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Personalization in early stages of psychosis: Cognitive subtypes and the relevance of learning performance and resting-state functional MRI for neurocognitive training response

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1. List of abbreviations

APS	Auditory Processing Plateau
CCT	Computerized Cognitive Training
EMT	Emotion Matching Task
HC	Healthy Control
ML	Machine Learning
ROP	Recent Onset Psychosis
rsFC	resting-state Functional Connectivity
SP	Sensory Processing
SVM	Support Vector Machine

2. List of publications

2.1. Original publications of the doctoral thesis

Haas, S. S., Antonucci, L. A., **Wenzel, J.**, Ruef, A., Biagianti, B., Paolini, M., Rauchmann, B. S., Weiske, J., Kambeitz, J., Borgwardt, S., Brambilla, P., Meisenzahl, E., Salokangas, R. K. R., Upthegrove, R., Wood, S. J., Koutsouleris, N., & Kambeitz-Ilankovic, L. (2020). A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis. *Neuropsychopharmacology*, *0*(September), 1–8. https://doi.org/10.1038/s41386-020-00877-4

Wenzel, J., Haas, S. S., Dwyer, D. B., Ruef, A., Oeztuerk, O. F., Antonucci, L. A., von Saldern, S., Bonivento, C., Garzitto, M., Ferro, A., Paolini, M., Blautzik, J., Borgwardt, S., Brambilla, P., Meisenzahl, E., Salokangas, R. K. R., Upthegrove, R., Wood, S. J., Kambeitz, J., … PRONIA consortium. (2021). Cognitive subtypes in recent onset psychosis: distinct neurobiological fingerprints? *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *January*. https://doi.org/10.1038/s41386-021-00963-1

2.2. Publications related to the doctoral thesis

Kambeitz-Ilankovic, L., **Wenzel, J.**, Haas, S. S., Ruef, A., Antonucci, L. A., Sanfelici, R., Paolini, M., Koutsouleris, N., & Biagianti, B. (2020). Modeling Social Sensory Processing During Social Computerized Cognitive Training for Psychosis Spectrum: The Resting-State Approach. *Frontiers in Psychiatry*, *11*(November), 1–11. https://doi.org/10.3389/fpsyt.2020.554475

2.3. Conference abstracts related to the doctoral thesis

Wenzel, J., Dwyer, D. B., Ruef, A., Öztürk, Ö., Haas, S., Kambeitz, J., ... & Kambeitz-Ilankovic, L. (2020). S44. NEUROBIOLOGICAL FINGERPRINTS OF COGNITIVE SUBTYPES IN RECENT ONSET PSYCHOSIS PATIENTS. *Schizophrenia Bulletin*, *46*(Supplement_1), S49-S49.

3. Introduction

3.1. Personalization in psychiatry

Personalized medicine strives to assess proneness to disease, specify diagnosis and optimize response to intervention by taking into account individual phenomenology, (patho-)physiology, genetic predisposition and environment (Ozomaro et al., 2013). In comparison to other medical disciplines, e.g. oncology, psychiatry lags behind (Ozomaro et al., 2013). Psychiatry is particularly challenged by personalization (Marquand et al., 2016; Wardenaar & de Jonge, 2013) as most psychiatric constructs are defined by their phenomenological nature rather than based on etiological mechanisms.

Major psychiatric diagnoses, e.g. schizophrenia, comprise heterogeneous clinical symptoms (Widiger & Clark, 2000; Widiger & Samuel, 2005) which might be the result of different underlying psychopathological substrates. Furthermore, high heterogeneity in pharmacological (Wong et al., 2010) and non-pharmacological (Hofmann et al., 2012; Isaac & Januel, 2016) treatment response occurs due to heterogeneous clinical phenotypes. For this reason psychiatric syndromes are being stratified beyond phenomenology, including neurobiology and genetics to better understand possible etiological mechanisms or endophenotypes present in subtypes of the disease (Marquand et al., 2016; Wium-Andersen et al., 2017). Further, studies investigated predictors of treatment outcome related to cognitive and neural mechanisms (figure 1).

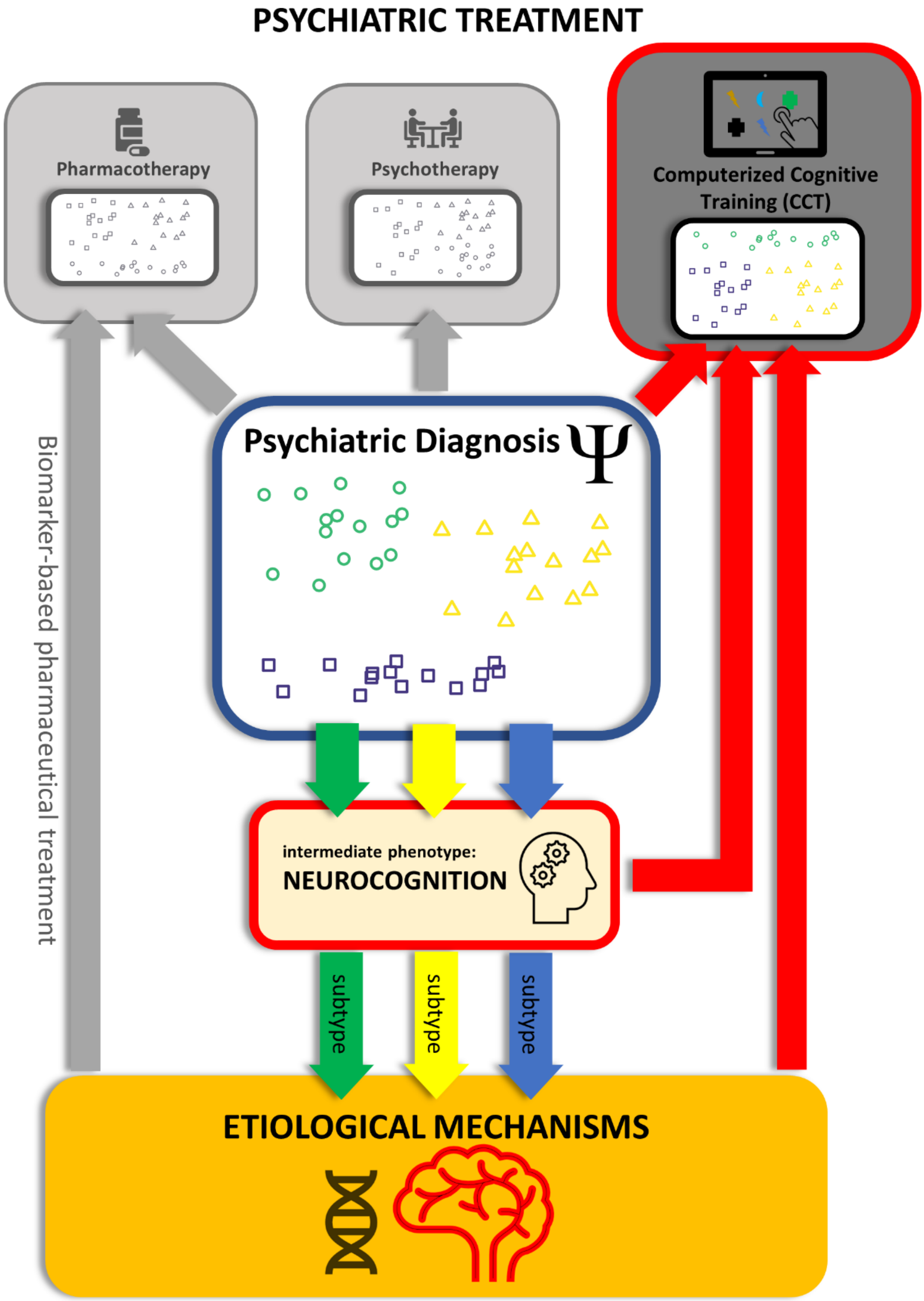

Figure 1. Research has stratified heterogeneous psychiatric diagnoses into subtypes to better understand underlying etiological mechanisms and improve response to psychiatric treatment. In schizophrenia neurocognition attracted attention as an important intermediate phenotype. The current doctoral thesis focusses on (1) neurocognitive subgroups and their relation to brain structure in ROP and (2) the impact of learning performance and functional brain characteristics on CCT.

In recent years progress in biomarker research and availability of advanced statistical techniques in psychiatry brought forward research on stratification of mental disorders (Marquand et al., 2016). Machine learning (ML) has been a major catalyst due to its potential to extract discriminant patterns of information among a large pool of (multimodal) input characteristics (Dwyer et al., 2018; Hebart & Baker, 2018). Furthermore, it approximates complex systems, e.g. the brain, where relationships appear more widespread and (non-linearly) interrelated (Davatzikos, 2004; Hebart & Baker, 2018; Lessov-Schlaggar et al., 2016).

Large multicentric initiatives benefit from statistical advances as they acquire rich data bases allowing to characterize complex and generalizable cross-modal relationships. For example, the PRONIA (Personalized Prognostic Tools for Early Psychosis Management; www.pronia.eu) consortium, a European research project with study sites in Europe and Australia, has recruited individuals suffering from recent onset psychosis (ROP), recent onset depression or at clinical high risk for psychosis. Those individuals were characterized based on clinical, neurocognitive, neurobiological and genetical data over a period of 36 months. A main goal of the consortium is to identify subgroups of patients with homogeneous profiles and link them to clinical and functional outcome. ML can be a useful tool to disentangle the complex interplay between the different data modalities obtained and generate important knowledge to understand heterogeneity in psychiatric diseases.

3.2. Neurocognition in schizophrenia

In schizophrenia the relevance of a cross-modal perspective is founded on the developmental hypothesis (Murray et al., 2017) which understands the disease as the result of maturational maladaptation and differentiates genetical, neurobiological and environmental influences. Neurocognition attracted attention as an intermediate phenotype in recent years (Gur et al., 2007; Kahn & Keefe, 2013). Dysfunctional interactions between neurocognition and social functioning or brain physiology perpetuate adverse conditions and behavior (e.g. difficulties in learning, social isolation, drug abuse etc.) which ultimately increase vulnerability to schizophrenia (Kahn & Keefe, 2013; Murray et al., 2017).

Importantly, neurocognitive deficits strongly relate to functioning and functional outcome (Gur et al., 2007; Kahn & Keefe, 2013). Patients show general (Reichenberg in Payne et al., 2011) and specific neurocognitive impairment which interferes with social and occupational functioning (Bowie et al., 2006; Kahn & Keefe, 2013; Mohamed et al., 2008). Verbal memory and processing speed exhibit strongest deficits (Sheffield et al., 2018). Further, they are associated with poor community functioning, social skill acquisition and problem solving (Green, 1996).

However, heterogeneity in neurocognitive impairment in schizophrenia has been reported in numerous studies (Green et al., 2019) and dates back to Kraepelin describing 'dementia praecox' in a group of individuals with schizophrenia (Kraepelin et al., 1919). Affective and non-affective psychosis clustering studies, that use unsupervised ML to detect homogenous subtypes (see 3.3.2 for an explanation of the clustering method), often show three-subtype-solutions with different neurocognitive profiles. Findings in schizophrenia derive no clear consensus on number of subtypes and distinctive cognitive domains. Neurocognitive impairment varies from near-normal functioning to severe impairment and evidence converges only regarding the existence of a severely impaired subtype (Green et al., 2019).

Severely impaired neurocognitive subtypes show mixed clinical profiles across studies. While in some studies (Lewandowski et al., 2014; Wells et al., 2015) severe cognitive impairment includes burden on positive, negative and general symptoms, others find high negative symptoms in the impaired subgroup but significantly lower positive symptoms (Green et al., 2013). However, they are associated with a clear profile of general (Dickinson et al., 2020; Green et al., 2013; Van Rheenen et al., 2018; Wells et al., 2015) and occupational functioning deficits (Dickinson et al., 2020; Lewandowski et al., 2014) emphasizing the relevance for targeted clinical care.

Neurocognitive impairments have commonly been associated with structural and functional brain alterations in schizophrenia (Antonova et al., 2004; Fornito et al., 2011; Kim et al., 2018; Sheffield et al., 2017). Likewise, varying cognitive impairment in subgroups is reflected in differences in structural neural substrates suggesting differences in etiology (Geisler et al., 2015; Gould et al., 2014; Van Rheenen et al., 2018; Weinberg et al., 2016). For example, a study investigated grey matter differences (Van Rheenen et al., 2017) in a cross-diagnostic sample of individuals with schizophrenia and schizoaffective disorder which was clustered into 'preserved', 'deteriorated' and 'compromised' subtypes previously (Wells et al., 2015). A unique pattern of brain volume atrophy across frontal, temporal, and occipital regions and significant overall brain volume reduction differentiated the most severely impaired subtype from the others.

Most of the studies investigated neurocognitive heterogeneity in patients who suffer from chronic schizophrenia. In this case, prolonged antipsychotic medication intake might have influenced cognitive performance (Van Rheenen et al., 2017) and brain structure (Haijma et al., 2013). It remains unclear if cognitive heterogeneity is the consequence of illness progression and medication effects and if it is present early, i.e. at the illness onset, or even prior to outbreak of psychotic symptomatology.

3.2.1. Heterogeneity in treatment response to computerized cognitive trainings

Cognitive deficits in psychotic disorders can be ameliorated through neuroplasticity-based computerized cognitive training (CCT; Biagianti et al., 2016; Harvey et al., 2018). CCT shows small to medium effect sizes on cognition (Kambeitz-Ilankovic et al., 2019; Keefe et al., 2012; McGurk et al., 2007; Medalia & Saperstein, 2013; Prikken et al., 2019; Wykes et al., 2011) and functioning (Kambeitz-Ilankovic et al., 2019; McGurk et al., 2007; Medalia & Saperstein, 2013; Prikken et al., 2019; Wykes et al., 2011) in schizophrenia-spectrum patients.

It uses a 'drill and practice' strategy to stimulate neuro-plastic responses in maldeveloped brain areas (Dale et al., 2016, 2020; Subramaniam et al., 2012; Vinogradov et al., 2012). Repetitive training of low-level perceptual processes engages primary sensory areas in visual or auditory cortex which propagate their input to higher-level brain regions. Therefore, CCT exploits neuroplasticity, i.e. the brain's adaptability to stimulation (Keshavan et al., 2015), to specifically drive modulatory responses in the brain which ultimately translate to improvements in cognitive functioning (Vinogradov et al., 2012). For example, it has been shown to increase activity in frontal, parietal, occipital and thalamic regions implicated in working memory, attention and executive functioning (Matsuda et al., 2019; Ramsay & Macdonald, 2015). Importantly, the induced plastic modulation in such regions correlates with behavioral gains (Bor et al., 2011; Haut et al., 2010; Ramsay et al., 2017; Subramaniam et al., 2012, 2014; Wexler et al., 2000; Wykes et al., 2002).

