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Clinical Deep Phenotyping From Cognition to Brain and Retina in Severe Mental Illnesses

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Lenka Krčmář

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Banska Bystrica (Slowakei)

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Erstes Gutachten:	Prof. Dr. Andrea Schmitt
Zweites Gutachten:	Dr. Daniel Keeser
Drittes Gutachten:	Prof. Dr. Frank Wollenweber
Viertes Gutachten:	Priv. Doz. Dr. Urs Heilbronner

Dekan: Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 17.06.2024

Affidavit

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_____Krčmář, Lenka_____

Surname, first name

_____Nußbaumstraße 7_____

Street

_____80 336 München_____

Zip code, town, country

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_____Krčmář, Lenka _____

Surname, first name

_____Nußbaumstraße 7_____

Street

_____80 336 München _____

Zip code, town, country

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Table of contents

Affidavit **3**

Confirmation of congruency **4**

Table of contents **5**

List of abbreviations **6**

List of publications **7**

1. Introductory summary **8**

1.1 Introduction 8

1.1.1 Severe mental illnesses – clinical background 8

1.1.2 Deep phenotyping cohort and multimodal assessment 9

1.1.2.1 Establishing a translational cohort for the CDP study 9

1.1.2.2 Importance of retinal assessments in patients with SMIs 12

1.1.2.3 mMRI and EEG examinations and findings in patients with SMIs and their associations with cognitive functioning 13

1.2 Project's aims 15

1.3 Project's conclusions 16

1.3.1 Summary of results and their relevance for the field 16

2. Contribution to the PhD publications **18**

2.1 Contribution to Paper I 18

2.2 Contribution to Paper II 19

3. Paper I **20**

4. Paper II **36**

References **51**

Acknowledgements **58**

Curriculum vitae **59**

List of abbreviations

AD, Alzheimer's disease; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BMI, body mass index; BrPsyD, brief psychotic disorder; CDP, Clinical Deep Phenotyping; CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; CNS, central nervous system; CPZeq, chlorpromazine equivalent doses; CTQ-Screen, Childhood Trauma Screener; DD, delusional disorder; DIP, drug-induced psychosis; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision; DTI, diffusion tensor imaging; EEG, electroencephalography; ENIGMA, Enhancing Neuro Imaging Genetics Through Meta-Analysis; ERG, electroretinography; GAF, Global Assessment of Functioning; HC, healthy controls; HCP, Human Connectome Project; ICD-10, International Classification of Diseases, 10th revision; IDS-C30, Inventory of Depressive Symptomatology clinician-rated version with 30 items; M.I.N.I., Mini-International Neuropsychiatric Interview; MCTQ, Munich Chronotype Questionnaire; MDD, major depressive disorder; MIMICSS, Multimodal Imaging in Chronic Schizophrenia Study; MRS, magnetic resonance spectroscopy; MS, Multiple Sclerosis; MT, macular thickness; NAKO, German National Cohort Study; OCD, obsessive-compulsive disorder; OCT, optical coherence tomography; OCT-A, OCT angiography; PANSS, Positive and Negative Syndrome Scale; PD, Parkinson's disease; PHQ-9, Patient Health Questionnaire-9; RDoC, Research Domain Criteria; RNFL, retinal nerve fibre layer; RSWG, Remission in Schizophrenia Working Group; SMIs, severe mental illnesses; SN, salience network; SSDs, schizophrenia spectrum disorders; SZ, schizophrenia; SZA, schizoaffective disorder; T1-MPRAGE, T1-weighted magnetization prepared-rapid acquisition gradient echo; T2-FLAIR, T2-weighted-fluid-attenuated inversion recovery; T2-SPACE, T2 sampling perfection with application-optimized contrasts using different flip angle evolution; TMS, transcranial magnetic stimulation; TR, treatment resistance; UR, unaffected relatives; WHO-5, World Health Organization-5 Well-Being Index; WHOQOL-BREF, World Health Organization Quality of Life Scale, abbreviated version; YMRS, Young Mania Rating Scale; fMRI, task-based functional MRI; hiPSCs, human induced pluripotent stem cells; mGCIPL, macular ganglion cell–inner plexiform layer; mMRI, multimodal magnetic resonance imaging; mRNFL, macular retinal nerve fibre layer; pRNFL, peripapillary retinal nerve fibre layer; rsfMRI, resting-state functional MRI

List of publications

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Falkai, P., Raabe, F., Bogerts, B., Schneider-Axmann, T., Malchow, B., Tatsch, L., Huber, V.; **Slapakova, L**.; Dobrowolny, H.; Schmitz, Ch.; Cantuti-Castelvetri, L.; Simons, M.; Steiner, J.; Schmitt, A. (2020). Association between altered hippocampal oligodendrocyte number and neuronal circuit structures in schizophrenia: a postmortem analysis. *Eur Arch Psychiatry Clin Neurosci.* doi:10.1007/s00406-019-01067-0

1. Introductory summary

1.1 Introduction

1.1.1 Severe mental illnesses – clinical background

Severe mental illnesses (SMIs) such as major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ) are heterogenous conditions with a high global burden [1]. Over the past few years, the understanding of treatment of SMIs has been notably improved [2]. Mental illnesses have a high risk of comorbidity [3], and each mental illness increases the likelihood of developing another mental illness [4]. Patients with SZ experience deficiencies in their everyday functioning associated with neurocognitive impairment, which is often described as a core feature of SMIs [5]. The cognitive function of patients with SMIs is impaired mainly in the areas of verbal and working memory [6]; interestingly, some patients show good cognitive performance, but others have severe cognitive impairments [7]. Understanding the underlying neurobiology of cognitive dysfunction is crucial to improving the functioning of patients with SMIs [6].

Treatment of SZ is challenging and response to pharmacotherapy is variable. For example, some patients respond only partially to treatment and others do not respond at all [8]. Importantly, treatment is often ineffective in patients with negative symptoms [6]. Patients with schizophrenia spectrum disorders (SSDs) are often refractory to pharmacological treatment, especially regarding their cognitive deficits, despite advances in psychopharmacology [9-11]. Psychiatric illnesses are characterized by multiple different pathophysiological mechanisms and treatment refractoriness also appears to be due to the fact that medications target only specific mechanisms [12]. Although patients with SSDs are known to respond differently to pharmacological interventions because of interindividual heterogeneity [8], treatment personalisation and targeted therapy for SSDs are lacking and stereotypical treatment approaches are common [13]. The low response rate may be due to the combining of distinct pathophysiological mechanisms into one disorder, but targeted therapy can increase the benefit of treatment for patients [12].

A significant number of people with SZ or first-episode psychosis develop treatment resistance (TR) early in their illness, and TR is associated with a high level of functional impairment [14]. There are several definitions of TR in SZ [15], MDD [16], and BD [17] and there is still a need for a better understanding of TR. Several years ago, the term *remission* was introduced as the absence of clinically important symptoms over a period of time [18]. Since then, remission has been widely endorsed in the literature as the outcome endpoint; however, only a small proportion of patients can achieve it [18]. For these reasons, research towards new treatment strategies is needed [1].

SZ is most commonly detected in members of one family line [19] so knowledge of neuronal circuits, genetics and epigenetics is essential and needs to be incorporated into clinical studies [12]. Migration, complications during childbirth, urbanicity, childhood trauma and abuse of

cannabis are associated with psychotic disorders [20] and there is a significant connection between environmental and genetic factors, which influence the occurrence of symptoms of SMIs [21]. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and the International Classification of Diseases, 10th revision (ICD-10), reflect symptoms of psychiatric disorders but not findings from genetics, neuroscience and behavioural science [12]. Therefore, the US National Institute of Mental Health established the Research Domain Criteria (RDoC) in 2010 [22]. The RDoC framework enables detailed investigation of SMIs by using combination of different methods of neuroscience termed units of analysis[1] and six major domains estimated in a functionality scale[2].

Studies performed to date included only a selection of the RDoC assessment tools or had a relatively smaller number of participants. The aim of the Clinical Deep Phenotyping (CDP) study (see attached Paper I) is to overcome this limitation by collecting data with multiple assessment tools from over 1000 healthy controls (HC) and patients with SMIs. In Paper I, we report that we already enrolled 381 participants from October 1, 2020, to October 31, 2022.

1.1.2 Deep phenotyping cohort and multimodal assessment

1.1.2.1 Establishing a translational cohort for the CDP study

As we note in Paper I, the single-centre CDP study was initiated at the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, after being approved by the local ethics committee at the LMU Munich, Germany (project number 20-528). The study is registered in the German Clinical Trials Register (ID: DRKS00024177). Multimodal data gained from the CDP study are stored in the Munich Mental Health Biobank [23] of the LMU Munich (project number: 18-716), where safety and organisation of these data is assured by the high standards of the biobank. In the initiation phase as described in the Paper I, from October 1, 2020, until October 31, 2022, we examined 381 participants, of whom 187 are HC (including 6 unaffected relatives [UR]) and 194 are patients with SMIs. As remarked in Paper I, of 167 patients with SSDs, 110 patients had a diagnosis of SZ; 44, schizoaffective disorder (SZA); 6, brief psychotic disorder (BrPsyD); 5, drug-induced psychosis (DIP); and 2, delusional disorder (DD). Of the other patients, 18 had a diagnosis of MDD and 9, BD. Data continue to be collected in the CDP study.

[1] National Institute of Mental Health. RDoC Matrix. Important Notes on the Matrix. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix [Accessed November 19, 2023].

[2] National Institute of Mental Health. Definitions of the RDoC Domains and Constructs. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs [Accessed November 19, 2023].

Examination of participants from two earlier studies allowed us to conduct longitudinal and translational research, i.e. the studies, a) the Multimodal Imaging in Chronic Schizophrenia Study (MIMICSS) [24, 25] and b) an add-on study of PsyCourse, where the group of donors of human induced pluripotent stem cells (hiPSCs) was secured [26]. Further information about the cohorts is provided in the Paper I.

Participants in the CDP study are assessed with the Mini-International Neuropsychiatric Interview (M.I.N.I.) [27] in line with the DSM-5, text revision (DSM-5-TR, Version 7.0.2) and ICD-10. To enable deep characterization of the cohort, participants undergo basic Munich Mental Health Biobank phenotyping. Participants fill out cross-diagnostic self-ratings: Childhood Trauma Screener (CTQ-Screen) [28], Brief Resilience Scale [29], Loneliness Scale [30], Lubben Social Network Scale [31], World Health Organization-5 Well-Being Index (WHO-5) [32], World Health Organization Quality of Life Scale, abbreviated version (WHOQOL-BREF) [33], Patient Health Questionnaire-9 (PHQ-9) [34] and Munich Chronotype Questionnaire (MCTQ) [35]. Psychiatric and medical history are assessed and current and lifetime psychiatric medication is recorded. Data gained from performed assessments are validated with the electronic medical database in our hospital.

The following disease-related scales are used in all participants regardless of their psychiatric diagnosis: The Positive and Negative Syndrome Scale (PANSS) is utilized to examine SZ symptoms in all participants [36] and the PANSS Remission in Schizophrenia Working Group (RSWG) is used to assess remission without the time criterion (“Andreasen criteria”) [37]. Other scales are the Calgary Depression Rating Scale for Schizophrenia (CDSS) [38], Young Mania Rating Scale (YMRS) [39] and the Inventory of Depressive Symptomatology clinician-rated version with 30 items (IDS-C30) [40]. We assess general functioning with the Global Assessment of Functioning (GAF) [41] and global disease severity with the Clinical Global Impression (CGI) [41]. These scales are used to assess psychopathology and to enable a transdiagnostic approach. A detailed description and explanation of the assessments can be found in Paper I.

To evaluate the level of cognitive ability we use the Brief Assessment of Cognition in Schizophrenia (BACS, German version) [42, 43]. As we also described in Paper I, to complete the deep phenotyping, participants undergo multimodal magnetic resonance imaging (mMRI) with a Siemens Magnetom Prisma 3T MRI scanner (Siemens Healthineers, Erlangen, Germany). mMRI includes anatomical MRI measurements, i.e., T1-weighted magnetization prepared-rapid acquisition gradient echo (T1-MPRAGE), T2 sampling perfection with application-optimized contrasts using different flip angle evolution (T2-SPACE), T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) and diffusion tensor imaging (DTI). Functional MRI measurements are also performed, i.e., resting-state functional MRI (rsfMRI), task-based functional MRI (fMRI) and magnetic resonance spectroscopy (MRS). Resting-state electroencephalography (EEG) and activation EEG are recorded and transcranial magnetic stimulation (TMS) is also performed. Retinal anatomy is assessed by optical coherence tomography (OCT), retinal microvasculature by OCT angiography (OCT-A) and electrophysiology of retina by electroretinography (ERG). Blood-based biobanking is performed in all participants and samples are stored in the Munich

Mental Health Biobank [23], allowing us to access longitudinal clinical data. After the successful completion of the initiation phase, we intend to conduct reassessment of participants with a follow-up of six months in patients with first-episode SZ and a follow-up of two years in all patients.

1.1.2.2 Importance of retinal assessments in patients with SMIs

It is known that in diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS), neurodegenerative changes of the central nervous system (CNS) are visible and detectable in the retina, e.g., the retinal nerve fibre layer (RNFL) is thinner in MS than in HC [44]. The retina also reflects changes in AD and PD [45-47]. Although SSDs are associated with retinal alterations [48-52], retinal assessments are not yet used in psychiatric diagnostics.

In this thesis, I will discuss whether the eye can be used in psychiatry to study CNS processes as a complement to the already widely used mMRI and EEG examinations [45]. As claimed also by London et al. [45] the retina can be regarded as a window into the brain and the blood-brain barrier is very similar to the inner blood-retinal barrier [53]. Aqueous humour in the anterior chamber of the eye is enriched with immunoregulatory mediators and is similar to cerebrospinal fluid [54, 55]. Studies published in recent years describe retinal changes in patients with SSDs [49, 52, 56]. Even though the retina was found to be thinner in patients with SSDs than in HC [52, 56], evidence for RNFL changes in SZ is still limited. Moreover, studies that used OCT to assess RNFL thickness in SZ and HC found inconsistent results [57]. Whether pathophysiological mechanisms of psychiatric diseases or effects of concordant somatic diseases such as diabetes and hypertension are responsible for retinal changes found in SSDs is still not known because diabetes and hypertension are also associated with reduced RNFL [58]. According to Bannai et al. [48], patients with SSDs show a connection between cortical measures and outer nuclear layer thinning.

In the CDP study, we examined retinal changes in 65 patients with SSDs and 72 HC from a structural and vascular perspective. We identified which specific layers of the retina are affected and also attempted to determine whether retinal thinning can be partially attributed to changes in the vascular system in SSDs. As mentioned in Paper II (attached below) we used the following covariates: sex, age, intraocular pressure, spherical equivalent, diabetes, hypertension, smoking status and body mass index (BMI) [49, 59-62], as well as OCT signal strength [63, 64], all of which affect OCT and OCT-A. After analysis of retinal microstructure in SSDs, which included parafoveal macular thickness (MT), the macular ganglion cell–inner plexiform layer (mGCIPL), macular retinal nerve fibre layer (mRNFL) thickness and peripapillary RNFL (pRNFL), broadened thinning of these retinal layers was observed. A detailed explanation of the examined retinal layers can be found in Paper II. We also remark in that paper that thinning of MT in some parafoveal fields and thinning of mean mRNFL was found to be connected to some clinical parameters, such as longer duration of illness (in years) and higher chlorpromazine equivalent doses (CPZeq). In patients treated with clozapine, a negative association was found between clozapine dose and mean pRNFL thickness.

The goal pursued in Paper II was to evaluate retinal changes associated with SSDs with the data collected within the framework of multimodal deep phenotyping in order to improve understanding of the not yet fully comprehended pathophysiological retinal alterations in psychiatric disorders.

1.1.2.3 mMRI and EEG examinations and findings in patients with SMIs and their associations with cognitive functioning

To investigate how structural and functional brain changes are related to changes in EEG data and cognition data in SMIs, studies need to examine these modalities in a large number of individuals. However, studies are frequently limited by sample size or the small number of assessed modalities. So far, several studies have highlighted global alterations in brain structure, e.g., bilateral volume reduction of the hippocampus (left > right) in SZ [65, 66] or increase in size of ventricles and reduction of the volume of corticostriatal-thalamic networks in SMIs [67, 68]. Structural brain changes [69, 70], changes in microstructure [71] and disturbances in connectivity [72-74] were examined in SSDs

The salience network (SN) was found in several studies to be a critical component in the pathogenesis of psychiatric diseases. The SN has strong functional connectivity, and a theory about insular dysfunction in psychosis was already proposed [75]. One article [76] points out that grey matter reduction in the dorsal anterior cingulate, right insula and left insula in BD, MDD, SZ, anxiety disorders, addiction and obsessive-compulsive disorder (OCD) implicates transdiagnostic morphometric similarities in these disorders. As examined in Opel et al. [77], four psychiatric disorders, i.e., MDD, BD, SZ and OCD, were confirmed to be strongly correlated in brain structural abnormalities.

The transdiagnostic model of psychiatric disorders is important in pharmaceutical research aiming to improve cognitive and affective dysfunctions in SMIs [76-79]. The neurobiology of cognitive deficits in patients with SMIs is still unclear [80], so research needs to consider that patients with various psychiatric disorders have similar cognitive deficits [81-83] and that neurocognitive networks show similar changes of functional connectivity in psychiatric disorders, indicating that a common path of network interactions appears to be associated with cognitive deterioration of psychiatric patients [80]. Similar functional connectivity changes were found in these networks: default mode network, frontoparietal network, and SN [80]. Similar to structural mMRI and functional connectivity studies, EEG studies [84] also detected change in the power within selected subset of EEG frequency bands in several psychiatric diseases. For example, patients with SZ, OCD and attention deficit-hyperactivity disorder showed an increase in the power of low frequency bands (delta and theta) and a decrease in the power in higher frequency bands (alpha, beta, gamma), as reported by Newson et al. [84]. Gamma oscillations maintain cognitive processes [85]. Cognitive dysfunction in SMIs can be explained by dysfunctional gamma oscillations, and these oscillations may be associated with excitatory/inhibitory imbalance [86-88]. Taken together, alterations of brain structure and disturbances in connectivity have a negative impact on cognition of patients [6].

