benefit from CT interventions. ML techniques are a promising and increasingly used approach as they are particularly well suited to predict and stratify clinical outcomes and therefore promise future clinical applicability at the single-subject level [70].

3.3. Machine Learning

ML is a computational approach characterized by the automatic determination of optimal problem-solving methods, as opposed to explicit human programming for predefined solutions [4]. Situated within the broader domain of artificial intelligence (AI), ML replicates aspects of human intelligence through its learning processes, facilitating ostensibly intelligent applications. ML methods, functioning algorithmically, seek to discern general principles governing observed phenomena without reliance on explicit instructions [71].

Originally, ML techniques have been developed to establish predictive associations between observed data features and variables of interest [72]. In the realm of healthcare, ML approaches have been shown to perform as well or even better than clinicians at tasks involving pattern recognition in images, such as detecting skin cancer, lung cancer, and eye disease [4]. In recent years, ML techniques have been employed with increasing frequency to identify intricate patterns within expansive and heterogeneous data sets, often outperforming human clinicians. In psychiatry, excellent results have been achieved using ML approaches to classify diseases or predict clinical outcomes.

ML techniques include supervised methods, such as Support Vector Machines (SVM) specialized for best-possible outcome prediction; and unsupervised methods, such as algorithms for data clustering and dimensionality reduction, effective at discovering unknown statistical configurations in data [71].

3.3.1. Support Vector Machines

The SVM is a multivariate, supervised learning method for classifying individuals using a margin-based framework [73]. Cases are represented in a two-dimensional space to establish a linear boundary, or hyperplane, that efficiently classifies existing known cases and generalizes them to future, unknown cases. Support Vectors (SVs) are those cases located closest to the external borders of the distributions. SVs define a margin to optimize the distance between the margins and the hyperplane for optimal classification accuracy [4].

To provide predictive models that are generalizable to unknown patients, volumes of large and complex measurements including clinical, sociodemographic, environmental, or molecular data are needed. This so-called “big data” is processed and identified through pattern recognition, enabling predictions and stratification of clinical outcomes at the single-subject level [16]. During data processing, all variables are categorized into features, which are then presented in a numerical matrix that can be understood by the algorithm [74]. After organizing a dataset into features, an SVM algorithm can be iteratively applied to it to reduce prediction errors through iterations.

In clinical practice, SVM classification algorithms are preferably used to categorize outcomes such as disease transition or therapy response. Currently, classification models based on neuroanatomical, clinical, sociodemographic, and also cognitive data have shown good results in identifying markers that influence a good therapy response [14,75].

3.3.2. Examples

In the following, recent ML studies are presented in order to provide examples of the utility of ML algorithms in predicting clinical outcomes in psychosis at the single-subject level.

The first example is a naturalistic, multisite study from 2018 called PRONIA (Personalized Prognostic Tools for Early Psychosis Management) [76]. The study aimed to predict the disease onset in patients with CHR status for depression and psychosis as well as to predict functional outcomes in patients with Recent Onset Depression (ROD) and ROP. ML prediction models were built based on clinical data, including sociodemographic, somatic, environmental, diagnostic, psychopathological, functional, and quality-of-life related data, and neuroimaging data based on magnetic resonance imaging (MRI) measures. Models that integrated both clinical and neuroanatomical data achieved the highest predictive accuracy for social functional outcomes, with balanced accuracies (BACs) of up to 82.7%. These models outperformed human clinical raters, indicating the potential of ML to enhance prognostic accuracy beyond current clinical assessments.

In the context of ML studies predicting the therapy response to CT in patients with psychosis, two recent studies have yielded promising results:

In a proof-of-concept (PoC) study from 2020 [14], Haas et al. investigated the potential of resting-state Functional Connectivity (rsFC) measures to predict the therapy response to CT in an intervention sample of 26 ROP patients using multivariate pattern analysis (MVPA). Accordingly, ROP patients were divided into maintainers and improvers based on individual changes in sensory processing throughout CT. An initial classification model was built in an independent sample to differentiate between ROP patients and HC based on MRI-acquired rsFC measures. Subsequently, the classifier was applied to the CT-intervention sample to evaluate associations between rsFC pattern changes, changes in sensory processing, and cognitive gains, revealing that alterations in rsFC to a more healthy-like pattern correlated with attentional gains in improvers. Moreover, improvements in attention were associated with better general functioning.

In another neuroimaging-based MVPA from 2021 [75], Kambeitz-Ilankovic et al. predicted global functioning following 40 hours of CT based on gray matter patterns in patients with schizophrenia. The SVM classifier predicted higher vs. lower global functioning after CT intervention with a BAC of 69.4%. In particular, greater baseline gray matter volumes in specific

brain regions predicted improved functioning at the single-subject level following CT in patients with schizophrenia, providing a neuroanatomical fingerprint predictive of a good therapy response.

While the aforementioned examples elucidate the utility of neuroanatomical measures for the prediction of therapy response in patients with psychotic disorders, the evidence for cognition-based ML prediction models is limited. There are several arguments in favor of employing cognitive data to predict functional outcomes: cognitive features are easy to acquire, show a high availability and applicability in everyday clinical practice [1], and exhibit high inter-rater reliability [8]. The evidence for the association between cognitive impairments and functional outcomes is broad and well-established [69,77,78]. In addition, cognitive data has proven to be an effective target for ML prediction models:

In 2012, Koutsouleris et al. [24] performed an ML analysis using MVPA to predict the disease transition in patients of different at-risk mental states (ARMS) for psychosis based on neurocognitive data comprising a test battery of 9 neurocognitive tests. This classification model was able to discriminate converters from non-converters to frank psychosis over the course of 4 years with a BAC of 77.5%. The discriminative neurocognitive pattern primarily involved premorbid verbal intelligence quotient (IQ), executive functions, and verbal learning abilities.

In a recent ML study from 2022 [79], Squarcina et al. predicted functional outcome measures based on cognitive baseline data in a sample of patients with CHR for psychosis and ROD. Both global functioning and role functioning could be predicted successfully.

These findings suggest that individual predictions can be achieved based on cognitive data. However, there is still a lack of robust evidence that could provide translation to everyday clinical practice.

3.4. Research question and objectives

CT provides an effective therapeutic approach to ameliorate cognitive deficits and impairments in social functioning in patients with ROP. However, the response to CT is heterogeneous, and the factors influencing a positive therapeutic response at the individual level remain unclear. ML studies have demonstrated promising results with models based on neuroanatomical and clinical data in identifying markers that influence the therapy response to CT. Cognitive data could be a suitable candidate for predicting the therapy response to CT at the single-subject level, as it exhibits good inter-rater reliability, is easy to acquire, and shows high availability and applicability in everyday clinical practice.

In this PoC study, we tried to monitor changes in social functioning following CT in order to define a cognitive pattern predictive of a good therapy response to CT. Finding a cognitive pattern predictive of a good therapy response could help to identify those who benefit from cognitive remediation at the single-subject level.

To achieve this, we conducted a CT study with a sample of 54 ROP patients. Participants were randomly assigned to either an active training group (n=27) undergoing social cognitive training (SCT) or a control group (n=27) receiving treatment as usual (TAU). Standardized clinical assessments and neurocognitive tests were conducted at the study baseline (T0) and after 6 weeks at FU. Using a test battery comprising 9 cognitive tests, a total of 73 cognitive features were extracted for further analysis.

Participants were categorized into patients with good social functioning (GF) and patients with poor social functioning (PF) based on their social functioning levels at FU. The aim of the study was to predict future social functioning at an individual level based on baseline cognitive data.

An ML classification model was developed using cognitive baseline data from 70 ROP patients from the naturalistic PRONIA study. Both the PRONIA study and the CT intervention study did not differ in terms of inclusion criteria or clinical and cognitive assessments. The resulting model served as the original classification model for classifying ROP patients into GF and PF.

Subsequently, we applied this classification model to the participants in the intervention study, assuming that the level of social functioning would be higher in the SCT participants than in the TAU control group. By applying the classification model to the intervention sample, we aimed to test the generalizability of our initial model and to establish a benchmark model for predicting functional outcomes in a naturalistic sample, capable of measuring the development of social functioning following CT in the intervention group using ML.

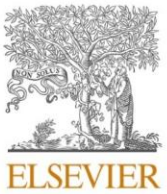
In the final step, we examined the cognitive patterns predictive of a good functional outcome at FU. This exploration aimed to identify cognitive patterns or markers that favorably influence a positive therapeutic response at an individual level.

4. Publication

Underlying reference of this dissertation (see below):

Walter, Nina; Wenzel, Julian; Haas, Shalaila S.; Squarcina, Letizia; Bonivento, Carolina; Ruef, Anne et al. (2023): A multivariate cognitive approach to predict social functioning in recent onset psychosis in response to computerized cognitive training. In: Progress in neuro-psychopharmacology & biological psychiatry, S. 110864. DOI: 10.1016/j.pnpbp.2023.110864. Reprinted with the publisher's permission.

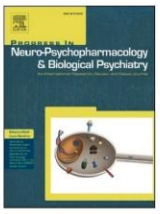
Progress in Neuropsychopharmacology & Biological Psychiatry 128 (2024) 110864



Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



A multivariate cognitive approach to predict social functioning in recent onset psychosis in response to computerized cognitive training

Nina Walter [a], Julian Wenzel [a], Shalaila S. Haas [b], Letizia Squarcina [c], Carolina Bonivento [c], Anne Ruef [d], Dominic Dwyer [d,e,j], Theresa Lichtenstein [a], Öznur Bastrük [a], Alexandra Stainton [e,j], Linda A. Antonucci [f], Paolo Brambilla [g,h], Stephen J. Wood [e,i,j], Rachel Upthegrove [i,k], Stefan Borgwardt [l], Rebekka Lencer [l], Eva Meisenzahl [m], Raimo K.R. Salokangas [n], Christos Pantelis [o], Alessandro Bertolino [f], Nikolaos Koutsouleris [d,p,q], Joseph Kambeitz [a], Lana Kambeitz-Ilankovic [a,r,*], the PRONIA consortium

[a] Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital, University of Cologne, Kerpenerstr.62, 50931, Cologne, Germany
[b] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, NY, New York, United States of America
[c] Scientific Institute, IRCCS E. Medea, Pasian di Prato, Udine, Italy
[d] Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University, Munich, Germany
[e] Orygen Youth Health, Melbourne, Australia
[f] Department of Translational Biomedicine and Neuroscience, University of Bari Aldo Moro, Bari, Italy
[g] Department of Neuosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[h] Department of Pathophysiology and Mental Health, University of Milan, Milan, Italy
[i] School of Psychology, University of Birmingham, United Kingdom
[j] Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia
[k] Institute of Mental Health, University of Birmingham, Birmingham, United Kingdom
[l] Translational Psychiatry Unit (TPU), Department of Psychiatry and Psychotherapy, University of Luebeck, Germany
[m] Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany
[n] Department of Psychiatry, University of Turku, Turku, Finland
[o] Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne & NorthWestern Mental Health, Melbourne, Australia
[p] Max Planck Institute for Psychiatry, Munich, Germany
[q] Institute of Psychiatry, Psychology & Neuroscience, Department of Psychosis Studies, King's College London, London, United Kingdom
[r] Faculty of Psychology and Educational Sciences, Department of Psychology, Ludwig-Maximilian University, Munich, Germany

ARTICLE INFO

Keywords:
Social functioning
Recent onset psychosis
Social cognitive training
Machine learning
Treatment response

ABSTRACT

Clinical and neuroimaging data has been increasingly used in recent years to disentangle heterogeneity of treatment response to cognitive training (CT) and predict which individuals may achieve the highest benefits. CT has small to medium effects on improving cognitive and social functioning in recent onset psychosis (ROP) patients, who show the most profound cognitive and social functioning deficits among psychiatric patients. We employed multivariate pattern analysis (MVPA) to investigate the potential of cognitive data to predict social functioning improvement in response to 10 h of CT in patients with ROP. A support vector machine (SVM) classifier was trained on the naturalistic data of the Personalized Prognostic Tools for Early Psychosis Management (PRONIA) study sample to predict functioning in an independent sample of 70 ROP patients using baseline cognitive data. PRONIA is a part of a FP7 EU grant program that involved 7 sites across 5 European countries, designed and conducted with the main aim of identifying (bio)markers associated with an enhanced risk of developing psychosis in order to improve early detection and prognosis. Social functioning was predicted with a balanced accuracy (BAC) of 66.4% (Sensitivity 78.8%; Specificity 54.1%; PPV 60.5%; NPV 74.1%; AUC 0.64; $P = 0.01$). The most frequently selected cognitive features (mean feature weights $> \pm 0.2$) included the (1) correct number of symbol matchings within the Digit Symbol Substitution Test, (2) the number of distracting stimuli leading to an error within 300 and 200 trials in the Continuous Performance Test and (3) the dynamics of verbal fluency between 15 and 30 s within the Verbal Fluency Test, phonetic part. Next, the SVM classifier

* Corresponding author at: Department of Psychiatry and Psychotherapy, University Hospital Cologne, Kerpener Str. 62, 50937 Cologne, Germany.
E-mail address: lana.kambeitz-ilankovic@uk-koeln.de (L. Kambeitz-Ilankovic).

https://doi.org/10.1016/j.pnpbp.2023.110864
Received 9 May 2023; Received in revised form 1 August 2023; Accepted 13 September 2023
Available online 17 September 2023

generated on the PRONIA sample was applied to the intervention sample, that obtained 54 ROP patients who were randomly assigned to a social cognitive training (SCT) or treatment as usual (TAU) group and dichotomized into good (GF-S $\geq$ 7) and poor (GF-S $<$ 7) functioning patients based on their level of Global Functioning-Social (GF-S) score at follow-up (FU). By applying the initial PRONIA classifier, using out-of-sample cross-validation (OOCV) to the sample of ROP patients who have undergone the CT intervention, a BAC of 59.3% (Sensitivity 70.4%; Specificity 48.1%; PPV 57.6%; NPV 61.9%; AUC 0.63) was achieved at T0 and a BAC of 64.8% (Sensitivity 66.7%; Specificity 63.0%; PPV 64.3%; NPV 65.4%; AUC 0.66) at FU. After SCT intervention, a significant improvement in predicted social functioning values was observed in the SCT compared to TAU group ($P \leq 0.05$; ES[Cohens' d] = 0.18). Due to a small sample size and modest variance of social functioning of the intervention sample it was not feasible to predict individual response to SCT in the current study. Our findings suggest that the use of baseline cognitive data could provide a robust individual estimate of future social functioning, while prediction of individual response to SCT using cognitive data that can be generated in the routine patient care remains to be addressed in large-scale cognitive training trials.