Not only local changes in activity but specifically the strengthening of connections between sensory and higher-order brain areas promote response to CCT. Studies (Fan et al., 2017; Matsuda et al., 2019) support this assumption by e.g. reporting specific resting-state Functional Connectivity (rsFC) patterns in frontal and temporal brain regions after CCT which mediate global cognition and emotion perception and regulation (Eack et al., 2016; Keshavan et al., 2017). Additionally, low baseline cognitive performance has been associated with stronger increases in thalamo-frontal connectivity after cognitive intervention (Ramsay et al., 2017). Likewise, studies tested the relevance of white matter micro-structure integrity (Subramaniam et al., 2018) and functional network modularity (Arnemann et al., 2015) in CCT and found a modulatory effect on attention and executive functioning. In sum, evidence suggests that rsFC together with white matter and brain network characteristics are important determinants for CCT success.

Learning performance during neurocognitive intervention, which determines the quality of the learning stimulus administered to the brain, might be another important modulator of treatment response. A study evaluated the effects of training an auditory processing task in patients with schizophrenia (Biagianti et al., 2016). The results suggested that the average participant reached an auditory processing plateau (APS) after around 20 hours of training. Critically, the amount of training hours needed to reach APS, was highly variable between participants and significantly correlated with global gain in cognition. This suggests that learning performance, i.e. amount of sensory processing (SP) change during the intervention, influences improvements to untrained cognitive domains in CCT.

CCT shows heterogeneity in treatment response (Isaac & Januel, 2016) which might be explained by differences in the brain's susceptibility to neuroplastic processes and the quality of the learning stimulus (induced through different learning behavior) it is exposed to. Studies are needed to simultaneously account for both aspects when evaluating its treatment response.

3.3. Machine learning as tool to improve personalization

ML can be described as a computational strategy that learns parameters at various stages of the analysis to find an optimal statistical model representative of the problem (Dwyer et al., 2018). Rooted in different philosophies (Bzdok & Meyer-Lindenberg, 2018; Hebart & Baker, 2018) classical statistics and ML provide complementary perspectives though several aspects of ML are especially suitable to improve personalization (Bzdok & Meyer-Lindenberg, 2018; Dwyer et al., 2018; Hebart & Baker, 2018):

First, ML aims at prediction of conditions by learning from data rather than predicting data based on given conditions and fixed model parameters. Complex and highly interrelated multi-dimensional concepts, like psychopathology, are more likely to be approximated by such approaches as they are less constrained by apriori assumptions. Second, ML uses mutual information from many input variables, so-called features, and enables to find their most discriminative combination. Thus it supports the development of statistical models combining high-dimensional information from behavioral, neurobiological and genetical modalities. Third, ML predicts on the level of the individual rather than reporting average measures on the level of the group. Finally, ML models are evaluated based on the performance in a test data set excluded from the model generation (out-of-sample estimate). Therefore it increases generalizability as the model can be tested across different cultural backgrounds (e.g. eastern vs. western culture) and technical standards (e.g. magnetic resonance imaging [MRI] scanner properties) which is especially valuable in multicentric initiatives (Chen et al., 2014).

ML techniques are commonly subdivided into supervised methods, that base the generation of the model on given categorical or continuous labels, and unsupervised methods, that are used to infer underlying labels in the data set based on criteria of similarity. The current doctoral thesis applied Support Vector Machine (SVM) algorithms (supervised ML) and K-means clustering (unsupervised ML), which will be described in a nutshell in the following paragraphs (figure 2).

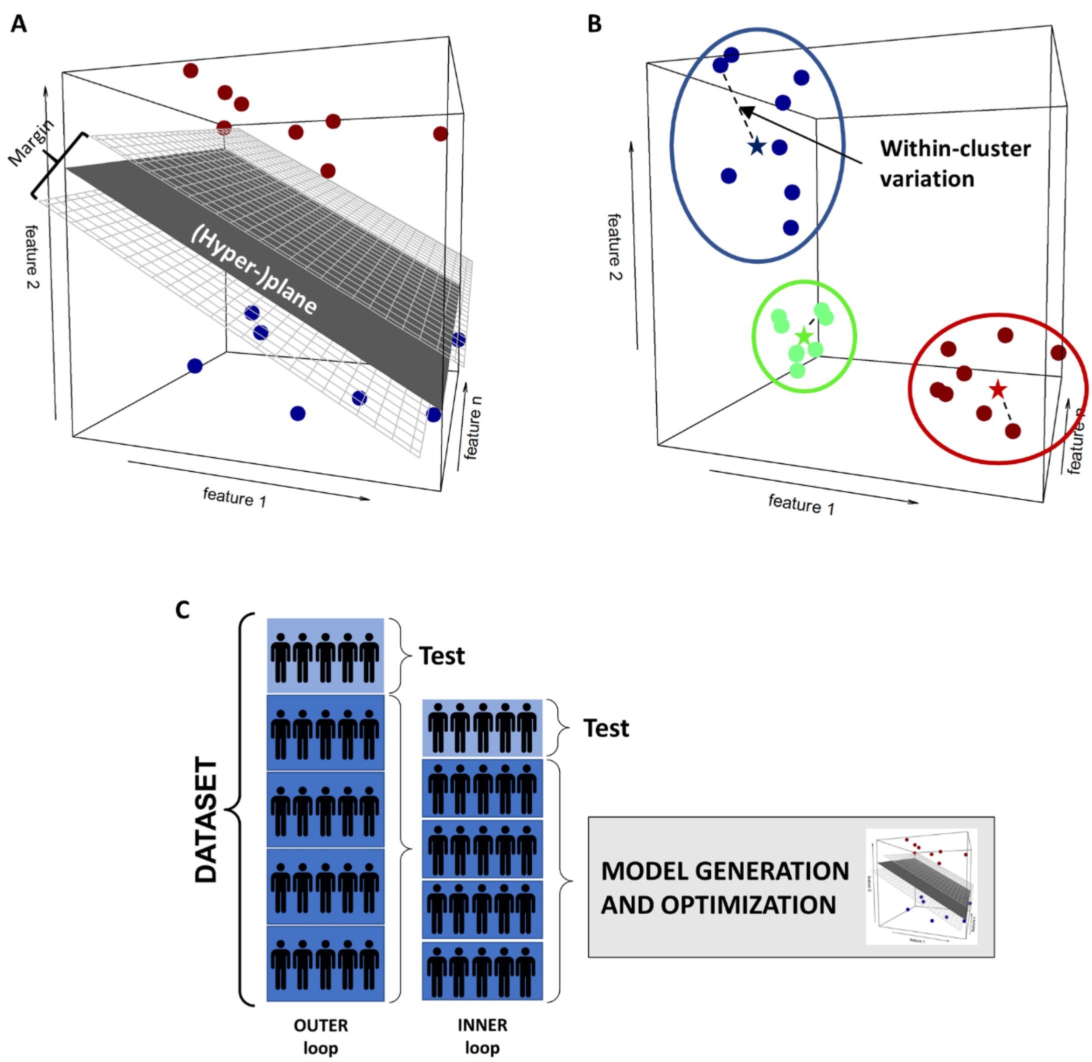

Figure 2. ML techniques and nested cross-validation. (A) SVM algorithms fit a (hyper-)plane into a n-dimensional space by optimizing the margin, i.e. the distance between the hyperplane and the observations of each label (blue and red dots). (B) K-means clustering partitions a given data set into an apriori defined number k of subgroups by minimizing the within-cluster variation, i.e. the distance between the cluster centroid (asterisk) and individual observations. (C) Nested cross-validation splits the data set into training and test folds both on an outer and inner loop. Models generated on the inner loop training folds are first evaluated on the inner loop test fold and subsequently on the outer loop test fold. This procedure is repeated until each fold has been test fold. Nested cross-validation is conducted to (1) minimize overfitting, (2) assess model generalizability and (3) optimize model parameters.

3.3.1. Supervised machine learning

A SVM algorithm is a ML technique commonly used in psychiatry due to its high interpretability (Dwyer et al., 2018). The linear SVM approach fits a decision boundary in the form of a plane ('hyperplane' when fitting to n > 3 dimensions) to classify two given labels, e.g. diagnostic entities (figure 2A; Cortes & Vapnik, 1995). The decision boundary describes an imagined border in high-dimensional space (e.g. in brain imaging data each voxel represents a dimension) separating the observations of the labels. The highest classification performance of an SVM is achieved by maximizing the distance of the decision boundary to the observations of each label (maximum margin SVM) and thereby maximizing the separation between the two groups (Cortes & Vapnik, 1995).

In complex real-world data, however, a separation of groups using a linear kernel is often not possible. Therefore, the extent of the margin is optimized by manipulating the cost parameter (soft margin SVM; Cortes & Vapnik, 1995; Dwyer et al., 2018) to balance classification accuracy and generalizability. In detail, a high cost parameter leads to a narrow margin, fits the hyperplane closely to the observations and results in a high classification accuracy. In contrast, a low cost parameter extends the margin, tolerates a certain amount of misclassifications but is less likely to model noise in the data. Therefore, it increases generalizability to observations that have not been included in model generation.

The process of optimization is commonly embedded into a scheme, e.g. nested cross-validation (figure 2C), that strictly separates the data set for model generation (training data set) from the data set for model evaluation (test data set). Nested cross-validation splits the data set into training and test folds on an outer loop and additionally, on a nested inner loop. Models are generated on the training folds of the inner loop and evaluated on the inner loop test fold. Models revealing the highest performance are then tested against the test fold of the outer loop. This procedure is repeated until each fold of both outer and inner loop has been test fold. Nested cross-validation is established to (1) minimize overfitting, (2) evaluate the generalizability to external data (e.g. from another study site or acquired using different technical devices), and (3) allow for optimization of model parameters (e.g. cost parameter). A comprehensive description of the nested cross-validation scheme applied in the papers of the doctoral thesis can be found in Koutsouleris et al. (2018).

The SVM approach enables to integrate information from a multiplicity of inputs as the algorithm 'learns' the weight of each feature when determining the position of the (hyper-)plane in the analyzed data space (Cortes & Vapnik, 1995). The weight holds information about how discriminative its associated feature is with respect to the investigated labels. The cumulative information of all features and weights for a given observation is represented by the decision value. This value captures the reliability of an observation to be classified as one label or the other.

Therefore, SVM algorithms are capable of extracting the most informative features of multivariate data and express them in a single continuous scale. This property can be useful to monitor 'multivariate' changes over time in response to interventions which is shown in the second paper of the current thesis.

3.3.2. Unsupervised machine learning

Unsupervised (ML) methods, particularly clustering (Hastie et al., 2009) and finite mixture models (Bishop, 2006; Lazarsfeld, 1957; Muthén, 2002), are prominent tools for stratification in large data sets in psychiatry (Marquand et al., 2016). Such approaches automatically identify intrinsic structures in a data set based on statistical similarity and sort observations with the most coherent characteristics in multi-dimensional space.

In K-means clustering single observations of a given data set are assigned to an apriori defined number k of subgroups with the objective to minimize the variation within a subgroup (James et al., 2021). Similarly to supervised ML, K-means clustering handles information from a multitude of variables by placing observations in high-dimensional space. During the optimization process, the algorithm determines the distance of each observation to the centroids, which represent the center position of the k subgroups. Observations are assigned to the subgroup with the closest centroid to minimize the variation.

Owed to the exploratory nature of the approach, free parameters, such as k, the measure of distance between the observations, and the definition of the centroid position, require extensive validation to hold meaningful results (Kassambara, 2015; Monti et al., 2003). Indices, e.g. the Calinski-Harabasz index (Caliñski & Harabasz, 1974) or the average silhouette width (Rousseeuw, 1987), measure the ratio between within-group closeness and between-group distance. Therefore, they provide means to evaluate the statistical separability. Furthermore, resampling, i.e. the process of repetitively drawing subsamples from a data set, can be used to obtain an estimate of stability of the subgroup assignments under varied conditions (Hennig, 2007). Importantly, as most unsupervised algorithms will output a partitioning result with potentially high statistical validity, external validation showing the discriminability of the subgroups with respect to other criteria is recommended.

The first paper of the doctoral thesis uses K-means clustering to identify subgroups of patients based on their neurocognitive performance. To meet the demands for cluster validation, this approach is incorporated in a resampling scheme that tests the stability of the solution over several clustering iterations. The generalizability of the cluster solution is further assessed through validation in an independent sample. Finally, subgroups are evaluated by comparing clinical and functional characteristics and their grey matter brain structure.

3.4. Research questions: Heterogeneity in neurocognition and CCT response

In schizophrenia, heterogeneity in neurocognitive impairment and in therapeutic response to CCT has drawn attention to neurocognition and brain connectivity as potential markers for stratification and improvement of treatment. Recent implementation of ML in psychiatric research has promoted such findings.

However, studies mainly investigated patients suffering from chronic schizophrenia and only a minority of studies characterized neurocognitive subtypes and response to cognitive intervention in early stages of the disease when patients are minimally affected by pharmacological treatment. Further, as yet no study has implemented information of both brain and learning phenotypes when investigating response to CCT. The doctoral thesis uses supervised and unsupervised ML to address the following research questions:

1) **Do ROP patients early in the course of the disease map onto different neurocognitive profiles?**
2) **Can training response to 10 hours of CCT in ROP patients be monitored using rsFC patterns and learning performance?**

3.5. Publication summaries

3.5.1. 'Cognitive subtypes in recent onset psychosis: Distinct neurobiological fingerprints?'