In today's psychiatry, diseases are unfortunately seen as separate, unrelated categories [80]. Despite the knowledge of structural and functional brain changes in SMIs, results are still conflicting and the exact neurobiological correlates of cognitive deficits and other psychiatric symptoms are still not known. There is also a need to correlate mMRI, EEG and cognition data with clinical examination data; e.g., one study [70] took into account a number of factors, such as the age at which SZ first manifested, illness duration and medication dose, and examined the relationship of these clinical factors with the thickness of the cortex. The RDoC system allows SMIs to be examined from the genetic to the behavioural level [12] and thus enables the underlying cause and neurobiological correlates of psychiatric deficits [81-83] to be carefully evaluated.

To better understand the neurobiological mechanisms underlying SMIs, we examined multivariate associations between cognition, brain electrophysiology and mMRI-based measurements. We performed an analysis within each modality and also used a joint analysis of all three modalities to investigate how they correlate with each other.

1.2 Project's aims

The purpose of this thesis is to highlight several aims; these aims were also discussed in Papers I and II. The purpose of our research assignment (Paper I) is to perform multimodal analysis of data obtained from the CDP study. There is a strong need to consider genetics findings and multimodal findings from neuroscience in the development of new treatment approaches. For this reason, we aim to map CNS non-invasively at different levels with the use of brain and retina examinations and to combine these data with other genetic, cellular, clinical and cognitive data. Important aims are not only to find relations within and between different assessed modalities, but also to assess how our data relate to the data from other larger studies, for instance the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA), German National Cohort Study (NAKO) and Human Connectome Project (HCP) [89-91]. We believe that as a neurobiology-based, research-orientated classification framework, the RDoC system needs to be implemented in the current diagnosis of psychiatric disorders.

Another aim (Paper I) is to study a large bottleneck of translational psychiatry: According to current findings in psychiatric research, genetic factors contribute to SZ risk, but the mechanisms by which this occurs are still not understood. In the past, it was difficult to use model human test systems to study genetic and pharmacological changes and pathomechanisms of psychiatric disorders [92] and until recently, research in psychiatry was limited to imaging studies, molecular and genetic analyses of peripheral tissues and studies of postmortem brain material [92]. Nowadays the mechanism of psychiatric disorders can be studied by using hiPSCs as patient-specific cellular systems [93-95]. There is great potential in studying pathomechanisms of psychiatric diseases by examining hiPSCs and their ability to differentiate into neuronal or glial cells [96]. In contrast to current hiPSC studies, which tend to only focus on basic clinical characteristics, we use hiPSCs derived from our deeply characterized cohorts. Because multimodal phenotyping data would be very relevant [92], we focussed on a thorough characterization of participants. We investigate hiPSCs, which are well characterized, to provide biological insight into the pathophysiology of psychiatric disorders. From a pharmacological perspective, these test models make a significant contribution to pharmacological research [97, 98]. In Paper I we explain that we aim to use the results from hiPSC analyses from our suitably sampled and well characterised group of CDP study participants to effectively incorporate such analyses into the clinical research domain. The sampling strategies will be applied on the CDP data by using multilayer neural networks.

Limited biomarkers are available for psychiatric research, and psychiatric diseases are currently diagnosed through interviews and observations. However, this approach is frequently inaccurate so it is critical to identify objective biomarkers that would tell us more about presence of and changes in disease and the effectiveness of treatment [99]. Brain imaging has some limitations, e.g., low image resolution and patient burden [100]. Therefore, we would like to evaluate whether OCT can be used as a non-invasive technology to detect retinal biomarkers of brain pathology [48]. One study discovered [100] that using OCT allows the degree or pathophysiology of neurodegeneration in psychosis to be objectively assessed. We aimed at filling the gaps in the application of OCT and OCT-A in psychiatric disorders (Paper II). To do so, we used OCT and OCT-A techniques to examine how SSDs affect retinal structure and microvasculature. In Paper II, we describe our evaluations of retinal parameters, but the link between changes in the cytoarchitecture of retina and brain functions or structure remains to be further investigated, which we plan to perform in SMIs. Longitudinal studies would also be important to replicate our findings.

1.3 Project's conclusions

1.3.1 Summary of results and their relevance for the field

The first publication (Paper I) that resulted from this PhD project is essential for comprehending the use of the RDoC approach in clinical studies. The analysis of multimodal data as discussed above and of the highly complex interactions between these data enabled us to gain an understanding of the neurobiology underlying psychiatric diseases. This approach can be used to identify biomarkers, which will allow meaningful subgroups of patients to be identified and will then be helpful in clinical trials and interventions that will prepare the way for personalization and precision medicine research [101-103]. Furthermore, our research emphasizes the importance of understanding that different clinical conditions, such as different illness severities, aspects of remission and treatment response, and different illness duration can be associated with different neurobiological types.

Our first publication also nicely illustrates several problems in the field, e.g., that no biomarkers have been defined that can assist in the better identification of psychiatric disorders and that the treatment of negative symptoms and cognitive dysfunction remains challenging. The development of drugs is also affected by the fact that hiPSC studies are limited by basic clinical characterization. For this reason, the use of multiple assessment tools is one of the key features that makes the CDP study unique. Results of genetic analyses are also relatively rarely reported, as mentioned in Raabe et al. [92]. The second publication (Paper II) that resulted from this PhD project is essential for understanding changes of retinal cytoarchitecture in SSDs. In the cohort of SSDs, we discovered significantly lower parafoveal mGCIPL and mRNFL thickness and lower mean pRNFL. The OCT-A investigations did not reveal any significant differences between groups. Retinal thinning was typically measured within the SSDs cohort. Factoring out covariates representing changes in the structure of small blood vessels and diseases such as hypertension and diabetes still showed statistically significant retinal thinning for the cohort, indicating validity of the tested relation.

Furthermore, as regards the pathophysiology of psychiatric diseases, our findings imply a deeper connection between retinal thinning and SSDs. As described in Paper II, OCT is a widely available tool for examining retinal cytoarchitecture that might result in a number of new scientific findings. We would like to emphasize that OCT can be used as an additional examination technique and diagnostic tool in the field of psychiatry.

Our second publication also reflects several key problems in the field. For example, pathophysiological mechanisms of the given SSDs and antipsychotic medication may both lead to retinal deterioration. The effect of medical treatment can be avoided by collecting large amounts of data from newly diagnosed patients with SSDs to gain a better understanding of a potential effect of antipsychotic medication on retinal thinning. Importantly, future research should thoroughly investigate cardiometabolic effects on retinal changes. Despite evidence of retinal thinning in patients with SSDs, the exact underlying mechanism is still not clear. This study presents retinal parameters and does not assess the relationship between retinal changes and changes in brain structure or brain function, so we plan to examine such interactions in our future studies on SSDs.

In summary, this thesis and our published papers present evidence that by combining multimodal data and identifying biotype-informed subgroups of patients we are able to overcome the lack of

progress in the treatment of SMIs. This work also contributes to the progress of personalized medical interventions, including the use of artificial intelligence-supported interventions, which are still not available in modern psychiatry.

2. Contribution to the PhD publications

2.1 Contribution to Paper I

I served as first and corresponding author of this paper, which reported on the clinical study that offers phenotyping data across most of the RDoC domains transdiagnostically from hundreds of participants to explore complex neurobiological coherence with regard to patients with SMIs.

The CDP cohort was assembled at the Department of Psychiatry and Psychotherapy, LMU Munich, Germany. I personally recruited approx. 200 participants and performed CDP phenotyping by using a number of assessment techniques I verified the data with electronic medical records and was in charge of organizing mMRI investigations, neurocognitive assessments, EEG investigations, measurements of retina and blood analyses (omics-based). My tasks also included helping to define the exclusion and inclusion criteria for the study. I was part of the core team of people who focused on the analysis of data from mMRI, electrophysiological and neurocognitive assessments. I performed de-artifacting of resting-state EEG data with a semi-automatic independent component analysis that used BrainVisionAnalyzer to reject a minimum possible number of EEG segments. I also converted mMRI data into the conform international uniform Brain Imaging Data Structure (BIDS) format. I performed the data preparation procedure and the necessary calculations. The required data transformations included merging the tables originating from the distinct modalities, adding the data consistently to the data from a large Biobank database and several MIMICSS databases and performing a large number of subsequent data cleaning and data-related reorganization steps. Afterwards I performed the statistical analysis of the prepared data, i.e., descriptive statistics and statistical hypothesis testing. I calculated the numbers of patients and HC in distinct modalities, the numbers of patients with distinct diagnoses and the demographic details of the CDP and MIMICSS studies. I also visualized data in the form of bar plots and a Venn diagram, as included in the paper. I presented these results at several national and international conferences as part of my PhD program. I supervised medical students who were working on the study and also helped them with their data analysis. I wrote the initial draft of the manuscript with the core team. As the corresponding author, I organized manuscript handling with the other co-authors, I personally edited the article in the specific style of Frontiers publications and managed the submission and publishing process.

2.2 Contribution to Paper II

I served as third author of this paper. This paper, which was based on our CDP data (Paper I), explores the possible use of OCT-A and OCT techniques to analyse changes that can be induced in the cytoarchitecture of retina in SSDs.

As mentioned above, I personally recruited approx. 200 participants and performed CDP phenotyping by using a battery of structured assessments, ratings and examinations. I verified the data with electronic medical records and was in charge of organizing the retinal investigations. I discussed clinically relevant exclusion criteria with the first author and helped with the data analysis procedures. I supervised the students to ensure that they performed assessments and collected data correctly and I loaded the data consistently and regularly into our databases. I also merged the CDP and Biobank databases and cleaned the resulting data table. Finally, I critically reviewed the draft manuscript and approved the final version.

3. Paper I

The multimodal Munich Clinical Deep Phenotyping study to bridge the translational gap in severe mental illness treatment research

Lenka Krčmář[1,2,*], Iris Jäger[1], Emanuel Boudriot[1], Katharina Hanken[1], Vanessa Gabriel[1], Julian Melcher[1], Nicole Klimas[1], Fanny Dengl[1], Susanne Schmoelz[1], Pauline Pingen[1], Mattia Campana[1], Joanna Moussiopoulou[1], Vladislav Yakimov[1], Georgios Ioannou[1], Sven Wichert[1], Silvia DeJonge[1], Peter Zill[1], Boris Papazov[1], Valéria de Almeida[1], Sabrina Galinski[1], Nadja Gabellini[1], Genc Hasanaj[1], Matin Mortazavi[1], Temmuz Karali[1], Alexandra Hisch[1], Marcel S Kallweit[1], Verena J. Meisinger[1], Lisa Löhrs[1], Karin Neumeier[1], Stephanie Behrens[1], Susanne Karch[1], Benedikt Schworm[3], Christoph Kern[3], Siegfried Priglinger[3], Berend Malchow[4], Johann Steiner[5,6,7,8], Alkomiet Hasan[9], Frank Padberg[1], Oliver Pogarell[1], Peter Falkai[1,10], Andrea Schmitt[1,11,†], Elias Wagner[1,†], Daniel Keeser[1,12, 13†], Florian J. Raabe[1,2,†]

[1]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany
[2]International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany
[3]Department of Ophthalmology, University Hospital, LMU Munich, Munich, Germany
[4]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany
[5]Department of Psychiatry and Psychotherapy, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
[6]Laboratory of Translational Psychiatry, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
[7]Center for Behavioral Brain Sciences (CBBS), Magdeburg, Germany
[8]Center for Health and Medical Prevention (CHaMP), Magdeburg, Germany
[9]Department of Psychiatry, Psychotherapy and Psychosomatics of the University Augsburg, Medical Faculty, University of Augsburg, Augsburg, Germany
[10]Max Planck Institute of Psychiatry, Munich, Germany
[11]Laboratory of Neurosciences (LIM-27), Institute of Psychiatry, University of São Paulo (USP), São Paulo-SP, Brazil
[12]NeuroImaging Core Unit Munich (NICUM), University Hospital, LMU Munich, Munich, Germany
[13]Munich Center for Neurosciences (MCN), LMU Munich, Munich, Germany

† These authors contributed equally to this work

* Correspondence:

Lenka Krčmář, Lenka.Krcmar@med.uni-muenchen.de

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EDITED BY
Giuseppe Carrà,
University of Milano-Bicocca, Italy

REVIEWED BY
Armida Mucci,
University of Campania Luigi Vanvitelli, Italy
Jurjen Luykx,
University Medical Center Utrecht, Netherlands

*CORRESPONDENCE
Lenka Krčmář
✉ Lenka.Krcmar@med.uni-muenchen.de

†These authors have contributed equally to this work

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The multimodal Munich Clinical Deep Phenotyping study to bridge the translational gap in severe mental illness treatment research

Lenka Krčmář[1,2]*, Iris Jäger[1], Emanuel Boudriot[1], Katharina Hanken[1], Vanessa Gabriel[1], Julian Melcher[1], Nicole Klimas[1], Fanny Dengl[1], Susanne Schmoelz[1], Pauline Pingen[1], Mattia Campana[1], Joanna Moussiopoulou[1], Vladislav Yakimov[1], Georgios Ioannou[1], Sven Wichert[1], Silvia DeJonge[1], Peter Zill[1], Boris Papazov[1], Valéria de Almeida[1], Sabrina Galinski[1], Nadja Gabellini[1], Genc Hasanaj[1], Matin Mortazavi[1], Temmuz Karali[1], Alexandra Hisch[1], Marcel S Kallweit[1], Verena J. Meisinger[1], Lisa Löhrs[1], Karin Neumeier[1], Stephanie Behrens[1], Susanne Karch[1], Benedikt Schworm[3], Christoph Kern[3], Siegfried Priglinger[3], Berend Malchow[4], Johann Steiner[5,6,7,8], Alkomiet Hasan[9], Frank Padberg[1], Oliver Pogarell[1], Peter Falkai[1,10], Andrea Schmitt[1,11†], Elias Wagner[1†], Daniel Keeser[1,12,13†] and Florian J. Raabe[1,2,10†]

[1]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, [2]International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany, [3]Department of Ophthalmology, University Hospital, LMU Munich, Munich, Germany, [4]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany, [5]Department of Psychiatry and Psychotherapy, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany, [6]Laboratory of Translational Psychiatry, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany, [7]Center for Behavioral Brain Sciences, Magdeburg, Germany, [8]Center for Health and Medical Prevention, Magdeburg, Germany, [9]Department of Psychiatry, Psychotherapy and Psychosomatics of the University Augsburg, Medical Faculty, University of Augsburg, Augsburg, Germany, [10]Max Planck Institute of Psychiatry, Munich, Germany, [11]Laboratory of Neurosciences (LIM-27), Institute of Psychiatry, University of São Paulo, São Paulo, Brazil, [12]NeuroImaging Core Unit Munich, University Hospital, LMU Munich, Munich, Germany, [13]Munich Center for Neurosciences, LMU Munich, Munich, Germany

Introduction: Treatment of severe mental illness (SMI) symptoms, especially negative symptoms and cognitive dysfunction in schizophrenia, remains a major unmet need. There is good evidence that SMIs have a strong genetic background and are characterized by multiple biological alterations, including disturbed brain circuits and connectivity, dysregulated neuronal excitation-inhibition, disturbed dopaminergic and glutamatergic pathways, and partially dysregulated inflammatory processes. The ways in which the dysregulated signaling pathways are interconnected remains largely unknown, in part because well-characterized clinical studies on comprehensive biomaterial are lacking. Furthermore, the development of drugs to treat SMIs such as schizophrenia is limited by the use of operationalized symptom-based clusters for diagnosis.

Methods: In line with the Research Domain Criteria initiative, the Clinical Deep Phenotyping (CDP) study is using a multimodal approach to reveal the neurobiological underpinnings of clinically relevant schizophrenia subgroups by performing broad transdiagnostic clinical characterization with standardized neurocognitive assessments, multimodal neuroimaging, electrophysiological

assessments, retinal investigations, and omics-based analyzes of blood and cerebrospinal fluid. Moreover, to bridge the translational gap in biological psychiatry the study includes *in vitro* investigations on human-induced pluripotent stem cells, which are available from a subset of participants.

Results: Here, we report on the feasibility of this multimodal approach, which has been successfully initiated in the first participants in the CDP cohort; to date, the cohort comprises over 194 individuals with SMI and 187 age and gender matched healthy controls. In addition, we describe the applied research modalities and study objectives.

Discussion: The identification of cross-diagnostic and diagnosis-specific biotype-informed subgroups of patients and the translational dissection of those subgroups may help to pave the way toward precision medicine with artificial intelligence-supported tailored interventions and treatment. This aim is particularly important in psychiatry, a field where innovation is urgently needed because specific symptom domains, such as negative symptoms and cognitive dysfunction, and treatment-resistant symptoms in general are still difficult to treat.

KEYWORDS

schizophrenia, research domain criteria, retina, electrophysiology, multimodal magnetic resonance imaging, electroencephalography

1. Introduction

Over the last century, advances in psychopharmacological medication have improved the outcome of severe mental illnesses (SMIs), including schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD) (1). However, despite these efforts, SMIs remain debilitating and have a high global disease burden because they first manifest usually in young adults and a third to a half of patients continue to experience symptoms even after they fulfill criteria for remission (2–5). Moreover, response to pharmacological interventions is highly variable (6), and a substantial number of individuals develop treatment resistance early in the course of an SMI (7). Treatment resistance is defined as reduced or non-response to an adequate treatment and is associated with increased healthcare burden, although in some disorders, criteria for treatment resistance still vary (8). A recent meta-analysis found rates of almost 25% for early treatment resistance in first-episode psychosis and SZ (7). Treatment-resistant schizophrenia (TRS) is defined as "nonresponse to at least 2 sequential antipsychotic trials of sufficient dose, duration, and adherence" (9). A 5-year prospective evaluation of outcome in individuals with a first-episode of a schizophrenia spectrum disorder (SSD, $N = 246$) found that 23% were treatment resistant from the start of the illness and that this was also the case in 70% of those with treatment resistance (10). Two types of TRS have been defined (10, 11): primary TRS, i.e., SZ that shows treatment resistance from the start of antipsychotic treatment, and secondary TRS, i.e., SZ where antipsychotics have initial effects but patients later develop TRS (9).