1. Introduction

Cognitive impairments commonly accompany the clinical manifestation of psychotic disorders (Sheffield et al., 2018). However, despite years of clinical research, these impairments are often targeted inefficiently (Harvey et al., 2022). Studies have shown that cognitive impairments are in general associated with poor social long-term functioning (Green et al., 2004; Cassetta and Goghari, 2016; Velthorst et al., 2017) and worsening of negative symptoms (Fett et al., 2020), while impairments in social cognition serve as a good prognostic indicator of poor outcome (Fett et al., 2011). Cognitive Training (CT) is recommended by clinical guidelines as one of the main supplementary therapies to ameliorate cognitive deficits in schizophrenia (Wykes et al., 2011; Barlati et al., 2013; Bellani et al., 2019) and it is considered to be particularly effective if implemented in the early course of the disorder (Bellani et al., 2019; Rocha et al., 2020; Bowie et al., 2014). Previous meta-analyses report small to moderate effects of CT in the cognitive domains of attention, working memory, executive functioning and social cognition (Wykes et al., 2011; Kambeitz-Ilankovic et al., 2019; Harvey et al., 2018). In addition to improvements in cognitive domains, two recent large-scale meta-analyses found small to moderate effects of CT on global functioning (Vita et al., 2021) and psychosocial functioning (Lejeune et al., 2021) in patients with schizophrenia, strengthening the evidence for CT to improve cognitive and functional deficits in patients with psychotic disorders. Significant improvements in social and daily functioning show durability of up to 1 year after CT-intervention alongside significant improvements observed in several cognitive domains (Katsumi et al., 2019).

Social CT has been confirmed as effective for improvement of several social-cognitive outcomes, including social cognition and social functioning (Tang et al., 2022; Tan et al., 2018; Nahum et al., 2021; Kurtz and Richardson, 2012). It has been suggested to produce greater benefits in neurocognition relative to classical CT, targeting only working memory(Lindenmayer et al., 2018). While group-level evidence of CT efficacy is robust and well-replicated, the effects at the individual level remain a challenge to predict (Kambeitz-Ilankovic et al., 2019; Biagianti et al., 2021; Haas et al., 2020). Machine learning (ML) approaches are increasingly used in psychiatric research as they are particularly well suited to predict and stratify clinical outcomes and therefore promise future clinical applicability at the single-subject level (Ophey et al., 2022; Koutsouleris et al., 2012). In the European multisite study PRONIA (Prognostic Tools for Psychosis Management), social functioning in patients with clinical high risk (CHR) for psychosis was predicted with a balanced accuracy (BAC) of 82.7% by combining neuroimaging and clinical data (Koutsouleris et al., 2018). These models outperformed human clinical raters, suggesting that prognostic improvements beyond current clinical routine may be possible if validated and generalizable ML models are available in the future (Koutsouleris et al., 2018).

In a recent study using ML to predict response to CT in first episode psychosis patients, we showed that in Recent Onset Psychosis (ROP) patients with intact social sensory processing and more healthy-like Resting-State Functional Connectivity (rsFC) patterns, attention significantly improves after 10 h of CT (Haas et al., 2020). Additionally, the improvement in attention was associated with better general functioning of patients. Following the same approach, a recent ML study identified neuroanatomical patterns at baseline indicative of poor or good general functioning at follow-up (FU) in patients with chronic schizophrenia following CT (Kambeitz-Ilankovic et al., 2021). The subgroup of good functioning patients showed cognitive gains in verbal learning and working memory as compared to poor functioning patients.

These proof- of -concept studies suggest that identification of patients who will benefit from CT at a single-subject level might be possible, and highlight the use of ML techniques for individual predictions (MacEachern and Forkert, 2021; Bzdok and Meyer-Lindenberg, 2018). While several neuroimaging-based ML approaches for predicting clinical outcomes are available in the research literature, the evidence regarding cognition-based ML predictions in psychosis is limited. Cognitive features are easy to acquire and show a high applicability and availability in real-world clinical scenarios (Sheffield et al., 2018). Moreover, cognitive impairment is relatively stable over time, present before illness onset (Fett et al., 2011) and associated with functional outcome (Hedges et al., 2022; Lindgren et al., 2020; Stouten et al., 2014). Furthermore, social and functional level of patients with psychosis is commonly a primary or secondary outcome in randomized clinical trials (RCT) and has been suggested to improve through CT intervention with small to medium effect sizes (Halverson et al., 2019). The study of Squarcina et al. that recently used an ML approach to predict role functioning in patients with CHR for psychosis and Recent Onset Depression (ROD) with a BAC of 61% (Squarcina et al., 2022), shows that predictions can be achieved using only cognitive measures. However, there is still a lack of robust evidence for individualized prediction that could provide translation to everyday clinical practice.

The aim of the current study was to develop a benchmark model using cognitive data at baseline to predict social functioning at FU and in the next step to test its generalisability in predicting future social functioning in response to CT intervention in ROP patients. We followed the assumption that social functioning predicted by cognitive performance will be higher in ROP that receive social cognitive training (SCT) as compared to treatment as usual (TAU).

2. Methods

2.1. Sample

A sample of 70 ROP patients of the European multicenter PRONIA study (Koutsouleris et al., 2018) recruited from five different study sites (supplementary information, Section 1.1) was used to generate a prognostic support vector machine (SVM) classification model that could later classify patients with good social functioning (GF) from patients with poor social functioning (PF) (Table 1).

The level of future social functioning was defined based on the individual score at FU, 3 months after study inclusion, on the Global

Table 1
Baseline demographic and clinical characteristics for ROP patients in the PRONIA sample and in the CT intervention sample.

	PRONIA sample ($n = 70$)	Intervention sample ($n = 54$)	T / X^2	P-value
Number of female (%)	20 (29%)	22 (41%)	1.51	0.22
Age (mean(sd))	25.09 (5.45)	26.16 (6.16)	1.02	0.31
Years of Education[a] (mean(sd))	14.01 (3.32)	14.31 (3.59)	0.48	0.63
Medication dosage[b] (mean(sd))	423.02 (1206.17)	68.53 (87.82)	−2.91	0.005*
PANSS[a] (mean(sd))				
Total	70.19 (19.58)	67.91 (17.01)	−0.69	0.49
Positive	17.97 (6.20)	20.04 (5.22)	2.00	0.05*
Negative	16.46 (7.48)	14.57 (6.10)	−1.54	0.13
General	35.76 (9.70)	33.30 (10.10)	−1.36	0.18
GF-S current (mean (sd))	5.64 (1.40)	5.85 (1.39)	0.83	0.41

PANSS (= Positive and Negative Syndrome Scale), GF-S (= Global Functioning – Social).

[a] Three participants of the intervention sample did not provide total years of education at baseline and for 1 participant of the intervention sample PANSS was not assessed.

[b] Medication dosage is calculated from the cumulative sum of chlorpromazine equivalent divided by number of days treated.

Table 2
Demographic and clinical variables at baseline in CT intervention sample.

	SCT group (n = 27)	TAU group (n = 27)	T / X^2	P-value
Number of female (%)	11 (41%)	11 (41%)	0	1
Age (mean(sd))	26.77 (6.03)	25.58 (6.17)	−0.70	0.49
Years of Education[a] (mean (sd))	15.24 (3.75)	13.42 (3.26)	−1.84	0.07
Medication dosage[b] (mean (sd))	65.91 (72.81)	71.14 (102.01)	0.22	0.83
PANSS[a] (mean(sd))				
Total	66.96 (15.91)	68.88 (18.35)	0.41	0.69
Positive	18.96 (5.69)	21.15 (4.51)	1.56	0.13
Negative	14.48 (5.61)	14.65 (6.67)	0.10	0.92
General	33.52 (8.86)	33.08 (11.43)	−0.16	0.88
GF-S current (mean(sd))	5.96 (1.13)	5.74 (1.63)	−0.58	0.56

PANSS (= Positive and Negative Syndrome Scale), GF-S (= Global Functioning – Social).

[a] Two participants of the SCT group and 1 participant of the TAU group did not provide total years of education at baseline and for 1 participant of the TAU group PANSS was not assessed.

Functioning: Social (GF-S) (Carrión et al., 2019) Scale. The classification model was built based on the naturalistic PRONIA sample to provide a benchmark model for prediction of social functioning based on cognitive baseline data. To validate the obtained model and to investigate whether the model is able to monitor individual social functioning in patients who have received intervention, an intervention sample of 54 ROP patients undergoing CT independent from the PRONIA cohort was used (Table 1; supplementary information, Section 1.1). Participants of both samples were therefore dichotomized by using median split into GF (GF-S $\geq$ 7) and PF (GF-S $<$ 7). This threshold has been validated in the previous PRONIA study (Koutsouleris et al., 2018). The cut-off value of <7 selected marks a mild but already existent and clinically relevant social-functioning impairment (Koutsouleris et al., 2018; Lo Cascio et al., 2017). The recruitment of the intervention sample took place at the Early Diagnosis and Intervention Centre at the Department of Psychiatry and Psychotherapy of the Ludwig Maximilian University (LMU) in Munich. The participants of both samples had to meet criteria for an affective or non-affective psychotic episode according to the DSM-IV (Bell, 1994) and be within 2 years of onset of first illness episode. Specific exclusion criteria were (1) history of neurological disease, head trauma with loss of consciousness (>5 min), alcoholism or polysubstance abuse; (2) insufficient intellectual capacity tested with the Wechsler Intelligence Scale for Adults (WAIS) (Wechsler, 1997); (3) insufficient German or English language skills or (4) prior CT within the last 3 years (supplementary information, Section 1.1). The study was approved by the Local Research Ethics Committee of the LMU and five PRONIA EU centers and all participants provided their written informed consent prior to study inclusion. A total of $n = 27$ participants of the intervention sample were randomly assigned by research assistants to an active intervention group receiving SCT and completed an average of 10 h. Participants who were not included in the active intervention group (n = 27) have undergone TAU (Table 2, Fig. S1).

2.2. Procedures

CT Intervention was performed within individual sessions of 30–45 min over 5 weeks and consisted of four different tasks addressing attention and processing speed in the social cognitive domains of visual affect perception and social cue perception (supplementary information, Section 1.2). Thus all tasks target early social sensory processing, which is associated with widespread impairments in cognitive and psychosocial functioning in schizophrenia (Koshiyama et al., 2021; Fisher et al., 2017). The individual training sessions were structured in four blocks with early blocks using stimuli meant to strengthen basic reaction times and subsequent blocks using stimuli with naturalistic properties to ensure processing improvements of more complex real-world stimuli. The exercises of the different blocks are described in supplementary information, Table 1. Measured at the individual patient level, task difficulty was adjusted by constantly adapting presentation time of displayed facial stimuli and stimulus complexity maintaining 75–80% accuracy of the participants' responses. Therefore, adaptive tracking methods based on a statistically optimal Bayesian approach were used to adjust single dimensions of the tasks within each block to the participant's ability. In this process, difficulty levels of all exercises were adapted in terms of 1) stimulus complexity; 2) number of response alternatives; 3) stimulus and response presentation times. For randomization, 1 set of 60 numbers ranging from 1 to 2 for each condition was generated by the research randomizer (https://www.randomizer.org/). For sample size estimation, a statistical power analysis based on data from a comparable study with medium-to-large effect size using CT (Kambeitz-Ilankovic et al., 2020) was performed. To achieve this effect size with an $\alpha = 0.05$ and power = 0.80, our sample size of 27 participants was considered adequate (supplementary information, Section 1.1).

2.3. Clinical and cognitive assessment

At baseline (T0) and at FU post-intervention, clinical assessment was administered including following test instruments: The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered in order to assess the presence and severity of symptoms while social functioning was assessed using the GF-S (Carrión et al., 2019). The full test battery has been previously described elsewhere (Koutsouleris et al., 2018). The GF-S quantifies social functioning in everyday life on a scale of 1–10 with 10 indicating superior functioning and 1 representing extreme dysfunction (Lo Cascio et al., 2017). It has been previously proposed as an effective predictor of functional outcome with excellent inter-rater reliability and accuracy in multi-site studies (Koutsouleris et al., 2018; Carrión et al., 2019; Lo Cascio et al., 2017) allowing us to use GF-S as target variable for good versus poor functioning. A cross-domain cognitive test battery including the (1) Diagnostical Analysis of Non-verbal Accuracy (DANVA) (Nowicki and Duke, 2023), the (2) Forward and Backward digit span test (FDS, BDS) (Jensen and Figueroa, 1975), the (3) Semantic/Phonemic Verbal Fluency Task (VFT-P/-S) (Lehtinen et al., 2021), the (4) Rey Auditory Verbal Learning Test

(RAVLT) (Britt et al., 1995), the (5) Trail Making Test (TMT-A/-B) (Llinàs-Reglà et al., 2017), the (6) Continuous Performance Test (CPT-IP) (Cornblatt et al., 1988), the (7) Self-Ordered Pointing Task (SOPT) (Gillett, 2007), the (8) Digit-Symbol Substitution Test (DSST) (Jaeger, 2018) and the (9) third version of the WAIS (Wechsler, 1997) were administered to patients in the intervention sample at T0 and FU (supplementary information, Section 1.3). All the tests were assigned to cognitive domains comparable to the Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) domains (Nuechterlein et al., 2008). To closely reflect the cognitive domains, we z-score transformed the tests based on the MATRICS recommended procedures (supplementary information, Table 2). 73 cognitive features were extracted from the test battery that were used in the further analysis (supplementary information, Table 3).

