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List of contents

List of figures

List of tables

List of abbreviations

AKT-1	serine-threonine protein kinase
CHR	clinical high-risk for psychosis
CIP	cannabis-induced psychosis study
COMT	catechol-O-methyltransferase
DRD2	dopamine receptor D2
DSM	The Diagnostic and Statistical Manual of Mental Disorders
Gig-ICA	group-information guided independent component analysis
GMV	grey matter volume
ICD	International Classification of Disorders
ML	machine learning
PRONIA	Personalized Prognostic Tools for Early Recognition
ROP	recent-onset psychosis
SBM	source-based morphometry
SCZ	schizophrenia
sMRI	structural magnetic resonance imaging

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1. Abstract

Cannabis use is among the most important environmental risk factors for developing a psychotic disorder, i.e., one of the most burdensome mental disorders worldwide, and a poor long-term clinical outcome. However, inter-individual differences exist in the reaction to harmful effects of the substance, with 0.4 %- 22.1 % of the general population varying across countries consuming cannabis but only a small fraction of individuals developing psychotic symptoms (~1.0 %). Besides genetic predisposition and additive effects of several harmful environmental exposures, specific patterns of cannabis use have been associated with more severe harmful effects, such as an initiation of cannabis use during critical periods of brain development (e.g., adolescence) and continued use after the first episode of psychosis or first attenuated psychotic symptoms. Given current legalization or de-criminalization of cannabis use in several countries across the world, the investigation of specifically harmful use patterns and underlying biological mechanisms ('cannabis use initiation age' - paper I) and the identification of individuals at particular risk for harmful use ('continued cannabis use' - paper II) gain relevance. As cannabis use is a modifiable risk factor for psychosis, in-depth research on patterns of consumption, along with preventive efforts and information via public health campaigns is further emphasized.

In our first study, we found structural abnormal brain development in a cerebellar network associated with an earlier consumption of cannabis in individuals at particularly high risk for experiencing harmful effects of the substance, i.e., individuals with recent-onset psychosis (ROP) with concurrent clinically meaningful cannabis use. Specifically, earlier initiation of cannabis use was associated with higher grey matter volume in the cerebellar network, an abnormal brain pattern which has previously been associated with psychosis. Further, earlier initiation of cannabis use was associated with more severe positive psychotic symptoms, i.e., more severe hallucinations and/or delusions. These findings highlight the risk of cannabis use initiation during adolescence and link them with possible interference with typical brain development.

To identify individuals at elevated risk for cannabis use during known critical periods for the harmful effects of the substance, such as after experiencing the first episode of psychosis or individuals at clinical high-risk for developing psychosis (CHR), we further aimed at developing a generalizable predictor of continued cannabis use. Our machine

learning model correctly classified 73% of ROP and 59% of CHR individuals as continued or discontinued users based on clinical information, such as substance use patterns and lower global functioning. Providing a test of the generalisable power for prediction of continued cannabis use in patients in the early stages of psychosis and CHR, our model might pave the way for further improvements in prevention approaches.

This thesis emphasizes the importance of specific cannabis use patterns for psychosis risk trajectories. Targeting specifically harmful cannabis use characteristics, such as the consumption of the substance during critical periods of brain development or after symptom onset might be an important focus of preventive efforts within mental health campaigns. The predictive model developed in our study might represent a first effort in this direction and shall be further tested in larger and more diverse clinical populations.