In scientific and clinical communities, the most widely accepted definition of treatment-resistant depression is a depressive episode that shows "a minimum of two prior treatment failures and confirmation of prior adequate dose and duration" (12). Defining treatment resistance in BD is challenging because course episodes are not uniform but have a complex clinical picture and complex treatment options (13). Some patients do not tolerate therapeutic trials

Abbreviations: ACC, anterior cingulate cortex; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BrPsyD, brief psychotic disorder; CDP, Clinical Deep Phenotyping; CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; CSF, cerebrospinal fluid; CTQ-Screen, Childhood Trauma Screener; DD, delusional disorder; DIP, drug-induced psychosis; DLPFC, left dorsolateral prefrontal cortex; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DTI, diffusion tensor imaging; EEG, electroencephalography; EMG, surface electromyography; ENIGMA, Enhancing Neuro Imaging Genetics Through Meta-Analysis; ERG, electroretinography; FRPS, Framingham Risk Prediction Score; GAF, Global Assessment of Functioning; GWASs, genome-wide association studies; HC, healthy controls; HCP, Human Connectome Project; ICD-10, International Classification of Diseases, 10th revision; IDS-C30, Inventory of Depressive Symptomatology version with 30 items; M. I. N. I., Mini-International Neuropsychiatric Interview; MCTQ, Munich Chronotype Questionnaire; MDD, major depressive disorder; MEPs, motor evoked potentials; MIMICSS, Multimodal Imaging in Chronic Schizophrenia Study; MRS, magnetic resonance spectroscopy; NAKO, German National Cohort Study; OCT, optical coherence tomography; OCT-A, OCT angiography; PANSS, Positive and Negative Syndrome Scale; PBMC, peripheral blood mononuclear cells; PHQ-9, Patient Health Questionnaire – 9; PROCAM, Prospective Cardiovascular Münster Score; RDoC, Research Domain Criteria; RSWG, Remission in Schizophrenia Working Group; SMI, severe mental illness; SNP, single nucleotide polymorphism; SSD, schizophrenia spectrum disorder; SZ, schizophrenia; SZA, schizoaffective disorder; T1-MPRAGE, T1-weighted magnetization prepared-rapid acquisition gradient echo; T2-FLAIR, T2-weighted-fluid-attenuated inversion recovery; T2-SPACE, T2 sampling perfection with application-optimized contrasts using different flip angle evolution; TMS, transcranial magnetic stimulation; TRS, treatment-resistant schizophrenia; UR, unaffected relatives; WHO-5, World Health Organization-5 Well-Being Index; WHOQOL-BREF, World Health Organization Quality of Life Scale, abbreviated version; YMRS, Young Mania Rating Scale; fMRI, task-based functional MRI; hiPSCs, human induced pluripotent stem cells; mMRI, multimodal magnetic resonance imaging; r_g, genetic correlation; rsfMRI, resting-state functional MRI.

or are noncompliant and are referred to as "pseudorefractory" (13). Treatment-resistant BD is defined as a "failure of symptoms improvement despite an adequate trial of two therapeutic agents" (14). Better knowledge about the neurobiological background of treatment resistance is urgently needed.

Before the revolutionary advances of molecular genetics, epidemiological studies already observed that first-degree relatives of SZ patients had a 10% lifetime risk to develop SZ, in contrast to the 1% risk in the general population. Therefore, the best-known risk factor for SZ is first-degree positive family history (15). The genetic heritability is estimated to be about 79% for SZ and 73% for SSD (16), and over the last decade, genome-wide association studies (GWASs) have found over 270 risk loci for SZ (17). The liability-based single nucleotide polymorphism (SNP) heritability (SNP-h^2, i.e., additive genetic variance explained by all SNPs) has been estimated to be 18.6% for BD and 24% for SZ (17, 18). A recent meta-analysis of GWASs in various mental disorders showed a strong genetic correlation (r_g) between SZ and BD ($r_g = 0.70$) and SZ and MDD ($r_g = 0.34$) (19). In addition, it showed that of the formerly 109 pleiotropic genome-wide loci identified in psychiatric traits, 83% were associated with SZ, 72% with BD, and 48% with MDD. Moreover, environmental factors, such as complications during childbirth, trauma during childhood, urban living, migration, and abuse of cannabis (20), are suggested to be part of the dynamic interplay that leads to the onset of SMI on the basis of a high-risk genetic background (21).

Despite the above, the pathophysiological background of SMIs is only poorly understood. The age of onset in SZ and BD is mostly during adolescence and early adulthood, i.e., during phases in which neurodevelopment switches from the production of new synapses to synaptic pruning, in which the number of synapses is reduced. In SMIs, neurodevelopmental disturbances may lead to synaptic deficits in connected brain regions (21–25), which could partly explain the deficits in connectivity and gray matter loss seen in SMIs (26, 27).

Besides the enlargement of ventricles, studies on SMI have also detected volume loss in corticostriatal-thalamic networks, which include the dorsolateral prefrontal cortex and temporal, parietal, and limbic regions (28, 29). A meta-analysis of more than 16,000 patients across psychiatric disorders and healthy controls (HC) showed alterations of gray matter volumes and resting-state functional connectivity in salience network areas, such as the anterior cingulate cortex and left and right insula, and in the default mode network, including the anterior cingulate cortex and frontoparietal cortex, providing evidence for a biologically driven transdiagnostic marker in SMIs (30, 31). Mature neuronal circuits are essential for brain functioning and required for higher cognitive processes such as attention and working memory, which are maintained by synchronized neuronal oscillations, especially at approximately 40 Hertz (gamma oscillations) (32). In SMIs, dysfunctional gamma oscillations are the basis of cognitive dysfunction and may be associated with an excitatory/inhibitory imbalance (33–35). However, despite the neurobiological background of SMIs, their diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and the International Classification of Diseases, 10th revision (ICD-10), is still based only on operationalized, symptom-based clusters, and there is a great need to identify biomarkers for each individual SMI (36).

SMIs are considered to be highly heterogeneous. For example, impairments in cognition are often thought to be present in all SMIs, but in clinical practice, only a subgroup of patients is affected by severe cognitive impairments and other subgroups have good cognitive performance (37). However, the underlying differences in neurobiology between those subgroups remain unclear. Another topic of discussion is whether pathophysiologic processes are the same in treatment-responsive and treatment-resistant individuals or whether these processes are more severe or progressive in treatment-resistant patients and whether treatment resistance is, at least partially, pathophysiologically distinct or even a transdiagnostic phenomenon (8). Noteworthy in this context is that psychiatric diagnoses often shift over time (38). Moreover, some individuals reach a state of remission relatively soon after an exacerbation of first-episode psychosis, whereas others report persisting symptoms (39).

Affective disorders such as MDD and BD not only clinically overlap with SSDs (38) but are also on a polygenetic spectrum (40–42). This commonality may explain why existing drug treatments for SMIs like MDD or SZ are often beneficial in a broader spectrum of diseases and supports the theory that transdiagnostic phenomenological approaches might help to reveal the underling neurobiology (43).

Hence, DSM-5 and ICD-11 do not reflect findings from the fields of genetics and neuroscience, but these findings should be considered when developing treatment approaches in terms of biology-based, individualized precision medicine (43). In 2010, the US National Institute of Mental Health launched the Research Domain Criteria (RDoC) (44), a neurobiology-based, research-orientated classification framework that investigates mental health and pathological states of six neurobehavioral major *domains* (negative valence systems, positive valence systems, cognitive systems, social processes, arousal/regulatory systems, and sensorimotor systems) and their *(sub) constructs* (e.g., attention, perception, declarative memory, language, cognitive control, and working memory for the cognitive domain) within a full functional range of variation from abnormal to normal[1] by using various clinical and translational neuroscience tools that are termed *units of analysis*.[2] The RDoC *units of analysis* include, e.g., genetic analyzes, electrophysiology, multimodal imaging, and neurocognitive assessments. The RDoC reflect mental disorders from a bottom-up, translational perspective (from genes to behavior) and use a transdiagnostic approach (43). This method is in contrast to the DSM-5 and ICD-10 top-down approach, which differentiates between "healthy" states and various "pathological" ones (43). By systematically assessing RDoC *domains* with neuroscience tools, the RDoC initiative aims to improve the diagnostic approach by identifying biotype-informed (sub)groups that may pave the way toward subgroup-specific treatment in psychiatry (43).

Ongoing discussions are considering whether and how RDoC-based research could fit into a clinical environment that uses DSM-5 and ICD-11, whether the use of RDoC would limit translational

1 National Institute of Mental Health. Definitions of the RDoC Domains and Constructs. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs (Accessed January 01, 2023).

2 National Institute of Mental Health. RDoC Matrix. Important Notes on the Matrix. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix (Accessed January 01, 2023).

communication, and whether a more psychopathology-based transdiagnostic classification system such as the Hierarchical Taxonomy of Psychopathology (45) would be even more beneficial (46). However, the RDoC system does not aim to replace the existing clinical classification systems, and combining RDoC with established clinical classification systems might enable (RDoC-based) neurobiological dissection with clinically meaningful outcomes and thus be beneficial for both affected individuals with ongoing symptoms despite adequate treatment and clinicians confronted with fluid diagnoses over time and heterogeneous symptoms despite identical disease entities (47). This approach may also help to develop biomarker-based stratification strategies for identifying clinically meaningful subgroups of patients and thus pave the way for personalized and tailored neurobiologically informed clinical trials and interventions (48–50).

Therefore, the multimodal Clinical Deep Phenotyping (CDP) study at the Department of Psychiatry, University Hospital, LMU Munich, Munich, Germany, aims to apply the RDoC framework in a broad naturalistic and transdiagnostic approach in a cohort of patients with MDD, BD, SSD, and HC, to gain a deeper understanding of the underlying neurobiology of SMI. To do so, it will investigate the existing disease hypotheses (disturbed circuits, brain volume loss, impaired connectivity, dysregulated excitation-inhibition ratio, inflammation, and neuroinflammation) of SMI and address the question whether certain clinically relevant subpopulations (e.g., those with certain clinical outcomes, such as cognitive impairment, those who fulfill Positive and Negative Syndrome Scale [PANSS] remission criteria (51) or have treatment resistance, or those with patient-reported outcomes, such as real-life functioning) are represented in neurobiological biotypes defined with available clinical and translational neuroscience methods. To enable the identification of clinically relevant subgroups, we aim to perform deep phenotyping in over 500 participants with SMI and in over 500 HC. Here, we report on the protocol of the multimodal CDP study and also show the feasibility of the applied multimodal characterization by presenting results in 381 participants who were enrolled in the initiation phase, October 1, 2020, to October 31, 2022.

TABLE 1 Evaluation plan.

Evaluations	
Clinical characterization	*
Psychiatric history	*
Physical examination	*
Transdiagnostic self-ratings	CTQ-Screen, Brief Resilience Scale, Loneliness Scale, Lubben Social Network Scale, WHO-5, PHQ-9, MCTQ, WHOQOL-BREF, GAF, CGI
Disease-related scales	PANSS, PANSS RSWG criteria, CDSS, YMRS, IDS-C30
Cognitive assessment	BACS
Cerebral assessment	MRI, EEG, TMS
Retinal assessment	OCT, OCT-A, ERG
Biobanking (Munich Mental Health Biobank)	*

BACS, Brief Assessment of Cognition in Schizophrenia; CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression; CTQ-Screen, Childhood Trauma Screener; EEG, electroencephalography; ERG, electroretinogram; GAF, Global Assessment of Functioning; IDS-C30, Inventory of Depressive Symptomatology-clinician-rated version with 30 items; MCTQ, Munich Chronotype Questionnaire; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PANSS, Positive and Negative Syndrome Scale; PHQ-9, Patient Health Questionnaire-9; RSWG, Remission in Schizophrenia Working Group; TMS, transcranial magnetic stimulation; WHO-5, Well-Being Index scale; WHOQOL-BREF, WHO-Quality of Life Scale; YMRS, Young Mania Rating Scale¸ MRI, multimodal magnetic resonance imaging.* See Supplementary Table S1 for details.

2. Materials and methods

After being approved by the local ethics committee at the LMU Munich, Germany (project number 20–528), the CDP study was initiated as a naturalistic, prospective, single-center study at the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany. The study is registered in the German Clinical Trials Register (ID: DRKS00024177). Data handling in the CDP study is embedded into the Munich Mental Health Biobank (52) of the LMU Munich (project number: 18–716) and uses their approved data storage and data safety concept. The CDP study includes multilayer, transdiagnostic assessments (Table 1; Supplementary Table S1), which are described in more detail below. To enable a transdiagnostic approach, all assessments are performed in all study participants, including HC.

2.1. Study recruitment and inclusion and exclusion criteria

The cross-diagnostic CDP study includes patients with a diagnosis of SSD, e.g., SZ, schizoaffective disorder (SZA), brief psychotic disorder (BrPsyD), drug-induced psychosis (DIP), and delusional disorder (DD); patients with a diagnosis of BD and MDD; and individuals without a past or current psychiatric disorder (HC). Patients are diagnosed with the Mini-International Neuropsychiatric Interview (M.I.N.I.) (53) according to the DSM-5, text revision (DSM-5-TR, Version 7.0.2), and ICD-10. All participants are aged 18 to 65 years and fluent in German [German language skills are required for the cognitive assessment with the Brief Assessment of Cognition in Schizophrenia (BACS, German version)] (54, 55).

Patients with a primary psychiatric disorder other than SSD, BD, and MDD, candidates younger than 18 years or older than 65 years, pregnant women, and patients with a concurrent clinically relevant neurological or neuropsychiatric disorder that affects the central nervous system (CNS; e.g., epilepsy, stroke, multiple sclerosis, dementia, meningitis, encephalitis, structural brain deficits, and organic psychosis/mania) or other severe somatic comorbidities are excluded. Additional exclusion criteria are the inability to provide written informed consent and relevant non-compliance that would interfere with the ability to participate in the study.

Participants are screened for inclusion and exclusion criteria, and written informed consent is obtained before any study-related procedures are performed.

2.2. Clinical assessments

The CDP assessments include the basic Munich Mental Health Biobank phenotyping, which comprises (1) a structured assessment that records socioeconomic background and psychiatric and medical history and screens for a family history of psychiatric disorders and (2) the following transdiagnostic self-ratings: Childhood Trauma Screener (CTQ-Screen) (56), Brief Resilience Scale (57), Loneliness Scale (58), Lubben Social Network Scale (59), World Health Organization-5 Well-Being Index (WHO-5) (60), World Health Organization Quality of Life Scale, abbreviated version (WHOQOL-BREF) (61), Patient Health Questionnaire - 9 (PHQ-9) (62), and Munich Chronotype Questionnaire (MCTQ) (63).

The specific CDP phenotyping includes an additional battery of structured assessments, ratings, examinations, and self-ratings that are performed or administered by trained mental health professionals. If available and applicable, electronic medical records are used to verify the collected data. Medical history includes age at first symptom onset, age at first psychotic, depressive, or manic episode, duration of illness, duration of untreated illness, time of first contact with the mental health care system, number and duration of illness episodes, number of past hospitalizations because of mental illness, and information on whether the current episode is the first one. The phenotyping also includes a structured assessment of current and lifetime psychiatric medication, including previous or current treatment with clozapine (the first-line medication for treatment-resistant SZ) (64) or ketamine; dosages of current antipsychotic medications are transformed into chlorpromazine equivalents (65). In addition, previous or current electroconvulsive therapy is assessed.

The clinical assessment covers the assessment of any past and current physical comorbidities, including CNS conditions, cardiometabolic conditions, and risk factors (i.e., body mass index, resting heart rate, blood pressure, and smoking status), and ophthalmological conditions that may potentially affect vision. Moreover, medication prescribed for physical illnesses is recorded. Cardiovascular risk scores, such as the Prospective Cardiovascular Münster (PROCAM) Score (66) and the body mass index-based Framingham Risk Prediction Score (FRPS) (67), are calculated. The intensity of physical addiction to nicotine is assessed with the Fagerström test (68). Handedness is assessed with the short form of the Edinburgh Handedness Inventory (69), and any shift work or time zone crossings with a time difference of more than 2 h within the last month is noted.

2.3. Psychometrics

To enable a transdiagnostic approach, all study participants (including HC) undergo a battery of psychometric tools, independent of the DSM-5-TR and ICD-10 psychiatric diagnosis. Thus, SZ symptoms are assessed in all participants by the PANSS (70). Remission is evaluated on the basis of the PANSS Remission in Schizophrenia Working Group (RSWG) items without the time criterion ("Andreasen criteria") (51). The Calgary Depression Rating Scale for Schizophrenia (CDSS) (71), the Inventory of Depressive Symptomatology version with 30 items (IDS-C30), clinician-rated version (72), and the Young Mania Rating Scale (YMRS) (73) are also used to assess affective symptoms in all participants.

Global disease severity is evaluated with the Clinical Global Impression (CGI) scale (74), and level of general functioning, with the Global Assessment of Functioning (GAF) scale (74).

2.4. Neurocognitive assessment

To assess study participants' neurocognitive performance within a feasible time (about 30–45 min), we use the BACS battery (55), which covers multiple cognitive domains that are characteristically impaired in psychosis, such as verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency.

2.5. Multimodal brain imaging

Multimodal magnetic resonance imaging (mMRI) is performed with a Siemens Magnetom Prisma 3 T MRI scanner (Siemens Healthineers, Erlangen, Germany) and includes anatomical MRI measurements, i.e., T1-weighted magnetization prepared-rapid acquisition gradient echo (T1-MPRAGE), T2 sampling perfection with application-optimized contrasts using different flip angle evolution (T2-SPACE), T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR), and diffusion tensor imaging (DTI), and functional MRI measurements, i.e., resting-state functional MRI (rsfMRI), task-based functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) (Supplementary Figure S1). The Human Connectome Project (HCP) protocol (75) is used for the mMRI measurements; detailed imaging parameters can be found in Supplementary Table S2. In addition, single-voxel spectroscopy is used to collect data at the left dorsolateral prefrontal cortex (DLPFC)/insula and anterior cingulate cortex (ACC). Task-based fMRI uses an HCP visuomotor task; we chose this task to allow comparability of task-based fMRI with other CDP modalities, such as the eye examinations and motor evoked potentials (MEPs) assessed by transcranial magnetic stimulation (TMS, see also section 2.7).