2.4. ML analysis pipeline

The ML software NeuroMiner (NM) (Koutsouleris et al., 2018) version 1.05 was used to create a SVM classification model differentiating between GF and PF in the PRONIA sample based on baseline cognitive data. To produce an unbiased estimate of the expected diagnostic and prognostic accuracy of the SVM model on new individuals, the model was applied to the intervention sample (Koutsouleris et al., 2009). Within the process of model creation, repeated-nested double cross-validation (CV) was employed to prevent information leakage, to avoid overfitting and to enable the unbiased estimation of the predictive system's generalizability to new patients (Dwyer et al., 2018; Ruschhaupt et al., 2004; Koutsouleris et al., 2016). This CV-structure, currently considered the gold-standard in translational science (Dwyer et al., 2018; Walter et al., 2019), provides an estimate of the expected diagnostic accuracy on unknown cases (Koutsouleris et al., 2015; Varma and Simon, 2006) by including an inner, k-fold CV cycle (CV1) within another, superordinate outer k-fold CV cycle (CV2). In CV1, models are generated and their generalizability is then tested in CV2 (Filzmoser et al., 2009). Both inner and outer CV cycles were randomly split into 10 folds and permuted 10 iterations. Within CV1, all features were preprocessed before being tested in CV2: Matrices were pruned of zero-variance features to reduce the variable cognitive battery to a clinically manageable predictor set (Koutsouleris et al., 2016) and standardized to the mean (Inza et al., 2010). Matrices with missing values were imputed to the k = 7 nearest neighbor (Troyanskaya et al., 2001). A linear, kernel based class-weighted SVM algorithm (LIBSVM 3.1.2 L1-Loss SVM) (Dwyer et al., 2018) was fed with the preprocessed CV1 data in order to generate a hyperplane that could optimally predict the dichotomized training and test cases' labels in a given CV1 partition. Due to the nonlinear kernel, the nonlinear input space was mapped into a new, linearly separable space (Kwak, 2013). By maximizing the geometric distance between the most similar subjects of opposite groups (Vapnik, 1999; Burges, 1998), the SVM algorithm was able to find the optimal between-group boundary. This maximum margin principle in conjunction with the nonlinear projection leads to classification rules that are adapted to subtle between-group differences resulting in a good generalizability to new individuals (Vapnik, 1999). To avoid any bias caused by unequal group sizes, i.e. producing a high predictive accuracy over the majority class but a poor predictive accuracy over the minority class (Garde et al., 2013), the hyperplane was weighted. The default regularization parameter of C = 1 controlling the margin and misclassification allowance (Dwyer et al., 2018) was used within CV1 (Cabral et al., 2016). The most predictive analysis pipeline was finally applied to each k-fold and N-permutation CV2 cycle whereby the participants' outcome class (GF vs. PF) was determined by majority vote across all ensemble models. Through permutation testing (Golland and Fischl, 2003), statistical significance was assessed with $\alpha = 0.05$ and 1000 permutations. Model's performance was measured by BAC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC).

2.5. Statistical analyses

In order to test the external validity, the obtained GF-PF classifier was applied to the intervention sample at T0 and FU without any in-between training steps using out-of-sample cross-validation (OOCV). After applying the classifier, a continuous (Walter et al., 2019), subject-specific linear SVM decision score was extracted for each patient in the intervention sample estimating the participant's class label based on their baseline cognitive performance (Spüler et al., 2012). A more positive decision score indicates that a given individual is prototypical of the GF class while a more negative decision score indicates that a given individual is prototypical of the PF class. The difference in decision scores between the two timepoints (FU-T0) and between the groups (SCT-TAU) provided an estimate of the direction of cognitive pattern shift across the SVM hyperplane following CT. Accordingly, we addressed increasing individual decision scores between T0 and FU as a shift from predicted prototypically poor-functioning-likeness to prototypically good-functioning-likeness.

Data analysis was performed using RStudio v. 1.3.1056 software with a significance level of $\alpha = 0.05$. To control for family-wise type I error rate (FWER), Holm correction of multiple comparisons was applied for the statistical analyses (Vickerstaff et al., 2019). Demographic differences between groups were assessed using independent *t*-tests for continuous variables and chi-square tests for categorical variables. Repeated measures Analysis of Variance (ANOVA) was used to assess (1) changes in social functioning in ROP patients of the intervention sample

Table 3
Cognitive, clinical and social functioning outcomes at baseline and follow-up in the intervention sample.

	SCT (n = 27)		TAU (*n* = 27)		ANOVA	
	T0 (mean(sd))	FU (mean(sd))	T0 (mean(sd))	FU (mean(sd))	Main Effect of Time F(P)	Interaction (Group x Time) F(P)
Functional outcomes						
GF-S	5.96 (1.13)	6.52 (1.09)	5.74 (1.63)	6.15 (1.56)	10.639 (0.002)*	0.252 (0.618)
PANSS						
Total	66.69 (15.91)	43.74 (14.55)	68.88 (18.35)	51.81 (17.29)	58.831 (4.78e-10)*	0.687 (4.11e-01)
Positive	18.96 (5.69)	10.26 (6.10)	21.15 (4.51)	12.56 (4.67)	38.032 (1.12e-07)*	0.942 (3.36e-01)
Negative	14.48 (5.61)	10.74 (4.47)	14.65 (6.67)	13.33 (6.32)	12.018 (0.001)*	1.238 (0.271)
General	33.52 (8.86)	22.74 (7.77)	33.08 (11.43)	25.93 (9.22)	94.056 (3.63e-13)*	0.015 (9.04e-01)
Cognitive domains						
Global cognition	0.16 (0.61)	0.11 (0.71)	−0.24 (0.91)	−0.10 (0.78)	0.176 (0.676)	1.550 (0.219)
Social cognition	0.12 (0.68)	0.11 (0.79)	−0.12 (1.24)	−0.11 (1.18)	0.000 (1.000)	0.002 (0.969)
Speed of Processing	0.07 (0.82)	0.11 (0.77)	−0.08 (0.81)	−0.11 (0.83)	0.099 (0.754)	0.069 (0.793)
Working memory	0.12 (0.81)	0.16 (0.82)	−0.12 (1.01)	−0.16 (0.89)	0.000 (1.000)	0.191 (0.664)
Verbal Learning	−0.02 (1.07)	0.11 (1.21)	0.02 (0.95)	−0.11 (0.75)	0.007 (0.932)	1.633 (0.207)
Attention	0.51 (1.33)	0.03 (1.76)	−0.51 (1.83)	−0.03 (1.60)	0.000 (1.000)	5.832 (0.019)*

over time (T0-FU) (2) cognitive pattern changes in ROP patients of the intervention sample over time (T0-FU) and (3) changes in predicted social functioning between the SCT and TAU group over time (T0-FU). We conducted additional correlational analyses between gender, age, years of education, positive and negative symptoms and social functioning and SVM decision scores using a Pearson's correlation method (Pearson's r) to exclude bias possibility (supplementary information, table 4). We also ran ANOVA to assess the association between the intervention and functional and cognitive measures (Table 3). Effect sizes were reported using Cohen's d (Cohen, 2013).

3. Results

Table 1 summarizes demographic and clinical characteristics of the PRONIA sample in comparison to the CT intervention sample. Participants in the PRONIA sample received a significantly higher dosage of antipsychotic medication in comparison to participants in the CT intervention sample (Table 1). Participants in the intervention sample showed significantly higher positive symptoms as measured by the PANSS – Positive than participants in the PRONIA sample (Table 1). No further significant differences were observed between the two samples in terms of clinical and demographic characteristics at baseline. Importantly, no significant differences between the PRONIA and intervention sample regarding the outcome variable social outcome were observed (GF-S at FU, Table 1).

Table 2 summarizes demographic and clinical characteristics of the CT intervention sample. At baseline, no significant differences on sex, age, years of education or social functioning between SCT and TAU subjects were found (Table 2). After intervention, social functioning had increased in both groups ($F = 10.64$; $df = 52$; $P = 0.002$; Fig. 1) without significant interactions between the groups ($F = 0.25$; $df = 52$; $P = 0.62$).

Symptom severity as measured by the PANSS improved significantly in both groups after the intervention in all measures including PANSS – Total ($F = 58.83$, $df = 51$, $P = 4.78e\text{-}10$), – Positive ($F = 94.06$, $df = 51$, $P = 3.63e\text{-}13$) – Negative ($F = 12.02$, $df = 51$, $P = 0.001$) and – General ($F = 38.02$, $df = 51$, $P = 1.12e\text{-}07$) yet lacking significant interactions between the groups (Table 3). A significant group by time interaction was observed on the cognitive domain of attention ($F = 5.83$, $df = 52$, $P = 0.019$, ES[Cohen's d] = 0.33) in the intervention group. Detailed information on the ANOVA assessing cognitive and functional outcomes in SCT and TAU groups can be found in Table 3.

Building SVM model on the PRONIA sample. The SVM correctly classified GF and PF with a BAC of 66.4% (Sensitivity 78.8%; Specificity 54.1%; PPV 60.5%; NPV 74.1%; AUC 0.64; $P = 0.01$). The most frequently selected cognitive features (mean feature weights $> \pm 0.2$) included the (1) correct number of symbol matchings within the DSST, (2) the number of distracting stimuli leading to an error within 300 and 200 trials in the CPT-IP and (3) the dynamics of verbal fluency between 15 and 30 s within the VFT—P.

SVM Model validation. Applying the GF-PF classifier generated on PRONIA sample to the intervention sample, a BAC of 59.3% (Sensitivity 70.4%; Specificity 48.1%; PPV 57.6%; NPV 61.9%; AUC 0.63) was achieved at T0 and a BAC of 64.8% (Sensitivity 66.7%; Specificity 63.0%; PPV 64.3%; NPV 65.4%; AUC 0.66) at FU. When applying the GF-PF classifier further to the separate subgroups, the following results were obtained: In the SCT group, a BAC of 50.0% (Sensitivity 66.7%; Specificity 33.3%; PPV 55.6%; NPV 44.4%; AUC 0.52) was achieved at T0 and a BAC of 55.0% (Sensitivity 60.0%; Specificity 50.0%; PPV 60.0%; NPV 50.0%; AUC 0.55) at FU. In the TAU group, a BAC of 67.5% (Sensitivity 75.0%; Specificity 60.0%; PPV 60.0%; NPV 75.0%; AUC 0.73) was obtained at T0 and a BAC of 74.2% (Sensitivity 75.0%; Specificity 73.3%; PPV 69.2%; NPV 78.6%; AUC 0.77) at FU.

After deriving decision scores from the SVM models at FU and baseline and comparing the SCT and TAU participants, no significant differences in decision scores between the groups were observed at T0 ($t = -0.06$; $df = 51.17$; $P = 0.95$). The main effect of the group ($F = 0.35$, $df = 37$, $P = 0.56$) and of cognitive pattern changes ($F = 0.22$, $df = 37$, $P = 0.64$) on social functioning were not significant. However, we found a significant interaction effect of the group and cognitive pattern changes on the predicted social functioning in response to the intervention ($F = 5.97$, $df = 37$, $P = 0.02$, ES[Cohen's d] = 0.18; Fig. 2).

While a tendency of improved predicted social functioning was indicated through increase in decision scores in the SCT group (M_T0 = 0.09 (SD = 0.74); M_ FU = 0.17 (SD = 0.83); ES[Cohen's d] = −0.10), decreasing decision scores in the TAU group (M_T0 = −0.08 (SD = 0.85); M_FU = −0.10 (SD = 0.75); ES[Cohen's d] = 0.23) indicated

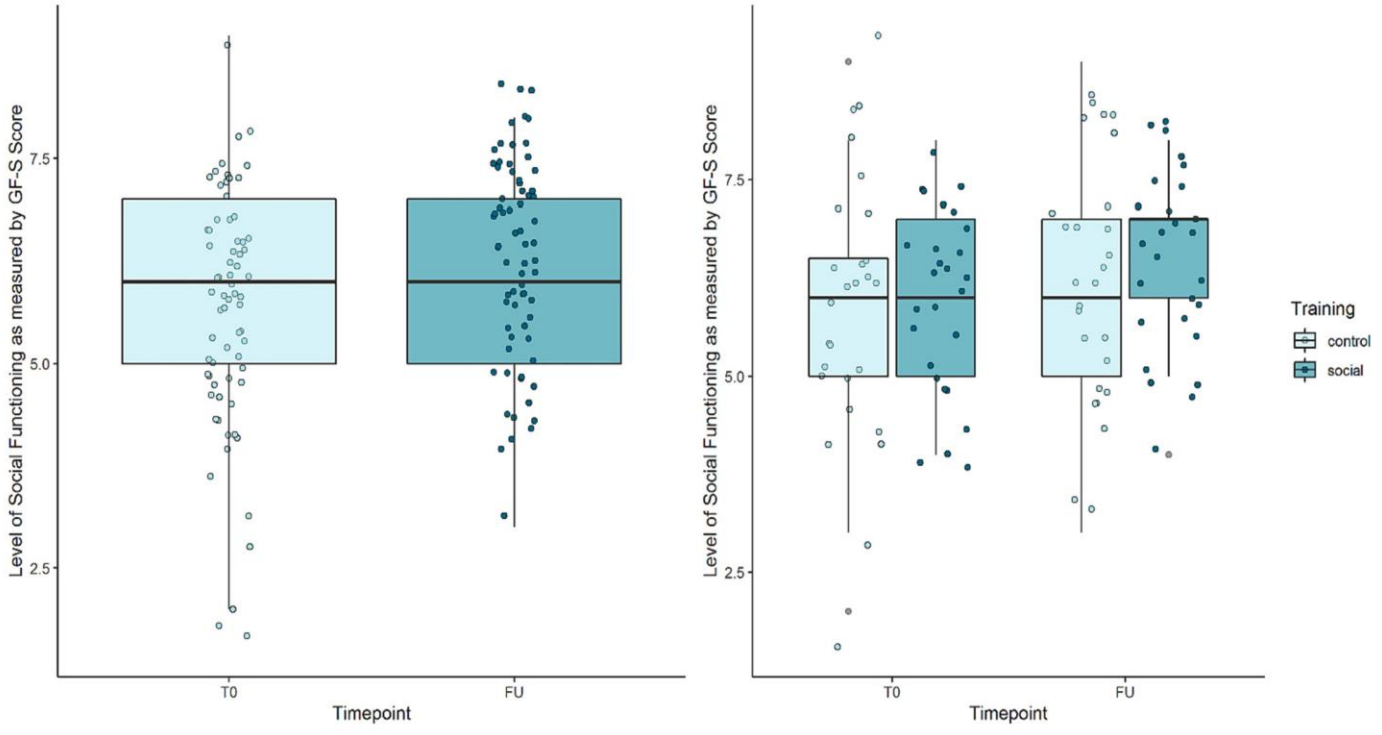


Fig. 1. Social Functioning measured by GF-S score in the PRONIA sample (left) and the intervention sample (right) at T0 and FU.