2. Zusammenfassung

Der Konsum von Cannabis ist einer der wichtigsten Risikofaktoren sowohl für die Entwicklung einer Psychose als auch für einen schlechten langfristigen klinischen Verlauf in Bezug auf psychotische Symptomatik, Rückfallquote und Re-hospitalisierung. Allerdings bestehen große interindividuelle Unterschiede in der Reaktion auf schädliche Wirkungen der Substanz. Je nach Region konsumieren 0.4 % - 22.1 % der Bevölkerung Cannabis, aber nur ein kleiner Anteil der Konsument*innen entwickelt letztlich psychotische Symptome (~1.0 %). Neben einer genetischen Veranlagung und der kombinierten Wirkung mehrerer schädlicher Umweltbelastungen wurden bestimmte Muster des Cannabiskonsums mit schwerwiegenderen schädlichen Auswirkungen in Verbindung gebracht. Zum Beispiel wird der Beginn des Cannabiskonsums während kritischer Phasen der Gehirnentwicklung als besonders schädlich angesehen. Auch ein fortgesetzter Konsum nach einer psychotischen Episode oder nach dem Einsetzen erster psychotischer Risikosymptome ist nachweislich mit besonders schädlichen Auswirkungen von Cannabis assoziiert. In Anbetracht aktueller Legalisierung oder De-kriminalisierung des Cannabiskonsums in mehreren Ländern ist die Untersuchung von schädlichen Konsummustern und deren zugrunde liegenden biologischen Mechanismen („Cannabis-Einstiegsalter“ - Papier I) sowie die Identifizierung von Personen mit besonderem Risiko für einen schädlichen Konsum („Prädiktion der Fortsetzung des Cannabiskonsums“ – Papier II) von besonderer Relevanz. Anders als die Prädisposition für psychische Erkrankungen oder manche Umwelteinflüsse wie Kindheitstraumata kann der Cannabiskonsum prinzipiell von jedem Individuum selbst beeinflusst werden. Dies hebt die Notwendigkeit der Aufklärung durch öffentliche Gesundheitskampagnen hervor, die durch die Wissenschaft unterstützt werden können indem als besonders schädlich betrachtete Konsummuster aufgezeigt werden und bestenfalls auch die zugrundeliegenden biologischen Wirkmechanismen erklärt werden können. Hierfür untersuchten wir ob strukturelle Hirnanomalien mit einem frühen Beginn des Cannabiskonsums in Personen mit besonderem Risiko einhergehen. Personen mit besonderem Risiko für die schädliche Wirkung von Cannabis waren definiert als Personen mit Psychose, die gleichzeitig einen klinisch bedeutsamen Cannabiskonsum berichten. Unsere Untersuchung ergab, dass ein früherer Beginn des Cannabiskonsums war mit vermehrter grauer Substanz im Kleinhirnnetzwerk assoziiert. Frühere Studien hatten vermehrte graue Substanz in diesem Gehirnnetzwerk mit Psychose in Verbindung gebracht. Darüber hinaus war ein früherer Beginn des Cannabiskonsums mit schwereren positiven psychotischen Symptomen verbunden. Diese Ergebnisse

unterstreichen das Risiko des Cannabiskonsums während der Adoleszenz und bringen sie mit einer möglichen Beeinträchtigung der typischen Gehirnentwicklung in Verbindung.

Um Personen mit erhöhtem Risiko für Cannabiskonsum während bekannter kritischer Phasen zu identifizieren (hier nach Erleben einer ersten Episode einer Psychose oder nach ersten Hochrisikosymptomen für die Entwicklung einer Psychose), zielten wir ferner darauf ab, einen verallgemeinerbaren Prädiktor für den fortgesetzten Cannabiskonsum zu entwickeln. Dreiundsiebzig % der Personen mit Psychose und 59 % der Personen mit klinischen Hochrisiko wurden korrekt entweder als fortgesetzte*r oder abstinente*r Nutzer*innen klassifiziert. Neben spezifischen Substanzkonsummustern war vor allem ein niedriges allgemeines Funktionsniveau prädiktiv für einen fortgesetzten Cannabiskonsum. Auch wenn diese Prädiktoren vorerst in diversen klinischen Populationen getestet werden müssen, könnten sie den Weg für weitere Verbesserungen der Vorhersage des fortgesetzten Cannabiskonsums ebnen.

Zusammengenommen unterstreichen unsere Ergebnisse die Bedeutung bestimmter Cannabiskonsummuster für das Risiko einer Psychose. Insbesondere der Konsum in kritischen Phasen der Gehirnentwicklung oder nach Symptombeginn könnte ein Schwerpunkt präventiver Bemühungen sein. Öffentliche Gesundheitskampagnen könnten in der Zukunft versuchen vor allem die Personen zu adressieren, die ein besonders hohes Risiko haben trotz nachgewiesener schädlicher Effekte weiterhin Cannabis zu konsumieren. Das in unserer Studie entwickelte Vorhersagemodell könnte einen ersten Versuch in diese Richtung darstellen und soll in größeren und vielfältigeren klinischen Populationen weiter getestet werden.