2.6. Electroencephalography

Study participants undergo digitized electroencephalography (EEG) recordings lasting approximately 30 min. Recordings are performed with a standardized set-up (BrainAmp amplifier, Brain Products, Martinsried, Germany) with 32 scalp electrodes (10/20 system). After resting-state EEG has been recorded with eyes closed for 5 min and open for 5 min, activation EEG is recorded with an auditory stimulus (P300) (76, 77) for an additional 18 min.

2.7. Transcranial magnetic stimulation

For the diagnostic TMS, participants are examined in a half-reclined seated position. For surface electromyography (EMG), electrodes are placed on the first dorsal interosseous muscle of the right hand. Raw EMG signals are amplified and bandpass filtered (2 Hz-3 kHz) with a Digitimer D-360 amplifier (Digitimer Ltd., Welwyn Garden City, United Kingdom), digitized at 5 kHz, and then processed with Signal Software (version 5, Cambridge Electronic

Design, Cambridge, United Kingdom). TMS-induced MEPs are evoked by stimulating the left primary motor cortex (M1) with a flat figure-eight coil (outer diameter: 70 mm) connected to a Magstim Bistim2 stimulator (Magstim Company Ltd., Whitland, United Kingdom). Different cortical excitability parameters are investigated with different TMS protocols that use single and paired pulses. More specifically, resting motor threshold, the intensity required to evoke a 1 mV MEP, short-and long-interval intracortical inhibition, and intracortical facilitation are assessed in each participant (Supplementary Table S3). TMS is performed according to established international safety guidelines (78), and each participant undergoes a screening TMS questionnaire prior to participating (79).

A smaller sample of patients with SZ or MDD and some HC undergo simultaneous TMS-fMRI examination. In a test–retest design, the left DLPFC is stimulated with a 10-Hz repetitive TMS protocol with intensities of 40 and 80% of the resting motor threshold. Simultaneous TMS-fMRI is a new technique that enables more causal interpretations of the blood oxygenation level-dependent response (80).

2.8. Retinal anatomy and electrophysiology

From a developmental perspective, the retina is part of the brain and therefore considered as an accessible "window to the brain" (81). Moreover, pioneer studies and meta-analyzes have reported retinal alterations in psychiatric disorders (82–85). Therefore, CDP phenotyping includes an assessment of retinal anatomy by optical coherence tomography (OCT), of retinal microvasculature by OCT angiography (OCT-A), and of retinal electrophysiology by electroretinography (ERG). Before the retinal assessments, refraction and visual acuity are determined with an OCULUS/NIDEK AR 1-s autorefractor (OCULUS Optikgeräte GmbH, Wetzlar, Germany) and intraocular pressure is measured with an OCULUS/NIDEK Tonoref II (OCULUS Optikgeräte GmbH, Wetzlar, Germany). OCT and OCT-A are performed on a ZEISS CIRRUS HD-OCT 5000 with AngioPlex (Carl Zeiss Meditec AG, Jena, Germany), and ERG is performed with a mobile RETeval electroretinograph (LKC Technologies, Inc., Gaithersburg, MD, United States).

2.9. Overlap with previous deep phenotyping and translational studies

To enable longitudinal and translational investigations to be performed right at the start of the CDP study, we invited those participants from previous deep phenotyping studies at the Department of Psychiatry and Psychotherapy, LMU Munich, who had agreed to be re-contacted for new studies at the Department to participate in the CDP study. These individuals had participated in one or both of the following studies: (a) the Multimodal Imaging in Chronic Schizophrenia Study (MIMICSS), a pilot study that was part of the longitudinal PsyCourse study (86, 87) (local ethics committee of the LMU Munich, Munich, Germany, project no. 17–13; see Supplemental Text), and (b) an add-on study of PsyCourse that established a cohort of donors of human induced pluripotent stem cells (hiPSCs) [ethics committee project no. 17–880; (88)].

2.10. Biobanking in the CDP study

The Munich Mental Health Biobank (52) provides the biobanking of samples in the CDP study. For all participants, blood-based biobanking comprises the following: 1 × 7.5 ml K3EDTA Monovette (Fa Sarstedt, Cat no 01.1605.001) for DNA extraction, 1 x PaxGene blood RNA tube (Fa BD, Cat no 762165) for RNA extraction, 1 × 9 ml K3EDTA Monovette (Fa Sarstedt, Cat no 02.1066.001) for plasma-based analysis, and 1 × 9 ml Monovette with coagulation activator (Fa Sarstedt, Cat no 02.1063.001) for serum-based analysis; after initial processing, all samples are stored at −80°C. If laboratory capacities allow additional biobanking, additional vials (BD Vacutainer 10 ml Glass Sodium Heparin Tubes, BD, Cat no 368480) are used for isolating peripheral blood mononuclear cells (PBMC) and stored in liquid nitrogen; the banking of PBMCs in liquid nitrogen enables later generation of hiPSCs (89). We also collect cerebrospinal fluid (CSF) from patients with psychosis in whom a diagnostic lumbar puncture is clinically recommended.

2.11. Genetic and epigenetic analyzes

To assess the genetic risk background of these individuals, the DNA isolated during biobanking of the samples will be genetically analyzed by using SNP genotyping platforms. After quality control and genetic imputation of these data, polygenic risk scores will be calculated with advanced methods such as continuous shrinkage (90). This approach will allow us to quantitatively estimate the genetic burden of the mental disorders in our sample. Such a genetic load index will be the basis for genetic analyzes of the impact of polygenic risk scores on different clinical traits and the degree of genetic overlap between the various diagnostic groups in the CDP study. In blood RNA collected in PaxGene tubes, we will specifically assess levels of microRNAs and mRNAs, including histone deacetylase 1 and 2. Subsequently, we will perform univariate and multivariate pathway analyzes to identify disturbed genetic and epigenetic pathways within biotype-stratified subgroups of patients. We will investigate all pathways and epigenetic markers with individual models or tests as part of advanced longitudinal and cross-sectional machine learning methods (49).

2.12. Longitudinal assessment

The CDP study is mainly a cross-sectional investigation; however, after a successful initiation phase, we will initiate a longitudinal re-assessment with a six-month follow-up only in patients with first-episode SZ and a regular two-year follow-up period in all patients. Moreover, because the study data are embedded in the Munich Mental Health Biobank (52), we will have access to the longitudinal clinical data from participants' medical records.

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TABLE 2 Participants in the Clinical Deep Phenotyping study.

CDP cohort		
	Healthy controls	Patients
Participants, *n*	187	194
Age, mean (SD), y	34.5 (12.3)	39.5 (11.1)
Female, *n*	100	67
Male, *n*	87	127
DSM-5-TR diagnosis, *n*		
Schizophrenia		110
Schizoaffective disorder		44
Major depression		18
Brief psychotic disorder		6
Drug induced psychosis		5
Delusional disorder		2
Bipolar disorder		9
Unaffected relatives	6	
Modalities, *n*		
BACS test	178	181
MRI	162	153
Resting-state EEG	164	170
P300 (EEG)	162	167
TMS	9	9
ERG	175	181
OCT	177	178
Blood sampling	185	190
PBMC	161	133
hiPSC	10	14
CSF		18
Agreed to be recontacted	178	169
CDP follow-up of MIMICSS participants		
MIMICSS participants, *n*	10	15
Time between MIMICSS and CDP, mean (SD), *y*	5.9 (0.7)	5.7 (1.0)

BACS, Brief Assessment of Cognition in Schizophrenia; CDP, Clinical Deep Phenotyping; CSF, cerebrospinal fluid; DSM5, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; ERG, electroretinogram; hiPSC, human induced pluripotent stem cells; MIMICSS, Multimodal Imaging in Chronic Schizophrenia Study; MRI, magnetic resonance imaging; OCT, optical coherence tomography; p300, EEG with an auditory stimulus; PBMC, peripheral blood mononuclear cells; SD, standard deviation; TMS, transcranial magnetic stimulation.

3. Results

3.1. Establishing a deep phenotyping cohort

From the start of the study on October 1, 2020, until the end of the initiation phase on October 31, 2022, 381 participants were enrolled in the ongoing CDP study. Background characteristics are shown in Table 2, including the numbers of patients for each diagnosis and the numbers of HC and unaffected relatives (UR). Among the patients, 65.5% were male, and among the HC, 46.5%. Table 2 also shows the modalities performed in patients and HC. We performed Fischer's exact test to investigate whether any CDP assessments were affected by group and found that insufficient evidence is available to show whether the decision to participate or inclusion in any of the mentioned examinations was significantly dependent on whether the participant was a patient or HC (*p* values: MRI, 0.06; EEG, 1.00; OCT, 0.31; ERG, 1.0; BACS, 0.51; blood sampling 0.69; and TMS, 1; Figure 1).

3.2. Enabling a longitudinal, translational cohort based on previous studies

The MIMICSS included 154 individuals (76 participants with a diagnosis of SZ, 56 HC, and 22 UR of patients with SZ). MIMICSS participants underwent multimodal imaging and a cognitive test battery. Of the MIMICSS participants, 15 patients with SZ and 10 HC accepted our invitation to join the CDP study. These individuals were enrolled in the CDP study a mean of 5.7 (± 1.0) years and 5.9 (± 0.7) years after their participation in MIMICSS. We continue to invite MIMICSS participants to the CDP study because their participation might allow us to perform longitudinal examinations in a subgroup at the start of the CDP study.

PBMC were isolated from 35 patients with SZ, 20 HC, and 5 UR who participated in the PsyCourse-based hiPSC cohort study. hiPSCs were generated from 20 patients with SZ, 12 HC, and 3 UR (Supplemental Text; Supplementary Table S4).

The successful inclusion of MIMICSS participants and participants from the hiPSC cohort from the PsyCourse study enables that the CDP study already contains longitudinal and translational subcohorts (Table 2; Figure 2).

3.3. Clinical deep phenotyping study covers several RDoC analysis units

The multimodal approach of the CDP study is similar to the approach of the RDoC initiative. Thus, all investigations and assessments are performed in all participants independent of their clinical diagnosis. For example, the PANSS is assessed in all patients and HC. In this way, the CDP study, which focuses in particular on the cognitive systems of the RDoC matrix, covers multiple layers of the RDoC analysis units (Genes, Molecules, Cells, Circuits, Physiology, Self-Reports, and paradigms; Table 3) and might provide novel findings on the neurobiological underpinnings of cognitive impairments in SMI (Figure 3).

4. Discussion

This article presents the protocol and initiation phase of the ongoing CDP study. Between October 1, 2020, and October 31, 2022, 381 participants, mostly with SSD, were recruited into the CDP cohort. In the CDP study, all participants undergo deep phenotyping, e.g., by multimodal MRI imaging, resting-state EEG, activation EEG, retinal anatomical and electrophysiological measurements, and blood and hiPSC biobanking and postprocessing.

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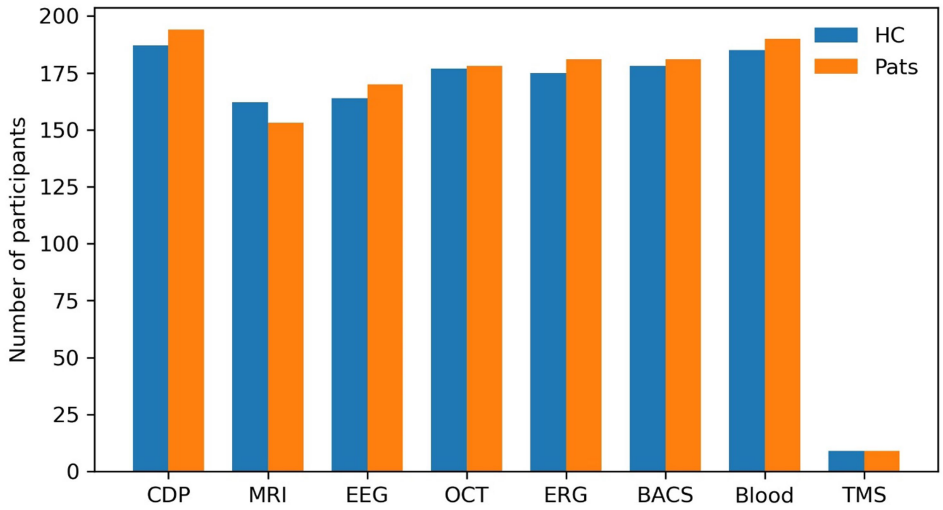

FIGURE 1
Numbers of patients and healthy controls in the Clinical Deep Phenotyping study grouped by modalities. Bar plots indicate the number of patients (orange bars) and healthy controls (blue bars) in the Clinical Deep Phenotyping (CDP) study who participated in the CDP study in general and in the various study examinations. BACS, Brief Assessment of Cognition in Schizophrenia; CDP, clinical deep phenotyping; EEG, electroencephalography; ERG, electroretinogram; HC, healthy controls; OCT, optical coherence tomography; Pats, patients; MRI, magnetic resonance imaging; TMS, transcranial magnetic stimulation.

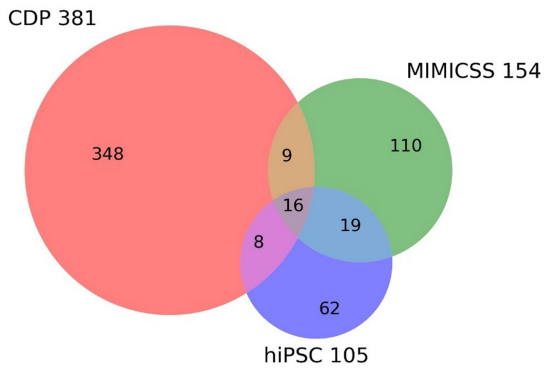

FIGURE 2
Overlap between longitudinal and translational subcohorts in the Clinical Deep Phenotyping study. The Venn diagram shows the inclusion in the Clinical Deep Phenotyping (CDP) study of participants who previously participated in the Multimodal Imaging in Chronic Schizophrenia Study (MIMICSS) and/or the human induced pluripotent stem cells (hiPSC) cohort of the PsyCourse study. The CDP, MMICSS, and hiPSC cohorts currently have a total of 381, 154, and 105 participants, respectively. CDP, Clinical deep phenotyping; hiPSC, human induced pluripotent stem cells; MIMICSS, Multimodal Imaging in Chronic Schizophrenia Study.

TABLE 3 Examples of Research Domain Criteria units of analysis in the Clinical Deep Phenotyping study.

RDoC Units of analysis	CDP Source / Method	Underlying principle
Genes	Blood biobanking	Genotyping
Molecules	Blood biobanking	Transcriptomics
		Proteomics
	MRS	Spectroscopy of candidate molecules in specific brain areas
Cells	Blood biobanking	hiPSC-derived brain cells
	OCT imaging	Analysis of retinal cytoarchitecture
Circuits	mMRI	T1, T2, DTI
Physiology	EEG	Auditory stimulus (p300), resting state
	TMS	Short-interval cortical inhibition
	fMRI	Functional resting MRI
Behavior	--	--
Self-reports	PANSS	Positive, negative symptoms
Paradigms	BACS	Cognitive tasks

BACS, Brief Assessment of Cognition in Schizophrenia; CDP, Clinical Deep Phenotyping; DTI, diffusion tensor imaging; EEG, electroencephalography; fMRI, functional resting MRI; hiPSC, human induced pluripotent stem cells; mMRI, multimodal magnetic resonance imaging; MRS, magnetic resonance spectroscopy; OCT, optical coherence tomography; PANSS, Positive and Negative Syndrome Scale; RDoC, Research Domain Criteria; T1, T1-weighted images; T2, T2-weighted images; TMS, transcranial magnetic stimulation.

The cross-diagnostic CDP study was inspired by the RDoC initiative (44). Although, the clinical diagnostic systems DSM-5 and ICD-10 do not reflect neurobiology, there are no plans to change them in the near future. Therefore, the CDP study uses both systems in parallel to allow potential clinical translation and aims to reveal the neurobiological underpinnings of clinically relevant subgroups across SMI disease courses, such as treatment resistance, remission, and cognitive impairments, by using a multimodal approach with RDoC-orientated clinical neuroscience tools.