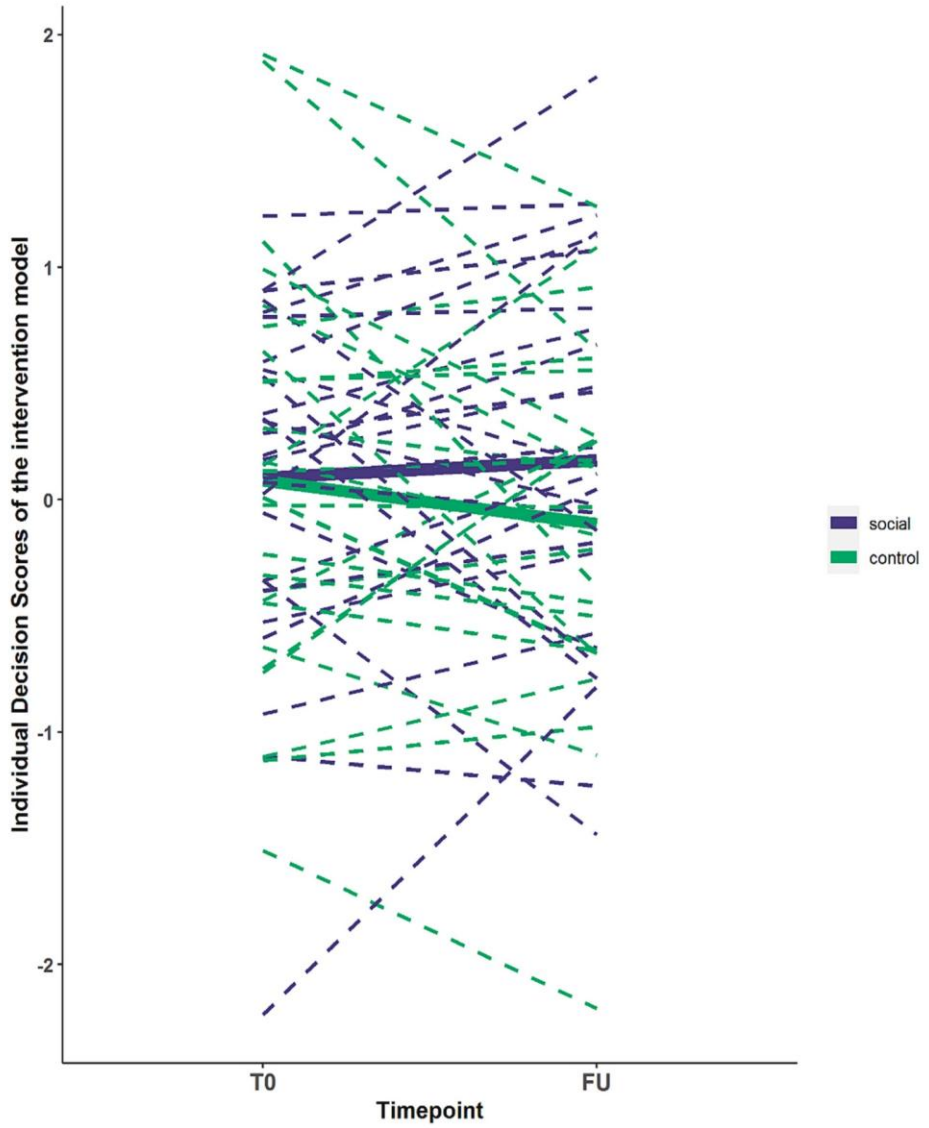


Fig. 2. Individual decision scores of the participants of SCT and TAU groups at T0 and FU.

slight deterioration of the cognitive pattern predictive of social functioning. We observed a significant correlation between decision scores and the number of years of education in the intervention sample at T0 ($r = 0.37$, df = 52, $P = 0.006$) whereby a high number of years of education at T0 correlated with increased decision scores at FU ($r = 0.33$, df = 49, $P = 0.02$). Further, we found significant associations between decision scores and measures of symptom severity including PANSS – Total ($r = -0.36$, df = 51, $P = 0.009$) and PANSS – Negative ($r = -0.34$, df = 51, $P = 0.01$). No associations were found between decision scores and gender and decision scores and age (supplementary information, table 4).

When looking further at social functioning in the subgroups of GF and PF, we observed a significant group by time interaction between the groups (F = 10.92; df = 52; $P = 2.00e\text{-}03$) with GF showing significant improvements in social functioning in response to the intervention ($t = 3.81$; df = 38.86; $P = 0.0005$) while social functioning in PF stayed unchanged after the intervention ($t = 0.12$; df = 45.42; $P = 0.90$).

4. Discussion

In this study, we performed ML analysis to investigate the utility of cognitive data to predict future social functioning in patients with ROP in response to SCT. To the best of our knowledge, this is the first study utilizing a multivariate cognitive model to investigate changes in social functioning in response to CT in a sample of ROP patients. In order to achieve this, we built a model based on the ROP patients of the PRONIA study sample with a BAC of 66.4% indicating poor versus good social functioning at an individual patient level.

In the cognitive pattern predictive of improvement in social functioning in the PRONIA model, cognitive domains of processing speed, attention and vigilance and verbal fluency had most prominent feature weights. These results are in line with the findings of a meta-analysis, in which community functioning was most strongly associated with verbal fluency, verbal learning and memory, and processing speed (Fett et al., 2011). In addition, preserved processing speed (Eack et al., 2010a) and attention (Lahera et al., 2017) have been shown to be critical for facial emotion recognition, which is strongly correlated with social functioning (Lahera et al., 2017; Sánchez et al., 2009). According to a recent RCT, processing speed is of further importance as the effects of cognitive rehabilitation on functional improvement seem to be partially mediated by changes in processing speed and verbal memory (Peña et al., 2018). In this context, the treatment of multi-domain cognitive impairments at early disease stages is of particular importance as early interventions may favor better long-term outcomes (Bellani et al., 2019) and lead to more adaptive brain responses and reduced symptoms (Fisher et al., 2013). We showed that it is possible to use baseline cognitive patterns to predict social functioning at FU in the short-term. In a recent study, only the occupational- and role functioning but not social functioning was successfully predicted in patients with CHR for psychosis based on neurocognitive performance with a BAC of 61% (Squarcina et al., 2022). Our current social functioning model may be providing better BAC due

to our use of a slightly larger set of predictors. These included not only correct responses but also omissions and errors of working memory and attention tests. The impairment in executive functions on the verbal fluency task, may be additionally boosting social functioning prediction. Executive function is involved in problem solving, inhibition of inappropriate responses and cognitive flexibility, which are all of great relevance to maintaining a satisfactory and age-appropriate level of social functioning. Another possible explanation is that the CHR group is characterized by more profound impairments in processing speed and memory (Velthorst et al., 2019), which are particularly associated with social functioning (Fett et al., 2011; Eack et al., 2010a; Peña et al., 2018).

When it comes to generalizability, our model was applied to the CT intervention sample which allowed us to compare the predicted individual social functioning changes between the SCT and the TAU groups following intervention. Our findings showed a significant difference regarding the cognitive pattern predictive of functioning as measured by the individual decision scores between SCT and TAU groups after the intervention. Though we found no significant difference in GF-S scores reflecting social functioning between the SCT and TAU groups with the classical statistical approach, it may be feasible to recognize individual cognitive-patterns predictive of response to CT using SVM. This assumption is consistent with previous findings that CT restores cognitive functions and leads to neurobiological reinforcement effects (Eack et al., 2010b) with the results of previous studies demonstrating cognitive improvements after 10 h of CT due to a "drill-and-practice" approach (Haas et al., 2020; Koshiyama et al., 2021) applied in the exercises. Despite high BAC of our model in predicting social functioning and its potential to generalize it remains challenging to predict individual therapy responses to CT. Only a few participants have improved their social functioning from a moderate to mild social impairment level as measured by the GF-S scale. Due to limited modulation of social functioning in both SCT and TAU group between T0 and FU it was not possible to clearly define and separate responders from non-responders. However, not only an improvement in GF-S score but also the maintenance of a moderate level of social functioning, despite undergoing a psychotic episode, may be seen as a response to CT.

Several limitations of the current study need to be considered. First, despite good generalizability, our model of functioning showed rather poor specificity when applied to the CT intervention sample, resulting in an inaccurate classification of patients with poor social functioning. This can be explained by reduced specificity of our original model of functioning resulting in poorer applicability to patients with poor social functioning. However, as our study is a smaller scale proof-of-concept study with the aim to application of new methodological approaches to determine individual therapy response to CT. We would like to address the validation of our findings in larger scale multi-centric trials to come. Second, our median split approach applied to the PRONIA ROP sample of 70 participants and a rather small intervention sample of 54 participants may have limited the generalizability of our findings. Thus, our proof-of-concept study needs to be validated in larger scale studies. Third, the current study used a relatively short intervention period of 10 h of CT over the course of 5 weeks with the aim to keep the intervention duration comparable to the duration of clinical treatment. To create a closer resemblance to the real clinical setting, we oriented towards treatment and intervention length that seems to be common across many health centers in Europe (Ajnakina et al., 2020). Furthermore, there is no evidence that the number of hours of completed CT is related to the extent of overall cognitive improvement (McGurk et al., 2007), or is assocaited to symptoms, cognitive- or functional outcomes (Lejeune et al., 2021). Finally, the main focus of our analyses related to the intervention sample were not primary (cognition) and secondary (functioning) outcomes per se, but rather the identification of early therapy response to CT and how it can be effectively identified in order to 1) provide CT to those who benefit and 2) find alternative or more integrative therapy approaches to those patients with ROP who are more likely not to benefit. However, it is possible that participants who did not respond with an improvement in social functioning and did not show a positive change in cognitive patterns in our study, may show functional 'recovery' with a longer duration, or with a slightly different form of intervention, or with implementation of other intervention protocols (Koutsouleris et al., 2016). Fourth, participants in the intervention sample show relatively modest variability in the prediction target, social functioning, in response to the CT intervention which could have potentially limited the model's predictiveness. We would like to address this issue in future studies with a larger intervention sample showing greater variability in functioning. Finally, due to the lack of long-term FU, future studies will need to investigate whether the cognitive pattern changes we have shown are durable after a longer observation period. As early individual identification and intervention programs progress to pave the way towards individualized therapy approaches (Behan et al., 2015; Patel et al., 2010), implementation of such proof-of-concept approaches as ours should be further validated and integrated. Finally, large-scale cognitive trials should enable the research field to investigate prediction of functioning beyond the indirect markers of response.

CRediT author statement

A multivariate cognitive approach to predict social functioning in recent onset psychosis in response to computerized cognitive training LK-I, NW and JW conceptualized the paper. LK-I and NK oversaw data collection and project development. NW was responsible for statistical analyses. LK-I and NW drafted the manuscript and provided data interpretation. JW, DD, and JK assisted with statistical analyses and data interpretation. JW, SH, LS, CB, AR, TL, ÖB, LA, PB, SJW, RU, SB, RL, EM, RKRS, CP, AB and JK assisted in data collection and data entry. NW, LK-I, JW, JK, DD and NK were involved in developing the classification pipeline. SH, DD, SJW, RU, RL, RKRS and CP revised the manuscript and assisted in conceptualizing the project. All authors revised and agreed upon the final version of the manuscript.

Code availability

The NeuroMiner Software code is available for download at https://github.com/neurominer-git.

Declaration of Competing Interest

This study was supported by EU-FP7 project PRONIA (Personalized Prognostic Tools for Early Psychosis Management) under the Grant Agreement No° 602152 (PI: NK), NARSAD Young Investigator Award of the Brain & Behavior Research Foundation No° 28474 (PI: LK-I) and LMU excellent (LKI). NK, JK and RKRA are currently honorary speakers for Otsuka/Lundbeck. RU received grants from Medical Research Council, grants from the National Institute for Health Research, and personal fees from Sunovion. C Pantelis was supported by a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellowship (1105825), an aNHMRC L3 Investigator Grant (1196508), and NHMRC-EU grant (1075379). SSH is supported by NIH National Institute of Mental Health, grant T32MH122394. The remaining authors including members of the PRONIA consortium have nothing to disclose.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

LKI and NK The data are not publicly available due to ethical restrictions protecting patients' privacy and consent.

Acknowledgements

The project has been conducted in the framework of LMU Excellent Funding Scheme, received by LK-I. Clinical recruitment and data preprocessing for this project have been carried out in the scope of the doctoral thesis of SSH at Ludwig Maximilian University and International Max Planck Research School for Translational Psychiatry.

The PRONIA consortium: Prof. Nikolaos Koutsouleris, MD, Lana Kambeitz-Ilankovic, PhD, Mark Sen Dong, MSc, Anne Erkens, Eva Gussmann, MSc, Shalaila Haas, PhD, Dominic Dwyer, Prof. Alkomiet Hasan, Claudius Hoff, MD, Ifrah Khanyaree, MSc, Aylin Melo, MSc, Susanna Muckenhuber-Sternbauer, MD, Janis Kohler, Omer Faruk Ozturk, MD, David Popovic, MD, Nora Penzel, PhD, Adrian Rangnick, BSc, Sebastian von Saldern, MD, Rachele Sanfelici, PhD, Moritz Spangemacher, Ana Tupac, MSc, Maria Fernanda Urquijo, MSc, Johanna Weiske, MSc, Julian Wenzel, PhD, Antonia Wosgien, Prof. Joseph Kambeitz, MD, Prof. Stephan Ruhrmann, MD, Marlene Rosen, PhD, Linda Betz, PhD, Theresa Lichtenstein, MD, Karsten Blume, Mauro Seves, MSc, Nathalie Kaiser, MSc, Tanja Pilgram, MSc, Thorsten Lichtenstein, MD, Christiane Woopen, MD, Prof. Stefan Borgwardt, MD, André Schmidt, PhD, Prof. Anita Riecher-Rössler, MD, Christina Andreou, MD, PhD, Laura Egloff, PhD, Fabienne Harrisberger, PhD, Claudia Lenz, PhD, Letizia Leanza, MSc, Amatya Mackintosh, MSc, Renata Smieskova, PhD, Erich Studerus, PhD, Anna Walter, MD, Sonja Widmayer, MSc., Prof. Rachel Upthegrove, MBBS FRCPsych, PhD, Prof. Stephen J. Wood, PhD, Katharine Chisholm, PhD, Chris Day, BSc, Sian Lowri Griffiths, PhD, Mariam Iqbal, BSc, Mirabel Pelton, MSc, Pavan Mallikarjun, MBBS, DPM, MRCPsych, PhD, Alexandra Stainton, PhD, Prof. Ashleigh Lin, PhD, Prof. Raimo K. R. Salokangas, MD, PhD, MSc, Alexander Denissoff, MD, Anu Ellila, RN, Tiina From, MSc, Markus Heinimaa, MD, PhD, Tuula Ilonen, PhD, Paivi Jalo, RN, Heikki Laurikainen, MD, Maarit Lehtinen, RN, Antti Luutonen, BA, Akseli Makela, BA, Janina Paju, MSc, Henri Pesonen, PhD, Reetta-Liina Armio (Säilä), MD, Elina Sormunen, MD, Anna Toivonen, MSc, Otto Turtonen, MD, Jarmo Hietala, MD, PhD, Mirka Kolkka, Sinikka Luutonen, MD, PhD, Maija Walta, MD, Lauri Tuominen, MD, PhD, Ana Beatriz Solana, PhD, Manuela Abraham, MBA, Nicolas Hehn, PhD, Timo Schirmer, PhD, Prof. Paolo Brambilla, MD, Carlo Altamura, MD, Marika Belleri, PsychD, Francesca Bottinelli, PsychD, Adele Ferro, PsychD, PhD, Marta Re, PhD, Emiliano Monzani, MD, Mauro Percudani, MD, Maurizio Sberna, MD, Armando D'Agostino, MD, Lorenzo Del Fabro, MD, Villa San Benedetto Menni, Giampaolo Perna, MD, Maria Nobile, MD, PhD, Alessandra Alciati, MD, Matteo Balestrieri, MD, Carolina Bonivento, PsychD, PhD, Giuseppe Cabras, PhD, Franco Fabbro, MD, PhD, Marco Garzitto, PsychD, PhD, Sara Piccin, PsychD, PhD, Prof. Alessandro Bertolino, Prof. Giuseppe Blasi, Prof. Linda A. Antonucci, Prof. Giulio Pergola, Grazia Caforio, PhD, Leonardo Faio, PhD, Tiziana Quarto, PhD, Barbara Gelao, PhD, Raffaella Romano, PhD, Ileana Andriola, MD, Andrea Falsetti, MD, Marina Barone, MD, Roberta Passatiore, M.Sc., Marina Sangiuliano, MD, Prof. Rebekka Lencer, Marian Surman, M.Sc., Olga Bienek, MD, Prof. Georg Romer, MD, Prof. Udo Dannlowski, MD, PhD, Prof. Eva Meisenzahl, MD, Frauke Schultze-Lutter, PhD, Christian Schmidt-Kraepelin, MD, Susanne Neufang, PhD, Alexandra Korda, PhD, Henrik Rohner, MD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110864.