Previous studies suggest neurocognitive subtypes in chronic schizophrenia samples (Green et al., 2019). Neurocognitive subtypes have been associated with structural brain correlates (Geisler et al., 2015; Gould et al., 2014; Van Rheenen et al., 2018; Weinberg et al., 2016). Most studies included patients with chronic schizophrenia that have been treated with extensive antipsychotic medication affecting cognitive performance (Lewandowski et al., 2011) and brain structure (Haijma et al., 2013). Therefore, we investigated 108 patients with a recent psychotic episode (ROP) who were recruited in the multi-site EU project PRONIA (Prognostic tools for early psychosis management) and minimally exposed to antipsychotic treatment due to recent onset. We analyzed 8 neurocognitive domains capturing performance in social cognition, executive functioning, processing speed, attention, salience, working memory and verbal and visual memory. All domains were corrected for age, sex, education years and study site. A K-means algorithm clustered the sample into subtypes based on neurocognitive (dis-)abilities. We assessed stability of the cluster solution using resampling. Further, we characterized the obtained neurocognitive subtypes and healthy controls (HC; N=195) based on their grey matter volume of the brain using SVM classification. The clustering algorithm yielded a cognitively impaired (N=41) and a cognitively spared (N=67) subtype which were functionally distinct and validated in an independent psychosis sample (N=53). The cognitively impaired subtype showed widespread deficits in cognitive performance and social and occupational functioning in comparison to the cognitively spared subtype and HC. The impaired subtype showed significant increases and decreases across several fronto-temporal-parietal brain areas, including basal ganglia and cerebellum relative to HC (balanced accuracy = 60.1%; p = 0.01) whereas no significant grey matter differences were found for the other comparisons (spared vs HC: BAC = 55.4%, p = 0.09; impaired vs spared: BAC = 47.2%, p = 0.79). Our findings are in line with previous clustering results in chronic schizophrenia patients (Green et al., 2019). Our impaired subgroup reveals neurocognitive and functional difficulties together with a significant neuroanatomical signature presumably present prior to florid psychotic symptoms. It supports the developmental hypothesis of psychosis (Murray et al., 2017) by showing decline in premorbid intelligence, general cognition and lower level of occupational functioning in early stages of the disease (Dickinson et al., 2020; Lewandowski, 2020). Our findings emphasize the relevance for early targeted treatment, e.g. through neurocognitive training, to improve the deteriorative course of the disease.

3.5.2. ‘A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis’

Research has shown marked variability in response to CCT potentially due to different learning performance (Biagianti et al., 2016) and brain phenotypes (Arnemann et al., 2015; Subramaniam et al., 2018). We investigated the effects of a neurocognitive intervention as function of individual SP change, i.e. learning performance, and rsFC patterns in 26 ROP patients. SP change during 10h of CCT was modeled during an emotion matching task (EMT). Presentation times of the stimuli, i.e. faces, during training were indicator for difficulty level, i.e. short presentation times refer to high difficulty while longer presentation times refer to lower difficulty. ROP patients showing high presentation times at baseline but reaching EMT psychophysical threshold over the course of the level, were classified as improver (N=12) whereas ROP patients sustaining low presentation times throughout the level, were classified as maintainer (N=14). To account for individual differences in rsFC, we trained a SVM hyperplane on a naturalistic sample of 35 ROPs and 56 HC of the PRONIA study (balanced accuracy = 65.5%, $p < 0.01$). The rsFC hyperplane was applied to the 26 patients of the intervention study marking their position on a hypothetical continuum between ROP-likeness and HC-likeness before and after training. Our main results show that maintainers improve in attention though keeping their ROP status on the rsFC hyperplane at follow-up ($p < 0.05$). In contrast, improver’s attentional gains occurred only for those shifting to the HC-like side of the hyperplane. The study indicates that in early course of psychotic disorders learning performance and individual rsFC are likely modulators of cognitive training gains. Further, it shows the methodological feasibility to track individual brain characteristics to monitor success in neurocognitive interventions. The ML approach used might be a way to integrate complex data in early recognition and intervention programs, to develop targeted and effective neurocognitive treatments.

3.6. Contribution to the publications

Both publications are based on data sets acquired within the frameworks of the PRONIA (PI: Prof. Dr. Nikolaos Koutsouleris) and PNKT (‘Personalisiertes Neurokognitives Training zur Verbesserung des Funktionsniveaus bei Psychosen’; PI: Dr. Lana Kambeitz-Ilankovic) project. I have been involved in the acquisition of the PRONIA data set through recruitment of ROP patients from March 2018 until September 2019 in the working group for Neurodiagnostic Applications at the Ludwig Maximilian University of Munich (PI: Prof. Dr. Nikolaos Koutsouleris). In parallel, I have been involved in the recruitment of ROP patients for the PNKT project at the same study site. In both PRONIA (study site Munich) and PNKT project I have been responsible for the quality control of the magnetic resonance imaging data, which comprised documentation, artefact inspection and server upload of the generated brain images.

I am the first author of the publication ‘Cognitive subtypes in recent onset psychosis: Distinct neurobiological fingerprints?‘. I have been involved in each step of the generation process of the publication. I have developed the concrete research question guided by literature search and an analysis proposal of the PRONIA consortium. Furthermore, I have derived the research hypotheses and developed the unsupervised clustering framework for the analysis using the programming languages R (https://cran.r-project.org/bin/windows/base/) and MATLAB (https://de.mathworks.com/products/matlab.html). Supervised by Dr. Kambeitz-Ilankovic and Prof. Dr. Koutsouleris I generated and interpreted the results of the analysis pipeline. I produced the draft of the manuscript and revised it in accordance with comments of the coauthors. I was responsible for the submission process to the journal and adapted the manuscript in accordance with suggestions by the reviewers.

I am co-author of the publication ‘A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis’. Besides the measurement of rsFC changes in response to CCT, the modulation due to learning performance has been a critical element of the publication. I was responsible for the quality control of the learning performance data in the PNKT project. Furthermore, I contributed to the publication by developing the methodological framework to analyze the learning performance in the data set. I assisted in further data analysis and in the interpretation of the results. Finally, I revised the draft of the manuscript.

4. Summary

High heterogeneity in psychiatric diagnoses (Widiger & Clark, 2000; Widiger & Samuel, 2005) and treatment response (Hofmann et al., 2012; Isaac & Januel, 2016; Wong et al., 2010) pose challenges in the process of personalization (Marquand et al., 2016; Wardenaar & de Jonge, 2013). Nonetheless, large multicentric initiatives and recent implementation of ML in psychiatric research have stimulated work on stratification of psychiatric diagnoses (Marquand et al., 2016).

Neurocognition is a promising marker for stratification in schizophrenia. Recent findings of subgroups with differential neurocognitive impairment (Green et al., 2019), specific clinical (e.g. Lewandowski et al., 2014), and neurobiological correlates (e.g. Van Rheenen et al., 2018) underline this. However, the main body of evidence refers to samples of chronic schizophrenic patients often treated with extensive antipsychotic medication influencing cognitive performance (Lewandowski et al., 2011) and the brain (Haijma et al., 2013). The current work presents evidence on cognitive subtypes and their clinical, functional, and brain correlates in a sample of ROP patients using unsupervised and supervised ML techniques:

Wenzel, J., Haas, S. S., Dwyer, D. B., Ruef, A., Oeztuerk, O. F., Antonucci, L. A., von Saldern, S., Bonivento, C., Garzitto, M., Ferro, A., Paolini, M., Blautzik, J., Borgwardt, S., Brambilla, P., Meisenzahl, E., Salokangas, R. K. R., Upthegrove, R., Wood, S. J., Kambeitz, J., … PRONIA consortium. (2021). Cognitive subtypes in recent onset psychosis: distinct neurobiological fingerprints? *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *January*. https://doi.org/10.1038/s41386-021-00963-1

We find a cognitively impaired and cognitively spared subtype with clinically and functionally distinct characteristics accompanied by brain morphological changes. The characteristics of the impaired cognitive subtype support the developmental hypothesis of psychosis (Murray et al., 2017) by showing decline in premorbid intelligence, general cognition and lower level of occupational functioning in early stages of the disease (Dickinson et al., 2020; Lewandowski, 2020).

Cognitive deficits in psychotic disorders can be ameliorated through CCT (Biagianti et al., 2016; Harvey et al., 2018). However, rsFC between sensory and higher-order brain areas, e.g. between temporal and frontal regions, modulates neurocognitive gains in response to CCT (Eack et al., 2016; Keshavan et al., 2017). Furthermore, a study indicates that different learning performance during the intervention (Biagianti et al., 2016) relates to untrained neurocognitive improvements. In a proof-of-concept study we investigated the effects of CCT as a function of individual rsFC and SP change, i.e. learning performance:

Haas, S. S., Antonucci, L. A., Wenzel, J., Ruef, A., Biagianti, B., Paolini, M., Rauchmann, B. S., Weiske, J., Kambeitz, J., Borgwardt, S., Brambilla, P., Meisenzahl, E., Salokangas, R. K. R., Upthegrove, R., Wood, S. J., Koutsouleris, N., & Kambeitz-Ilankovic, L. (2020). A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis. *Neuropsychopharmacology*, *0*(September), 1–8.

Both individual rsFC and SP change during the intervention modulate cognitive gains in attention. Our findings show both methodological feasibility and clinical relevance of tracking individual rsFC and SP changes in the process of CCT response evaluation. This is, to the best of our knowledge, the first study using ML to monitor changes in neuro-functional characteristics and their association with learning behavior and cognitive gains in CCT.

Patients in early stages of a psychotic disease show marked heterogeneity in neurocognitive functioning, learning performance and brain structure and possibly experience different paths on their way into the illness. Our ML approach has proven feasible to (neuro-)monitor heterogeneity in relevant characteristics in ROP undergoing CCT. In summary, the current doctoral thesis emphasizes the relevance for personalization in diagnostics and treatment in early stages of psychotic disorders and promotes the utility of ML in this process.

Note: The data of publication #2 (‘A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis’) has been part of the PhD project from Shalaila Haas which has been submitted as a monography.

5. Zusammenfassung

Hohe Heterogenität bei psychiatrischen Erkrankungen (Widiger & Clark, 2000; Widiger & Samuel, 2005) und beim Ansprechen auf die Behandlung (Hofmann et al., 2012; Isaac & Januel, 2016; Wong et al., 2010) erschweren die Personalisierung von Diagnostik und Behandlung in der Psychiatrie. Große Multizentrumstudien und die Implementierung maschineller Lernverfahren in die psychiatrische Forschung ermöglichen Studien zur Stratifizierung psychiatrischer Diagnosen (Marquand et al., 2016).

Bisher gewonnene Erkenntnisse betonen die Bedeutung von Neurokognition bei der Stratifikation von Patienten mit Schizophrenie. Studien die Subgruppen mit unterschiedlicher neurokognitiver Beeinträchtigung identifizieren (Green et al., 2019) und mit klinischen (z.B. Lewandowski et al., 2014) und neurobiologischen Markern (z.B. Van Rheenen et al., 2018) assoziieren konnten, bestätigen diese. Ein Großteil der bisher durchgeführten Forschungsvorhaben untersuchte schizophrene Patienten, deren Hirnphysiologie (Haijma et al., 2013) und kognitive Leistungsfähigkeit (Lewandowski et al., 2011) bereits durch antipsychotische Medikation beeinflusst wurde. Daher nutzt die erste Studie supervidierte und unsupervidierte maschinelle Lernverfahren, um kognitive Subtypen bei Patienten, die an einer kürzlich aufgetretenen psychotischen Episode leiden, zu identifizieren und diese durch klinische Symptomatik, Funktionsniveau und Veränderungen der grauen Substanz im Gehirn zu unterscheiden:

Wenzel J., Haas, S. S., Dwyer, D. B., Ruef, A., Oeztuerk, O. F., Antonucci, L. A., von Saldern, S., Bonivento, C., Garzitto, M., Ferro, A., Paolini, M., Blautzik, J., Borgwardt, S., Brambilla, P., Meisenzahl, E., Salokangas, R. K. R., Upthegrove, R., Wood, S. J., Kambeitz, J., Koutsouleris, N., Kambeitz-Ilankovic, L. (in press). Cognitive Subtypes in Recent Onset Psychosis: Distinct neurobiological fingerprints? *Neuropsychopharmacology*, *X*, X–X.

Die Analyse zeigt eine Subgruppe mit starker neurokognitiver Beeinträchtigung und eine Subgruppe, die in ihrer kognitiven Leistung gesunden Probanden ähnelt. Die Subgruppen unterscheiden sich hinsichtlich klinischer und funktioneller Charakteristika voneinander. Die Subgruppe mit starken neurokognitiven Einbußen zeigte zusätzlich hirnstrukturelle Unterschiede im Vergleich zu gesunden Probanden. Die Charakteristika der neurokognitiv stark beeinträchtigten Subgruppe bestätigen die Neuroentwicklungshypothese (Murray et al., 2017), welche einen beeinträchtigten prämorbiden IQ, reduzierte kognitive Fähigkeiten während des Krankheitsbeginnes und geringes Rollen-Funktionieren beschreibt (Dickinson et al., 2020; Lewandowski, 2020).

Kognitive Einschränkungen in psychotischen Erkrankungen können durch CCT verbessert werden (Biagianti et al., 2016; Harvey et al., 2018). Forschung zeigt, dass die rsFC zwischen sensorischen und höher-rangigen Hirnarealen, z.B. temporalen und frontalen Regionen, einen modulierenden Einfluss auf die neurokognitive Verbesserung nach CCT ausübt. Eine Studie konnte zeigen, dass zusätzlich unterschiedliches Lernverhalten während des Trainings das Ansprechen auf die Intervention beeinflusst (Biagianti et al., 2016). Daher ist es das Ziel in der zweiten Studie, die Effekte eines CCT in Abhängigkeit der individuellen rsFC und des individuellen Lernverhaltens (SP change) zu betrachten:

Haas, S. S., Antonucci, L. A., Wenzel, J., Ruef, A., Biagianti, B., Paolini, M., Rauchmann, B. S., Weiske, J., Kambeitz, J., Borgwardt, S., Brambilla, P., Meisenzahl, E., Salokangas, R. K. R., Upthegrove, R., Wood, S. J., Koutsouleris, N., & Kambeitz-Ilankovic, L. (2020). A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis. *Neuropsychopharmacology*, *0*(September), 1–8. https://doi.org/10.1038/s41386-020-00877-4

Sowohl die individuelle rsFC als auch das Lernverhalten während der Intervention beeinflussen die Verbesserung der Aufmerksamkeit. Unsere Ergebnisse verdeutlichen die Sinnhaftigkeit individuelle rsFC und individuelles Lernverhalten (SP change) im Rahmen eines CCT zu charakterisieren, um kognitive Veränderungen zu untersuchen. Nach bestem Wissen ist diese Studie die Erste, die maschinelle Lernverfahren verwendet, um Veränderungen in funktionellen Gehirneigenschaften nach CCT zu messen und diese mit Lernverhalten und kognitiven Verbesserungen assoziiert.