3. Contribution to publications

Both studies presented in this thesis were carried out on two combined patient samples including individuals recruited within the multi-site longitudinal Personalized Prognostic Tools for Early Recognition (PRONIA) study (www.pronia.eu) and the longitudinal 'Cannabis-induced psychosis' (CIP) study. I was the main recruiter of the CIP study (recruitment of N ~ 50 patients with cannabis-associated recent-onset psychosis) and contributed to the recruitment of the PRONIA study (N ~ 33 participants). This task involved carrying out differential diagnostics, exhaustive clinical assessments, neurocognitive, and magnetic resonance imaging assessments as well as controlling the quality of all data domains. Further, I supervised other colleagues in all these tasks. Additionally, I was responsible for the longitudinal assessments, thus, to re-contact participants and repeat assessments over a period of up to nine months and up to 36 months in intervals of three months-contacts for the CIP and PRONIA study, respectively. Besides, I was responsible for the advertisement of the CIP study and its study-organisation.

3.1 Contribution to Paper I

This publication focuses on the impact of early cannabis consumption in patients particularly at risk for the substances' harmful effects. I was in charge of an exhaustive literature search on the topic, developed the main research idea as well as the methodological strategy and I performed all analyses independently under supervision. More specifically, in order to perform literature-informed neuroimaging analyses, I implemented a group-information guided independent component analysis (see Chapter 4.3.1). I established a fruitful collaboration with Prof. Vince Calhoun, director of the Translational Research in Neuroimaging and Data Science, so that I could implement some key results of one of his previous studies in my methods. I autonomously wrote the manuscript, created figures and performed extensive supplemental analyses during the revision process, with support from co-authors. Along with the manuscript I have published our final components of interest for replicability (https://github.com/nora6591/thc_initiationage_psychosis) and I maintain this webpage.

3.2 Contribution to Paper II

This publication focuses on the prediction of continued cannabis use in patients with recent-onset psychosis and individuals at clinical high-risk for psychosis. Based on exhaustive literature review on the topic and on the relevant methodological approaches I developed the research idea and the main methodological strategy. My supervisors encouraged me to include additional data modalities, namely neuropsychological cognitive tests and structural magnetic resonance imaging. After defining the labels ('continued cannabis use' and 'discontinued cannabis use') based on thorough investigation of all follow-up visits, I generated a robust machine learning pipeline using the publicly available toolbox NeuroMiner (www.neurominer.de) developed by my supervisor, Prof. Dr. Nikolaos Koutsouleris. Due to our finding that one grey matter volume network (cerebellar component) was affected in recent-onset psychosis by a specific pattern of cannabis use ('early initiation of cannabis use'), I implemented the group-information guided independent component analysis in the pre-existing NeuroMiner-toolbox. This step was critical, as only the algorithm's implementation in a robust cross-validation assures a strict separation between training and testing phases. Again, I autonomously wrote the manuscript, created figures and performed extensive supplemental analyses during the revision process, with support from co-authors.

4. Introduction

4.1 Psychotic disorders

Psychotic disorders constitute a subset of mental illnesses characterized by various combinations of delusional, hallucinatory, negative, and disorganization symptoms, as well as functional impairment [1,2]. According to diagnostic manuals commonly used in clinical and research contexts (e.g., The Diagnostic and Statistical Manual of Mental Disorders [DSM [2]] and the International Classification of Disorders [ICD [3]]) psychotic disorders are differently classified based on the presence or absence of affective symptoms, the severity and duration of the episode, and the potential influence of substances on symptom onset [4]. Here, schizophrenia (SCZ) remarks the poor outcome category [5] with persisting symptoms for at least one or six months defined by the ICD-11 [3] and DSM-V [2], respectively.

The lifetime prevalence for psychotic disorders pooled across populations is about 0.8 %, but the reported prevalence varies depending on the reference sample, diagnostic criteria, and calculation method [6]. Despite its relatively low prevalence, the Global Burden of Disease study lists SCZ in the top ten causes of disability worldwide [7]. The consequences of the disorder are multifaceted [8], affecting the individuals directly, as well as relatives [9] and society [8,10]. Because of the typical disorder onset during early adulthood and the high rate of poor long-term outcomes, individuals with psychosis suffer many years of disability [11]. Further, psychosis reduces life expectancy by about 10-20 years [8,12], partly explained by high rates of suicide [13] and (secondary) cardiovascular diseases [14,15]. Besides the direct burden from symptoms, individuals with psychosis are frequently diagnosed with comorbidities [16,17], have a lower income [10], higher unemployment rates [18], and a poorer global and social functioning [19] compared with healthy individuals. In addition, both individuals with psychosis and their relatives experience stigma [9,20], whereas societal burden is mainly driven by economic costs [8,21]. Indeed, among mental illnesses, psychotic disorders cause the highest cost of care per patient [8].