References

Ajnakina, O., Stubbs, B., Francis, E., Gaughran, F., David, A.S., Murray, R.M., Lally, J., 2020. Hospitalisation and length of hospital stay following first-episode psychosis: systematic review and meta-analysis of longitudinal studies. Psychol. Med. 50, 991–1001. https://doi.org/10.1017/S0033291719000904.

Barlati, S., Deste, G., Peri, L., Ariu, C., Vita, A., 2013. Cognitive remediation in schizophrenia: current status and future perspectives. Schizophr. Res. Treat. 2013, 156084. https://doi.org/10.1155/2013/156084.

Behan, C., Cullinan, J., Kennelly, B., Turner, N., Owens, E., Lau, A., et al., 2015. Estimating the cost and effect of early intervention on in-patient admission in first episode psychosis. J. Ment. Health Policy Econ. 18, 57–61.

Bell, C.C., 1994. DSM-IV: diagnostic and statistical manual of mental disorders. JAMA. 272, 828. https://doi.org/10.1001/jama.1994.03520100096046.

Bellani, M., Ricciardi, C., Rossetti, M.G., Zovetti, N., Perlini, C., Brambilla, P., 2019. Cognitive remediation in schizophrenia: the earlier the better? Epidemiol. Psychiatr. Sci. 29, e57 https://doi.org/10.1017/S2045796019000532.

Biagianti, B., Castellaro, G.A., Brambilla, P., 2021. Predictors of response to cognitive remediation in patients with major psychotic disorders: a narrative review. J. Affect. Disord. 281, 264–270. https://doi.org/10.1016/j.jad.2020.12.011.

Bowie, C.R., Grossman, M., Gupta, M., Oyewumi, L.K., Harvey, P.D., 2014. Cognitive remediation in schizophrenia: efficacy and effectiveness in patients with early versus long-term course of illness. Early Interv. Psychiatry 8, 32–38. https://doi.org/10.1111/eip.12029.

Britt, D.M., Adams, S.G., Godding, P.R., Grothues, C.A., Varnado, P., 1995. Clinical differentiation of the Rey auditory-verbal learning test. Am. J. Alzheimers Dis. 10, 7–18. https://doi.org/10.1177/153331759501000603.

Burges, C.J., 1998. A tutorial on support vector machines for pattern recognition. Data Min. Knowl. Disc. 2, 121–167. https://doi.org/10.1023/A:1009715923555.

Bzdok, D., Meyer-Lindenberg, A., 2018. Machine learning for precision psychiatry: opportunities and challenges. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 223–230. https://doi.org/10.1016/j.bpsc.2017.11.007.

Cabral, C., Kambeitz-Ilankovic, L., Kambeitz, J., Calhoun, V.D., Dwyer, D.B., von Saldern, S., et al., 2016. Classifying schizophrenia using multimodal multivariate pattern recognition analysis: evaluating the impact of individual clinical profiles on the Neurodiagnostic performance. Schizophr. Bull. 42 (Suppl. 1), S110–S117. https://doi.org/10.1093/schbul/sbw053.

Carrión, R.E., Auther, A.M., McLaughlin, D., Olsen, R., Addington, J., Bearden, C.E., et al., 2019. The global functioning: social and role scales-further validation in a large sample of adolescents and young adults at clinical high risk for psychosis. Schizophr. Bull. 45, 763–772. https://doi.org/10.1093/schbul/sby126.

Cassetta, B.D., Goghari, V.M., 2016. Working memory and processing speed training in schizophrenia: study protocol for a randomized controlled trial. Trials. https://doi.org/10.1186/s13063-016-1188-5.

Cohen, J., 2013. Statistical Power Analysis for the Behavioral Sciences. Routledge.

Cornblatt, B.A., Risch, N.J., Faris, G., Friedman, D., Erlenmeyer-Kimling, L., 1988. The continuous performance test, identical pairs version (CPT-IP): I. new findings about sustained attention in normal families. Psychiatry Res. 26, 223–238. https://doi.org/10.1016/0165-1781(88)90076-5.

Dwyer, D.B., Falkai, P., Koutsouleris, N., 2018. Machine learning approaches for clinical psychology and psychiatry. Annu. Rev. Clin. Psychol. 91–118.

Eack, S.M., Mermon, D.E., Montrose, D.M., Miewald, J., Gur, R.E., Gur, R.C., et al., 2010a. Social cognition deficits among individuals at familial high risk for schizophrenia. Schizophr. Bull. 36, 1081–1088. https://doi.org/10.1093/schbul/sbp026.

Eack, S.M., Hogarty, G.E., Cho, R.Y., Prasad, K.M.R., Greenwald, D.P., Hogarty, S.S., Keshavan, M.S., 2010b. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch. Gen. Psychiatry 67, 674–682. https://doi.org/10.1001/archgenpsychiatry.2010.63.

Fett, A.-K.J., Viechtbauer, W., Dominguez, M.-G., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35, 573–588. https://doi.org/10.1016/j.neubiorev.2010.07.001.

Fett, A.-K.J., Velthorst, E., Reichenberg, A., Ruggero, C.J., Callahan, J.L., Fochtmann, L. J., et al., 2020. Long-term changes in cognitive functioning in individuals with psychotic disorders: findings from the Suffolk County mental health project. JAMA Psychiatry 77, 387–396. https://doi.org/10.1001/jamapsychiatry.2019.3993.

Filzmoser, P., Liebmann, B., Varmuza, K., 2009. Repeated double cross validation. Aust. J. Chem. 23, 160–171. https://doi.org/10.1002/cem.1225.

Fisher, M., Loewy, R., Hardy, K., Schlosser, D., Vinogradov, S., 2013. Cognitive interventions targeting brain plasticity in the prodromal and early phases of schizophrenia. Annu. Rev. Clin. Psychol. 9, 435–463. https://doi.org/10.1146/annurev-clinpsy-032511-143134.

Fisher, M., Nahum, M., Howard, E., Rowlands, A., Brandrett, B., Kermott, A., et al., 2017. Supplementing intensive targeted computerized cognitive training with social cognitive exercises for people with schizophrenia: an interim report. Psychiatr. Rehabil. J. 40, 21–32. https://doi.org/10.1037/prj0000244.

Garde, A., Voss, A., Caminal, P., Benito, S., Giraldo, B.F., 2013. SVM-based feature selection to optimize sensitivity-specificity balance applied to weaning. Comput. Biol. Med. 43, 533–540. https://doi.org/10.1016/j.compbiomed.2013.01.014.

Gillett, R., 2007. Assessment of working memory performance in self-ordered selection tests. Cortex. 43, 1047–1056. https://doi.org/10.1016/s0010-9452(08)70702-0.

Golland, P., Fischl, B., 2003. Permutation tests for classification: towards statistical significance in image-based studies. Inf. Process. Med. Imaging 18, 330–341. https://doi.org/10.1007/978-3-540-45087-0_28.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72, 41–51. https://doi.org/10.1016/j.schres.2004.09.009.

Haas, S.S., Antonucci, L.A., Wenzel, J., Ruef, A., Biagianti, B., Paolini, M., et al., 2020. A multivariate neuromonitoring approach to neuroplasticity-based computerized