To identify patient subgroups, WHOQOL-BREF and GAF are used to stratify patients according to social functioning and quality of life, both of which can differentiate between genetically different

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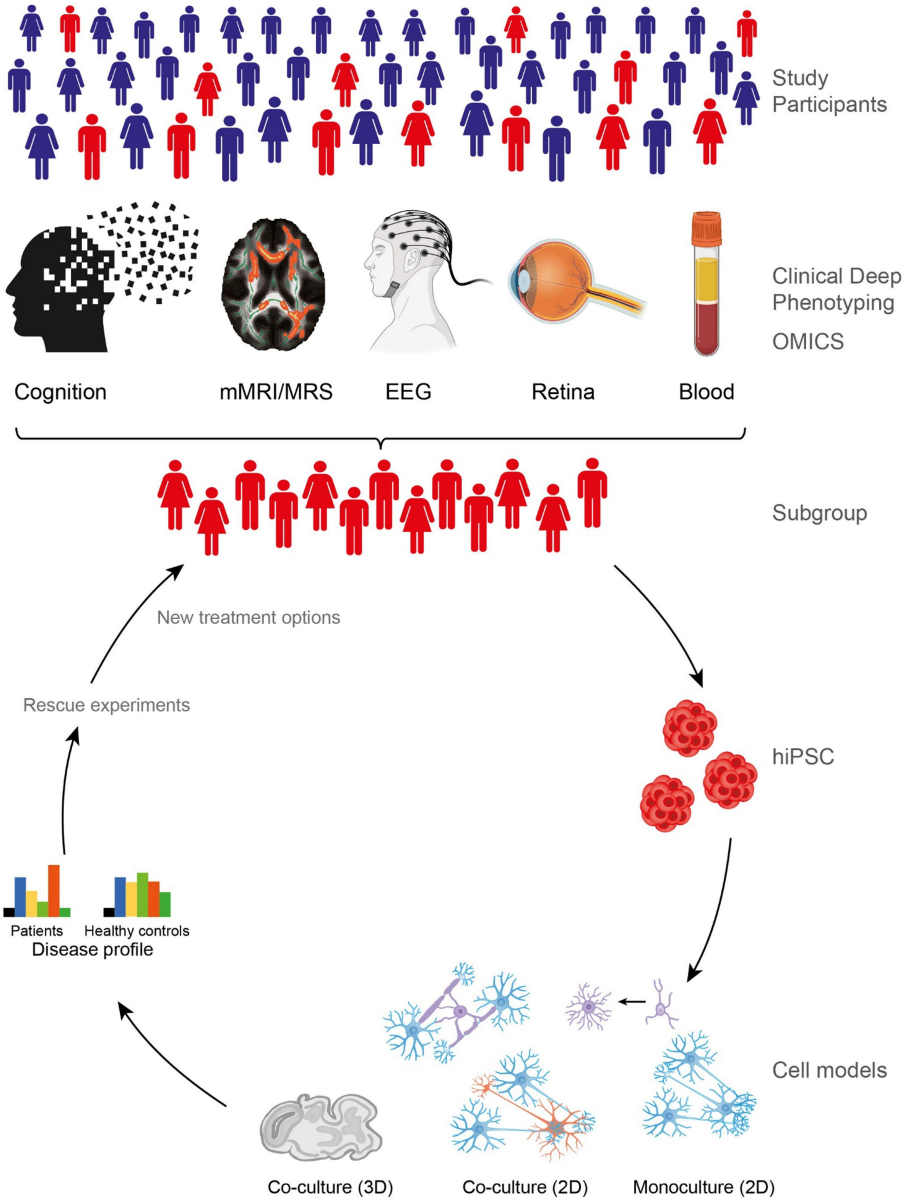

FIGURE 3
Summary of the approach of the Clinical Deep Phenotyping study. Clinical deep phenotyping of patients with severe mental illness and healthy controls includes cognitive, cerebral, and retinal assessments and blood-based biobanking; when space allows, isolated peripheral blood mononuclear cells are also added to the biobank, enabling later generation of human induced pluripotent stem cells (hiPSCs) from selected participants. After sufficient patient stratification, e.g., based on genetic subtypes and/or subphenotypes, subsequent hiPSC reprogramming from representative patients remains a bottleneck because of the high costs and time required. hiPSC models enable experimental validation and investigations of generated hypotheses in cellular 2D/3D monoculture and co-culture systems to reveal disease-specific molecular profiles. These models also allow treatment options to be screened, paving the way for new treatments that can be introduced into clinical practice after being verified in clinical trials with increasing numbers of patients; such trials are best performed in patient subgroups that are aligned with the initial stratification strategy. Adapted from (84). EEG, electroencephalography; hiPSC, human induced pluripotent stem cells; mMRI, multimodal magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

subgroups of psychosis (91). We aim to investigate potential neurobiological alterations in treatment-resistant patients by assessing lifetime clozapine treatment as a proxy (8). Moreover, we categorize remission by applying the established "Andreasen criteria" (51).

Cognitive functioning is often impaired in patients with SSD (92) but is only marginally influenced by antipsychotic treatment (93). Furthermore, it may predict treatment response and remission (94–96). Therefore, one aim of the CDP study is to investigate whether cognitive impairments in SMI are reflected in neurobiological patterns because finding such patterns might help to identify patients at cognitive risk in future investigations or clinical trials.

Previous studies have investigated biological aspects of remission and treatment response. For example, one study found that patients with TRS had a more pronounced reduction in gray matter and lower perfusion of frontotemporal regions than treatment-responsive patients (97). Moreover, another study showed that non-remitted

patients with first-episode SZ have smaller hippocampal tail volumes than remitted first-episode patients, whereas hippocampal head and body volumes did not significantly differ between groups (98).

Most studies that investigate SMI from a biological perspective are limited by low sample sizes or the use of only a few assessment modalities. For example, the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) initiative aims to dissect neuropsychiatric disorders by combining only structural MRI, DTI, and fMRI data with genetic analyzes in large-scale cohorts (99). On the other hand, studies with retinal assessments, which represent an easily accessible window to the CNS and provide high-resolution data that might help to provide a deeper pathophysiological understanding, use mostly only methods such as OCT and ERG (84, 100). The only study to date that used both retinal and cerebral assessments in the same individuals had a low sample size ($n = 24$), which limited subsequent subgroup stratification (101). To enable the identification of clinically relevant subgroups, we aim to overcome these disadvantages in study designs (102, 103) and to consider the variability within and across individuals by performing deep phenotyping in over 500 participants with SMI.

To study and validate whether clinically relevant subgroups are reflected, at least to a certain extent, by altered biotypes, we aim to analyze multimodal data from the CDP assessments, including brain and retinal electrophysiology and anatomy and neurocognitive data, and combine them with blood- and CSF-derived data, such as transcriptomics and proteomics, and genetic information. This aim will be supported by biobanking of biomaterial from CDP participants at the Munich Mental Health Biobank.

Brain structure is heritable (104), and twin and family studies in UR show that UR have brain volume abnormalities similar to those found in patients (105). Moreover, SMI are associated with global brain structure alterations (106). For this reason, the CDP uses multiple brain imaging modalities to investigate the underlying anatomy and physiology.

The cross-diagnostic design of the CDP study will allow us to not only evaluate differences in the results of each type of assessment between patients with SMI and HC and between subgroups of patients with SMI, but also to examine the complex relations between the assessed modalities. We understand multilevel research as the simultaneous investigation of different domains of neurophysiological investigations and the subsequent confirmation of plausible findings, e.g., the significant distinction between patients and HC. Content validity is increased if matches are shown, e.g., in regions of the frontal brain, and reflected across modalities (e.g., structural alterations in mMRI and electrophysiological alterations in EEG). Furthermore, MRS can be used to distinguish between regional excitatory and inhibitory effects.

Environmental factors also play an important role in structural brain alterations (107). One confounding factor that may influence brain volume is medication intake, and it is difficult to determine whether brain volume changes are a consequence of disease-specific processes or antipsychotic treatment (108). Taking into account the confounding role of psychotropic drugs, the CDP study records current and past drug intake in all participants. To disentangle the complex nature of morphological and functional brain changes in SMI and control for antipsychotic treatment effects that might impact physiological parameters or blood–brain barrier alterations, for example, we intend to include also a substantial number of drug-naïve and first-episode patients in the CDP cohort.

The German national schizophrenia guidelines recommend that a lumbar puncture with routine CSF analysis is performed in all patients with the first episode of an SMI.[3] Of interest in this context is a large-scale retrospective study that postulated that CSF shows distinct, psychosis-specific patterns that include markers of inflammation or infection (109, 110). Hence, when clinically indicated, lumbar punctures are performed in a substantial subgroup of CDP patients to investigate CSF signatures in patients with SMI and assess the associations of such signatures with other assessed modalities (i.e., imaging, electrophysiology, and cognitive performance). To date, no large-scale cross-sectional study has examined the relationship between cognitive performance and CSF abnormalities in SMI. Furthermore, we aim to conduct an RDoC-conform longitudinal observational follow-up in patients with SMI to assess neuroinflammatory markers and glia-derived neurotrophic factors in CSF and the effect of these substances on cognition and symptomatic outcomes over the course of the disease. Moreover, in a subgroup of patients with SSD we also aim to evaluate the blood–brain barrier *via* contrast-enhanced MRI.

4.1. Relationship of the CDP study to international cohort studies

Comparability of the CDP study with other large cohort studies, such as NAKO (German National Cohort Study), ENIGMA (The Enhancing NeuroImaging Genetics through Meta-Analysis), the United Kingdom Biobank (United Kingdom Biobank), and the HCP, offers the possibility to study the relationship between the CDP data and those of much larger samples (99, 111–113). For example, ENIGMA provides data on various disorders, including SZ and MDD (114). Previously published work shows multicenter efforts to link genetics to brain structures, for example (106). Most recently, a multicenter ENIGMA effort identified 15 "hotspots" in the genome that either accelerate or slow brain aging–a finding that could potentially provide new targets for medications for psychiatric disorders (106). The CDP study uses a 3 T Prisma Magnetom Siemens scanner and the same MRI protocols as used in the HCP sample (75) and thus provides technically good conditions for obtaining normative reference values for multimodal MRI recordings. The HCP and CDP study collect similar cognition parameters and sociodemographic information. Thus, the use of the HCP protocol for multimodal MRI also allows direct comparison of the CDP sample with the HCP lifespan samples, the HCP young adult S1200 sample, and the HCP aging sample, covering individuals aged from 5 to over 100 years (75, 115).[4] In the future, clinical HCP studies will also allow for direct comparison and referencing of clinical diseases.

3 AWMF online. S3-Leitlinie Schizophrenie. https://register.awmf.org/de/leitlinien/detail/038-009 (Accessed January 01, 2023).

4 Connectome coordination facility. 1,200 Subjects Data Release. https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release (Accessed January 01, 2023).

4.2. Validating the potential of retina measurements as a window to the brain

Numerous studies on neurodegenerative disorders, including multiple sclerosis (116), Alzheimer disease (117), and Parkinson disease (118), have applied retinal OCT to assess how the retinal nerve fiber layer gradually thins. Interestingly, the retina shows typical changes in neurochemistry, morphology, electrophysiology, and function that reflect several pathomechanisms of neurodegenerative disorders and stroke (81).

Although OCT and ERG are broadly available, quick evaluation techniques, retinal measurements are not an established feature of research in biological psychiatry and are a long way from being used as diagnostic tools. Nevertheless, recent meta-analyzes provided evidence for the phenomenon of retinal thinning in SZ and BD (82–85). Moreover, one study found that the outer nuclear layer, which was altered in psychosis, was associated with total brain and white matter volume in a small cohort of 25 patients with psychosis and 15 HC (101).

Of note, the majority of retinal studies in SMI are limited by small sample sizes. Therefore, the large-scale CDP study aims to deliver further evidence for the potential and feasibility of retinal investigations in psychiatric research by validating the initial findings of retinal alterations presented here in the full CDP cohort.

As a preliminary finding from the CDP study, we recently published OCT findings in 65 patients with an SSD and 72 HC that provided evidence of thinner inner retinal layers and thinner total macular thickness in SSDs (119). These changes could not be explained by comorbidities such as hypertension, diabetes, or higher body mass index (BMI), all of which also affect retinal thickness and are enriched in patients with SSD.

As the next step, the CDP study will investigate in the future to what extent the retinal findings are related to brain-based CDP modalities and whether retinal investigations could be used as follow-up investigations.

4.3. Bridging the translational gap of micro- and macrocircuit research

Previously, the biological causes of SMI could be studied only by examining peripheral tissues, comparing imaging results with other findings, comparing genetic data, and analyzing postmortem brain samples. However, there is now great optimism that hiPSCs (120) will allow researchers to create almost any type of neuronal or glial cell and thus perform *in vitro* research on the brain. Technologies related to hiPSCs are expected to lead to advances in translational psychiatry (89, 121). To date, hiPSC models have enabled the investigation of hypotheses from GWASs, which have found more than 200 genes with a potential role in SZ (122, 123). Studies of hiPSCs have shown dysfunctions in neurons and glial cells in SZ (88, 121, 124). Currently, most hiPSC experiments enable identification of only basic clinical features, in particular variables such as age and diagnosis. Reports of genetic findings are rare and do not describe detailed clinical features. Thus, patient samples with extensive data on a broad range of characteristics are required to enable translation of clinical findings to the laboratory and from the laboratory back into clinical practice (89). Such extensively characterized samples would enable us to understand the underlying biology of neuropsychiatric diseases such as SZ and translate the biological findings into clinically relevant phenotypes. Therefore, we aim to use representative subgroups of our deeply phenotyped cohort to close the translational gap between hiPSC models and clinical symptomatology in patients. To this end, we will apply stratification strategies with deep learning algorithms based on the examined multi-layer data. Thus, after performing big data analysis, we will evaluate only meaningful subgroups of representative patients with hiPSC-based technology (89). In the long term, by using initial stratification strategies we expect to be able to develop new personalized therapeutic approaches with the help of clusters that are built from examined datasets with an RDoC approach and also with the help of patient-derived cell systems. We believe that this approach will help to push the boundaries of translational psychiatry (89, 125).

4.4. Summary and outlook

In summary, the multi-and interdisciplinary CDP study aims to non-invasively map the CNS in detail at different levels by using various examinations of the brain and retina to gain biological insights into disease patterns and manifestations in SMI and to merge them with genetic, cellular, clinical, and cognitive data. The study follows a confirmatory approach that aims on the one hand to find multimodal similarities and differences in terms of content and, on the other hand, to examine how our study data relate to those of larger cohorts. In small, well-designed subsamples, we aim to integrate our macroscopic assessments with hiPSC-based *in vitro* investigations and examinations of inflammatory markers in blood, brain, and CSF.

As mentioned above, so far only preliminary retinal data from the CDP cohort have been published (119) because the sample size is not large enough to obtain sound results for all the variables examined. Of note, similar to the data in the initial OCT paper (119), we plan to make published data available to enable open research exchange. However, the fact that no further preliminary findings have been published is a limitation of the current status of the CDP study. In the long term, we plan to pool our data with data from other centers and to participate in global efforts to better understand brain structure and function and cellular mechanisms in SMI by using multivariate data. The CDP study might support the scientific endeavor to identify neurobiology-informed SMI subgroups of patients who could benefit from personalized and tailored treatment in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty of the Ludwig-Maximilian-University, number: 20–528. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DK, EW, AS, BM, and FR designed and conceptualized the CDP study. LK, EB, KH, IJ, GI, JMe, JMo, and VG recruited patients and collected study data. EW trained staff on diagnostic and clinical assessments. LK performed data preparation and statistical analysis. LK and FR performed data visualization. LK, DK, AS, PF, and FR wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1179811/full#supplementary-material

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4. Paper II

Optical coherence tomography reveals retinal thinning in schizophrenia spectrum disorders

Emanuel Boudriot[1], Benedikt Schworm[2], Lenka Slapakova[1,3], Katharina Hanken[1], Iris Jäger[1], Marius Stephan[1,3], Vanessa Gabriel[1], Georgios Ioannou[1], Julian Melcher[1], Genc Hasanaj[1], Mattia Campana[1], Joanna Moussiopoulou[1], Lisa Löhrs[1], Alkomiet Hasan[4], Peter Falkai[1,5], Oliver Pogarell[1], Siegfried Priglinger[2], Daniel Keeser[1,6,7], Christoph Kern[2], Elias Wagner[1], Florian J. Raabe[1,3,*]

[1]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Nußbaumstraße 7, 80336 Munich, Germany
[2]Department of Ophthalmology, University Hospital, LMU Munich, 80336 Munich, Germany
[3]International Max Planck Research School for Translational Psychiatry (IMPRS-TP), 80804 Munich, Germany
[4]Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, 86156 Augsburg, Germany
[5]Max Planck Institute of Psychiatry, 80804 Munich, Germany
[6]NeuroImaging Core Unit Munich (NICUM), University Hospital, LMU Munich, 80336 Munich, Germany
[7]Munich Center for Neurosciences (MCN), LMU Munich, 82152 Planegg-Martinsried, Germany

Emanuel Boudriot, Benedikt Schworm, Christoph Kern, Elias Wagner, and Florian J. Raabe contributed equally.

***** Correspondence:

Florian J. Raabe, florian.raabe@med.uni-muenchen.de

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ORIGINAL PAPER

Optical coherence tomography reveals retinal thinning in schizophrenia spectrum disorders

Emanuel Boudriot[1] · Benedikt Schworm[2] · Lenka Slapakova[1,3] · Katharina Hanken[1] · Iris Jäger[1] · Marius Stephan[1,3] · Vanessa Gabriel[1] · Georgios Ioannou[1] · Julian Melcher[1] · Genc Hasanaj[1] · Mattia Campana[1] · Joanna Moussiopoulou[1] · Lisa Löhrs[1] · Alkomiet Hasan[4] · Peter Falkai[1,5] · Oliver Pogarell[1] · Siegfried Priglinger[2] · Daniel Keeser[1,6,7] · Christoph Kern[2] · Elias Wagner[1] · Florian J. Raabe[1,3]

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Abstract

Background Schizophrenia spectrum disorders (SSDs) are presumed to be associated with retinal thinning. However, evidence is lacking as to whether these retinal alterations reflect a disease-specific process or are rather a consequence of comorbid diseases or concomitant microvascular impairment.

Methods The study included 126 eyes of 65 patients with SSDs and 143 eyes of 72 healthy controls. We examined macula and optic disc measures by optical coherence tomography (OCT) and OCT angiography (OCT-A). Additive mixed models were used to assess the impact of SSDs on retinal thickness and perfusion and to explore the association of retinal and clinical disease-related parameters by controlling for several ocular and systemic covariates (age, sex, spherical equivalent, intraocular pressure, body mass index, diabetes, hypertension, smoking status, and OCT signal strength).

Results OCT revealed significantly lower parafoveal macular, macular ganglion cell–inner plexiform layer (GCIPL), and macular retinal nerve fiber layer (RNFL) thickness and thinner mean and superior peripapillary RNFL in SSDs. In contrast, the applied OCT-A investigations, which included macular and peripapillary perfusion density, macular vessel density, and size of the foveal avascular zone, did not reveal any significant between-group differences. Finally, a longer duration of illness and higher chlorpromazine equivalent doses were associated with lower parafoveal macular and macular RNFL thickness.

Conclusions This study strengthens the evidence for disease-related retinal thinning in SSDs.

Keywords OCT · Angiography · Schizophrenia · Retina · Thickness · Perfusion

Introduction

Schizophrenia spectrum disorders (SSDs) are associated with significant global and widespread alterations in brain structure [1, 2], microstructure [3], and connectivity [4–6] and have a severe impact on cognition and social functioning [7]. Neurodevelopment is presumed to be atypical in SSDs

Emanuel Boudriot, Benedikt Schworm, Christoph Kern, Elias Wagner, and Florian J. Raabe contributed equally.