Bereits Patienten in frühen Stadien von psychotischen Erkrankungen zeigen deutliche Unterschiede in ihrer Neurokognition, ihrem Lernverhalten und ihren hirnstrukturellen Eigenschaften, welche unterschiedliche pathophysiologische Prozess andeuten. ML erweiset sich als nützliche Methode, um neurobiologische Heterogenität bei psychotischen Patienten im Hinblick auf das Ansprechen bei CCTs zu betrachten. Zusammenfassend betont die vorliegende Doktorarbeit die Relevanz von Personalisierung bei der Diagnostik und Behandlung von Psychosen im frühen Verlauf und den Nutzen von ML, um diese Aspekte weiter zu untersuchen.

Notiz: Die Daten von Publikation #2 (‘A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis’) sind Bestandteil des als Monographie eingereichten Phd-Projektes von Shalaila Haas.

6. Original Publications

6.1. Publication #1

Neuropsychopharmacology www.nature.com/npp

ARTICLE OPEN

Cognitive subtypes in recent onset psychosis: distinct neurobiological fingerprints?

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In schizophrenia, neurocognitive subtypes can be distinguished based on cognitive performance and they are associated with neuroanatomical alterations. We investigated the existence of cognitive subtypes in shortly medicated recent onset psychosis patients, their underlying gray matter volume patterns and clinical characteristics. We used a K-means algorithm to cluster 108 psychosis patients from the multi-site EU PRONIA (Prognostic tools for early psychosis management) study based on cognitive performance and validated the solution independently ($N = 53$). Cognitive subgroups and healthy controls (HC; $n = 195$) were classified based on gray matter volume (GMV) using Support Vector Machine classification. A cognitively spared ($N = 67$) and impaired ($N = 41$) subgroup were revealed and partially independently validated ($N_{spared} = 40$, $N_{impaired} = 13$). Impaired patients showed significantly increased negative symptomatology ($p_{fdr} = 0.003$), reduced cognitive performance ($p_{fdr} < 0.001$) and general functioning ($p_{fdr} < 0.035$) in comparison to spared patients. Neurocognitive deficits of the impaired subgroup persist in both discovery and validation sample across several domains, including verbal memory and processing speed. A GMV pattern (balanced accuracy = 60.1%, $p = 0.01$) separating impaired patients from HC revealed increases and decreases across several fronto-temporal-parietal brain areas, including basal ganglia and cerebellum. Cognitive and functional disturbances alongside brain morphological changes in the impaired subgroup are consistent with a neurodevelopmental origin of psychosis. Our findings emphasize the relevance of tailored intervention early in the course of psychosis for patients suffering from the likely stronger neurodevelopmental character of the disease.

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INTRODUCTION

In accordance with the neurodevelopmental hypothesis [1] the majority of patients suffering from psychosis show general and specific neurocognitive impairments [2, 3] as premorbid signs of early developmental insults and brain alterations [4]. However, studies report substantial heterogeneity regarding the severity of neurocognitive impairments [2] putatively representing different underlying disease trajectories marked by specific (neuro-) biological, clinical and functional characteristics [5].

Impaired cognitive and psychosocial functioning represent the top of the dysfunctional pyramid of schizophrenia (SZ) [6]. For a number of patients with psychosis, cognitive impairment persists beyond the presence of positive and negative symptoms and relates to reduced psychosocial outcome [6]. For this reason, identifying homogeneous subgroups of patients showing specific cognitive profiles may enhance the effects of promising novel treatments including neurocognitive interventions [7]. Previous studies using unsupervised machine learning (ML) found between two and four cognitive subgroups in SZ samples, ranging from unimpaired to severely deteriorated patient subgroups [8–11]. These subgroups differed not only with respect to their cognitive performance yet also in clinical symptomatology [8, 9, 11], general [8, 10, 11] and occupational functioning [9, 11]. Furthermore, they were linked to different patterns of alterations in brain morphology [10, 12]. Complementary, studies using unsupervised ML identified neuroanatomical subgroups that were related to

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differences in premorbid functioning [13, 14] and neuropsychological performance [14].

Existing evidence on cognitive subgroups is mainly based on chronic SZ samples presenting with clinical symptoms for a prolonged period. These findings could be limited as patients may already be susceptible to change due to the effects of antipsychotic medication on cognitive performance [15] and brain structure [16].

The current study aims at disentangling variability in neurocognitive impairment. To achieve this, we (1) subgroup a recent onset psychosis (ROP) sample based on neurocognitive performance using cluster analysis and validate the cluster solution on neurocognitive data of an independent validation sample [17], (2) associate obtained ROP subgroups to symptom burden and functional disability and (3) investigate morphological brain differences between the cognitive subgroups and healthy controls (HC) using gray matter volume (GMV) within a supervised ML framework.

MATERIALS AND METHODS

Sample

In the discovery sample 121 ROP patients and 201 HC, age between 15 and 40 years, were recruited within the PRONIA study (Personalized Prognostic tools for early psychosis management; www.pronia.eu; German Clinical Trials Register: DRKS00005042) at seven sites across Europe. Patients were included in the study if they fulfilled DSM-IV-TR criteria [18] for a psychotic episode present in the last 3 months, lasting longer than 1 week and with first onset in the last 24 months [19]. HC volunteers were required to not fulfill any current or past DSM-IV-TR axis I or II diagnosis, clinical high-risk (CHR) status for psychosis as defined by the Structured Interview for Prodromal Syndromes [20] and Schizophrenia Proneness Instrument [21] or positive familial history (1st degree relatives) for psychosis accompanied by a drop in functioning in the last year. HC participants with any intake of psychotropic medications more than five times/year or in the month before study entry were excluded. Written informed consent was obtained from the subjects. The study received ethical approval by each Local Research Ethics Committee at every study site separately (Supplementary Materials and Methods) [19].

The independent validation sample comprised baseline data of a monocentric, longitudinal cognitive intervention study called Personalized Neurocognitive Training (ClinicalTrials.gov Identifier: NCT03962426). Overall, 58 ROP patients were recruited at the Early Detection and Intervention Center at the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilians-University in Munich, Germany. Inclusion and exclusion criteria were identical to those required for the discovery sample of the PRONIA study.

The analysis data set consisted of 108 ROP patients and 195 HC for the discovery sample and 53 ROP patients for the independent validation sample (Table 1, Fig. S8, Supplementary Materials and Methods).

Clinical and neurocognitive assessment

Participants were assessed using multiple clinical scales and neuropsychological tests focusing on the General Assessment of Functioning Scale (GAF) [22], split into two subscales (symptoms and disability), the Global Functioning Scale (GF social and occupational) [23] and the Positive and Negative Syndrome Scale (PANSS) [24]. The neuropsychological test battery comprised of ten tests that were assigned to cognitive domains comparable to the MATRICS Consensus Cognitive Battery (MCCB) domains [25] including visual memory (Rey–Osterrieth Complex Figure test [26]), social cognition (Diagnostic Analysis of Non-Verbal Accuracy [27]), working memory (Auditory Digit Span Task [28], Self-ordered Pointing Task [29]), processing speed (Verbal Fluency Test [30], Trail Making Test A [31], Digit-Symbol-Substitution Test [28]), verbal learning and memory (Rey Auditory Verbal Learning Test [32]), executive functioning (Trail Making Test B [31]), attention and vigilance (Continuous Performance Test, Identical Pairs version [33]) and one psychosis-specific domain: aberrant salience [34] (Tables S1, S2 and Supplementary Materials and Methods).

Preprocessing and clustering of neurocognitive data

All selected neurocognitive variables were used. Preprocessing followed the steps of (1) imputing missing values by median and (2) linear regression of effects of age, sex, years of education and study site to account for site and demographic differences [35]. In addition, we used (3) principal component analyses (PCA) for dimensionality reduction on each group of neuropsychological variables associated with a certain cognitive domain (Table S1) and retained the first PCA component of each domain for cluster analysis (Fig. S1).

A K-means clustering algorithm [36] was applied to the neurocognitive domain values (PCA components) using Euclidean distance. Two independent resampling strategies were followed to assess cluster stability [37].

Preprocessing of the validation sample followed procedures identical to the discovery sample. To estimate the generalizability of the discovery clustering model to new observations, cluster assignment in the validation data set was based on the minimum Euclidean distance of a single observation to the centroids of the discovery sample cluster solution.

Demographic, clinical and neuropsychological characteristics of the obtained ROP subgroups and the HC sample were compared using one-way permutation and chi-squared tests. *P* values were corrected using the Benjamini–Hochberg false discovery rate method [38] (Supplementary Materials and Methods).

Preprocessing, clustering and statistical analyses were conducted in R version 3.6.1 (https://cran.r-project.org/bin/windows/base/). Cluster stability was assessed using the 'clusterboot'-function [37] contained in the 'fpc' package [39]. Cluster assignments of the validation observations were predicted using the 'flexclust' package [40]. Characteristics of subgroups were compared using non-parametric statistical tests from the 'coin'- and the 'rcompanion'-package [41, 42].

Preprocessing of neuroimaging data

MRI data were inspected for scanner artefacts and anatomical abnormalities by a trained radiologist. Images were preprocessed using the open-source CAT12 toolbox (version > r1200; http://dbm.neuro.uni-jena.de/cat12/), an extension of the SPM12 software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) following previously described steps [19] and the CAT12 manual (www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) (Supplementary Materials and Methods).

Neuroimaging classification analysis

A ML pipeline was employed to compare GMV between the obtained clusters and the HC population. Model generation and testing were embedded in a tenfold × tenfold nested cross-validation pipeline with ten permutations on inner (CV1) and outer (CV2) loop using the in-house ML tool NeuroMiner (http://www.pronia.eu/neurominer) running in MATLAB 2019a (MathWorks Inc.).

Within CV1 modulated, normalized GMV images were (1) smoothed with a Gaussian kernel (optimized for 4, 6 and 8 mm), (2) corrected for total intracranial volume and (3) pruned by removing zero-variance voxels. Moreover, images were (4) pruned for voxels with low reliability across study sites using a G coefficient map to account for scanner differences [19], (5) dimensionality was reduced by PCA (optimizing the retainment

Table 1. Demographic and clinical characteristics of the discovery and validation sample used in the study.

	Discovery				Validation			Validation vs. discovery	
			ROP vs. HC			ROP vs. HC		ROP (val) vs. ROP (disc)	
	ROP (*N* = 108)	HC (*N* = 195)	t/X^2	*p*	ROP (*N* = 53)	t/X^2	*p*	*t*	*p*
Demographics									
Age	24.91 (5.11)	25.32 (6.23)	−0.63	0.53	25.74 (6.39)	0.42	0.68	0.82	0.41
Site[a]	39/20/28/8/13	48/39/60/35/13	11.62	0.02*	53/0/0/0/0	98.1	<0.001***	59.26	<0.001***
Sex[a]	Female = 35	Female = 121	23.28	<0.001***	Female = 21	7.67	0.01*	0.53	0.47
Years of education	14.08 (3.3)	16.02 (3.43)	−4.83	<0.001***	14.05 (3.54)	−3.62	<0.001***	−0.06	0.96
Illness duration in days	181.51 (187.46)	–	–	–	186.38 (203.88)	–	–	−0.15	0.88
Chlorpromazine equivalent[b]	388.18 (1020.61)	–	–	–	1208.09 (5205.17)			−1.06	0.29
Premorbid intelligence									
WAIS (Vocabulary)	9.89 (3.64)	12.11 (2.85)	−5.48	<0.001***	9.22 (3.3)	−5.61	<0.001***	−1.13	0.26
WAIS (Matrices)	9.35 (2.7)	11.23 (2.25)	−6.14	<0.001***	10.35 (2.73)	−2.15	0.03*	2.16	0.03*
GAF (symptoms)									
Lifetime	77.77 (10.09)	88.48 (5.63)	−10.15	<0.001***	77.22 (8.79)	−8.61	<0.001***	−0.35	0.73
Past year	59.12 (15.79)	87.43 (6.1)	−17.83	<0.001***	62.3 (14.19)	−12.24	<0.001***	1.26	0.21
Past month	41.85 (13.52)	86.98 (6.48)	−32.54	<0.001***	39.86 (13.02)	−24.81	<0.001***	−0.88	0.38
GAF (disability)									
Lifetime	77.11 (8.99)	86.84 (5.21)	−10.29	<0.001***	75.78 (9.74)	−7.75	<0.001***	−0.82	0.42
Past year	61.36 (13.66)	85.95 (5.82)	−17.76	<0.001***	61.82 (14.21)	−11.76	<0.001***	0.19	0.85
Past month	45.39 (12.24)	85.51 (6.16)	−31.78	<0.001***	42.8 (11.77)	−24.8	<0.001***	−1.27	0.21
PANSS									
Positive scale	18.07 (6.43)	–	–	–	20.27 (4.72)	–	–	−2.39	0.02*
Negative scale	16.75 (8.11)	–	–	–	15.33 (6.21)	–	–	1.2	0.23
General scale	36.05 (10.6)	–	–	–	34.02 (10.02)	–	–	1.15	0.25
BDI score	20.91 (11.41)	2.80 (4.73)	−14.91	<0.001***	22.44 (12.79)	−10.14	<0.001***	−0.69	0.49

ROP recent onset psychosis, *HC* healthy control, *WAIS Wechsler Adult Intelligence Scale, GAF* General Assessment of Functioning, *PANSS* Positive and Negative Syndrome Scale, *BDI* Beck Depression Inventory.
[a]Chi-squared test.
[b]Cumulative sum of Chlorpromazine equivalents divided by number of days treated.
*$p < 0.05$, ***$p < 0.001$.

of the highest ranking components optimizing 40, 60 and 80%) and (6) values were scaled between zero and one.

To find a discriminative pattern of GMV between groups, a linear support vector machine (SVM) algorithm (optimized c-parameter range between 0.015625 and 16; 11 parameters) weighted by group sizes was applied on the GMV maps. Model performance was assessed by calculating the balanced accuracy (BAC). Statistical significance of the overall winning model was assessed using permutation tests ($N_{perm} = 1000$; alpha = 0.05) [43]. Reliability of discriminative voxels contributing to the classification performance of the winning model was inspected by the cross-validation ratio (Supplementary Materials and Methods).