cognitive training in recent onset psychosis. Neuropsychopharmacology. https://doi.org/10.1038/s41386-020-00877-4.
Halverson, T.F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A.-K., Penn, D.L., 2019. Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors. Neurosci. Biobehav. Rev. 105, 212–219. https://doi.org/10.1016/j.neubiorev.2019.07.020.
Harvey, P.D., Bosia, M., Cavallaro, R., Howes, O.D., Kahn, R.S., Leucht, S., et al., 2022. Cognitive dysfunction in schizophrenia: An expert group paper on the current state of the art. Schizophr Res. Cogn. 29, 100249. https://doi.org/10.1016/j.scog.2022.100249. https://www.sciencedirect.com/science/article/pii/S2215001322000142.
Harvey, P.D., McGurk, S.R., Mahncke, H., Wykes, T., 2018. Controversies in computerized cognitive training. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 907–915. https://doi.org/10.1016/j.bpsc.2018.06.008.
Hedges, E.P., Dickson, H., Tognin, S., Modinos, G., Antoniades, M., van der Gaag, M., et al., 2022. Verbal memory performance predicts remission and functional outcome in people at clinical high-risk for psychosis. Schizophr. Res. Cogn. 28, 100222. https://doi.org/10.1016/j.scog.2021.100222.
Inza, I., Calvo, B., Armañanzas, R., Bengoetxea, E., Larrañaga, P., Lozano, J.A., 2010. Machine learning: an indispensable tool in bioinformatics. Methods Mol. Biol. 593, 25–48. https://doi.org/10.1007/978-1-60327-194-3_2.
Jaeger, J., 2018. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. J. Clin. Psychopharmacol. 38, 513–519. https://doi.org/10.1097/JCP.0000000000000941.
Jensen, A.R., Figueroa, R.A., 1975. Forward and backward digit span interaction with race and IQ: predictions from Jensen's theory. J. Educ. Psychol. 67, 882–893.
Kambeitz-Ilankovic, L., Betz, L.T., Dominke, C., Haas, S.S., Subramaniam, K., Fisher, M., et al., 2019. Multi-outcome meta-analysis (MOMA) of cognitive remediation in schizophrenia: revisiting the relevance of human coaching and elucidating interplay between multiple outcomes. Neurosci. Biobehav. Rev. 107, 828–845. https://doi.org/10.1016/j.neubiorev.2019.09.031.
Kambeitz-Ilankovic, L., Wenzel, J., Haas, S.S., Ruef, A., Antonucci, L.A., Sanfelici, R., et al., 2020. Modeling social sensory processing during social computerized cognitive training for psychosis Spectrum: the resting-state approach. Front. Psychol. 11, 554475. https://doi.org/10.3389/fpsyt.2020.554475.
Kambeitz-Ilankovic, L., Vinogradov, S., Wenzel, J., Fisher, M., Haas, S.S., Betz, L., et al., 2021. Multivariate pattern analysis of brain structure predicts functional outcome after auditory-based cognitive training interventions. NPJ Schizophr. 7, 40. https://doi.org/10.1038/s41537-021-00165-0.
Katsumi, A., Hoshino, H., Fujimoto, S., Yabe, H., Ikebuchi, E., Nakagome, K., Niwa, S.-I., 2019. Effects of cognitive remediation on cognitive and social functions in individuals with schizophrenia. Neuropsychol. Rehabil. 29, 1475–1487. https://doi.org/10.1080/09602011.2017.1409639.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.
Koshiyama, D., Thomas, M.L., Miyakoshi, M., Joshi, Y.B., Molina, J.L., Tanaka-Koshiyama, K., et al., 2021. Hierarchical pathways from sensory processing to cognitive, clinical, and functional impairments in schizophrenia. Schizophr. Bull. 47, 373–385. https://doi.org/10.1093/schbul/sbaa116.
Koutsouleris, N., Meisenzahl, E.M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., et al., 2009. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. Arch. Gen. Psychiatry 66, 700–712. https://doi.org/10.1001/archgenpsychiatry.2009.62.
Koutsouleris, N., Davatzikos, C., Bottlender, R., Patschurek-Kliche, K., Scheuerecker, J., Decker, P., et al., 2012. Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. Schizophr. Bull. 38, 1200–1215. https://doi.org/10.1093/schbul/sbr037.
Koutsouleris, N., Riecher-Rössler, A., Meisenzahl, E.M., Smieskova, R., Studerus, E., Kambeitz-Ilankovic, L., et al., 2015. Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. Schizophr. Bull. 41, 471–482. https://doi.org/10.1093/schbul/sbu078.
Koutsouleris, N., Kahn, R.S., Chekroud, A.M., Leucht, S., Falkai, P., Wobrock, T., et al., 2016. Multisite prediction of 4-week and 52-week treatment outcomes in patients with first-episode psychosis: a machine learning approach. Lancet Psychiatry 3, 935–946. https://doi.org/10.1016/S2215-0366(16)30171-7.
Koutsouleris, N., Kambeitz-Ilankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D.B., et al., 2018. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. JAMA Psychiatry 75, 1156–1172. https://doi.org/10.1001/jamapsychiatry.2018.2165.
Kurtz, M.M., Richardson, C.L., 2012. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. Schizophr. Bull. 38, 1092–1104. https://doi.org/10.1093/schbul/sbr036.
Kwak, N., 2013. Nonlinear projection trick in kernel methods: an alternative to the kernel trick. IEEE Trans. Neural Netw. Learn. Syst. 24, 2113–2119. https://doi.org/10.1109/TNNLS.2013.2272292.
Lahera, G., Ruiz, A., Brañas, A., Vicens, M., Orozco, A., 2017. Tiempo de reacción, velocidad de procesamiento y atención sostenida en esquizofrenia: impacto sobre el funcionamiento social. [Reaction time, processing speed and sustained attention in schizophrenia: impact on social functioning]. Rev. Psiquiatr. Salud. Ment. 10, 197–205. https://doi.org/10.1016/j.rpsm.2017.04.001.
Lehtinen, N., Luotonen, I., Kautto, A., 2021. Systematic administration and analysis of verbal fluency tasks: preliminary evidence for reliable exploration of processes underlying task performance. Appl. Neuropsychol. Adult 1–13. https://doi.org/10.1080/23279095.2021.1973471.
Lejeune, J.A., Northrop, A., Kurtz, M.M., 2021. A Meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. Schizophr. Bull. 47, 997–1006. https://doi.org/10.1093/schbul/sbab022.
Lindenmayer, J.-P., Khan, A., McGurk, S.R., Kulsa, M.K.C., Ljuri, I., Ozog, V., et al., 2018. Does social cognition training augment response to computer-assisted cognitive remediation for schizophrenia? Schizophr. Res. 201, 180–186. https://doi.org/10.1016/j.schres.2018.06.012.
Lindgren, M., Holm, M., Kieseppä, T., Suvisaari, J., 2020. Neurocognition and social cognition predicting 1-year outcomes in first-episode psychosis. Front. Psychol. 11, 603933. https://doi.org/10.3389/fpsyt.2020.603933.
Llinàs-Reglà, J., Vilalta-Franch, J., López-Pousa, S., Calvó-Perxas, L., Torrents Rodas, D., Garre-Olmo, J., 2017. The trail making test. Assessment. 24, 183–196. https://doi.org/10.1177/1073191115602552.
Lo Cascio, N., Curto, M., Pasqualetti, P., Lindau, J.F., Girardi, N., Saba, R., et al., 2017. Impairment in social functioning differentiates youth meeting ultra-high risk for psychosis criteria from other mental health help-seekers: a validation of the Italian version of the global functioning: social and global functioning: role scales. Psychiatry Res. 253, 296–302. https://doi.org/10.1016/j.psychres.2017.04.008.
MacEachern, S.J., Forkert, N.D., 2021. Machine learning for precision medicine. Genome. 64, 416–425. https://doi.org/10.1139/gen-2020-0131.
McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164, 1791–1802. https://doi.org/10.1176/appi.ajp.2007.07060906.
Nahum, M., Lee, H., Fisher, M., Green, M.F., Hooker, C.I., Ventura, J., et al., 2021. Online social cognition training in schizophrenia: a double-blind, randomized. Controll. Multi-Site Clin. Trial Schizophr Bull. 47, 108–117. https://doi.org/10.1093/schbul/sbaa085.
Nowicki, S., Duke, M., 2023. Nonverbal receptivity: The Diagnostic Analysis of Nonverbal Accuracy (DANVA): Interpersonal Sensitivity: Theory and Measurement, pp. 183–198.
Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., et al., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165, 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042.
Ophey, A., Wenzel, J., Paul, R., Giehl, K., Rehberg, S., Eggers, C., et al., 2022. Cognitive performance and learning parameters predict response to working memory training in Parkinson's disease. J. Parkinsons Dis. 12, 2235–2247. https://doi.org/10.3233/JPD-223448.
Patel, A., Knapp, M., Romeo, R., Reeder, C., Matthiasson, P., Everitt, B., Wykes, T., 2010. Cognitive remediation therapy in schizophrenia: cost-effectiveness analysis. Schizophr. Res. 120, 217–224. https://doi.org/10.1016/j.schres.2009.12.003.
Peña, J., Ibarretxe-Bilbao, N., Sánchez, P., Uriarte, J.J., Elizagarate, E., Gutierrez, M., Ojeda, N., 2018. Mechanisms of functional improvement through cognitive rehabilitation in schizophrenia. J. Psychiatr. Res. 101, 21–27. https://doi.org/10.1016/j.jpsychires.2018.03.002.
Rocha, N.B., Campos, C., Figueiredo, J.M., Saraiva, S., Almeida, C., Moreira, C., et al., 2020. Social cognition and interaction training for recent-onset schizophrenia: a preliminary randomized trial. Early Interv. Psychiatry. https://doi.org/10.1111/eip.12944.
Ruschhaupt, M., Huber, W., Poustka, A., Mansmann, U., 2004. A compendium to ensure computational reproducibility in high-dimensional classification tasks. Stat. Appl. Genet. Mol. Biol. 3 https://doi.org/10.2202/1544-6115.1078. Article37.
Sánchez, P., Ojeda, N., Peña, J., Elizagárate, E., Yoller, A.B., Gutiérrez, M., Ezcurra, J., 2009. Predictors of longitudinal changes in schizophrenia: the role of processing speed. J. Clin. Psychiatry 70, 888–896. https://doi.org/10.4088/JCP.08m04294.
Sheffield, J.M., Karcher, N.R., Barch, D.M., 2018. Cognitive deficits in psychotic disorders: a lifespan perspective. Neuropsychol. Rev. 28, 509–533. https://doi.org/10.1007/s11065-018-9388-2.
Spüler, M., Rosenstiel, W., Bogdan, M., 2012. Adaptive SVM-based classification increases performance of a MEG-based brain-computer interface (BCI). In: Hutchison, D., Kanade, T., Kittler, J., Kleinberg, J.M., Mattern, F., Mitchell, J.C., et al. (Eds.), Artificial Neural Networks and Machine Learning – ICANN 2012. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 669–676. https://doi.org/10.1007/978-3-642-33269-2_84.
Squarcina, L., Kambeitz-Ilankovic, L., Bonivento, C., Prunas, C., Oldani, L., Wenzel, J., et al., 2022. Relationships between global functioning and neuropsychological predictors in subjects at high risk of psychosis or with a recent onset of depression. World J. Biol. Psychiatry 1–9. https://doi.org/10.1080/15622975.2021.2014955.
Stouten, L.H., Veling, W., Laan, W., van der Helm, M., van der Gaag, M., 2014. Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis. Schizophr. Res. 158, 113–119. https://doi.org/10.1016/j.schres.2014.06.023.
Tan, B.-L., Lee, S.-A., Lee, J., 2018. Social cognitive interventions for people with schizophrenia: a systematic review. Asian J. Psychiatr. 35, 115–131. https://doi.org/10.1016/j.ajp.2016.06.013.
Tang, Y., Yu, L., Zhang, D., Fang, F., Yuan, Z., 2022. The effect of social cognitive interaction training on schizophrenia: a systematic review and Meta-analysis of comparison with conventional treatment. Biomed. Res. Int. 2022, 3394978. https://doi.org/10.1155/2022/3394978.
Troyanskaya, O., Cantor, M., Sherlock, G., Brown, P., Hastie, T., Tibshirani, R., et al., 2001. Missing value estimation methods for DNA microarrays. Bioinformatics. 17, 520–525. https://doi.org/10.1093/bioinformatics/17.6.520.
Vapnik, V.N., 1999. An overview of statistical learning theory. IEEE Trans. Neural Netw. 10, 988–999. https://doi.org/10.1109/72.788640.

Varma, S., Simon, R., 2006. Bias in error estimation when using cross-validation for model selection. BMC Bioinformatics 7, 91. https://doi.org/10.1186/1471-2105-7-91.

Velthorst, E., Fett, A.-K.J., Reichenberg, A., Perlman, G., van Os, J., Bromet, E.J., Kotov, R., 2017. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. Am. J. Psychiatry 174, 1075–1085. https://doi.org/10.1176/appi.ajp.2016.15111419.

Velthorst, E., Meyer, E.C., Giuliano, A.J., Addington, J., Cadenhead, K.S., Cannon, T.D., et al., 2019. Neurocognitive profiles in the prodrome to psychosis in NAPLS-1. Schizophr. Res. 204, 311–319. https://doi.org/10.1016/j.schres.2018.07.038.

Vickerstaff, V., Omar, R.Z., Ambler, G., 2019. Methods to adjust for multiple comparisons in the analysis and sample size calculation of randomised controlled trials with multiple primary outcomes. BMC Med. Res. Methodol. 19, 129. https://doi.org/10.1186/s12874-019-0754-4.

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., Wykes, T., 2021. Effectiveness, Core elements, and moderators of response of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 78, 848–858. https://doi.org/10.1001/jamapsychiatry.2021.0620.

Walter, M., Alizadeh, S., Jamalabadi, H., Lueken, U., Dannlowski, U., Walter, H., et al., 2019. Translational machine learning for psychiatric neuroimaging. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 91, 113–121. https://doi.org/10.1016/j.pnpbp.2018.09.014.

Wechsler, D., 1997. Wechsler Adult Intelligence Scale. Psychological Corporation, San Antonio.

Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168, 472–485. https://doi.org/10.1176/appi.ajp.2010.10060855.

5. Discussion

Psychotic disorders are commonly accompanied by cognitive and functional decline. CT is an effective therapy approach to address these impairments, yet the response is heterogeneous. Several markers including sociodemographic, environmental, biological, functional, or cognitive characteristics are shown to be predictive of a good therapy response on a group-based level. However, it remains unclear who benefits from CT approaches on a single-subject level. ML studies using cognitive data may provide a useful approach to disentangle the treatment response to CT at the single subject level, yet robust evidence is needed to allow translation into everyday clinical practice.

In the present PoC study, we built an ML classification model predictive of social functioning in response to 10 hours of CT intervention based on cognitive data. By monitoring changes in social functioning following CT, we aimed to define a cognitive pattern predictive of a good therapy response in order to identify those who benefit from cognitive remediation at the individual level. The following discussion addresses previous research to provide context for our findings on predicting the individual treatment response to CT.

5.1. Machine learning classification model

Our ML classification model based on cognitive baseline data was able to discriminate between GF and PF in a naturalistic sample of ROP patients from the multicentric PRONIA study with a BAC of 66.4%. In order to test the model's predictive ability in response to CT, it was applied to the SCT and TAU groups of the intervention sample at T0 and FU. At T0, the model differentiated between GF and PF with a BAC of 59.3%. At FU, the BAC increased to 64.8%. These results suggest that cognitive baseline data alone can be used to predict treatment response to CT in patients with ROP.

Recent ML studies on predicting treatment response to CT or functional outcomes have yielded similar classification accuracies: in their neuroimaging-based ML classification study, Haas et al. differentiated between patients who either maintained or improved their level of social sensory processing through CT with a sensitivity of 65.4% [14]. The original classification model differentiating between patients with ROP and HC showed a BAC of 65.5%. This classification accuracy was shown to be within the expected range observed in several neuroimaging-based classification studies [80].

In the ML study predicting functional outcomes based on cognitive baseline data performed by Squarcina et al. [79] mentioned above, global- and role functioning could be predicted in patients with CHR for psychosis and ROD with a BAC of 61%. Interestingly, the classification model for predicting social functioning was not significant. Several reasons can be considered for this result deviating from ours.

First, the literature describes cognitive clusters for both patients with CHR for psychosis and ROP, which differ in terms of variability and severity of cognitive decline. Within patients with CHR for psychosis, four different cognitive clusters have been described [81]. Patients in the severely impaired cluster are characterized by profound impairments in the cognitive domains of processing speed and memory, which are particularly associated with social functioning [8,82,83]. In contrast, only 2 cognitive clusters were identified for patients with ROP, which are characterized by moderate to mild cognitive impairment in contrast to HC [40,41]. Cognitive impairments were seen in the domains of processing speed, executive functioning, verbal and visual memory, and social cognition. Impairments in social cognition have been shown to be a good prognostic indicator of poor social functional outcomes [8,69]. It must be considered that higher cognitive variability and more severe cognitive impairment in the CHR group for psychosis examined by Squarcina et al. may have limited ML prediction.

Second, we used a slightly larger set of cognitive predictors to predict social functioning. These included not only correct responses but also omissions and errors on working memory and attention tests, which might have led to a higher BAC of our classification model.

In conclusion, our cognition-based classification model for predicting treatment response to CT, as measured by improvements in social functioning, performs similarly or even better

than the studies mentioned above. This highlights the utility of cognitive baseline data in predicting therapy response to CT.

Current research has shown that particularly in FEP or ROP, cognitive data may provide an excellent proxy for outcome predictions. The authors of a recent multi-task deep learning study observed that neuroimaging approaches are less accurate in early psychosis, as there are mild structural brain changes in the early stages of the disease [84]. Using direct MRI data with and without cognitive assessment, they performed a deep learning classification that discriminated between patients with early psychosis and HC. When cognitive assessment was included in the analysis, accuracy, F1 score, and specificity were improved by 3.9, 4.4 and 8.5%, respectively.

These findings are consistent with the results of a recent ML study that employed clinical, neurocognitive, and neuroimaging data to differentiate patients with ROP from those with ROD [85]. The classification model based on clinical and neurocognitive data exhibited a BAC of 79% outperforming the neuroimaging model showing a BAC of 62.5%.

In a further ML study, SVMs were used to predict the diagnostic outcome at 2-year FU in patients with early-onset schizophrenia spectrum disorders (SSD). The authors found that clinical and neurocognitive variables had the highest predictive value for a diagnostic outcome of SSD, as opposed to neuroimaging and biochemical variables which did not provide additional predictive value [86].

In light of the findings presented and in consideration of the aforementioned studies, the use of cognitive data for the prediction of functional outcomes, particularly in the context of FEP or ROP, is a promising avenue that merits further investigation.

Upon closer examination of our model's predictive ability, it appears to be highly sensitive in predicting GF but lacks specificity resulting in a poor prediction of PF. In a longitudinal prognostic study, the authors compared risk estimates provided by algorithms and clinicians in predicting the transition to psychosis in CHR patients from the PRONIA sample using multimodal ML models [87]. It could be observed that clinicians attained a high BAC by effectively ruling out (high specificity) but ineffectively ruling in (low sensitivity) psychosis transition. In contrast, algorithms showed high sensitivity but low specificity. A cybernetic risk calculator combining all algorithmic and human components predicted psychosis with a high BAC, sensitivity, and specificity.

Consistent with these findings, the original PRONIA study [76] also demonstrated that the most effective prediction of social functioning in patients with CHR for psychosis was achieved through combined prediction models that incorporated both algorithmic information and information provided by clinicians.

In this context, it would be worthwhile to investigate whether our classification model predicting the treatment response to CT could be boosted by incorporating additional

algorithmic information from clinically assessed neurocognitive data. Once the findings of this small-scale PoC study are replicated in larger studies, it would be a valuable scientific objective to pursue.

5.2. Cognitive pattern predictive of individual social functional improvement

Applying our original classification model to the CT intervention sample allowed us to compare the predicted individual changes in social functioning between the SCT and the TAU groups following CT. Our results showed a significant interaction effect of the group and cognitive pattern changes on the predicted social functioning level in response to the intervention. This result suggests that it is possible to recognize individual cognitive patterns predictive of therapy response to CT using SVM.

Previous research aligns with our findings, though, to the best of our knowledge, no study has specifically examined the individual prediction of social functioning in response to CT in patients with ROP based on cognitive data. However, cognitive performance has been shown to predict functional outcomes on a group-based level.