✉ Florian J. Raabe
florian.raabe@med.uni-muenchen.de

1 Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Nußbaumstraße 7, 80336 Munich, Germany

2 Department of Ophthalmology, University Hospital, LMU Munich, 80336 Munich, Germany

3 International Max Planck Research School for Translational Psychiatry (IMPRS-TP), 80804 Munich, Germany

4 Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, 86156 Augsburg, Germany

5 Max Planck Institute of Psychiatry, 80804 Munich, Germany

6 NeuroImaging Core Unit Munich (NICUM), University Hospital, LMU Munich, 80336 Munich, Germany

7 Munich Center for Neurosciences (MCN), LMU Munich, 82152 Planegg-Martinsried, Germany

[8], and several lines of evidence suggest that the regenerative capacity of the brain is impaired [7].

From an embryological perspective, the retina is part of the central nervous system (CNS). It does not just mimic many cellular processes of the healthy brain but also reflects various pathophysiological changes in neurodegenerative conditions, such as Alzheimer's and Parkinson's disease [9–11]. However, in contrast to the complex and deeply enmeshed neuronal networks of the brain, the highly structured cytoarchitecture of the human retina can be studied easily, quickly, and with very high resolution in vivo. Limitations in brain imaging encouraged researchers to harness the retina as a "window to the brain" [9] and use the non-invasive technology of optical coherence tomography (OCT) to explore retinal biomarkers of brain pathology [12].

In the last years, several pioneering studies have described alterations in retinal cytoarchitecture in SSDs [12–16]. A recent systematic review and meta-analysis, which included 23 studies with a total of 2079 eyes of patients with SSDs and 1571 eyes of healthy controls, revealed a reduction in peripapillary retinal nerve fiber layer (pRNFL) thickness, average macular thickness (MT), macular ganglion cell–inner plexiform layer (mGCIPL) thickness, and macular volume, as well as enlarged cup volume in SSDs [16]. However, the quality of previous studies was highly heterogeneous [17], and some reported negative results (e.g., [18, 19]). Findings across SSD studies were inconsistent as to whether the retinal nerve fiber layer (RNFL), macula, or other structures show abnormalities, and most past studies were too small to generate robust estimates of between-group differences [13].

Interestingly, the retina is also one of the few sites where the human microvasculature can be studied directly in vivo. Advanced OCT devices offer the possibility to visualize the capillary network by OCT angiography (OCT-A), which can reveal altered microvasculature in somatic diseases, such as diabetes or hypertension, even in the absence of retinopathy [20, 21]. There are only a few studies with small sample sizes of 12–28 patients with schizophrenia and 15–37 controls that have explored potential vascular changes in schizophrenia by OCT-A [22–25]. They indicated changes in several parameters within the patient groups, including reduced superficial vessel and perfusion density of the macula and larger foveal avascular zone (FAZ) area [25], decreased vessel density in the deep vascular plexus of the macula [23], and lower peripapillary vascular density in the temporal quadrant [22]. In one study, increased skeletonized vessel density in the superficial vascular plexus and increased vessel density and skeletonized vessel density in the choriocapillaris of the right eyes of patients with schizophrenia were detected [24].

Importantly, retinal investigations in mental illness face several limitations: It has been shown that age, sex, spherical equivalent, intraocular pressure (IOP), body mass index (BMI), diabetes, hypertension, smoking status [13, 21, 26–28], and OCT signal strength [29, 30] affect OCT and OCT-A measurements. Thus, effects of concomitant somatic conditions and cardiovascular risk factors, such as obesity, diabetes, hypertension, and smoking, that are over-represented in SSDs [13], and an altered microvascular state might have contributed to the reported retinal disturbances in SSDs.

In this study, we aimed to provide further evidence for the applicability of OCT and OCT-A as tools to study disease-related retinal processes in SSDs. Using an exploratory approach, we aimed to identify effects of SSDs on retinal structure and microvasculature by systematically controlling for potential covariates (age, sex, spherical equivalent, IOP, BMI, diabetes, hypertension, smoking status, and OCT signal strength) with a multivariate analysis strategy.

Materials and methods

Sample characteristics

This study was part of the Munich Clinical Deep Phenotyping study, an ongoing naturalistic study that started in October 2020 and focuses on schizophrenia. It was approved by the local ethics committee of the LMU Munich (approval number: 20-528) and registered in the German Clinical Trials Register (DRKS, registration ID: DRKS00024177). All participants provided written informed consent. This study provides a preliminary data analysis of participants that were enrolled between October 9, 2020, and July 21, 2021. Patients were recruited at the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany. Both in- and outpatients were considered for inclusion. Healthy controls were recruited from the local community via online advertisements, flyers, and personal referrals.

Inclusion criteria for patients were a diagnosis of schizophrenia, schizoaffective disorder, or brief psychotic disorder according to the Mini International Neuropsychiatric Interview (M.I.N.I.) [31], and for the healthy controls, no past or current psychiatric disorder according to the M.I.N.I. Exclusion criteria were a primary psychiatric disorder other than those mentioned above; age younger than 18 years or older than 65 years; a concurrent clinically relevant CNS disorder; a history of encephalitis, meningitis, or stroke; retinal pathology (pre-known or detected by OCT, for individual exclusion details see Supplemental Text); elevated IOP ($\geq$ 21 mmHg); and pregnancy. Individual eyes were

excluded at a spherical equivalent of less than or equal to -6 diopter (D) or greater than or equal to 6 D [32].

Diagnosis and clinical assessment

All participants underwent the M.I.N.I. [31] for psychotic disorders studies, German version 7.0.2, according to *DSM-5* criteria. Symptom severity was assessed by the Positive and Negative Syndrome Scale (PANSS) [33]. Information on medications, disease history, concomitant conditions (e.g., diabetes, hypertension; defined as the presence of a medical diagnosis), height, weight, substance use in the past 7 days, and smoking status was collected through self-report and, if possible, verified by examining medical records. Current antipsychotic medication was converted to chlorpromazine equivalent doses (CPZeq) [34].

OCT and OCT-A imaging

Eye examinations were performed at the Department of Ophthalmology, University Hospital, LMU Munich, Munich, Germany. Refraction and best corrected visual acuity (BCVA) were determined with an OCULUS/NIDEK AR 1-s autorefractor (OCULUS Optikgeräte GmbH, Wetzlar, Germany), and IOP, with a non-contact tonometer (OCULUS/NIDEK Tonoref II; OCULUS Optikgeräte GmbH, Wetzlar, Germany). For participants with previous refractive surgery, preoperative refraction was obtained from medical records. Before OCT imaging, most pupils were pharmacologically dilated with 0.5% tropicamide eye drops. Spectral-domain OCT and OCT-A scans of both eyes were then performed with a ZEISS CIRRUS HD-OCT 5000 with AngioPlex (Carl Zeiss Meditec AG, Jena, Germany), which has an axial resolution of 5 microns. The protocol comprised several scans: a $6 \times 6 \times 2$ mm^3 volume scan of the macula centered on the fovea, whereby each scan consisted of 128 brightness (B) scans with 512 amplitude (A) scans each; a 6×6 mm^2 cube scan centered on the optic disc and consisting of 200 B-scans with 200 A-scans each; a 6×6 mm^2 angiography scan centered on the fovea; and a 4.5×4.5 mm^2 angiography scan of the peripapillary region. The angiography scans each consisted of 350 B-scan positions with 350 A-scans and two consecutive B-scans at each position. If necessary, individual scans were repeated to achieve adequate image quality. Scans were evaluated according to the OSCAR-IB criteria [32, 35] and excluded in case of notable artifacts. Only structural scans with a signal strength of at least 6 out of 10 and angiographies with a signal strength of at least 8 were accepted.

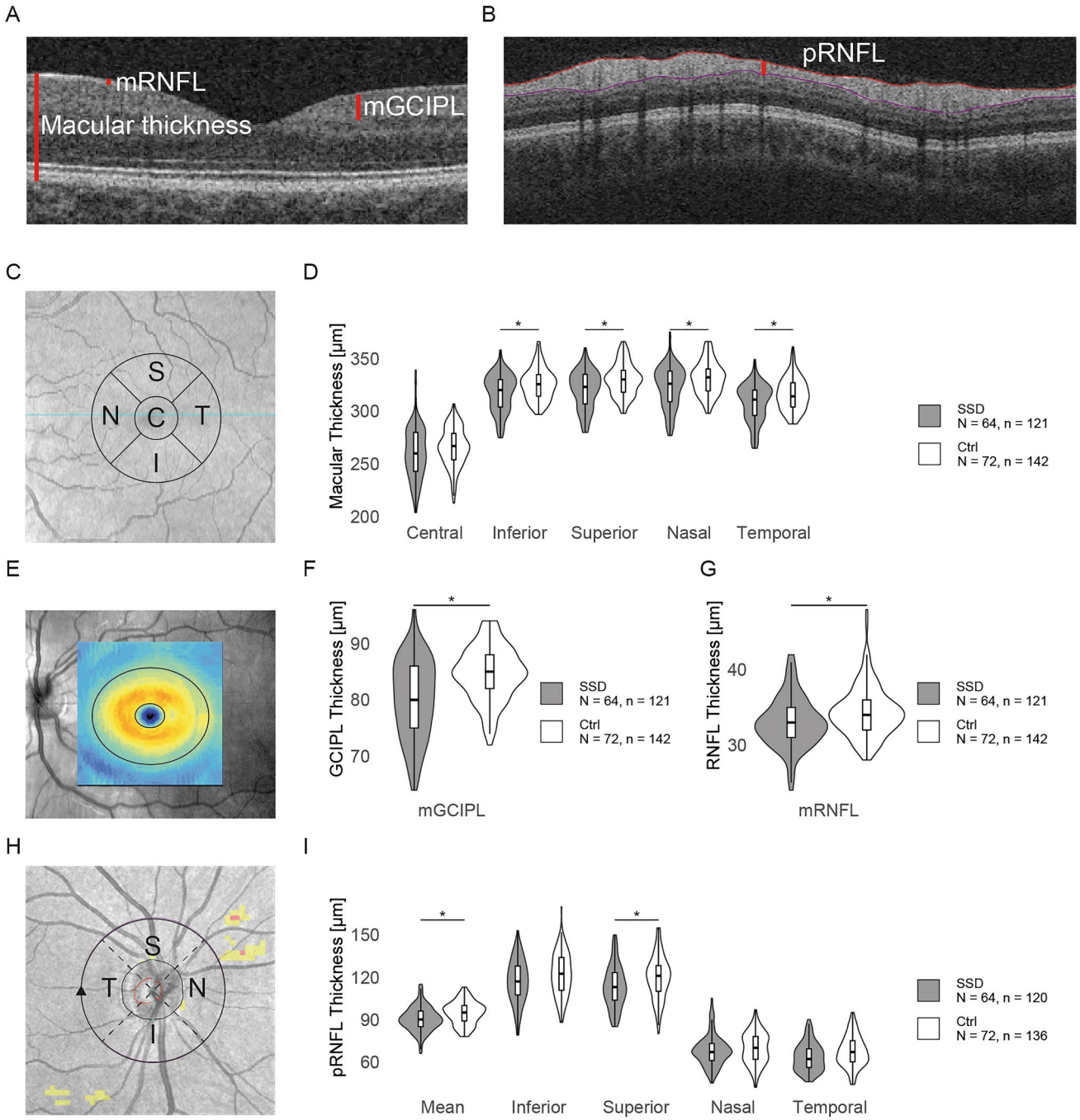
OCT data were automatically analyzed by the instrument's software (version 11.0.0.29946), and several parameters were evaluated in detail. The software calculated the MT—which equates to the distance between the internal limiting membrane and the posterior part of the retinal pigment epithelium (Fig. 1A)—according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Here, the retina is divided into 9 sectors that form inner and outer rings with outer diameters of 3 and 6 mm, respectively, around a 1-mm-diameter central foveal field. For the present work, we used only the values for the central and four adjacent subfields within the inner parafoveal ring (Fig. 1C). Mean mGCIPL and macular RNFL (mRNFL) thicknesses were determined by the instrument's software within an elliptical ring around the fovea with an inner diameter of 1 mm vertically and 1.2 mm horizontally and outer diameters of 4 mm and 4.8 mm (Fig. 1A, E). To determine pRNFL thickness (Fig. 1B), a circle with a radius of 1.73 mm was placed around the optic disc. We assessed the mean value for the whole pRNFL and the separate values for the inferior, superior, nasal, and temporal quadrants (Fig. 1H). Automatic layer segmentation was checked for all scans. Scans with segmentation errors were excluded.

OCT-A macular perfusion parameters included the perfusion and vessel densities of the superficial vascular plexus (Fig. 2A). Perfusion density was defined as the proportion of the area with blood flow, and vessel density, as the total length of all blood vessels per area. The software analyzed the corresponding values within the central foveal subfield, which included the FAZ, and inside the surrounding inner ring of the ETDRS grid. For peripapillary angiographies, perfusion density in the radial peripapillary capillary network was measured within an annulus with an outer diameter of 4.5 mm around the optic disc (Fig. 2E). Furthermore, the FAZ size was determined automatically by the software. The automatic FAZ detection was checked in each case and manually corrected on the OCT device if necessary. Individual scans were excluded from the FAZ analysis if the FAZ was not reasonably delineable, e.g., in anatomical variations in which the inner nuclear layer was not completely absent [36].

Statistical analysis

Statistical analyses were performed with R, version 4.1.1 [37]. Group differences in sample characteristics were explored with Fisher's exact test for categorical variables and with Welch's *t* test for normally distributed and Mann–Whitney *U* test for non-normally distributed continuous variables [38, 39]. Normality within groups was assessed with the Shapiro–Wilk test.

We studied the association between SSDs and retinal parameters from OCT and OCT-A measures with additive mixed models (AMMs). These models enable the inclusion of non-linear smooth effects of multiple covariates [40]. The regression models were estimated with the *gam* function of the *mgcv* package [41]. Both eyes (i.e., oculus uterque, OU)



were included if available. We adjusted for the correlation of the measurements of each participant's eyes by including a random intercept for participant identification number. It has been reported that age, sex, spherical equivalent, IOP, BMI, diabetes, hypertension, smoking status [13, 21, 26–28], and OCT signal strength [29, 30] affect OCT and OCT-A measurements. These variables were, therefore, considered as covariates. Non-linear effects were estimated on a P-spline basis with 10 basis functions; residuals were visually checked and showed no substantial deviation from the model assumptions. To address possible inter-eye differences, we additionally fitted separate additive models for the right (i.e., oculus dexter, OD) and left (i.e., oculus sinister, OS) eyes and included the mentioned covariates. The resulting *p* values of the group effects of the OU, OD, and OS models were jointly adjusted for multiple testing within one Benjamini–Hochberg procedure [42].

Next, we performed exploratory post hoc analyses and used separate additive mixed models to address the association of duration of illness, CPZeq, and lifetime history of

◂**Fig. 1** Optical coherence tomography reveals thinner retinal layers in patients with schizophrenia spectrum disorders compared with healthy controls. **A** Detail of a horizontal optical coherence tomography (OCT) brightness (B) scan of the macula. The red lines represent the macular thickness (MT), macular retinal nerve fiber layer (mRNFL), and combined ganglion cell–inner plexiform layer (mGCIPL). **B** Circular cut around the optic disc, illustrating the measurement of the peripapillary retinal nerve fiber layer (pRNFL; vertical red line). **C** OCT fundus image of the macular area of a left eye illustrating the central field ("C") and the adjacent superior ("S"), temporal ("T"), inferior ("I"), and nasal ("N") fields of the inner ring of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid, where the macular thickness was measured. **D** Violin plots showing the distribution of the macular thickness within the central field ($p=0.43$) and the inferior ($p=0.030$), superior ($p=0.015$), nasal ($p=0.016$), and temporal ($p=0.041$) fields of the inner ring of the ETDRS grid between the schizophrenia spectrum disorder (SSD) and the healthy control (Ctrl) group. **E** Fundus image of a left eye. The thicknesses of the mRNFL and mGCIPL were measured inside the area enclosed by the two concentric ellipses. **F** Distribution of the mGCIPL thickness in patients with SSDs and Ctrl ($p=0.008$), illustrated with violin plots. **G** Distribution of the mRNFL thickness in patients with SSDs and Ctrl ($p=0.008$), illustrated with violin plots. **H** Illustration of the pRNFL measurement circle (black) for a right eye. Values were obtained for the mean and the temporal ("T"), superior ("S"), nasal ("N") and inferior ("I") quadrants. **I** Violin plots comparing the distribution of the mean pRNFL thickness in patients with SSDs and Ctrl ($p=0.021$) and pRNFL thickness in the inferior ($p=0.54$), superior ($p=0.018$), nasal ($p=0.31$), and temporal ($p=0.42$) quadrants. If available, the measurements of both eyes are each included as separate observations. *p* values were obtained with additive mixed models and are false discovery rate adjusted. *N*, number of participants; *n*, number of eyes; $*p<0.05$. *GCIPL* ganglion cell–inner plexiform layer; *mGCIPL* macular GCIPL; *RNFL* retinal nerve fiber layer *mRNFL* macular RNFL; *pRNFL* peripapillary RNFL

treatment with clozapine with those parameters that were significantly altered in the OU analysis, controlling for the aforementioned covariates. Duration of illness and CPZeq were included as linear predictors. Because of the primarily hypothesis-generating nature of these post hoc analyses, they were not corrected for multiple testing.

For all analyses, a *p* value of less than or equal to 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

83 patients with SSDs and 89 healthy controls underwent OCT. After excluding ineligible scans (see Supplemental Text), the following scans from a total of 126 eyes of 65 patients and 143 eyes of 72 controls were available: macular OCT scans of 121 eyes of 64 patients and 142 eyes of 72 controls, papillary OCT scans of 120 eyes of 64 patients and 136 eyes of 72 controls, macular OCT-A scans of 115 eyes of 63 patients and 116 eyes of 62 controls, and papillary OCT-A scans of 104 eyes of 57 patients and 127 eyes of 68 controls. Sex distribution was not significantly different between groups (Table 1). Mean age was 4.64 years higher in patients, and mean BMI was 6.88 kg/m^2 higher. Nearly half (48%) of patients were smokers, compared with only 15% of controls. Five patients and none of the controls had a concomitant diagnosis of type 2 diabetes. The groups did not differ significantly in the frequency of hypertension. We observed that within our study cohort the mean spherical equivalent was 0.67 D lower in patients than in controls, and the mean IOP was 0.64 mmHg higher. BCVA showed no significant differences. OCT signal strength in the optic disc scans was slightly higher in patients than in controls, but no significant differences were observed for the other scans (Table 1).