So far, no curative treatment exists [22] and clinical trajectories and treatment responses vary greatly between individuals [23,24], with about 30 % of individuals experiencing persistent symptoms following a first episode of psychosis [24].

4.1.1 Early recognition of psychosis

Not only do about 30 % of individuals with psychosis have a poor long-term prognosis, but already a first (single) psychotic episode is accompanied by devastating effects for the individual and their relatives, especially in case of a long duration of untreated psychosis [25]. Thus, research over the past three decades increasingly shifted to early recognition and prevention of the disorder. By now the disorder's early stages and the so-called clinical high-risk (CHR) state for psychosis have become pivotal parts of research. The CHR state is commonly described by attenuated psychotic symptoms [26,27], basic symptoms i.e., self-experienced disturbances of cognition, perception and mood [28] and genetic liability accompanied by recent drop in functioning. In 1960, Huber and Gross [29] first formally described symptoms that commonly precede the onset of full-blown psychosis [30]. Then, in the 1980s the first studies investigated CHR individuals prospectively [29]. While earlier evidence pointed to a relatively good specificity of the recognition scales used for detecting transition to psychosis in at-risk individuals [26–28], transition rates declined across studies over the years [31]. At present, the transition rate in CHR detected using solely the diagnostic risk criteria is relatively low, with only about 25 % of individuals developing a full-blown psychosis within three years after baseline assessment [32]. To improve early detection of psychosis, more holistic models have been developed based on symptoms, cognitive abnormalities, and biological measures such as genetics and brain imaging [33–37]. Meta-analytic evidence highlights the relatively good performance of prognostic models (~67% specificity, [31]), nevertheless, the CHR field still remains very heterogeneous and models have still not been able to be implemented in clinical daily practice, mainly because of lack of generalizability and methodological issues [31,36].

4.1.2 Aetiology of psychosis

In order to develop reliable and generalizable predictive models, a clearer understanding of the underlying mechanisms and risk factors for psychosis seems critical. At the beginning of the last century, family studies pointed to a crucial role of genetics in SCZ risk, with heritability estimates of about 70-85 % [38,39]. However, a large gap exists between individual genetic liability for SCZ estimated based on twin studies versus genome-wide genotyping that explains just about 20% by the additive risk of the variance [40]. Until today the aetiology of psychosis remains largely unknown, and no single cause has been

pinpointed. Moreover, heterogeneous clinical presentation and outcome trajectories render different aetiologies likely.

Epidemiological studies have consistently linked several environmental exposures [41–43] with the development of psychotic disorders (see Figure 1 for some of the most important environmental risks factors). Rarely do risk factors occur in isolation, thus individuals are usually exposed to more than one risk factor. Environmental risk factors can be divided based on their occurrence in life with vulnerable windows during neurodevelopment [40]. For example, an early life factor would be the season of birth [40], whereas maltreatment is a typical harmful exposure during childhood [43]. Other risk factors such as cannabis or tobacco use are most commonly initiated during adolescence, even though some individuals might also initiate the consumption earlier or later [40]. Most risk factors do not only occur in a particular time window. Instead, the exposure might either last for a longer time (e.g., urban residence, low socioeconomic status) or could occur at several time points in life (e.g., migration).