A 2015 longitudinal study demonstrated that both social cognition and neurocognitive tasks predicted functional outcomes, including social functioning, with small to medium effect sizes after 2-4 weeks [88].

Similarly, a 2019 review by Silberstein and Harvey concluded that cognitive test performance is broadly related to functioning and more predictive of functional impairment than psychosis severity [89]. They further emphasized the role of introspective accuracy (IA)—the ability to assess one's cognitive abilities—in predicting everyday functional deficits. While IA of neurocognition predicts non-social outcomes, IA of social cognition better predicts social functioning.

In our classification model's cognitive pattern predictive of improvements in social functioning, the most prominent feature weights were found within the cognitive domains of processing speed, attention and vigilance, and verbal fluency.

These results are in line with previous findings. In their meta-analysis investigating the relationship between neuro- and social cognitive domains and functional outcome, Fett et al. found that social functioning was most strongly associated with the domain of attention and vigilance, while community functioning had the strongest associations with verbal fluency, verbal learning and memory, and processing speed [8].

In a longitudinal study investigating the predictive value of neurocognition and negative symptoms on functional outcome in FEP, the authors found that verbal memory, processing speed, and attention, as well as the severity of negative symptoms, were related to functional outcome [90]. Specifically, poor performance on cognitive tasks addressing attention, as well as high severity of negative symptoms at intake, were predictive of poor global psychosocial functioning and poor work performance. Verbal memory impairment was a significant predictor of relationship impairments, which are characteristic of impaired social functioning, while impairments in processing speed and attention domains were not.

In a recently published longitudinal study by Lindgren et al. investigating the associations between neurocognition, social cognition, and functional outcomes, higher levels of processing speed were associated with a better 1-year outcome in terms of remission, occupational status, and maintaining life goals [69]. Interestingly, verbal memory and motor performance factors did not show significant associations with 1-year clinical or functional outcomes.

The cognitive domain of processing speed seems to be of particular importance for the prediction of social functioning. In addition to the correlation between processing speed and social functioning [69,91], it appears to mediate impairments in attention, executive functions, verbal memory, verbal fluency, social cognition, and functional outcomes [6]. Furthermore, studies have demonstrated that preserved processing speed [82] and attention [92] are crucial for facial emotion recognition, which is strongly associated with social functioning [91,92]. In conjunction with our results, it can be assumed that the cognitive domain of processing speed can serve as an important predictor of social functioning and thus of treatment response to CT.

Although there is a general consensus on the cognitive domains that predict functional outcomes in psychosis, it is noteworthy that the various dimensions of global, social, and role functioning are linked to different cognitive domains. In a longitudinal study investigating the correlation between neurocognition and negative symptoms with social and role functioning, the authors observed that negative symptoms played a mediating role in the relationship between composite neurocognition and social and role functioning [61]. After removing negative symptom items that overlap with social and role functioning measures, the relationship between neurocognition and social and role functioning was strengthened. Further, regression analyses showed that negative symptoms accounted for a unique variance in social and role functioning at both baseline and FU. These findings suggest that negative symptoms might contribute to heightened variability within cognitive and functional domains, complicating the prediction of functional outcomes relying on cognitive information.

In conclusion, the cognitive domains of processing speed, attention and vigilance, and verbal fluency, appear to predict individual functional outcomes in psychosis. Negative symptoms contribute to cognitive variability and act as a mediator in the relationship between neurocognition and functional outcomes, thereby affecting the prediction of social functioning. Further research is required to ascertain the extent to which negative symptoms impact these cognitive domains and to validate our classification model. Furthermore, future studies should investigate whether the incorporation of IA measures could enhance our model's predictive accuracy.

5.3. Limitations

There are some limitations to the interpretation of our findings that need to be addressed. First, in our ML study, we were unable to sufficiently replicate the evidence-based effects of CT interventions on cognitive and functional outcomes in our intervention sample of 54 ROP patients. At FU, social functioning had increased significantly in both SCT and TAU groups, without showing significant interactions between the groups. However, upon examining social functioning within the subgroups of GF and PF, a significant group-by-time interaction was observed, with GF showing significant improvements in social functioning following CT while social functioning in PF remained unchanged. When looking at the cognitive domains within the intervention sample, no significant improvements in cognitive domains over the study period nor significant group-per-time interactions between SCT and TAU participants were observed. Due to the limited modulation of social functioning in both SCT and TAU groups between T0 and FU, clear differentiation between responders and non-responders to CT is challenging which could have potentially weakened the predictive ability of our classification model. However, this study should be understood as a small-scale PoC study aimed at determining the utility of cognitive baseline data for predicting social functioning in ROP. The primary objective of the statistical analyses conducted on the intervention sample was not to ascertain primary (cognitive) or secondary (social functioning) outcomes. Rather, the aim was to identify the characteristics of an early therapy response to CT and to determine how this can be effectively identified [70]. As our prediction model of social functioning was constructed using only cognitive baseline data, we can discount the possibility that the absence of cognitive variability in response to CT within the intervention sample has reduced the model's predictive capability. Nevertheless, this issue should be addressed in studies with larger intervention samples showing greater functional variability.

Second, we employed a relatively short intervention period of 10 hours of CT over the course of 5 weeks with the aim to keep the intervention duration comparable to that of clinical treatment [70], following the treatment and intervention length that appears to be common across many health centers in Europe [93]. The authors of a recent meta-analysis comparing 73 RCTs on CT remediation observed that CT duration did not affect cognitive, symptom, or functional outcomes [54]. However, we cannot claim that participants who did not exhibit improvements in social functioning or positive changes in cognitive patterns in our study might experience cognitive and functional enhancements with a longer duration or a slightly different form of intervention, or through the implementation of alternative intervention protocols.

Finally, due to the small sample size selected for this PoC study and the modest functional variability within participants in the intervention sample, it was not possible to identify direct markers beyond the indirect markers of good treatment response to CT that we found. Larger trials with more participants replicating the results of our study would allow us to validate

our study protocol. Additionally, once the study protocol is validated, those individuals showing the largest changes in cognitive patterns predictive of social functioning could be identified to analyze cognitive characteristics predictive of treatment response to CT.

5.4. Outlook

The present study shows that it is possible to predict individual social functioning in response to CT intervention using baseline cognitive data. Information contributing to the predictive cognitive pattern of good treatment response is found in the cognitive domains of processing speed, attention and vigilance, and verbal fluency. These findings highlight the utility of ML approaches for predicting clinical outcomes at the single-subject level, paving the way for more personalized therapy approaches. However, this is a small-scale PoC study with a small intervention sample showing relatively modest variability in cognitive domains and functional outcomes. To validate our findings and to define the cognitive and clinical characteristics of those individuals who respond well to CT intervention, larger studies with participants showing greater cognitive and functional variability in response to CT are needed. In further steps, it would be interesting to analyze whether the addition of algorithmic information to the predictive cognitive data could increase the specificity of our model in order to improve the identification of individuals who are more likely not to respond to CT. Furthermore, the addition of self-rating information to assess IA would be a worthwhile attempt to further improve the predictive power of the model, as cognitive IA has been found to be particularly predictive of functional outcome. A final interesting step would be to further analyze the relationship between negative symptoms and the cognitive domains predictive of social functioning, as negative symptoms seem to mediate the relationship between neurocognition and functional outcomes. Much more research is needed in this field to gain a better understanding of the factors that contribute to a good response to CT.

6. Literaturverzeichnis

1 Sheffield JM, Karcher NR, Barch DM. Cognitive Deficits in Psychotic Disorders: A Lifespan Perspective. *Neuropsychol Rev*. 2018;28(4):509-533. doi:10.1007/s11065-018-9388-2.

2 Chan V. Schizophrenia and Psychosis: Diagnosis, Current Research Trends, and Model Treatment Approaches with Implications for Transitional Age Youth. *Child Adolesc Psychiatr Clin N Am*. 2017;26(2):341-366. doi:10.1016/j.chc.2016.12.014.

3 Harvey PD, Bosia M, Cavallaro R, et al. Cognitive dysfunction in schizophrenia: An expert group paper on the current state of the art. *Schizophr Res Cogn*. 2022;29:100249. doi:10.1016/j.scog.2022.100249.

4 Dwyer DB, Falkai P, Koutsouleris N. Machine Learning Approaches for Clinical Psychology and Psychiatry. *Annual Review of Clinical Psychology*. 2018;(14):91-118. clinpsy.annualreviews.org.

5 Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research*. 2004;72(1):41-51. doi:10.1016/j.schres.2004.09.009.

6 Cassetta BD, Goghari VM. Working memory and processing speed training in schizophrenia: study protocol for a randomized controlled trial. *Trials*. 2016;17. doi:10.1186/s13063-016-1188-5.

7 Velthorst E, Fett A-KJ, Reichenberg A, et al. The 20-Year Longitudinal Trajectories of Social Functioning in Individuals With Psychotic Disorders. *American Journal of Psychiatry*. 2017;174(11):1075-1085. doi:10.1176/appi.ajp.2016.15111419.

8 Fett A-KJ, Viechtbauer W, Dominguez M-G, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev*. 2011;35(3):573-588. doi:10.1016/j.neubiorev.2010.07.001.

9 Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry*. 2011;168(5):472-485. doi:10.1176/appi.ajp.2010.10060855.

10 Barlati S, Deste G, Peri L de, Ariu C, Vita A. Cognitive remediation in schizophrenia: current status and future perspectives. *Schizophr Res Treatment*. 2013;2013:156084. doi:10.1155/2013/156084.

11 Bellani M, Ricciardi C, Rossetti MG, Zovetti N, Perlini C, Brambilla P. Cognitive remediation in schizophrenia: the earlier the better? *Epidemiol Psychiatr Sci*. 2019;29:e57. doi:10.1017/S2045796019000532.

12 Kambeitz-Ilankovic L, Betz LT, Dominke C, et al. Multi-outcome meta-analysis (MOMA) of cognitive remediation in schizophrenia: Revisiting the relevance of human coaching and elucidating interplay between multiple outcomes. *Neurosci Biobehav Rev*. 2019;107:828-845. doi:10.1016/j.neubiorev.2019.09.031.

13 Harvey PD, McGurk SR, Mahncke H, Wykes T. Controversies in Computerized Cognitive Training. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(11):907-915. doi:10.1016/j.bpsc.2018.06.008.

14 Haas SS, Antonucci LA, Wenzel J, et al. A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis. *Neuropsychopharmacology*. 2020. doi:10.1038/s41386-020-00877-4.

15 Biagianti B, Castellaro GA, Brambilla P. Predictors of response to cognitive remediation in patients with major psychotic disorders: A narrative review. *Journal of Affective Disorders*. 2021;281:264-270. doi:10.1016/j.jad.2020.12.011.

16 Passos IC, Mwangi B, Kapczinski F. Big data analytics and machine learning: 2015 and beyond. *The Lancet Psychiatry*. 2016;3(1):13-15. doi:10.1016/S2215-0366(15)00549-0.

17 Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry*. 2013;70(10):1107-1112. doi:10.1001/jamapsychiatry.2013.155.

18 Biedermann F, Fleischhacker WW. Psychotic disorders in DSM-5 and ICD-11. *CNS Spectr*. 2016;21(4):349-354. doi:10.1017/S1092852916000316.

19 Vita A, Gaebel W, Mucci A, et al. European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia. *Eur Psychiatry*. 2022;65(1):e57. doi:10.1192/j.eurpsy.2022.2315.

20 Keefe RSE. The longitudinal course of cognitive impairment in schizophrenia: an examination of data from premorbid through posttreatment phases of illness. *J Clin Psychiatry*. 2014;75 Suppl 2:8-13. doi:10.4088/JCP.13065su1.02.

21 Allott K, van-der-El K, Bryce S, et al. Compensatory Interventions for Cognitive Impairments in Psychosis: A Systematic Review and Meta-Analysis. *Schizophr Bull*. 2020;46(4):869-883. doi:10.1093/schbul/sbz134.

22 Miley K, Hadidi N, Kaas M, Yu F. Cognitive Training and Remediation in First-Episode Psychosis: A Literature Review. *J Am Psychiatr Nurses Assoc*. 2020;26(6):542-554. doi:10.1177/1078390319877952.

23 Ophey A, Wenzel J, Paul R, et al. Cognitive Performance and Learning Parameters Predict Response to Working Memory Training in Parkinson's Disease. *J Parkinsons Dis*. 2022;12(7):2235-2247. doi:10.3233/JPD-223448.

24 Koutsouleris N, Davatzikos C, Bottlender R, et al. Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. *Schizophr Bull*. 2012;38(6):1200-1215. doi:10.1093/schbul/sbr037.

25 Puntis S, Minichino A, Crescenzo F de, Cipriani A, Lennox B, Harrison R. Specialised early intervention teams for recent-onset psychosis. *Cochrane Database Syst Rev*. 2020;11(11):CD013288. doi:10.1002/14651858.CD013288.pub2.

26 Kirkbride JB, Hameed Y, Ankireddypalli G, et al. The Epidemiology of First-Episode Psychosis in Early Intervention in Psychosis Services: Findings From the Social Epidemiology of Psychoses in East Anglia SEPEA Study. *American Journal of Psychiatry*. 2017;174(2):143-153. doi:10.1176/appi.ajp.2016.16010103.

27 Arciniegas DB. Psychosis. *Continuum (Minneap Minn)*. 2015;21(3 Behavioral Neurology and Neuropsychiatry):715-736. doi:10.1212/01.CON.0000466662.89908.e7.

28 Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161(2 Suppl):1-56.

29 Lieberman JA, First MB. Psychotic Disorders. *N Engl J Med*. 2018;379(3):270-280. doi:10.1056/NEJMra1801490.

30 Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951-962. doi:10.1016/S0140-6736(13)60733-3.

31 Borison RL. The role of cognition in the risk--benefit and safety analysis of antipsychotic medication. *Acta Psychiatr Scand Suppl*. 1996;389:5-11. doi:10.1111/j.1600-0447.1996.tb05942.x.

32 Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology*. 2020;172:107704. doi:10.1016/j.neuropharm.2019.107704.

33 Uren J, Cotton SM, Killackey E, Saling MM, Allott K. Cognitive clusters in first-episode psychosis: Overlap with healthy controls and relationship to concurrent and prospective symptoms and functioning. *Neuropsychology*. 2017;31(7):787-797. doi:10.1037/neu0000367.

34 Mollon J, David AS, Zammit S, Lewis G, Reichenberg A. Course of Cognitive Development From Infancy to Early Adulthood in the Psychosis Spectrum. *JAMA Psychiatry*. 2018;75(3):270-279. doi:10.1001/jamapsychiatry.2017.4327.