RESULTS

Discovery sample

A two-cluster solution indicated maxima on the Calinski-Harabasz index [44] and the average silhouette width score [45]. Stability assessment revealed clusterwise Jaccard similarity [46] indices of 0.84 and 0.90 for the 'subset' and 0.90 and 0.93 for the 'noise'-method, respectively, indicating highly stable clusters (Fig. S3) [37].

Neurocognitive characteristics

Patients in cluster 1 ($N = 41$) showed significantly lower performance in processing speed ($p_{fdr} < 0.001$, $d = 1.89$), executive functioning ($p_{fdr} < 0.001$, $d = -1.60$), attention ($p_{fdr} < 0.001$, $d = 1.01$), working memory ($p_{fdr} = 0.004$, $d = 0.67$), verbal ($p_{fdr} < 0.001$, $d = -1.37$) and visual memory ($p_{fdr} < 0.001$, $d = 1.44$) as compared to patients belonging to cluster 2 ($N = 67$).

Cluster 1 patients showed significantly lower performance in processing speed ($p_{fdr} < 0.001$, $d = 2.11$), executive functioning ($p_{fdr} < 0.001$, $d = -0.77$), attention ($p_{fdr} < 0.001$, $d = 1.01$), working memory ($p_{fdr} < 0.001$, $d = 1.10$) and verbal ($p_{fdr} < 0.001$, $d = -2.43$) and visual memory ($p_{fdr} < 0.001$, $d = 1.66$) as compared to HC group. We refer to cluster 1 as 'impaired' due to its largely inferior cognitive performance in comparison to cluster 2 and HC.

Cluster 2 patients showed significantly decreased performance in attention ($p_{fdr} < 0.001$, $d = 0.65$) and verbal memory ($p_{fdr} = 0.001$, $d = -0.47$) as compared to HC. They showed improved performance in executive functioning ($p_{fdr} < 0.001$, $d = 0.53$), salience ($p_{fdr} = 0.003$, $d = 0.44$) and visual memory ($p_{fdr} = 0.003$, $d = 0.44$) compared to HC. We refer to this cluster as 'spared' as its performance was inferior to HC only in two cognitive domains (Table 2 and Fig. 1A).

Table 2. Neuropsychological domain-specific effects between impaired and spared cluster and healthy controls in discovery and validation sample.

	Overall			Impaired vs. spared		Impaired vs. HC		Spared vs. HC	
	T (max)	*p* (uncorr)	*p* (FDR)	*p* (FDR)	*Cohen's d*	*p* (FDR)	*Cohen's d*	*p* (FDR)	*Cohen's d*
Discovery									
Social cognition	0.980	0.583	0.583	–	–	–	–	–	–
Working memory	6.089	<0.001	<0.001***	0.004**	0.68	<0.001***	1.11	0.053	0.28
Processing speed	10.070	<0.001	<0.001***	<0.001***	1.90	<0.001***	2.12	0.223	−0.17
Executive functioning	5.416	<0.001	<0.001***	<0.001***	−1.62	<0.001***	−0.78	<0.001***	0.53
Attention	8.756	<0.001	<0.001***	<0.001***	1.02	<0.001***	2.05	<0.001***	0.65
Verbal memory	10.385	<0.001	<0.001***	<0.001***	−1.39	<0.001***	−2.44	0.001**	−0.48
Visual memory	8.423	<0.001	<0.001***	<0.001***	1.45	<0.001***	1.67	0.003**	−0.44
Salience	2.646	0.022	0.023*	0.175	−0.28	0.913	−0.02	0.003**	0.45
Validation									
Social_cognition	2.824	0.012	0.014*	0.008**	−1.13	0.010*	−0.75	0.159	–
Working_memory	0.792	0.700	0.720	–	–	–	–	–	–
Processing_speed	7.256	<0.001	<0.001***	<0.001***	1.91	<0.001***	2.48	0.007**	0.50
Executive_functioning	2.497	0.031	0.034*	0.020*	0.98	0.023*	0.67	0.212	–
Attention	0.249	0.965	0.965	–	–	–	–	–	–
Verbal_memory	7.112	<0.001	<0.001***	<0.001***	−1.48	<0.001***	−2.51	0.050	–
Visual_memory	8.628	<0.001	<0.001***	<0.001***	2.29	<0.001***	3.04	0.052	–
Salience	3.533	0.001	0.001**	0.008**	−1.12	<0.001***	−1.03	0.578	–

HC healthy control.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Demographic characteristics
Cognitively impaired patients showed significantly reduced number of years of education ($p_{fdr} < 0.001$) and a significantly decreased female-to-male ratio ($p_{fdr} = 0.009$) compared to HC. Patients in the spared cluster showed significantly lower number of years of education ($p_{fdr} = 0.002$) and lower female-to-male ratio ($p_{fdr} < 0.001$) as compared to HC. The number of patients recruited across sites differed significantly for the two clusters ($p_{fdr} = 0.046$) and when comparing the impaired group and HC ($p_{fdr} = 0.014$). Clusters did not differ regarding chlorpromazine equivalent level ($p_{fdr} < 0.100$) and illness duration ($p_{fdr} < 0.440$) (Table 3).

Clinical characteristics
Cognitively impaired patients showed significantly lower premorbid intelligence ($p_{fdr} < 0.001$, $d > 1.04$), lower GAF score in the last month ($p_{fdr} = 0.027$, $d = 0.49$), in the last year ($p_{fd} = 0.035$, $d = 0.46$) and lifetime ($p_{fdr} = 0.011$, $d = 0.59$) and lower GF scores at examination ($p_{fdr} < 0.045$, $d > 0.43$), last year ($p_{fdr} < 0.50$, $d > 0.42$) and across lifetime ($p_{fdr} < 0.024$, $d > 0.51$) when compared to patients in the spared cluster. Cognitively impaired patients showed significantly higher scores on the PANSS negative scale ($p_{fdr} = 0.003$, $d = -0.72$) (Table S4 and Fig. 1B–E).

Validation sample
Observations in the validation sample were assigned to the impaired (impaired$_{val}$, $N = 13$) and spared (spared$_{val}$; $N = 40$) cluster of the discovery sample.

Neurocognitive characteristics
Cognitively impaired$_{val}$ patients showed significantly worse performance in social cognition ($p_{fdr} = 0.008$, $d = -1.13$), processing speed ($p_{fdr} < 0.001$, $d = 1.91$), executive functioning ($p_{fdr} = 0.020$, $d = 0.98$), salience ($p_{fdr} = 0.008$, $d = -1.12$) and verbal ($p_{fdr} < 0.001$, $d = -1.48$) and visual memory ($p_{fdr} < 0.001$, $d = -2.29$) compared to cognitively spared$_{val}$ patients.

Cognitively impaired$_{val}$ patients performed significantly worse regarding social cognition ($p_{fdr} = 0.010$, $d = -0.75$), processing speed ($p_{fdr} < 0.001$, $d = 2.48$), executive functioning ($p_{fdr} = 0.023$, $d = 0.67$), salience ($p_{fdr} < 0.001$, $d = -1.03$) and verbal ($p_{fdr} < 0.001$, $d = -2.51$) and visual memory ($p_{fdr} < 0.001$, $d = 3.04$) when compared to HC.

Cognitively spared$_{val}$ patients showed significantly reduced performance in processing speed ($p_{fdr} = 0.007$, $d = 0.50$) in comparison to HC.

Demographic characteristics
Cognitively impaired$_{val}$ patients showed no significant differences to cognitively spared$_{val}$ patients and HC. Cognitively spared$_{val}$ patients showed a significantly lower number of years of education ($p_{fdr} = 0.001$) and lower female-to-male ratio ($p_{fdr} = 0.017$) compared to HC. Clusters did not differ regarding chlorpromazine equivalent level ($p_{fdr} = 0.535$) and illness duration ($p_{fdr} = 0.535$) (Table 3).

Clinical characteristics
Cognitively impaired$_{val}$ patients showed significantly lower premorbid intelligence ($p_{fdr} < 0.001$, $d = 1.66$) and lower GF scores for role functioning last year ($p_{fdr} = 0.042$, $d = 0.87$) and across life span ($p_{fdr} = 0.042$, $d = 0.87$) when compared to cognitively spared$_{val}$ patients (Table S4 and Fig. S5B–E).

sMRI classification results
A neuroanatomical SVM classification model discriminated the cognitively impaired patient group from HC (BAC = 60.1%, sensitivity = 56.1%, specificity = 64.1%, NND = 5.0; $p = 0.01$) in the discovery sample. The classification model of the cognitively spared group against the HC (BAC = 55.4%, sensitivity = 47.8%, specificity = 63.1%; $p = 0.09$) and the cognitively spared group against the cognitively impaired group (BAC = 47.2%, sensitivity = 31.7%, specificity = 62.7%; $p = 0.79$) remained non-significant (Fig. 2).

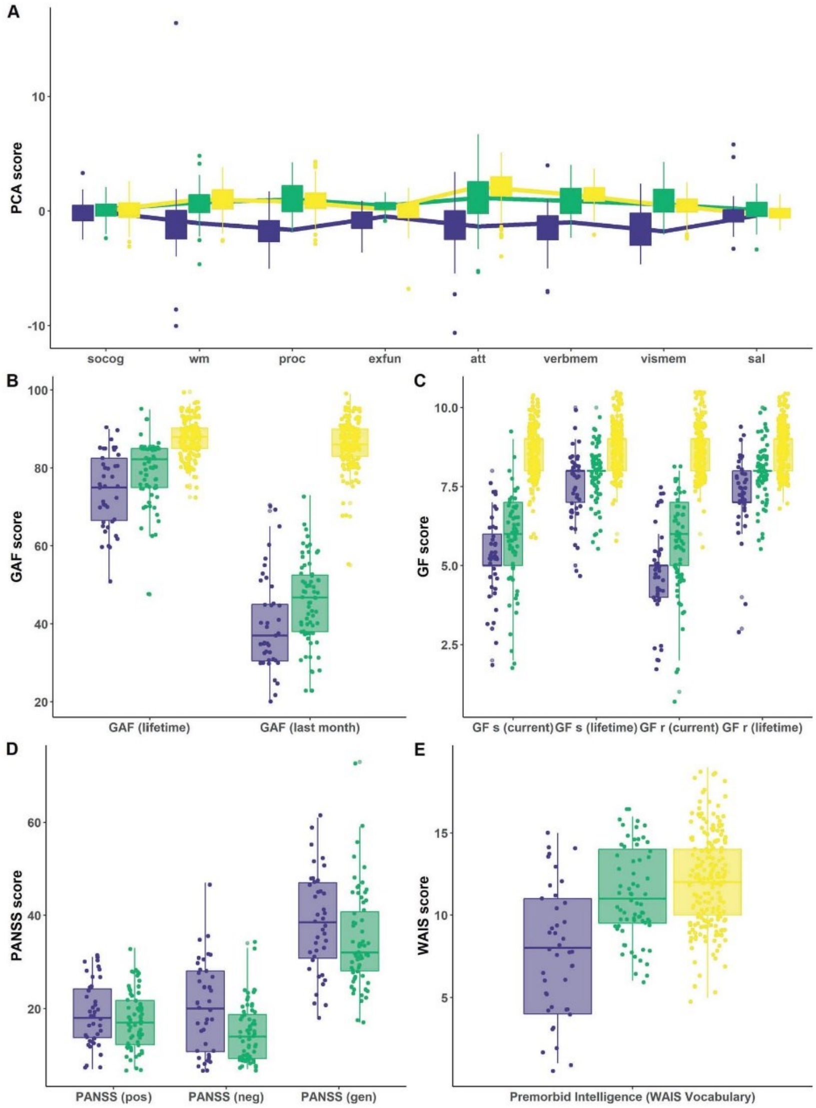

Fig. 1 Neuropsychological and clinical differences between clusters and HC in the discovery sample. Differences between the impaired (blue; $N = 41$) and spared cluster (green; $N = 67$) and HC (yellow; $N = 195$) regarding **A** the neuropsychological PCA components, **B** the General Assessment of Functioning score (GAF), **C** the General Functioning score (GF), **D** the Positive and Negative Syndrom Scale (PANSS) and **E** Premorbid Verbal Intelligence are shown. **A** High PCA scores represent high performance. PCA scales for cognitive domains where high PCA scores represent low performance, are inverted. socog social cognition, wm working memory, proc processing speed, exfun executive functioning, att attention, verbmem verbal memory, vismem visual memory, sal salience.

The neuroanatomical signature between cognitively impaired ROP and HC group comprised both cortical and subcortical regions. Bilateral GMV increases associated with 'cognitively impaired ROP' status were predominantly found in basal ganglia and cerebellum and to a lesser extent in the middle frontal and inferior temporal gyrus. The unilateral GMV decreases were localized in the right superior frontal, supplementary motor areas and anterior cingulum. Left lateralized reductions were found in inferior occipital and orbito-frontal gyrus and superior temporal pole.

Increases in GMV associated with HC status were found bilaterally in the Heschl's gyrus, supramarginal gyrus, superior

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Table 3. Demographical effects between *impaired* and *spared* cluster and healthy controls in discovery and validation sample.