Among the patients, mean duration of illness was 13.69 years ($SD=7.81$) and mean CPZeq was 366.03 mg ($SD=273.46$). Ten patients had missing data for CPZeq, and two, for duration of illness. Most patients were clinically stable according to the PANSS; mean PANSS total score was 47.75 ($SD=14.47$). According to the M.I.N.I., most patients had a diagnosis of schizophrenia (72%), followed by schizoaffective disorder (26%). Only one patient, a 63-year-old woman with first-episode psychosis, was diagnosed with brief psychotic disorder (Table 1). No healthy control and only one patient reported use of cannabis within the 7 days before the examination.

OCT reveals retinal thinning in SSDs

We examined the retinal cytoarchitecture in both groups by OCT (Fig. 1). To estimate the impact of SSDs on the measurements, we fitted additive mixed models, which enable adjustment for non-linear predictor variables [40]. We included age, sex, spherical equivalent, IOP, BMI, diabetes, hypertension, smoking status, and OCT signal strength as covariates in all analyses; except for diabetes and smoking status, all covariates were significantly associated with at least some of the OCT outcome measures. More detailed information of the partial effects of the included covariates on the respective OCT measurements is provided in the Supplemental Model Reports. The partial effects of the covariates on pRNFL thickness are highlighted as an example (Fig. S1).

Table 2 reports and Fig. S2A illustrates the estimates of the group effect on OCT measurements. Despite accounting for the effects of the aforementioned covariates, the analysis revealed a robust and significant thinning of the parafoveal MT in SSD (Fig. 1D; Table 2). MT was lower in the SSD group in the inferior (estimate [95% CI] = −8.80 µm [−15.62, −1.98]; $p=0.030$), superior (estimate [95% CI] = −11.13 µm [−18.48, −3.78]; $p=0.015$), nasal (estimate [95% CI] = −10.21 µm [−17.25, −3.18]; $p=0.016$), and temporal (estimate [95% CI] = −8.74 µm [−15.89,

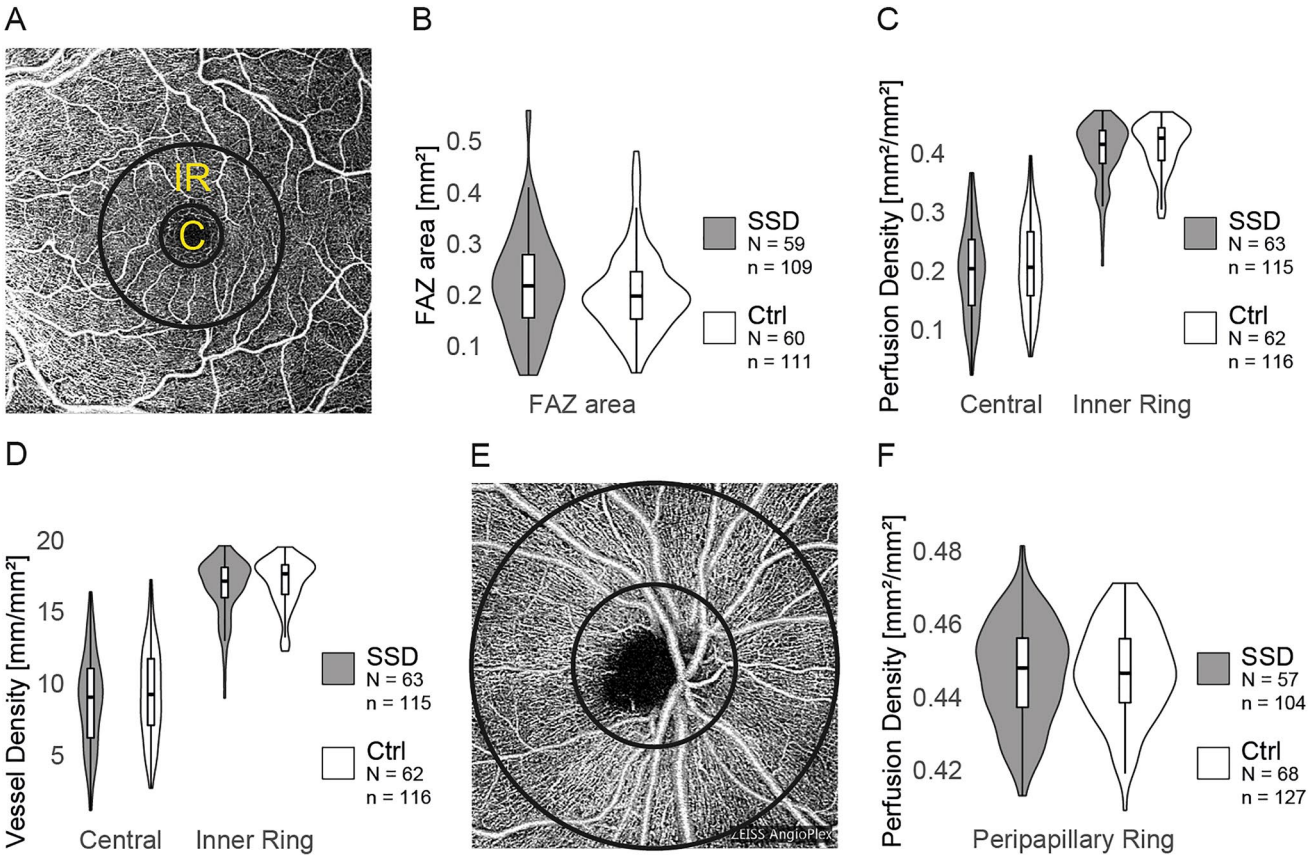


Fig. 2 Illustration of the coherence tomography angiography investigations and comparison between patients with schizophrenia spectrum disorders and healthy controls. **A** Exemplary en face image of the superficial vascular plexus of the left macula. The central field ("C") contains the foveal avascular zone (FAZ) and is surrounded by the inner ring ("IR") of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. **B** Violin plots comparing the distribution of the FAZ size in patients with schizophrenia spectrum disorders (SSDs) and healthy controls (Ctrl; $p=0.43$). **C** Violin plots comparing the distribution of the perfusion density in the macular area in patients with SSDs and Ctrl, separately for the central field ($p=0.96$) and the inner ring ($p=0.66$). **D** Distribution of the vessel density in the central field ($p=0.96$) and the inner ring ($p=0.55$) of the ETDRS grid, illustrated with violin plots. **E** En face image of a papillary optical coherence tomography angiography scan. The two black circles illustrate the annulus in which the peripapillary perfusion density was measured. **F** Violin plots comparing the distribution of the peripapillary perfusion density between patients with SSDs and Ctrl ($p=0.54$). If available, the measurements of both eyes are each included as separate observations. *p* values were obtained with additive mixed models and are false discovery rate adjusted. *N*, number of participants; *n*, number of eyes; $^*p<0.05$. *FAZ* foveal avascular zone

−1.59]; $p=0.041$) fields of the inner ring of the ETDRS grid, but no significant differences between groups were found in the central foveal field ($p=0.43$). Within the macular area, we found thinner mRNFL (estimate [95% CI] = −2.40 µm [−3.78, −1.03]; $p=0.008$) and mGCIPL (estimate [95% CI] = −4.46 µm [−6.95, −1.97]; $p=0.008$; Fig. 1F, G) in SSD. Mean pRNFL thickness (Fig. 1I) was also lower in patients (estimate [95% CI] = −4.72 µm [−8.14, −1.30]; $p=0.021$), driven mainly by a strong effect in the superior quadrant (estimate [95% CI] = −8.54 µm [−14.54, −2.55]; $p=0.018$), whereas SSD had no significant effect on pRNFL thickness in the inferior ($p=0.54$), nasal ($p=0.31$), or temporal ($p=0.42$) quadrants.

Transferring the estimated effects to an average male, nonsmoking patient without diabetes or hypertension, with all other covariates set to the SSD group median, the following percentage changes would be expected compared with a psychiatrically healthy control with otherwise similar characteristics: −2.7% for the inferior, −3.3% for the superior, −3.0% for the nasal, and −2.7% for the temporal inner MT; −7.0% for the mRNFL; −5.3% for the mGCIPL; and −5.0% for the mean and −7.0% for the superior pRNFL thickness.

Next, we fitted separate models for the right (OD) and left (OS) eyes. These analyses yielded very similar results compared to the OU analysis and the same parameters were significantly altered (Fig. S2; Table S1).

In summary, regardless of the effects of the various ocular and systemic covariates on retinal thickness, we observed widespread retinal thinning in SSDs.

Investigating the retinal microvasculature with OCT-A

To assess whether the observed retinal thinning in SSDs could be partly explained by an altered vascular state, OCT-A data were analyzed with additive mixed models (Fig. 2; Table 2) and, in line with the OCT analysis, age, sex, spherical equivalent, IOP, BMI, diabetes, hypertension, smoking status, and signal strength were included as covariates in all analyses. No differences between groups were found for perfusion density in the central foveal field ($p = 0.96$), in the 3-mm-diameter parafoveal ring ($p = 0.66$; Fig. 2C), or in the peripapillary area ($p = 0.54$; Fig. 2F) or for central ($p = 0.96$) or parafoveal ($p = 0.55$) vessel density (Fig. 2D). Moreover, the size of the FAZ did not differ between groups ($p = 0.43$; Fig. 2B). Table 2 reports and Fig. S2B illustrates the estimates and confidence intervals for these non-significant effects of SSD.

In addition, the vascular parameters were found to be associated (to varying degrees) with BMI, smoking status, sex, and OCT-A signal strength (Supplemental Model Reports). Similar to OCT data, the right and left eye exhibited comparable states (Fig. S2; Table S1).

Association of retinal thickness with clinical disease-related parameters

Last, we performed exploratory post hoc analyses to assess whether the retinal measures that were significantly altered in the SSD group in this study (only OCT measures) were associated with clinically relevant parameters by controlling for age, sex, spherical equivalent, IOP, BMI, diabetes, hypertension, smoking status, and signal strength as covariates.

Table S2 reports the estimates for the effects of duration of illness and CPZeq. Interestingly, although we controlled for covariate effects (including age), longer duration of illness (in years) was significantly associated with thinner MT in the inferior (estimate [95% CI] = −0.7078 µm/year [−1.2977, −0.1180]; $p = 0.022$), superior (estimate [95% CI] = −0.8307 µm/year [−1.4156, −0.2458]; $p = 0.007$), nasal (estimate [95% CI] = −0.6398 µm/year [−1.2503, −0.0292]; $p = 0.045$), and temporal (estimate [95% CI] = −0.7085 µm/year [−1.3297, −0.0874]; $p = 0.030$) parafoveal fields and with thinner mean mRNFL thickness (estimate [95% CI] = −0.1729 µm/year [−0.3025, −0.0432]; $p = 0.012$; Fig. 3). Moreover, higher CPZeq (in mg) was significantly associated with lower inferior (estimate [95% CI] = −0.0144 µm/mg [−0.0282, −0.0006]; $p = 0.047$), nasal (estimate [95% CI] = −0.0186 µm/mg [−0.0318, −0.0053]; $p = 0.009$), and temporal (estimate [95% CI] = −0.0169 µm/mg [−0.0302, −0.0037]; $p = 0.016$) parafoveal MT and mRNFL thickness (estimate [95% CI] = −0.0029 µm/mg [−0.0052, −0.0005]; $p = 0.020$; Fig. 3). Neither duration of illness nor CPZeq was significantly associated with mGCIPL or pRNFL thickness.

As a proxy for treatment resistance, we further assessed the effect of lifetime history of treatment with clozapine on OCT measures. The additive mixed models revealed a significant negative association with mean pRNFL thickness (estimate [95% CI] = −4.64 µm [−8.12, −1.15]; $p = 0.012$; Fig. S3; Table S3).

Discussion

This study presents a preliminary exploratory analysis of data from the ongoing Munich Clinical Deep Phenotyping Study. We systematically investigated the retina in a large cohort of patients with SSDs and healthy controls with the aims to explore differences in retinal thickness with OCT and to evaluate the retinal microvascular state with OCT-A by controlling for covariates associated with retinal alterations (age, sex, spherical equivalent, IOP, BMI, diabetes, hypertension, smoking status, and OCT signal strength). The multivariate analyses presented here revealed that SSDs were significantly associated with lower parafoveal macular, mGCIPL, mRNFL, and pRNFL thickness. In contrast, we could not detect accompanying microvascular alterations in SSDs regarding macular or peripapillary perfusion density, macular vessel density, and size of the foveal avascular zone.

The lack of between-group differences in the OCT-A parameters contrasts with previous smaller studies that showed several alterations in OCT-A parameters in SSDs [18, 22–24]. Of note, the previous findings were quite heterogeneous and ranged from reduced [18, 22, 23] to increased [24] perfusion in SSDs. Hence some previous OCT-A studies reported contradictory findings as to whether retinal alterations affect both eyes [25] or only one eye [24], we performed separate analyses for the right and left eyes that showed no relevant differences between the two eyes in either retinal thinning or the microvascular state.

Of note, several OCT-A studies in SSDs used different devices and image processing methods and are, therefore, not directly comparable with our study. A recent study of 28 patients with SSDs and 37 healthy controls that used the same OCT device as we did found that patients had lower macular perfusion density and larger FAZ areas in both eyes, as well as lower left macular vessel density [25]. However, the study used a different scanning protocol that had a higher resolution than ours, because it covered a smaller area of 3×3 mm^2 and each A-scan and B-scan was separated by 12.2 microns, whereas the A-scans and B-scans in our 6×6

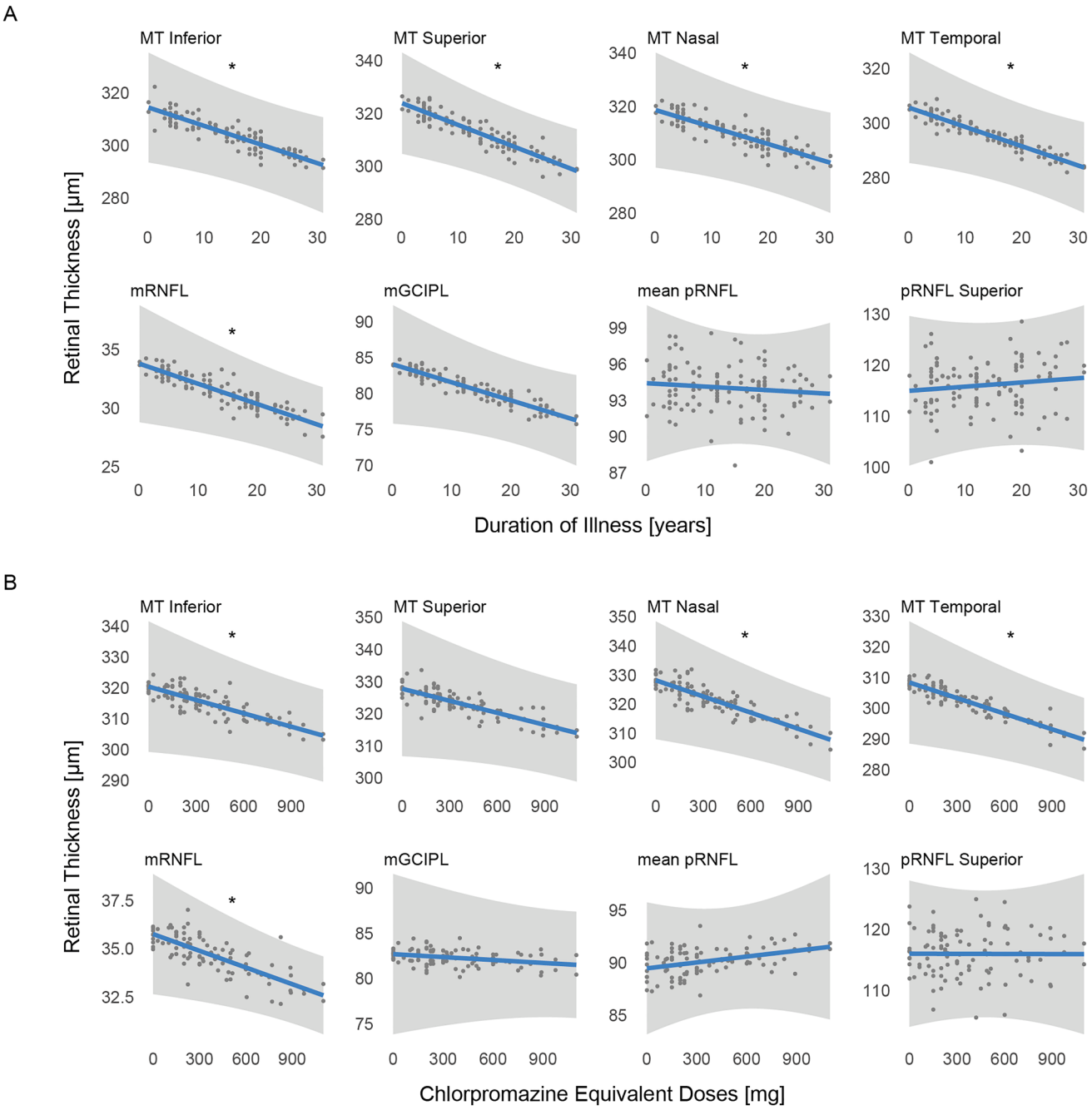


Fig. 3 Association between retinal measures and clinical disease features. **A** Association of duration of illness with significantly altered optical coherence tomography (OCT) parameters, estimated with additive mixed models. The plots show how the expected values of the outcome variables (blue lines) change as a function of the duration of illness when all other model terms are held fixed. Included are grey 95% confidence bands and dots for the partial residuals. $^*p < 0.05$. **B** Association of chlorpromazine equivalent doses with significantly altered OCT parameters, estimated with additive mixed models. The plots show how the expected values of the outcome variables (blue lines) change as a function of the chlorpromazine equivalent doses when all other model terms are held fixed. Included are grey 95% confidence bands and dots for the partial residuals. $^*p < 0.05$. *MT Central* macular thickness in the central subfield; *MT Inferior* macular thickness in the inner inferior subfield; *MT Superior* macular thickness in the inner superior subfield; *MT Nasal* macular thickness in the inner nasal subfield; *MT Temporal* macular thickness in the inner temporal subfield; *mGCIPL* macular ganglion cell–inner plexiform layer; *mRNFL* macular retinal nerve fiber layer; *pRNFL* peripapillary retinal nerve fiber layer