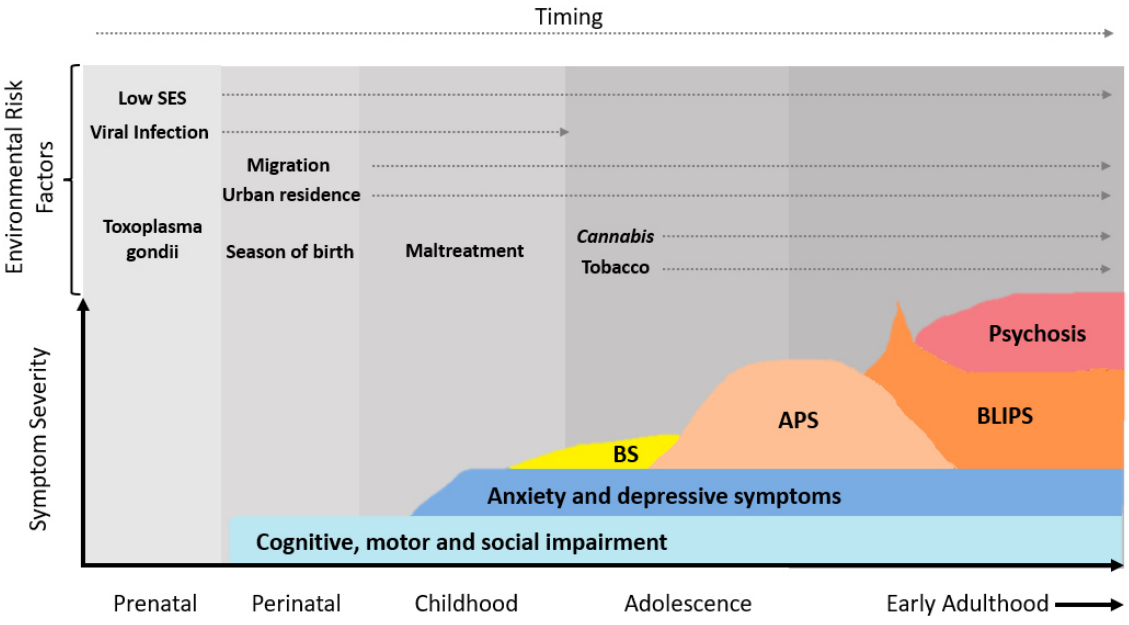

Figure 1: Environmental risk factors associated with psychosis risk trajectories.Figure adapted from [30,40,44]: Already years before the onset of a first episode of full-blown psychosis the occurrence of first only self-experienced and later attenuated psychotic symptoms have been reported by most psychotic patients. Psychosis as well as pre-clinical symptoms have consistently been linked with several environmental risk factors and genetic risk. Those risk factors might co-occur and together increase the likelihood for an outburst of full-blown psychosis. Abbreviations: BS=basic symptoms, APS=attenuated psychotic symptoms, BLIPS=brief limited intermittent psychotic symptoms.

By now, the most empirically supported model of the aetiology of psychosis highlights the importance of genetics, environmental risk factors, and their complex interplay [1,40,41,44,45]. In the current work, we focus on one specific environmental risk factor, namely cannabis use, that has shown robust links with psychosis [40,42,45]. Contrary to other risk factors, such as genetic risk or maltreatment, cannabis use is one of the most apparent *modifiable* risk factors [45,46]. Furthermore, recent debates about the legalization of cannabis use highlight the timely importance of investigating this risk factor as preventative efforts and public health information are particularly warranted [47,48].

4.2 Cannabis use: a risk factor for psychosis

Although earlier research [49] pointed out the causal effects of cannabis use on the development of psychosis, the predominant public opinion allocated low harm to the use of cannabis for several years after. While for about 15 years no research group has attempted to replicate the findings from Andréasson et al. (1987) [49], by now, multifaceted research suggests a pivotal role of cannabis in psychosis risk [50] (see Table 1 for an overview).

Table 1: Evidence linking cannabis use and risk for psychosis

	Cumulative evidence supports a crucial role of cannabis use in psychosis risk trajectories
1	Epidemiological studies support causal effects of cannabis use on psychosis risk (reviewed in [51])
2	Higher rates of cannabis users among patients with psychosis compared to the general population [52–54]
3	Cannabis-induced transient symptoms can be induced in controlled experimental design [55–57]
4	National states with more liberal cannabis laws have higher odds of hospital discharge due to cannabis associated psychosis [58]
5	Dose-dependent effect of cannabis use on psychosis risk [42,51,59–61]
6	Earlier age of onset of psychosis among cannabis users compared with non-users [62]
7	Negative impact of cannabis use on the long-term clinical outcome in individuals with psychosis [63–65]