	Impaired	Spared	Overall			Impaired vs. spared	Impaired vs. HC	Spared vs. HC
	Mean (sd)	Mean (sd)	*T*(max)/*Z*	*p* (uncorr)	*p* (FDR)	*p* (FDR)	*p* (FDR)	*p* (FDR)
Discovery								
N	41	67						
Age	23.5 (4.3)	25.8 (5.4)	2.015	0.106	0.109	–	–	–
Years of Education	13.5 (3.2)	14.5 (3.3)	4.612	<0.001	<0.001***	0.135	<0.001***	0.002**
Sex[a]	female = 16	female = 19	25.611	<0.001	<0.001***	0.302	0.009**	<0.001***
Site[a,b]	11/5/11/5/9	28/15/17/3/4	23.614	0.003	0.003**	0.046*	0.061	0.014*
Illness duration in days[c]	163.66 (153.82)	192.43 (205.69)	−0.770	0.440	0.440	–	–	–
Chlorpromazine equivalent[d]	685.65 (1596.42)	196.95 (125.38)	1.940	0.052	0.100	–	–	–
Validation								
N	13	40						
Age	24.2 (5.3)	26.2 (6.7)	0.899	0.630	0.673	–	–	–
Years of Education	14.3 (3.7)	14.0 (3.5)	3.594	<0.001	0.001**	0.858	0.081	0.001**
Sex[a]	Female = 5	Female = 16	8.575	0.014	0.016*	1.000	0.140	0.017*
Illness duration in days[c]	149.00 (91.46)	198.53 (228.55)	−0.761	0.447	0.535	–	–	–
Chlorpromazine equivalent[d]	127.80 (267.83)	1578.48 (6006.66)	−0.833	0.405	0.535	–	–	–

HC healthy control, *sd* standard deviation, *FDR* False Discovery Rate.
[a]Nominal permutation test are used; Fisher's exact *p* value is reported.
[b]Sites: Munich/Basel/Köln/Udine/Milan.
[c]Difference in time between first fulfillment of psychotic diagnosis according to Structured Clinical Interview for DSM-IV (SCID) and date of MRI examination.
[d]Cumulative sum of chlorpromazine equivalents divided by the number of days treated.
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

temporal gyrus and rolandic operculum. Further, bilateral increases in GMV were located in superior frontal and middle occipital regions, precuneus, in the cingulum and parahippocampal gyrus. The unilateral GMV increases were shown in left inferior frontal areas and cerebellum alongside with GMV increases in right superior parietal regions and angular gyrus, inferior orbital gyrus and hippocampus.

DISCUSSION

Our study reveals two cognitively and clinically distinct neurocognitive subgroups in ROP patients in line with previously reported cognitive subgroups in chronic SZ patients [8–11]. To the best of our knowledge, this is the first study showing altered cognitive, clinical and neuroanatomical features, using unsupervised ML methods, in the early stages of psychosis when patients are minimally affected by antipsychotic medication. We obtain a largely impaired and a spared subgroup and validate both in an independent behavioral data set of ROP patients. Whilst the applied neuroanatomical classification analysis was successful in distinguishing the cognitively and clinically impaired cluster from HC, it revealed no statistical differences between the spared subgroup and HC.

The current study found an impaired cluster presenting with more profound cognitive deficits in the domains of processing speed, working memory, executive functioning, attention and visual and verbal memory in comparison to HC. The spared cluster shows impairments in attention and verbal memory relative to HC, however, a similar performance in working memory, processing speed and social cognition. Conversely, this cluster shows increased performance in executive functioning, salience and visual memory relative to HC (Fig. 1 and Table 2). Increased performance in a psychosis subgroup relative to HC has been reported in a previous study [47]. The presence of cognitively and functionally preserved individuals in one subgroup might have been easier to identify due to our minimally medicated recent onset sample in comparison to previously employed chronic patient cohorts [8–11].

Analysis of the cognitive clusters' clinical characteristics revealed premorbid general functioning [8, 10, 11], social and occupational functioning [9, 11] difficulties in the impaired group which were less present in the spared group (Supplementary Table S4). In line with prior studies, we confirmed a higher level of negative symptoms in impaired ROP patients as compared to the spared ROP patients [8, 9] (Supplementary Table S4). Importantly, though making a major contribution to the cluster solution, cognitive subgroups were not entirely explained by premorbid intelligence (Supplementary Materials and Methods).

Similar as in the discovery sample, we found reduced performance in processing speed, executive functioning and verbal and visual memory alongside impaired premorbid intelligence level and partially impaired functioning for impaired_{val} patients when compared to spared_{val} patients and HC of the independent behavioral data set. The concordance on verbal memory and processing speed deficits between impaired patients across both samples supports recent efforts of the second phase of the North American Psychosis Longitudinal Study-II that generated a risk calculator for transition to psychosis integrating both domains in its prediction model [48].

Our classification analysis reliably showed patterns of GMV increases associated with impaired-cluster status predominantly in the subcortical area of putamen [13] while we observed smaller increases in cortical areas [49]. Basal ganglia enlargement seems to occur in medication-naive populations with clinical and genetic risk [50]. As our ROP patients were newly exposed to antipsychotic treatment, larger basal ganglia appear to reflect striatal hyperdopaminergia possibly related to acute psychotic symptoms [51]. In previous studies, unaffected family members have also shown larger putamen [51]. However, HC have shown increases in fronto-temporo-parietal cortical regions with an emphasis on Heschl's gyrus [52] and parahypocampal areas [53] which are particularly prone to GMV loss in psychosis [16, 49].

Previous studies propose a preadolescent decline trajectory for SZ, characterized by impaired premorbid intelligence, reduced general cognition at illness onset and lower level of occupational functioning [11]. First, impaired patients show high levels of

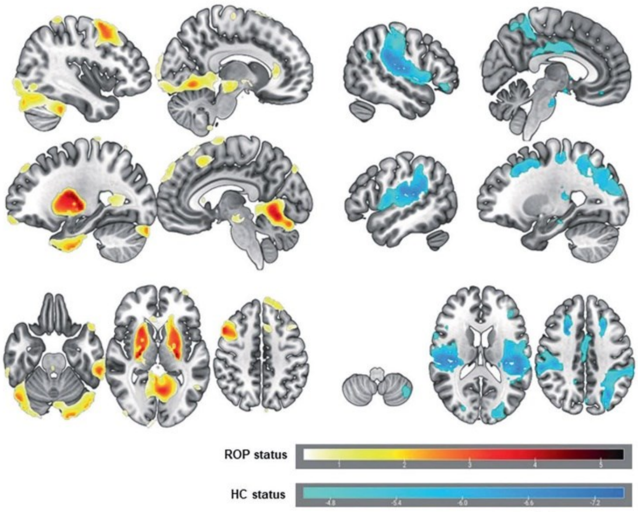

Fig. 2 Reliability of predictive voxels for the impaired vs. HC classification model. Voxel-wise reliabilities are represented by the cross-validation ratio. Warm colors represent the 10% most reliable voxels predicting impaired ROP status, i.e., areas with increased gray matter (GM) in ROP. Cool colors represent the 10% most reliable voxels predicting HC status, i.e., areas with increased GM in HC. Left and right hemisphere are reversed.

negative symptoms [8, 9] and gradual differences in social and occupational functioning in comparison to spared subgroup and HC. Second, studies demonstrate developmental lags relative to same-aged HC [54] in CHR individuals who go on to develop full-blown psychosis. Large cohort studies in CHR [55] implicate that immediate verbal learning, memory and processing speed are the most relevant domains for prediction of transition to psychosis. Those domains are significantly reduced in our impaired subgroup (Supplementary Fig. S9) and replicate in the validation sample. Third, previous cross-sectional findings on ultra-high risk (UHR) individuals who later transitioned to psychosis reported reduced GMV in prefrontal areas, temporal gyrus and cerebellum relative to HC and to UHR who did not transition to psychosis, respectively [56, 57]. In the current study, the impaired subgroup shows a significant neuroanatomical signature relative to HC. The presence of GMV reduction, despite the absence of chronicity and long-term medication effects, suggests these brain alterations may have emerged before the onset of florid psychotic symptoms. Finally, both behavioral and imaging effects persist after controlling for differences across subgroups regarding age, sex, educational years, study site and group sizes. In addition, post hoc examination of the relationship between decision scores of the 'impaired subgroup vs HC' neuroimaging classification model and study site ensures that our classification model is not mainly driven by site-specific scanner differences (Supplementary Materials and Methods).

The current study has several limitations. First, the applied neuropsychological tasks differed from the MCCB [25] and cognitive domains, e.g., social cognition and executive functioning, were underrepresented in comparison to other tests (Table S1). Second, we could only partially replicate the effects of the discovery cluster solution. This might be due to differences in sample characteristics and sizes (Table 1) or the monocentric characteristic of the validation sample. Third, while we suggest that the characteristics of the impaired subgroup align with early maladaptive processes as proposed in the neurodevelopmental hypothesis [1], our assessment of functioning is retrospective and cross-sectional. Future studies would benefit from a longitudinal design providing a more comprehensive answer. Fourth, as cross-site data acquisition differences arise as key issues in multi-center studies [58], we accounted for such effects in both behavioral and neuroimaging analysis. However, an effect of an unbalanced distribution of participants between subgroups and HC on our cluster findings cannot be ruled out entirely.

Cognitive and clinical differences in the psychosis subgroups of the discovery sample support the idea of distinct trajectories in early stages of the disease [5]. In accordance with this finding is the neurobiological separability of cognitively impaired patients from HC. Early detection of psychosis subgroups could help to tailor early interventions for ROP patients with likely stronger neurodevelopmental character of psychosis. A prime candidate to achieve this might be neurocognitive intervention showing positive effect on cognition and functioning in patients suffering from SZ [7]. Further studies should investigate if the suggested clusters are shared between different phenotypes, particularly affective psychosis, and if common transdiagnostic pathways can be found for patients with cognitive impairments.

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institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

DATA AVAILABILITY

The data models that support the findings of this study are available on request from the corresponding author [LK-I and NK]. The data are not publicly available due to ethical restrictions.

AUTHOR CONTRIBUTIONS

Analysis or interpretation of data: JW, LK-I, NK, DBD, JK. Concept and design: LK-I, NK, DBD, JK, RU, RKRS, EM, SJW, PB, Borgwardt. Drafting of the manuscript: JW, LK-I. Critical revision of the manuscript for important intellectual content: all authors. Data acquisition, analysis, quality control and MRI support: SSH, AR, OFO, LA, SvS, CB, MG, AF, MP, JB and the PRONIA consortium.

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ADDITIONAL INFORMATION

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THE PRONIA CONSORTIUM

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6.2. Publication #2

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ARTICLE OPEN

A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis

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Two decades of studies suggest that computerized cognitive training (CCT) has an effect on cognitive improvement and the restoration of brain activity. Nevertheless, individual response to CCT remains heterogenous, and the predictive potential of neuroimaging in gauging response to CCT remains unknown. We employed multivariate pattern analysis (MVPA) on whole-brain resting-state functional connectivity (rsFC) to (neuro)monitor clinical outcome defined as psychosis-likeness change after 10-hours of CCT in recent onset psychosis (ROP) patients. Additionally, we investigated if sensory processing (SP) change during CCT is associated with individual psychosis-likeness change and cognitive gains after CCT. 26 ROP patients were divided into maintainers and improvers based on their SP change during CCT. A support vector machine (SVM) classifier separating 56 healthy controls (HC) from 35 ROP patients using rsFC (balanced accuracy of 65.5%, $P < 0.01$) was built in an independent sample to create a naturalistic model representing the HC-ROP hyperplane. This model was out-of-sample cross-validated in the ROP patients from the CCT trial to assess associations between rsFC pattern change, cognitive gains and SP during CCT. Patients with intact SP threshold at baseline showed improved attention despite psychosis status on the SVM hyperplane at follow-up ($p < 0.05$). Contrarily, the attentional gains occurred in the ROP patients who showed impaired SP at baseline only if rsfMRI diagnosis status shifted to the healthy-like side of the SVM continuum. Our results reveal the utility of MVPA for elucidating treatment response neuromarkers based on rsFC-SP change and pave the road to more personalized interventions.

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INTRODUCTION

Neuroplasticity-based computerized cognitive training (CCT) has frequently been used as a supplementary treatment in psychotic illness [1, 2]. CCT implements learning-based neuroplasticity principles to restore neuromodulatory processes underlying the structure, function, and connections in the brain that support perceptual, cognitive, social, and motor abilities often disturbed in psychotic illness [3, 4]. This therapeutic approach received evidence in circumventing cognitive deficits [5–7] and poor functional outcome in psychosis [8, 9]. Previous meta-analyses indicate that cognitive remediation has a small to moderate effect on multiple cognitive domains including attention, working memory, executive functioning, and social cognition in the treatment of schizophrenia [6, 7, 10]. In particular, research has documented the neural plasticity of cortical responses as an individual acquires new perceptual and cognitive abilities [11, 12]. Further evidence suggests that preserved brain network modularity [13] and neuronal fiber integrity may be important determinants for training-induced neurocognitive plasticity, particularly in domains of attention [14], executive function [14], and social cognition [15]. Previous research on selective attention demonstrates marked malleability of neural systems in charge of potential changes in response to intervention [16]. Dysplasticity in schizophrenia has been known for decades, and while it has predominantly been reported in motor and frontal areas [17, 18], it is also expressed in multiple brain regions including sensory systems [19]. The underlying mechanism of neuroplasticity-based CCT is meant to induce widespread changes in both cortical and subcortical representations and may not be captured by single-region activation maps measured by task-based MRI [3, 20, 21].

Importantly, the variability in neuroplastic response induced by intermediate neurocognitive and brain phenotypes may moderate the neuroplastic response induced by respective training paradigms [22]. To mitigate the heterogeneity in response to CCT and

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multidimensionality of neuroimaging data, multivariate pattern analysis (MVPA) allows quantification of diagnostic group membership or treatment response at the individual level [23, 24], particularly when clinical data is complemented with neurobiological proxies [25]. These proxies may entail information on intermediate- and endo-phenotypes responsible for the high degree of variability in the response to CCT. Specifically, they may serve as "neuromarkers" [26, 27] that successfully aid in identifying disorders and factors determining not only illness progression [28, 29], but also monitoring response to treatment (theranostics) [27, 30–32]. Recently, brain connectivity measures derived from task-based functional Magnetic Resonance Imaging (fMRI) were used as a proxy for cognitive performance [33]. Resting-state functional connectivity (rsFC) has been used to predict diagnosis and clinical outcome of patients with psychosis and it demonstrated a high level of within-subject reproducibility that is relevant for longitudinal monitoring of treatment response [34, 35].

Finally, the high degree of variability in cognitive gains may be explained by individual differences in engagement level of the underlying neural system target and learning progress in CCT [36, 37]. These studies showed greater deficits in mismatch negativity, an event-related potential elicited pre-attentively, predicted greater improvements after auditory CCT. Still, it remains unknown whether inter-individual differences in sensory processing during CCT in combination with neuroimaging prediction on the single-subject level may inform more personalized CCT in patients at the earlier stages of psychosis [38] early in the course of CCT (first 10 h).