35 Carrión RE, Walder DJ, Auther AM, et al. From the psychosis prodrome to the first-episode of psychosis: No evidence of a cognitive decline. *J Psychiatr Res*. 2018;96:231-238. doi:10.1016/j.jpsychires.2017.10.014.

36 Fett A-KJ, Reichenberg A, Velthorst E. Lifespan evolution of neurocognitive impairment in schizophrenia - A narrative review. *Schizophr Res Cogn*. 2022;28:100237. doi:10.1016/j.scog.2022.100237.

37 Fett A-KJ, Velthorst E, Reichenberg A, et al. Long-term Changes in Cognitive Functioning in Individuals With Psychotic Disorders: Findings From the Suffolk County Mental Health Project. *JAMA Psychiatry*. 2020;77(4):387-396. doi:10.1001/jamapsychiatry.2019.3993.

38 Lui SSY, Zhang R-T, Lau WYS, et al. Prospective Memory Influences Social Functioning in People With First-Episode Schizophrenia: A Network Analysis and Longitudinal Study. *J Clin Psychiatry*. 2022;83(2). doi:10.4088/JCP.21m14114.

39 Veltro F, Mazza M, Vendittelli N, Alberti M, Casacchia M, Roncone R. A comparison of the effectiveness of problem solving training and of cognitive-emotional rehabilitation on neurocognition, social cognition and social functioning in people with schizophrenia. *Clin Pract Epidemiol Ment Health*. 2011;7:123-132. doi:10.2174/1745017901107010123.

40 Amoretti S, Rabelo-da-Ponte FD, Rosa AR, et al. Cognitive clusters in first-episode psychosis. *Schizophrenia Research*. 2021;237:31-39. doi:10.1016/j.schres.2021.08.021.

41 Wenzel J, Haas SS, Dwyer DB, et al. Cognitive subtypes in recent onset psychosis: distinct neurobiological fingerprints? *Neuropsychopharmacology*. 2021;46(8):1475-1483. doi:10.1038/s41386-021-00963-1.

42 Barder HE, Sundet K, Rund BR, et al. Neurocognitive development in first episode psychosis 5 years follow-up: associations between illness severity and cognitive course. *Schizophrenia Research*. 2013;149(1-3):63-69. doi:10.1016/j.schres.2013.06.016.

43 Hoff AL, Svetina C, Shields G, Stewart J, DeLisi LE. Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophrenia Research*. 2005;78(1):27-34. doi:10.1016/j.schres.2005.05.010.

44 Bonner-Jackson A, Grossman LS, Harrow M, Rosen C. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. *Compr Psychiatry*. 2010;51(5):471-479. doi:10.1016/j.comppsych.2010.02.005.

45 Øie M, Sundet K, Rund BR. Neurocognitive decline in early-onset schizophrenia compared with ADHD and normal controls: evidence from a 13-year follow-up study. *Schizophr Bull*. 2010;36(3):557-565. doi:10.1093/schbul/sbn127.

46 Zanelli J, Mollon J, Sandin S, et al. Cognitive Change in Schizophrenia and Other Psychoses in the Decade Following the First Episode. *American Journal of Psychiatry*. 2019;176(10):811-819. doi:10.1176/appi.ajp.2019.18091088.

47 Abdel-Baki A, Ouellet-Plamondon C, Salvat É, Grar K, Potvin S. Symptomatic and functional outcomes of substance use disorder persistence 2 years after admission to a first-episode psychosis program. *Psychiatry Research*. 2017;247:113-119. doi:10.1016/j.psychres.2016.11.007.

48 Hakulinen C, McGrath JJ, Timmerman A, et al. The association between early-onset schizophrenia with employment, income, education, and cohabitation status: nationwide

study with 35 years of follow-up. *Soc Psychiatry Psychiatr Epidemiol*. 2019;54(11):1343-1351. doi:10.1007/s00127-019-01756-0.

49 Schoenbaum M, Sutherland JM, Chappel A, et al. Twelve-Month Health Care Use and Mortality in Commercially Insured Young People With Incident Psychosis in the United States. *Schizophr Bull*. 2017;43(6):1262-1272. doi:10.1093/schbul/sbx009.

50 Lo Cascio N, Curto M, Pasqualetti P, et al. Impairment in Social Functioning differentiates youth meeting Ultra-High Risk for psychosis criteria from other mental health help-seekers: A validation of the Italian version of the Global Functioning: Social and Global Functioning: Role scales. *Psychiatry Research*. 2017;253:296-302. doi:10.1016/j.psychres.2017.04.008.

51 Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. *J Child Adolesc Psychopharmacol*. 2016;26(5):410-427. doi:10.1089/cap.2015.0097.

52 Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: update and future directions. *American Journal of Psychiatry*. 2014;171(5):510-522. doi:10.1176/appi.ajp.2013.13081075.

53 van der Ven E, Scodes J, Basaraba C, et al. Trajectories of occupational and social functioning in people with recent-onset non-affective psychosis enrolled in specialized early intervention services across New York state. *Schizophrenia Research*. 2020;222:218-226. doi:10.1016/j.schres.2020.05.051.

54 Lejeune JA, Northrop A, Kurtz MM. A Meta-analysis of Cognitive Remediation for Schizophrenia: Efficacy and the Role of Participant and Treatment Factors. *Schizophr Bull*. 2021;47(4):997-1006. doi:10.1093/schbul/sbab022.

55 McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry*. 2007;164(12):1791-1802. doi:10.1176/appi.ajp.2007.07060906.

56 Ueland T, Rund BR. Cognitive remediation for adolescents with early onset psychosis: a 1-year follow-up study. *Acta Psychiatrica Scandinavica*. 2005;111(3):193-201. doi:10.1111/j.1600-0447.2004.00503.x.

57 Fisher M, Holland C, Subramaniam K, Vinogradov S. Neuroplasticity-based cognitive training in schizophrenia: an interim report on the effects 6 months later. *Schizophr Bull*. 2010;36(4):869-879. doi:10.1093/schbul/sbn170.

58 Lindenmayer J-P, McGurk SR, Mueser KT, et al. A randomized controlled trial of cognitive remediation among inpatients with persistent mental illness. *Psychiatr Serv*. 2008;59(3):241-247. doi:10.1176/ps.2008.59.3.241.

59 Reeder C, Huddy V, Cella M, et al. A new generation computerised metacognitive cognitive remediation programme for schizophrenia (CIRCuiTS): a randomised controlled trial. *Psychological Medicine*. 2017;47(15):2720-2730. doi:10.1017/S0033291717001234.

60 Ventura J, Ered A, Gretchen-Doorly D, et al. Theory of mind in the early course of schizophrenia: stability, symptom and neurocognitive correlates, and relationship with functioning. *Psychological Medicine*. 2015;45(10):2031-2043. doi:10.1017/S0033291714003171.

61 Meyer EC, Carrión RE, Cornblatt BA, et al. The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal Study. *Schizophr Bull*. 2014;40(6):1452-1461. doi:10.1093/schbul/sbt235.

62 Vita A, Barlati S, Ceraso A, et al. Effectiveness, Core Elements, and Moderators of Response of Cognitive Remediation for Schizophrenia: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Psychiatry*. 2021;78(8):848-858. doi:10.1001/jamapsychiatry.2021.0620.

63 Katsumi A, Hoshino H, Fujimoto S, et al. Effects of cognitive remediation on cognitive and social functions in individuals with schizophrenia. *Neuropsychol Rehabil*. 2019;29(9):1475-1487. doi:10.1080/09602011.2017.1409639.

64 Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry*. 2005;62(9):975-983. doi:10.1001/archpsyc.62.9.975.

65 Kurtz MM, Seltzer JC, Fujimoto M, Shagan DS, Wexler BE. Predictors of change in life skills in schizophrenia after cognitive remediation. *Schizophrenia Research*. 2009;107(2-3):267-274. doi:10.1016/j.schres.2008.10.014.

66 Huddy V, Reeder C, Kontis D, Wykes T, Stahl D. The effect of working alliance on adherence and outcome in cognitive remediation therapy. *J Nerv Ment Dis*. 2012;200(7):614-619. doi:10.1097/NMD.0b013e31825bfc31.

67 Kontis D, Huddy V, Reeder C, Landau S, Wykes T. Effects of age and cognitive reserve on cognitive remediation therapy outcome in patients with schizophrenia. *Am J Geriatr Psychiatry*. 2013;21(3):218-230. doi:10.1016/j.jagp.2012.12.013.

68 Keshavan MS, Eack SM, Wojtalik JA, et al. A broad cortical reserve accelerates response to cognitive enhancement therapy in early course schizophrenia. *Schizophrenia Research*. 2011;130(1-3):123-129. doi:10.1016/j.schres.2011.05.001.

69 Lindgren M, Holm M, Kieseppä T, Suvisaari J. Neurocognition and Social Cognition Predicting 1-Year Outcomes in First-Episode Psychosis. *Front Psychiatry*. 2020;11:603933. doi:10.3389/fpsyt.2020.603933.

70 Walter N, Wenzel J, Haas SS, et al. A multivariate cognitive approach to predict social functioning in recent onset psychosis in response to computerized cognitive training. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023:110864. doi:10.1016/j.pnpbp.2023.110864.

71 Bzdok D, Meyer-Lindenberg A. Machine Learning for Precision Psychiatry: Opportunities and Challenges. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(3):223-230. doi:10.1016/j.bpsc.2017.11.007.

72 Stephan KE, Schlagenhauf F, Huys QJM, et al. Computational neuroimaging strategies for single patient predictions. *NeuroImage*. 2017;145(Pt B):180-199. doi:10.1016/j.neuroimage.2016.06.038.

73 James G, Witten D, Hastie T, Tibshirani R. *An Introduction to Statistical Learning*. New York, NY: Springer New York; 2013.

74 Sidey-Gibbons JAM, Sidey-Gibbons CJ. Machine learning in medicine: a practical introduction. *BMC Med Res Methodol*. 2019;19(1):64. doi:10.1186/s12874-019-0681-4.

75 Kambeitz-Ilankovic L, Vinogradov S, Wenzel J, et al. Multivariate pattern analysis of brain structure predicts functional outcome after auditory-based cognitive training interventions. *NPJ Schizophr*. 2021;7(1):40. doi:10.1038/s41537-021-00165-0.

76 Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, et al. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or With Recent-Onset Depression: A Multimodal, Multisite Machine Learning Analysis. *JAMA Psychiatry*. 2018;75(11):1156-1172. doi:10.1001/jamapsychiatry.2018.2165.

77 Hedges EP, Dickson H, Tognin S, et al. Verbal memory performance predicts remission and functional outcome in people at clinical high-risk for psychosis. *Schizophr Res Cogn*. 2022;28:100222. doi:10.1016/j.scog.2021.100222.

78 Stouten LH, Veling W, Laan W, van der Helm M, van der Gaag M. Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis. *Schizophrenia Research*. 2014;158(1-3):113-119. doi:10.1016/j.schres.2014.06.023.

79 Squarcina L, Kambeitz-Ilankovic L, Bonivento C, et al. Relationships between global functioning and neuropsychological predictors in subjects at high risk of psychosis or with a recent onset of depression. *World J Biol Psychiatry*. 2022:1-9. doi:10.1080/15622975.2021.2014955.

80 Kambeitz J, Kambeitz-Ilankovic L, Leucht S, et al. Detecting neuroimaging biomarkers for schizophrenia: a meta-analysis of multivariate pattern recognition studies. *Neuropsychopharmacology*. 2015;40(7):1742-1751. doi:10.1038/npp.2015.22.

81 Velthorst E, Meyer EC, Giuliano AJ, et al. Neurocognitive profiles in the prodrome to psychosis in NAPLS-1. *Schizophrenia Research*. 2019;204:311-319. doi:10.1016/j.schres.2018.07.038.

82 Eack SM, Mermon DE, Montrose DM, et al. Social cognition deficits among individuals at familial high risk for schizophrenia. *Schizophr Bull*. 2010;36(6):1081-1088. doi:10.1093/schbul/sbp026.

83 Peña J, Ibarretxe-Bilbao N, Sánchez P, et al. Mechanisms of functional improvement through cognitive rehabilitation in schizophrenia. *J Psychiatr Res*. 2018;101:21-27. doi:10.1016/j.jpsychires.2018.03.002.

84 Wen Y, Zhou C, Chen L, et al. Bridging structural MRI with cognitive function for individual level classification of early psychosis via deep learning. *Front Psychiatry*. 2022;13:1075564. doi:10.3389/fpsyt.2022.1075564.

85 Lalousis PA, Wood SJ, Schmaal L, et al. Heterogeneity and Classification of Recent Onset Psychosis and Depression: A Multimodal Machine Learning Approach. *Schizophr Bull*. 2021;47(4):1130-1140. doi:10.1093/schbul/sbaa185.

86 Pina-Camacho L, Garcia-Prieto J, Parellada M, et al. Predictors of schizophrenia spectrum disorders in early-onset first episodes of psychosis: a support vector machine model. *Eur Child Adolesc Psychiatry*. 2015;24(4):427-440. doi:10.1007/s00787-014-0593-0.

87 Koutsouleris N, Dwyer DB, Degenhardt F, et al. Multimodal Machine Learning Workflows for Prediction of Psychosis in Patients With Clinical High-Risk Syndromes and Recent-Onset Depression. *JAMA Psychiatry*. 2021;78(2):195-209. doi:10.1001/jamapsychiatry.2020.3604.

88 Pinkham AE, Penn DL, Green MF, Harvey PD. Social Cognition Psychometric Evaluation: Results of the Initial Psychometric Study. *Schizophr Bull*. 2016;42(2):494-504. doi:10.1093/schbul/sbv056.

89 Silberstein J, Harvey PD. Cognition, social cognition, and Self-assessment in schizophrenia: prediction of different elements of everyday functional outcomes. *CNS Spectr*. 2019;24(1):88-93. doi:10.1017/S1092852918001414.

90 Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry*. 2005;162(3):495-506. doi:10.1176/appi.ajp.162.3.495.

91 Sánchez P, Ojeda N, Peña J, et al. Predictors of longitudinal changes in schizophrenia: the role of processing speed. *J Clin Psychiatry*. 2009;70(6):888-896. doi:10.4088/JCP.08m04294.

92 Lahera G, Ruiz A, Brañas A, Vicens M, Orozco A. Tiempo de reacción, velocidad de procesamiento y atención sostenida en esquizofrenia: impacto sobre el funcionamiento social. *Rev Psiquiatr Salud Ment*. 2017;10(4):197-205. doi:10.1016/j.rpsm.2017.04.001.

93 Ajnakina O, Stubbs B, Francis E, et al. Hospitalisation and length of hospital stay following first-episode psychosis: systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*. 2020;50(6):991-1001. doi:10.1017/S0033291719000904.