Several longitudinal studies point to the importance of cannabis in psychosis risk trajectories [66]. Further, rates of cannabis users among psychotic patients are significantly higher compared to the general public [52,53]. For example, Di Forti et al. (2009) [54] estimated

that patients with a first episode of psychosis were about six-times more likely to consume cannabis daily compared with healthy controls at time of assessment. For a long time, the "self-medication" hypothesis, stating that individuals might consume cannabis in an attempt to reduce (attenuated) symptoms, would have questioned the meaning of this observation. However, by now, little evidence supports this hypothesis [50], whereas several studies favour a causal effect of cannabis on symptom development [56,67]. Indeed, in studies with a controlled experimental design, cannabis-induced transient symptoms resembled psychotic symptoms [55,57]. Currently, changes in legalization of recreational cannabis use in several states of the United States allowed a comparison of hospital discharges due to cannabis associated psychosis across different cannabis legality. The division with most liberal cannabis laws had significantly higher odds of hospital discharge due to cannabis associated psychosis compared with other division [58]. Conclusive evidence emphasizes a dose-dependent association between cannabis use and psychosis risk [42,51,59–61]. Regular cannabis users also experience their first psychotic episodes at an earlier age (about three years earlier) compared to abstinent patients [62]. However, it remains unknown whether a single occasion of cannabis use already elevates psychotic risk [61] or whether only heavy consumption elevates the risk [51]. Besides elevating the risk for an outburst of the first episode of psychosis, cannabis use negatively impacts the long-term clinical outcome of psychosis, especially if continuously consumed [63,68]. Along with this notion, 30 % of patients diagnosed with a first episode of primary psychosis develop SCZ, whereas 50 % of patients with cannabis-induced psychosis develop SCZ [65].

4.2.1 Inter-individual differences for the harmful effects of cannabis use

Notably, cannabis is the most commonly used illicit substance with varying prevalence rates across the world. In the age group of 15-34 years cannabis use in the last year was reported in 0.4 % - 22.1 % ranging significantly across countries [69]. However, only a small fraction of all consumers develops psychosis. This suggests that individuals react differently to the harmful effects of cannabis [70]. In support of a various vulnerability theory, inter-individual differences to the effects of cannabis arose in an experimental condition. Cannabis-intoxication increased psychotic experiences more severely in individuals with a psychosis than in healthy individuals [56]. Probably, complex interactions with genetic and environmental risk factors explain some of the variance in the vulnerability to the harmful effects [40,70,71].

Most studies on the interaction of genetic liability and cannabis use have investigated the genotypes of the serine-threonine protein kinase (AKT1) gene or the Catechol-O-Methyltransferase (COMT). Consistently, the C/C AKT1 genotype was associated with more severe effects of cannabis use on psychotic outcomes [72–74], whereas studies on COMT genotype yielded conflicting findings with carrying Val allele increasing likelihood of psychotic symptoms [75], and no interaction effect [76,77]. Recently, further genes have started to be investigated, such as the dopamine receptor D2 (DRD2) gene. Here, the interaction of using cannabis and carrying a DRD2, rs1076560, T allele increases the risk to develop psychosis three-fold for unregular users and five-fold in daily users [78]. Attempts to find new candidate genes for gene-environment interactions in a systematic manner are currently ongoing in the genome-wide environment interaction study [79–81].

Besides various genetic liability, the exposure to other environmental risk factors might explain some variability in the harmful effects of cannabis use. Instead of separately increasing the risk for psychotic disorders, different environmental risk factors might cumulate their negative effect [1,71,82–84].

Regardless of additional risk factors, the specific patterns of cannabis consumption seem to play a crucial role in the effect of the substance. As mentioned previously, the effect of cannabis on psychotic outcome follows a dose-response effect, i.e., frequency, duration, and the specific compound crucially contribute to the effect [42,59,60,66,85,86]. Indeed, the use of high-potency cannabis increases the risk to develop a psychotic disorder by an odds ratio of about three compared with individuals who never used the substance [86]. Further, an initiation of cannabis use during vulnerable periods of neurodevelopment, such as adolescence, has been associated with particularly harmful effects [60,87,88]. At the neurotransmitter level, the interaction between endogenous cannabinoids and cannabinoid-receptor type 1 is critically involved in brain development by regulating the release of glutamate [89]. Animal studies have provided evidence that cannabis use in this period may be more harmful due to its effects on the endocannabinoid system, possibly influencing the reorganization of grey and white matter [90]. In our first work (paper I) we focused on this hypothesis by investigating this pattern of use, i.e., the impact of ‘age of cannabis use initiation’ on GMV in individuals with ROP.