The aim was to investigate individual response to 10 h of CCT by measuring changes in psychosis-likeness based on rsFC patterns in relation to sensory processing. First, we developed an original multivariate model, able to distinguish HC from ROP patients using rsFC in a naturalistic sample. Second, this model was applied to the CCT intervention sample, to assess and monitor clinical outcome in response to CCT. Hereby, we measured the change of psychosis-likeness after 10 h of CCT at the single-subject level employing machine learning on rsFC pattern before and after CCT. In the third step, we investigated how psychosis-likeness change was related to sensory processing. In the final step, we investigated the effects of sensory processing change (SPC), psychosis-likeness change (ROP-HC continuum) and their association on cognitive gains, in response to the intervention. We expected to observe cognitive gains in lower-order cognitive functions due to the drill-and-practice approach used and short duration of the intervention.

Table 1. Baseline demographic and clinical characteristics for ROP patients and HC individuals included for the generation of a healthy-to-psychosis model based on resting-state functional connectivity.

	ROP (*N* = 35)	HC (*N* = 56)	*T*/ χ^2	*P* value
Number of female (%)	13 (37.14 %)	36 (64.29 %)	6.39	0.012*
Age (*SD*)	30.43 (6.15)	30.64 (6.78)	0.151	0.88
Years education (*SD*)[a]	13.88 (3.45)	15.73 (3.26)	2.51	0.014*
Premorbid IQ (*SD*)	100.29 (18.59)	109.64 (13.24)	2.80	0.006**
Handedness[a]	–	–	0.27	0.88
Right (%)	29	47	–	–
Mixed (%)	2	5	–	–
Left (%)	2	3	–	–
Diagnosis (%)				
No Axis I Diagnosis	0	56	–	–
Schizophrenia	19 (54.29 %)	–	–	–
Schizoaffective disorder	1 (2.63 %)	–	–	–
Schizophreniform disorder	3 (8.57 %)	–	–	–
Delusional disorder	5 (13.16 %)	–	–	–
Psychotic disorder NOS	5 (13.16 %)	–	–	–
Substance-induced psychotic disorder	2 (5.26 %)	–	–	–
GAF past month	41.18 (9.87)	83.7 (5.11)	26.91	<0.001***
GF current				
Role (*SD*)	5.06 (1.82)	8.29 (0.59)	12.24	<0.001***
Social (*SD*)	5.65 (1.32)	8.25 (0.69)	12.24	<0.001***
PANSS				
Total (SD)	67.03 (14.45)	–	–	–
Positive (SD)	18.00 (5.48)	–	–	–
Negative (SD)	15.06 (5.82)	–	–	–
General (SD)	33.97 (6.76)	–	–	–

MRI Magnetic Resonance Imaging, *NOS* not otherwise specified, *MDD* Major Depressive Disorder, *CPZ* chlorpromazine equivalent, *GAF* Global Assessment of Functioning, *GF* Global Functioning, *PANSS* Positive and Negative Syndrome Scale.
[a]Two participants did not provide total years of education at baseline and three did not complete the self-rating instrument which includes information regarding handedness.

MATERIALS AND METHODS

Sample

Two samples were included from the Early Detection and Intervention Center at the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilians-University (LMU) in Munich, Germany: (1) the original PRONIA study diagnostic sample of 35 ROP patients and 56 HC recruited from the LMU Munich site of the naturalistic, European multi-center PRONIA study [39] (Table 1) to generate the SVM classification HC-ROP model to create the psychosis-likeness hyperplane, and (2) the CCT intervention sample, independent from the original SVM sample cohort, that included 26 patients with ROP (Fig. S1) undergoing CCT in a randomized controlled trial (ClinicalTrials.gov Identifier: NCT03962426). Although PRONIA is a multi-center study, we included only the LMU, Munich site to generate our HC-ROP model as (1) the intervention sample was acquired from the same study site (2) neuroimaging site-effects can be an additional source of variability in SVM classification which is challenging to mitigate, especially for the resting-state modality [40–44]. For both the diagnostic classification and intervention samples, ROP patients were included if illness duration was below 2 years and if the criteria for an affective or non-affective psychotic episode according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [45] was fulfilled (supplementary information, Section 1.1). All participants provided written informed consent prior to study inclusion while all procedures performed in this study were in accordance with the ethical standards of the Local Research Ethics Committee of the LMU and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Procedures

CCT Intervention. Participants included in the active intervention group (*N* = 26, Table 2) completed an average of 9.98 h of CCT within 20 30-min individual sessions over 5 weeks (Supplementary Information, Fig. S1 and Section 1.2). The training consisted of four exercises (Table S1) that strike a balance in improving multiple cognitive domains including social cognition, processing speed, and attention. Task difficulty is adjusted to maintain 75–80% accuracy of the participants' responses by constantly adapting presentation times of the displayed facial stimulus [3, 46]. Difficulty levels are modulated based on a specific individual's

Table 2. Baseline demographic information of the intervention sample.

	Maintainers EMT ($N = 14$)	Improvers EMT ($N = 12$)	T/χ^2	P value
Number of female (%)	8 (57.14%)	3 (25.00%)	2.74	0.098
Age (*SD*)	27.46 (5.84)	26.10 (7.00)	0.54	0.594
Years education (*SD*)	14.96 (2.71)	15.79 (4.73)	−0.56	0.582
Premorbid IQ (*SD*)	97.14 (16.02)	100.83 (13.62)	−0.63	0.537
Handedness	–	–	2.20	0.333
Right (%)	9	11	–	–
Mixed (%)	2	0	–	–
Left (%)	1	1	–	–
Diagnosis	–	–	6.55	0.477
Schizophrenia (%)	4 (28.57 %)	4 (33.33 %)	–	–
Schizoaffective disorder (%)	1 (7.14 %)	-	–	–
Schizophreniform disorder (%)	1 (7.14 %)	2 (16.67 %)	–	–
Brief psychotic disorder (%)	3 (21.43 %)	3 (25.00 %)	–	–
Delusional disorder (%)	1 (7.14 %)	2 (16.67 %)	–	–
Psychotic disorder NOS (%)	1 (7.14%)	–	–	–
MDD with psychotic symptoms (%)	3 (21.43 %)	–	–	–
Substance-induced psychotic disorder (%)	–	1 (8.33 %)	–	–
Medication at baseline ($N = 39$)				
CPZ equivalent (SD)	142.68 (162.49)	278.44 (258.96)	−1.63	0.117
Days between assessments	51.29 (13.12)	47.42 (8.99)	0.86	0.397
Number of hours trained	9.91 (0.74)	10.10 (0.73)	−0.49	0.630
GAF past month	46.25 (13.86)	48.00 (16.87)	−0.29	0.774
GF current				
Role (*SD*)	4.57 (1.45)	4.25 (1.54)	0.55	0.590
Social (*SD*)	6.00 (1.30)	6.00 (0.95)	0.00	1.000
PANSS				
Total (SD)	66.07 (15.61)	69.83 (17.94)	−0.57	0.573
Positive (SD)	19.21 (6.12)	19.83 (5.88)	−0.26	0.796
Negative (SD)	13.43 (5.24)	15.83 (6.19)	−1.07	0.294
General (SD)	33.43 (9.10)	34.17 (9.11)	−0.21	0.839

EMT Emotion Matching Task, *MRI* Magnetic Resonance Imaging, *NOS* not otherwise specified, *MDD* Major Depressive Disorder, *CPZ* chlorpromazine equivalent, *GAF* Global Assessment of Functioning, *GF* Global Functioning, *PANSS* Positive and Negative Syndrome Scale.

rate of learning, represented by a 'learning score', are quantified by analyzing the stimulus presentation times for a specific level within a specific task (Supplementary Information, Section 1.3) and have previously been shown to influence neural plasticity and transfer of the training [47]. While all four exercises target early social sensory processing, we chose to study the Emotion Matching Task (EMT) as a potential proxy for target engagement, given its ability to capture the processing of basic social information while improving speeded facial emotion decision-making (Supplementary Information, Section 1.3). 26 patients that completed training on the Emotion Matching Task (EMT) were thus dichotomized into maintainers ($N = 14$) and improvers ($N = 12$) based on a median split of their learning scores (Supplementary Information, Section 1.3, Fig. S2). Improvers showed impaired performance at baseline and reached the psychophysical threshold (~31 ms) for EMT during training (high SPC), while maintainers showed intact psychophysical threshold for EMT at baseline that were sustained throughout the training (low SPC). The current analysis selected a level that was played by everyone and contained the most repetitions per participant.

Assessment procedure

Clinical assessment occurred during intake at baseline (T0) and again at follow-up (FU) post-intervention. Clinical diagnosis was assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) [45]. In order to assess clinical status and the presence and severity of symptoms, the Positive and Negative Syndrome Scale (PANSS) was administered [48]. Global rating of functioning was assessed using the Global Assessment of Functioning (GAF) Disability and Impairment Scale of the DSM-IV [49]. Additionally, the clinician-rated Global Functioning - Social (GF-S) and Global Functioning - Role (GF-R) Scales were used to assess social and role functioning separately [50].

A cross-domain neuropsychological test battery comprising 9 tests were administered to patients in the intervention sample at T0 and FU in a fixed order (Supplementary Information, Section 1.4). Tests were z-score transformed based on the study sample to closely reflect cognitive domains based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) recommended procedures [51] (Table S2).

Imaging procedure

All participants from both the original sample and intervention sample were scanned using the same 3 Tesla Philips Ingenia scanner with 32-channel radio-frequency coil at the Radiology Department in the university clinic of the LMU in Munich, Germany (Supplemental Information, Section 1.5). Both structural MRI (sMRI) and resting-state fMRI (rsfMRI) were acquired from all participants. T1 sMRI images were preprocessed using CAT12 (Supplementary Information, Section 1.6). rsfMRI preprocessing was divided into two main processes: core steps included realignment, coregistration, warping to Montreal Neurological Imaging (MNI) space and smoothing, whereas denoising steps comprised of motion correction using time series despiking with the BrainWavelet Toolbox (http://www.brainwavelet.org/) [52], background filtering and temporal band-pass filtering (0.01–0.08 Hz), extracting signal from white matter (WM) and cerebrospinal fluid (CSF), correcting for movement (Friston 24 movement parameters) [53] and calculating framewise displacement (FD) for each subject to determine inclusion [54] (Supplementary Information, Section 1.6).

Following sMRI and rsfMRI preprocessing, the brain was parcellated into 160 regions of interest (ROIs) according to the Dosenbach functional atlas [55]. We extracted the mean signal from 10 mm spheres centered at each ROI using the MarsBaR Toolbox [56] version 0.42. Next, the Pearson's correlation of average time series between pairwise ROIs was calculated within Matlab R2015 using in-house scripts—resulting in 12720 rsFC for each participant. Connectivity matrices were generated for each subject in both the intervention sample and the original diagnostic classification sample.

Machine learning strategy

The machine learning software NeuroMiner [39] version 1.0 was used to set up the machine learning analysis pipeline to extract multivariate decision rules from the rsFC data using an

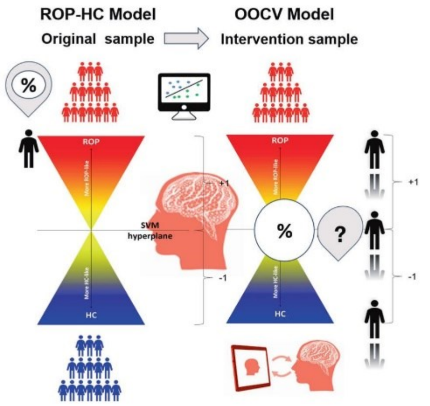

Fig. 1 Proposed model depicting the application of a healthy-to-psychosis-like spectrum that could be used for monitoring treatment response to CCT. rsFC correlation matrices are entered into the SVM classification model to distinguish HC from ROP in an external sample. Using OOCV, the model is validated on patients who underwent the intervention sample at two time-points. Changes in decision scores are compared at the two time-points (FU-T0) in order to measure the direction of shift across the hyperplane based on rsFC.

out-of-sample cross-validation (OOCV) strategy. First, a HC-ROP rsFC classifier was built to identify a disease-related rsFC signature. To investigate whether this disease-related signature could be used to track neural response to CCT in ROP patients, models generated for HC-ROP classification were applied to the intervention sample at both T0 and FU using OOCV. Here, we expected to identify a pattern of rsFC anomalies that not only classified HC and ROP with high accuracy, but that could also identify a set of individuals whose rsFC would shift to a more healthy-like rsFC pattern across the SVM hyperplane (Fig. 1).

Machine learning analysis pipeline

NeuroMiner was used to create a predictive model that could separate patients with ROP from HC based on rsFC in the original diagnostic classification sample. To avoid overfitting, test the estimation of the model's generalizability, and prevent information leakage between training and test participants, repeated-nested double cross-validation (CV) was employed [57, 58] (Supplementary Information, Section 1.7). This CV structure embeds a 10-fold inner CV cycle (CV1), where models are generated, in another super-ordinate 10-fold outer CV cycle (CV2), which is ultimately used to test the model's generalizability [59, 60]. Both inner and outer CV cycles were permuted 10 iterations. Within CV1, matrices were pruned of zero-variance features, and sex and IQ effects were regressed out of the feature set using a partial correlation method. Then, a dimensionality reduction procedure was applied using Principal Component Analysis (PCA) in the CV1 training data to reduce the risk of overfitting and increase the generalizability of classification models [61] following previous methods [62]. Principal component (PC) scores were 0–1 scaled and fed to a linear class-weighted Support Vector Machine (SVM) algorithm (LIBSVM 3.1.2 L1-Loss SVC) [39, 63] to detect a set of PCs that optimally predicted the training and test cases' labels in a given CV1 partition. The default regularization parameter of C = 1 was used within CV1 [64]. This analysis pipeline was subsequently applied to each k-fold and N-permutation CV2 cycle, determining the participant's classification (HC vs. ROP) through majority voting. Statistical significance was assessed through permutation testing [57, 65], with $\alpha = 0.05$ and 1000 permutations (Supplementary Information, Section 1.7).