Table 1 Cohort characteristics

Sociodemographic variables	SSD group		Ctrl group		
	Mean ± SD	*n*	Mean ± SD	*n*	*p*
Age, years	39.29 ± 10.8	65	34.65 ± 11.35	72	0.007[b]
	n (%)		*n* (%)		
Sex, male:female	42:23 (65%)		36:36 (50%)		0.12[a]
	Mean ± SD	*n*	Mean ± SD	*n*	
BMI, kg/m^2	30.41 ± 6.83	65	23.53 ± 3.03	72	< 0.001[b]
	n (%)		*n* (%)		
Diabetes[c], yes:no	5:60 (8%)		0:72 (0%)		0.022[a]
Hypertension[c], yes:no	9:56 (14%)		5:67 (7%)		0.26[a]
Smoking status, yes:no	31:34 (48%)		11:61 (15%)		< 0.001[a]
Treatment and severity of illness	Mean ± SD	*n*	Mean ± SD	*n*	*p*
CPZeq, mg	366.03 ± 273.46	55	–	–	–
Duration of illness, years	13.69 ± 7.81	63	–	–	–
PANSS positive symptoms	11.46 ± 4.15	65	7.14 ± 0.42	72	< 0.001[b]
PANSS negative symptoms	11.57 ± 4.68	65	7.53 ± 1.09	72	< 0.001[b]
PANSS general symptoms	24.86 ± 7.32	65	16.89 ± 1.42	72	< 0.001[b]
PANSS total score	47.75 ± 14.47	65	31.56 ± 2.26	72	< 0.001[b]
	n (%)		–		–
Lifetime clozapine treatment, yes:no	30:34 (47%)		–		–
Ophthalmic variables	Mean ± SD	*n* (eyes)	Mean ± SD	*n* (eyes)	*p*
Spherical equivalent, D	−1.64 ± 1.64	126	−0.97 ± 1.60	143	< 0.001[b]
IOP, mmHg	13.59 ± 2.72	126	12.95 ± 2.75	143	0.028[b]
BCVA	1.18 ± 0.15	126	1.20 ± 0.13	143	0.36[b]
Signal strength OCT, macula	8.59 ± 0.95	121	8.42 ± 0.99	142	0.15[b]
Signal strength OCT, optic disc	7.83 ± 0.91	120	7.57 ± 0.81	136	0.020[b]
Signal strength OCT-A, macula	8.90 ± 0.77	115	8.91 ± 0.79	116	0.88[b]
Signal strength OCT-A, optic disc	9.13 ± 0.80	104	8.97 ± 0.80	127	0.12[b]
Diagnosis (*DSM-5*)	*n* (%)		–		–
Schizophrenia	47 (72%)		–		–
Schizoaffective disorder	17 (26%)		–		–
Brief psychotic disorder	1 (2%)		–		–

BCVA best corrected visual acuity; *BMI* body mass index; *CPZeq* chlorpromazine equivalent doses; *Ctrl* healthy controls; *D* diopters; *IOP* intraocular pressure; *n* number of observations; *OCT* optical coherence tomography; *OCT-A* optical coherence tomography angiography; *p p* value; *PANSS* Positive and Negative Syndrome Scale; *SD* standard deviation; *SSD* schizophrenia spectrum disorder

[a]Fisher's exact test

[b]Mann–Whitney *U* test

[c]Information regarding concomitant diagnoses of somatic conditions was collected through self-report and by examining medical records

mm^2 protocol were separated by 17.1 microns; in addition, the protocol had more B-scan repetitions per position (4 vs 2) [43, 44]. Therefore, the measurements obtained with our 6 × 6 mm^2 scan might have lower repeatability [44]. OCT-A is a novel technology and still prone to artifacts [45–47]. This might explain part of the heterogeneity of previous findings. In the future, more sensitive OCT-A devices might be able to detect more subtle changes. A further technical limitation of our OCT-A analysis is that we included only the superficial vascular plexus. A previous smaller study that investigated the deeper vascular layers observed some increased vessel density and skeletonized vessel density in the choriocapillaris in SSDs [24]. Of interest is that other recent OCT studies found no differences in choroidal thickness between patients with SSDs and healthy controls [48–50]. A previous OCT-A study in SSDs found the most prominent differences for patients with early disease [24], whereas another study found no differences between first-episode and multi-episode

Table 2 Descriptive statistics and estimates for the retinal measures (oculus uterque)

	SSD		Ctrl		Estimate [95% CI]	*n*	*p*	*p* (FDR adj.)	
	Mean	SD	Mean	SD					
OCT measurements									
MT, central subfield (µm)	260.27	23.71	265.75	18.11	−4.3611 [−12.2245, 3.5023]	263	0.2792	0.4307	*ns*
MT, inner inferior subfield (µm)	317.33	17.62	325.47	14.79	−8.8016 [−15.6197, −1.9835]	263	0.0127	0.0297	*
MT, inner superior subfield (µm)	320.30	17.81	329.94	15.07	−11.1310 [−18.4817, −3.7803]	263	0.0036	0.0149	*
MT, inner nasal subfield (µm)	323.04	19.25	331.35	15.44	−10.2115 [−17.2475, −3.1754]	263	0.0052	0.0165	*
MT, inner temporal subfield (µm)	307.82	17.49	316.07	15.27	−8.7382 [−15.8902, −1.5862]	263	0.0181	0.0408	*
mRNFL thickness (µm)	32.98	3.34	34.39	3.29	−2.4031 [−3.7762, −1.0300]	263	0.0008	0.0079	*
mGCIPL thickness (µm)	80.17	6.90	84.66	4.75	−4.4632 [−6.9520, −1.9743]	263	0.0006	0.0079	*
pRNFL thickness, mean (µm)	90.44	8.66	94.71	8.08	−4.7171 [−8.1356, −1.2987]	256	0.0078	0.0211	*
pRNFL thickness, inferior (µm)	117.12	15.28	122.06	15.24	−2.4275 [−8.2082, 3.3533]	256	0.4120	0.5412	*ns*
pRNFL thickness, superior (µm)	113.33	14.85	119.86	15.35	−8.5430 [−14.5390, −2.5471]	256	0.0060	0.0180	*
pRNFL thickness, nasal (µm)	67.84	10.81	69.59	11.14	−3.6164 [−8.6257, 1.3928]	256	0.1595	0.3076	*ns*
pRNFL thickness, temporal (µm)	63.46	9.86	67.43	10.92	−2.6159 [−7.0151, 1.7833]	256	0.2460	0.4151	*ns*
OCT-A measurements									
FAZ area (mm^2)	0.22	0.10	0.21	0.08	0.0289 [−0.0227, 0.0806]	220	0.2743	0.4307	*ns*
Perfusion density, central (mm^2/mm^2)	0.20	0.08	0.21	0.07	0.0014 [−0.0258, 0.0285]	231	0.9211	0.9565	*ns*
Perfusion density, inner ring (mm^2/mm^2)	0.40	0.05	0.41	0.04	−0.0047 [−0.0202, 0.0107]	231	0.5487	0.6584	*ns*
Vessel density, central (mm/mm^2)	8.82	3.22	9.33	3.18	0.0671 [−1.0992, 1.2333]	231	0.9104	0.9565	*ns*
Vessel density, inner ring (mm/mm^2)	16.73	2.01	17.07	1.71	−0.2402 [−0.8438, 0.3634]	231	0.4364	0.5481	*ns*
Perfusion density, peripapillary (mm^2/mm^2)	0.45	0.01	0.45	0.01	0.0023 [−0.0033, 0.0079]	231	0.4210	0.5412	*ns*

Ctrl healthy controls; *FAZ* foveal avascular zone; *mGCIPL* macular ganglion cell–inner plexiform layer; *mRNFL* macular retinal nerve fiber layer; *MT* macular thickness; *n* number of eyes (SSDs and Ctrl); *ns* not significant; *p*, *p* value; *p* (FDR adj.), false discovery rate adjusted *p* value; *pRNFL* peripapillary retinal nerve fiber layer; *SD* standard deviation; *SSD* schizophrenia spectrum disorder. $*p < 0.05$

patients [25]. Importantly, the patients in our study, which could not reveal any SSD-driven alterations of the retinal microvasculature, were mostly chronically ill.

Despite some technical limitations of our OCT-A investigation, we included only high-quality scans in our study and were able to draw on a large and well-powered data set. Our negative results challenge the positive findings of previous studies that investigated retinal microvasculature in SSDs by OCT-A.

Effects of systemic diseases, smoking, or obesity [13] and neuroinflammatory processes [25] have been postulated as possible etiologies of retinal alterations in SSDs. Importantly, our finding of retinal thinning was robust even after controlling for various covariates including cardiovascular risk factors and, moreover, was not associated with altered retinal microvasculature. Thus, we presume that the retinal thinning observed in our SSDs cohort was most likely not due to comorbid somatic conditions or microvascular changes.

In contrast to previous findings of pronounced disturbances in the retinal photoreceptor complex in SSDs [15], we found no between-group differences for the central foveal field, the region with the highest cone density, where the inner retinal layers are almost absent [51]. Considering the observed simultaneous thinning of mGCIPL and mRNFL in the parafoveal area, we suspect an underlying process in the inner retinal layers that may involve retinal ganglion cells, synapse formation and neuropil of bipolar cells and retinal ganglion cells, amacrine cells and associated synapses, and horizontal cells [52, 53].

Overall, the effect of SSDs on retinal thickness parameters in our study was rather small (e.g., about 3% reduction in parafoveal MT) but comparable to the 2% reduction in brain volume found in imaging studies [1]. A recent preliminary study indicated an association between outer nuclear layer thinning and smaller total brain and white matter volume and cognitive dysfunction in psychosis probands [12]. However, in the field of retinal investigations in mental illness, there is still a lack of evidence that could reveal, at least in part, the mechanisms underlying the observed retinal alterations. Importantly, also the present study covered only retinal parameters, and it could neither address mechanistical questions nor investigate whether retinal changes are related to altered brain structure or function. Moreover, whether the observed retinal thinning is caused by anterograde or retrograde processes [54] could not be demonstrated in this or previous studies.

Interestingly, our exploratory post hoc analyses revealed a significant association of longer duration of illness with reduced MT measures, although we controlled for multiple covariates, including age. This finding adds to a growing body of evidence suggesting an association between the duration of illness and the extent of retinal changes in SSDs [16]. Alizadeh et al. found that a longer duration of illness was negatively associated with several retinal thickness measures in men with chronic SSDs, whereas in acute psychotic stages, a longer duration of illness was associated with higher thickness measures [55]. They suggested that retinal alterations in chronic SSDs could be due to both an acceleration of neurodegeneration and failed neuroregeneration [55].

However, medication effects on retinal structures cannot be ruled out. Further post hoc analyses indicated that higher CPZeq might be associated with reduced parafoveal MT and mRNFL thickness. Importantly, the results of these exploratory analyses were not adjusted for multiple testing and thus must be interpreted with caution; however, an impact of medication on retinal thickness seems plausible, because retinal cells widely express dopamine receptors [56–58] and retinal disturbances are a known adverse effect of some antipsychotics [13, 59]. Nevertheless, higher doses of medication could also reflect more severe disease courses. Of note, neither duration of illness nor medication was associated with pRNFL or mGCIPL thickness, suggesting that even if medication contributes to retinal thinning in SSDs, other factors including disease-specific pathophysiological mechanisms could be involved.

Subsequent analyses showed that a history of treatment with clozapine (lifetime) was significantly associated with lower mean pRNFL thickness but with none of the other parameters studied. Previous or current treatment with clozapine was considered a proxy for treatment resistance, as clozapine is the recommended first-line treatment for treatment-resistant schizophrenia [60, 61]. Whether treatment-resistant SSDs may be characterized by greater pRNFL thinning could be addressed in further studies. Importantly, it is hardly possible to distinguish between medication and disease effects with our cross-sectional study design. Thus, the potential mediator effect of antipsychotic medication needs to be addressed in larger and longitudinal studies with substantial numbers of treatment-naïve first-episode patients.

One important limitation of our OCT investigation is that we used the automated layer segmentation provided by the software of our OCT device, so we were not able to specifically examine the outer retinal layers. Thus, large-scale studies involving the segmentation of all retinal layers would be desirable for future research. Moreover, the number of participants with certain comorbidities such as diabetes was limited. In addition to that, diabetes and hypertension may be underdiagnosed in patients with schizophrenia [13]. Since our study relied on self-report and medical records to assess somatic comorbidities, we may have underestimated the impact of cardiometabolic risk factors on retinal structures. Furthermore, a multivariate analysis does not exclude potential effects of unmeasured confounders, such as chronic stress and various environmental risk factors [62], which could both increase the risk of developing psychosis and could have effects on retinal cells.

Finally, given the exploratory nature of our study, further well-designed studies including studies with a longitudinal design are warranted to replicate our findings and to elucidate the relationship between retina, brain, and clinical parameters in SSDs. Thus, for example replication studies in larger cohorts that systematically measure potential covariates and studies with non-affected relatives of patients with SSDs could be useful to reliably distinguish the effects of confounding environmental factors from directly SSD-driven effects.

Our study provides new evidence for thinning of retinal structures in SSDs. However, the causal mechanisms underlying this association remain to be determined. We suggest that a deeper understanding of the alterations in retinal cytoarchitecture could provide another piece of the puzzle for understanding the pathophysiology of SSDs and that the cost-effective, easy-to-perform method of OCT holds great potential for application in future clinical research.

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Author contributions DK, EW, and FJR designed and conceptualized the Clinical Deep Phenotyping Study. EB, BS, CK, EW, and FJR designed this study and wrote the protocol. EB, EW, GI, IJ, KH, and LS recruited patients and collected study data. EW trained staff on diagnostic and clinical assessments. Eye examinations were performed by EB and BS under the supervision of CK and SP. Statistical analyses were performed by EB with the support of MS and FJR. Data visualization was performed by EB and FJR. EB, EW, and FJR wrote the first draft of the manuscript. AH, BS, CK, JM, LS, LL, MC, MS, and OP provided critical review. EB and FJR prepared the final manuscript version with the help of all authors.

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Data availability The de-identified individual participant data of this study will be made available upon publication in the Zenodo repository at https://doi.org/10.5281/zenodo.5813675.

Declarations

Conflict of interest The authors declare that they have no biomedical financial interests or potential conflicts of interest regarding the content of this report. BS received speaker fees by Novartis Pharma GmbH. AH received paid speakership by Janssen, Otsuka, Lundbeck, and Recordati and was member of advisory boards of these companies and Rovi. PF received paid speakership by Boehringer-Ingelheim, Janssen, Otsuka, Lundbeck, Recordati, and Richter and was member of advisory boards of these companies and Rovi. SP received previous speaker fees and/or travel expenses from Novartis Pharma GmbH, Oertli AG, Bayer AG, Alcon Pharma GmbH, and Pharm-Allergan GmbH. CK received previous speaker fees from Bayer AG and received grants from Zeiss Meditech outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

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Curriculum vitae

Professional experience

Since 04/2023 –	Resident physician, Department of Neurology, Schön Klinik, Bad Aibling, Germany
Since 10/2020 –	Lab for Neurobiology of Psychoses, LMU Munich. Program: Else Kröner-Fresenius Forschungskolleg „Translationale Psychiatrie“. Research group leader Prof. Dr. med. Andrea Schmitt
Since 06/2019 –	Resident physician, Department of Psychiatry, LMU Munich Germany, MD/PhD Program, IMPRS-TP
02/2017 – 05/2019	Resident physician, Center for Neuropathology and Prion Research, (ZNP) Munich
	Medical approbation/License to practice, The Bavarian State Medical Association (BLÄK) (2017)
09/2016 – 12/2016	Internship as a resident physician, Institute of Neuropathology, University Hospital Zurich, Switzerland
09/2015 – 06/2016	Resident physician, Department of Psychiatry Solothurn, Switzerland (s. SIWF-Certificate)

Teaching experiences

	Academic teaching experiences in the field of Neuropathology and Psychiatry

Training and qualifications

2009 – 2015	University undergraduate doctoral, General Medicine (MUDr./M.D.), Faculty of Medicine, Comenius University in Bratislava, Bratislava, Slovak Republic, EU; degree/diploma verified by: Ministry of Health of the Slovak Republic
	Diploma thesis: *Novel Pharmacological Approaches to Hyper-tensive Heart Treatment*
2013 – 2014	**Clinical internships and experiences:**
07/2014	Internal Medicine – Gynaecology and Obstetrics, Regional Hospital Horn – Allentsteig, Horn, Teaching Hospital of the Medical University of Vienna and the Medical University of Graz, Austria; position: student (compulsory practice during the study at the Faculty of Medicine, Comenius University in Bratislava) Lions Austria Program “Medical

	Students Beyond Frontiers" (Em. Univ. Prof. Dr. med. Herbert Ehringer, Lions Club Wien – Europa)
10/2013 – 3/2014	General Medicine, Faculté de Médecine, Université Paris-Sud, Hôpital Bicêtre, Hôpitaux Universitaires Paris-Sud (Internal Medicine and Clinical Immunology, Nephrology, Infectious and Tropical Diseases, Ophthalmology, Gynaecology/Obstetrics, Surgery, Orthopaedics and Traumatology), Paris, France; position: student of international exchange program for higher education of the European Union (European Region Action Scheme for the Mobility of University Students, ERASMUS)
08/2013	Internal Medicine / Cardiology, MediClin Specialistic Clinic Rhein/Ruhr, Essen, Germany; position: student (compulsory practice during the study at the Faculty of Medicine, Comenius University in Bratislava)
2005 – 2009	High School, Vavrinec Benedikt Nedožerský, Prievidza, Slovak Republic

Research (diploma) thesis at the Faculty of Medicine, Comenius University in Bratislava

2012 – 2015	*Remodelling of the aorta in experimental models of L-NAME and 24- hour illumination induced hypertension* (with active participation in scientific conferences)