Another critical period for the harmful effects of cannabis use is the time during and after experiencing a first episode of psychosis or at-risk symptoms. Notably, changing cannabis use patterns even after a first episode of psychosis impacted the individuals’

long-term clinical outcome in terms of relapse rate, re-hospitalization and symptom severity [64] (see Figure 2).

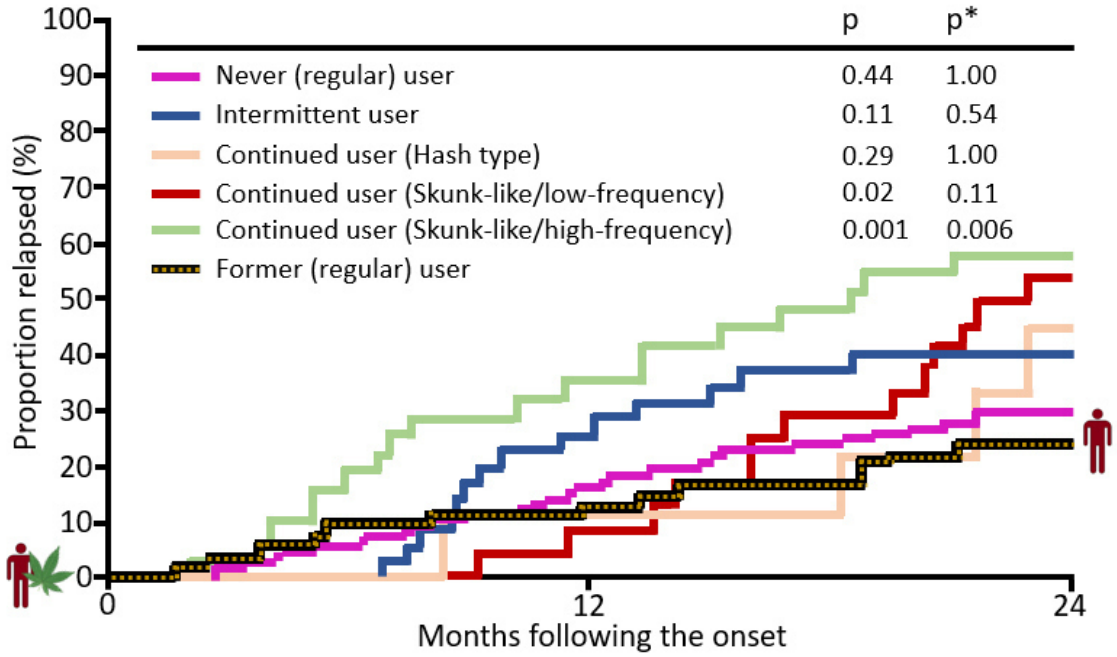

Figure 2: Continued versus discontinued cannabis use after a first episode of psychosis.Figure adapted from Schoeler et al., 2016 [64]. Patients with a first episode of psychosis have been reassessed for two years after first admission to the hospital. Associations between cannabis use patterns and relapse rates were tested with log-rank tests and were found to be significant. The former (regular) users were used as reference group for p-value representation. Notably, individuals with previous regular consumption presented with a comparable long-term outcome in terms of psychotic symptoms with never (regular) users. P* indicates Bonferroni-corrected p-values.

In our second work (paper II) we focused on this particular use pattern 'continued cannabis use' and aimed to build a model able to predict continued cannabis use in a sample of individuals with ROP and CHR individuals.

4.3 Machine learning

Until today studies investigating the effect of specific cannabis use patterns on psychosis risk trajectories and brain structural abnormalities have heavily relied on univariate statistics. While these studies have yielded great progress in understanding the impact of cannabis use on psychosis risk, univariate approaches entail some important limitations: First, approaches based on univariate statistics ignore the highly interconnected nature of the brain as well as the potential interplay of diverse risk factors [40,41,87]. Second, inferences are made only at the group level. Thus, they ignore interindividual differences but future

model implementation in clinical practice requires predictions being made at the single-subject level [31,91]. Last, previous studies using classical univariate statistics lacked a proper generalizability assessment that is a cornerstone of potential model implementation [91]. Machine learning (ML) constitutes a computational strategy able to tackle aforementioned shortcomings and is increasingly used across different fields of medicine [91–93]. ML can find an optimal solution to a given research problem by automatically "learning" underlying patterns in input data. Two main ML categories can be distinguished based on the learning objectives: 1.) Unsupervised techniques, that do not require any given label and algorithms discover unknown statistical configurations in the data, such as in clustering or dimensionality reduction approaches (e.g., source-based morphometry [SBM], chapter 4.3.1). 2.) Supervised techniques that are used to find patterns in data to best predict a 'label' given by the researcher (e.g., functional outcome) (chapter 4.3.2).