Validation analyses of classifier

The HC-ROP classifier built on the independent sample was subsequently applied to the intervention sample at T0 and FU without any in-between retraining using OOCV. The OOCV model provides a subject-specific linear SVM decision score at each timepoint for every ROP patient in the intervention sample. Positive decision scores indicate a predicted class membership of ROP, whereas negative decision scores indicate a predicted class membership belonging to HC. The difference in decision scores between the two time-points (FU-T0), that we address as psychosis-likeness change, provides an estimate of the direction of shift across the SVM hyperplane following CCT. Positive differences indicate a shift in the more psychosis-like direction, whereas negative differences indicate a shift in the more healthy-like direction across the SVM hyperplane. The measured changes in decision scores between the two time-points serve to verify if the multivariate rsFC signature from psychosis-like to healthy-like has been altered in the CCT intervention group. We performed platt scaling [66] to calibrate the decision score and assure that SVM predicted probabilities match the expected distribution of probabilities for each class. We calibrated the trained model by fitting the logistic regression to decision scores of the original HC-ROP model and applied this to the decision scores of the intervention data set. The HC-ROP classifier built on the LMU independent sample was additionally applied to three independent samples without any in-between retraining using OOCV in order to further assess generalizability of our model (Supplementary Information, Section 1.8, Table S5). We conducted additional correlational analyses to confirm our results are not biased by antipsychotic medication intake (Supplementary Information, Section 1.8, Table S6). We also ran additional correlational analyses to assess the associations between the psychosis-likeness model and 1) unhealthy consumption (e.g., cigarettes, alcohol), 2) variables indicative of socio-economic status (education and occupation of parents), patients functioning (GAF), traumatic experiences (Childhood trauma Questionnaire, CTQ [67, 68]) and age of illness onset (Supplementary Information, Section 1.8, Table S7).

Statistical analyses of clinical and cognitive data

The following analyses were carried out in Jamovi version 1.1.9 (https://www.jamovi.org/), with a significance level of $\alpha = 0.05$, with False Discovery Rate (FDR) correction for multiple comparisons [69]. Participants identified as outliers on cognitive domains (>2 SD) were excluded from further analyses. Demographic differences between groups were assessed using independent *t*-tests for continuous variables and chi-square tests for categorical variables. Repeated measures ANOVA was used to assess changes in cognition over time (1) based on SPC, (2) psychosis-likeness change, and (3) the interaction of SPC and psychosis-likeness change. Post-hoc analyses investigating the direction of effects were done using paired-samples t-tests. Effect sizes were reported using Cohen's d [70].

RESULTS

Group-level sociodemographic and clinical data

Independent sample (HC-ROP). At baseline there were significantly more females in the HC group as compared to the patient group ($df = 1$, $\chi^2 = 6.39$, $P = 0.012$). Patients had significantly fewer years of education ($T[86] = 2.51$, $P = 0.014$), and lower premorbid IQ ($T[89] = 2.80$, $P = 0.006$) than HC individuals (Table 1). Patients with ROP showed significantly lower levels of functioning in all measures at T0 including GAF Disability and

Impairment ($T[88] = 26.91$, $P < 0.001$), GF-R ($T[88] = 12.24$, $P < 0.001$), and GF-S ($T[88] = 12.24$, $P < 0.001$).

Intervention Sample (maintainers - improvers). At baseline, there were no significant differences between maintainers and improvers in demographic characteristics, symptom severity, functioning, number of days between assessments, training intensity or antipsychotic medication ($P > 0.05$) (Table 2). The performance on all cognitive domains, except for verbal learning at baseline ($T[24] = 2.18$, $P = 0.04$) was balanced between the maintainers and improvers. We observed a marginally significant between groups effect on social cognition FU scores ($F[1,25] = 4.45$, $P = 0.046$), while controlling for T0 performance ($F[1,25] = 4.08$, $P = 0.055$). Although symptoms and functioning improved over time in all measures, there were no differences based on SPC (Table S3).

Resting-state functional connectivity prediction performance. The HC-ROP classifier correctly discriminated patients with ROP from HC with a cross-validated balanced accuracy (BAC) of 65.54% (sensitivity = 54.29%, specificity = 76.79%) and was significant ($P = 0.01$). Detailed statistics of the classification model are reported in Table S4. Inspection of the mean feature weights generated within the CV framework revealed that the rsFC connections driving correct classification between ROP and HC were long-range connections between (1) left parietal and right frontal lobe and (2) bilateral parietal lobe and thalamus, and short-range connections between (1) left parietal and left occipital area (2) right temporal and right angular gyrus, (3) left inferior temporal with right insula and left cerebellum, and (4) bilateral temporal lobe with bilateral thalamus (Fig. 2, Table S7). The connectivity patterns were mainly characterized by stronger FC associations in patients as compared to HC (Fig. 2) whereas only a few fronto-parietal and temporal-insular connectivities showed stronger connectivity in HC as compared to ROP patients (Fig. 2).

Applying the ROP-HC model generated within the independent PRONIA sample to the intervention sample resulted in a model sensitivity of 65.38% at baseline and 57.69% at follow-up. When looking across all patients in the maintainer and improver subgroups, rsFC patterns shifted in the healthy-like direction (i.e., a decrease in decision scores from T0 to FU), with no significant differences in the number of patients whose rsFC shifted in the healthy-like direction (maintainers = 8, improvers = 8) as opposed to the psychosis-like direction (maintainers = 6, improvers = 4; $df = 1$, $\chi^2 = 0.25$, $P = 0.62$). Although there were no significant differences between maintainers and improvers in psychosis-likeness changes over time ($F[1,25] = 0.96$, $P = 0.34$), the overall shift to the healthy-like decision scores seems to be driven by a shift to the healthy-like part of SVM hyperplane in improvers (ES[Cohen's d] = −0.35), whereas maintainers showed rather stable decision score values from T0 to FU (ES[Cohen's d] = 0.03; Fig. 3a; Supplementary Information, Fig. S3 [A-B]).

Comparing maintainers and improvers further, we found a significant interaction between the group and the change in decision scores on the attentional gain ($F[1,23] = 8.13$, $P = 0.01$, [$P = 0.06$ with FDR correction]; Fig. 3b; Supplementary Information, Fig. S3 [C-D]). However, the effect of the group ($F[1,23] = 0.06$, $P = 0.81$) and decision score change ($F[1,23] = 0.13$, $P = 0.72$) alone on the attentional change was not significant. We observed a moderate effect size of improvement in attention despite psychosis-likeness change in the psychosis-like direction on the SVM hyperplane only in patients who showed intact SPC at baseline and maintained peak performance throughout the CCT ($T[13] = 1.26$, $P = 0.26$, ES = 0.51). Contrarily, attentional gains showed a large effect size in the ROP patients who showed impaired SPC at baseline only if the rsFC shifted to the healthy-like side of the SVM hyperplane ($T[11] = 2.29$, $P = 0.06$, ES = 0.87).

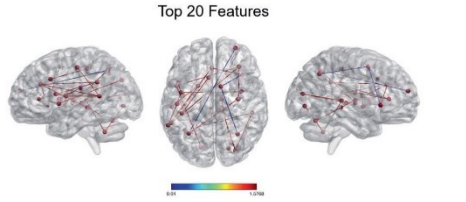

Fig. 2 Depiction of the cross-validation ratio-based most reliable connections driving the classification between HC and ROP. The inter- and intrahemispheric connectivities of the top 20 features were extracted using a percentile rank of ~99.99% mapped onto the brain using BrainNet Viewer. Details of the regions that comprise the top 20 features are depicted in Table S8 in the Supplement. Blue lines indicate higher connectivity degree in the HC group; red lines indicate greater connectivity in the ROP group. Reliability is defined as the mean value of the SVM weight divided by its standard error across all the generated models in the cross-validation scheme.

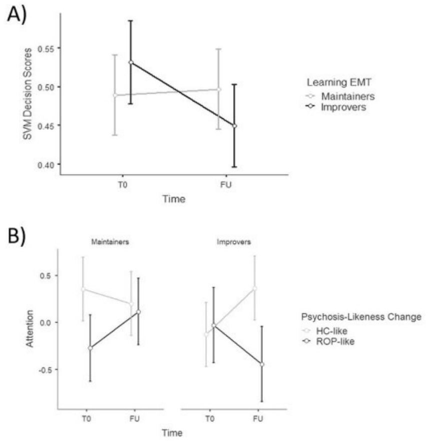

Fig. 3 Decision scores and cognitive changes following computerized cognitive training. a SVM decision score change, reflecting the degree of psychosis-likeness based on resting-state functional connectivity (rsFC), in maintainers versus improvers and **b** attentional change based on shift across the hyperplane using rsFC and sensory processing change. Higher SVM decision scores reflect more psychosis-like rsFC. Error bars represent standard error. EMT Emotion Matching Task, FU follow-up, HC healthy control, ROP recent onset psychosis, SVM Support Vector Machine, T0 baseline.

DISCUSSION

In this study, we performed a proof-of-concept analysis aimed at investigating the potential utility of rsFC to assess and monitor individual neural response to CCT. This is, to the best of our knowledge, the first study utilizing a machine learning rsFC model to investigate change of psychosis-likeness in response to CCT and associate it to changes in cognition and sensory processing.

To achieve this, we employed a model that was built on an independent sample of LMU ROP patients not undergoing the intervention, providing us with a quantifiable clinical outcome measure of psychosis-likeness change across the HC-ROP continuum with a BAC of 65.54%. This BAC is within the range of classification accuracies that utilize the resting-state modality for classifying chronic and first-episode psychosis patients from healthy controls [71].

After showing a solid generalizability of this model to the CCT sample, we followed the notion that various types of sensory [19] and multimodal plasticity impairments [72] may be differentially susceptible to interventions [37]. We used EMT as a proxy for sensory processing and created two patient groups based on the median split of SPC. We identified a subgroup of 'improvers' who initially presented with sensory processing impairments, however showed significant improvements in SPC throughout the course of the CCT. The other subgroup of 'maintainers' initially presented with unimpaired sensory processing and maintained peak performance throughout CCT at the optimal psychophysical level. We found that rsFC psychosis-likeness change in these two subgroups was differentially associated with attentional gains in response to CCT. Although we did not find a significant difference between improvers and maintainers in psychosis-likeness changes over time, the improvers showed a stronger change in psychosis-likeness to the healthy rsFC pattern. Importantly, these rsFC shifts seemed to be accompanied by attentional gains in improvers, while psychosis-likeness change in maintainers appeared compensated by efficient sensory processing that helped this subgroup nevertheless achieve attentional gains. Improvements in the attention domain after 10 h training is consistent with previous findings that improvements in low-order cognitive functions via drill-and-practice techniques precede gains in higher-order cognitive domains [73].

Stepping back to understand the resting-state pattern underlying psychosis-likeness in our original HC-ROP model, we observed widespread changes in both cortical and subcortical functional connectivities. We observed reduced rsFC between fronto-parietal regions and thalamo-cortical areas which successfully distinguished ROP patients from HC group, that may indicate less disturbed neuroplasticity in areas of top-down regulatory control, highly relevant for attentionally demanding cognitive tasks.

The importance of preserved fronto-parietal [13] and thalamo-cortical connectivity [66] is critical for normal cognitive functioning, in particular attention and sequential planning [74, 75], and relevant for mechanisms of learning in CCT. Our findings support this notion as the improvers, whose psychosis-likeness decreased or remained healthy-like, were able to translate cognitive skills acquired during CCT to attentional gains. Conversely, maintainers showed greater transfer effects to the domain of attention despite preserved psychosis-like rsFC, possibly due to their efficient sensory processing at baseline that served as cognitive reserve [14]. Our results suggest that improvement in attention may depend on an association between more healthy-like whole-brain rsFC patterns and efficient sensory processing during CCT and demonstrates feasibility of using resting-state as a valid biomarker. In line with our work, a recent fMRI study using resting-state connectivity networks was able to predict medication-class of response in hard-to-diagnose patients [76], further supporting the utility of resting-state fMRI in the 'real-world' clinical context. In the recent meta-analysis on the utility of resting-state as biomarker, the authors warn about its moderate test-retest variability, while at the same time highlighting the complexity of its application and circumstances that improve the reliability of this neuroimaging modality [40, 77]. Future studies are necessary to determine the exact methodological conditions necessary to optimize the utility of neuroimaging to reliably trace the response to pharmacological and non-pharmacological interventions.

Several limitations of the present study need to be considered. First, the current study used a relatively short CCT as we wanted to keep the intervention duration comparable to the duration of clinical treatment. Our intention was to provide greater resemblance to the real-world clinical setting that appears common in many other health centers across Europe [78], and provides a strong clinical care framework due to the initial stay of the patients at the ward or frequent clinical checks. However, we cannot claim that ROP patients who did not respond with an improvement of rsFC pattern and did not show efficient SPC learning would not achieve neural 'recovery' associated with enhancement of cognition with a slightly different form of intervention, longer duration, or implementing more diverse protocols [7]. Second, we attempted to operationalize sensory processing during CCT by using a median split to categorize patients into improvers and maintainers. However, our approach may limit the generalizability of our findings and needs to be further investigated in future studies. Third, while the CCT in this study uses social stimuli, we have not observed any interaction between psychosis-likeness change and social cognition. While we measured performance on facial affect recognition, which represents only one domain of social cognition, a greater number of social cognitive measures would be needed to capture social cognition improvement at a fine-grained level [79]. Fourth, though we were not able to assess long-term effects of the intervention in an additional follow-up session, investigating durability effects of the intervention would be crucial for future studies. Finally, though we followed the generalizability rule in MVPA, including an independent sample in the study to generate the model and tested the generalizability of this model to three additional independent samples across multiple sites, future studies replicating our findings in multi-site cohorts with larger numbers of participants are warranted.

Prospectively, this MVPA approach may be integrated into individual early identification and intervention programs, thus resulting in a likely cheaper and more effective personalized psychiatry application [80, 81]. Psychotic disorders are highly heterogeneous at many levels, from biological pathways to clinical presentation and usage of the neuromonitoring approach may lead to faster identification of individuals with shared biological pathways that show a greater potential to improve through CCT [82].

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AUTHOR CONTRIBUTIONS

SH, LK-I, and NK conceptualized the paper. LK-I and NK oversaw data collection and project development. SH was responsible for statistical analyses. SH and LK-I drafted the manuscript and provided data interpretation. LA, JuW, BB, and JK assisted with statistical analyses and data interpretation. SH, JuW, and JoW assisted in data collection and data entry. LA, SH, JoW, and AR were involved in developing the neuroimaging pipeline. MP and BSR were in charge of developing scanning protocols. JK, SB, EM, RS, RU, and SW revised the manuscript and assisted in conceptualizing the project. All authors revised and agreed upon the final version of the manuscript.

ADDITIONAL INFORMATION

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7. Literature

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