In the current work, both unsupervised (SBM, paper I and paper II, chapter 5 and chapter 6) and supervised (paper II, chapter 6) ML techniques are used and thus, shortly explained in this chapter.

4.3.1 Unsupervised machine learning: source-based morphometry

A commonly used univariate approach to invest the impact of cannabis use on brain structure is voxel-based morphometry (VBM). Due to normalization, voxels represent the same spatial location across brains [94,95], which allows a comparison of each voxel with the corresponding voxel across subjects. Depending on the smoothing kernel and resolution, this approach requires up to more than 100.000 comparisons, which challenges multiple comparison correction [96,97], and further it ignores the interconnected nature of the brain. Instead, unsupervised ML techniques utilize information across voxels [97]. In structural magnetic resonance imaging (sMRI) analysis inter-individual differences of GMV between topologically distinct brain regions are used to characterise GMV covariance [98]. Accounting for GMV covariance seems particularly relevant to detect disturbances of brain maturation due to environmental exposure (paper I), as GMV covariance is hypothesized to be in part driven by shared maturational processes [99–101].

SBM uses independent component analysis (ICA) to identify networks of common structural variation that are maximally spatially independent from each other [96,97]. Spatial independence is thought to emerge from underlying different "sources" of signal, such as

different developmental trajectories or noise [97]. Two matrices are the output of this procedure; one matrix represents each individuals loading coefficient; i.e., how the brain network contributes to the individual (a high loading coefficient indicates that the pattern of GMV variation is strongly weighted for the individual), and one matrix represents how the brain networks contribute to each voxel. After network creation, the participants' loadings for the different networks can be associated with, e.g., patient status or symptom severity [96,97,102–104].

Different algorithms have been used to identify independent networks. In our work, we focus on a semi-blind algorithm, thus an algorithm that combines hypothesis-free and hypothesis-driven approaches, namely group-information guided independent component analysis (Gig-ICA) [105,106]. Gig-ICA simultaneously optimizes the independency between components and the closeness to reference components; i.e., we used components of interest derived from a study that has revealed differences in these networks between individuals with SCZ and healthy individuals [102]. Importantly, Gig-ICA benefits from these priors. Here, they assure closeness to components derived from a study performed on a larger sample of the patient group of interest and already corrected for several confounds. Thus, we restricted our analysis to brain networks relevant in the context of psychosis. We have employed SBM in the form of Gig-ICA in both presented works. In paper I, we have associated the age of cannabis use initiation with the participants' loadings on each independent network. In paper II, we implemented the Gig-ICA in our ML pipeline as a dimensionality reduction step. We tested the predictive power of the GMV networks for continued cannabis use in repeated nested cross-validation. This implementation was necessary to verify generalizability, a cornerstone of ML analysis aiming at outcome prediction.

4.3.2 Supervised machine learning

Supervised ML is a promising statistical approach that can predict relevant clinical outcomes at the individual level. Since its introduction in the field of psychiatry, ML has generated several encouraging predictions of diverse clinical outcomes using a range of data modalities [31,35–37,107]. One cornerstone of ML analyses is the generalizability assessment of the predictive models. Cross-validation represents one frequently employed strategy for this aim [91]. By strictly separating the training from the testing phase of the model, all classifiers can be fine-tuned for good generalizability on unseen data, which is required

for ultimate model implementation in clinical practice on new help-seeking individuals. The features (e.g., voxels of an sMRI image, interview-based variables, cognitive variables) are pre-processed during the training phase. Afterward, the applied algorithm (e.g., logistic regression, random forest, support vector machine) *learns* predictive patterns of the features to predict the outcome of interest [91–93]. For this aim different parameters and hyperparameters are tested and the classification results are compared with real labels. Finally, the best performing models are chosen based on a researcher-defined metric such as balanced accuracy (see Figure 3).

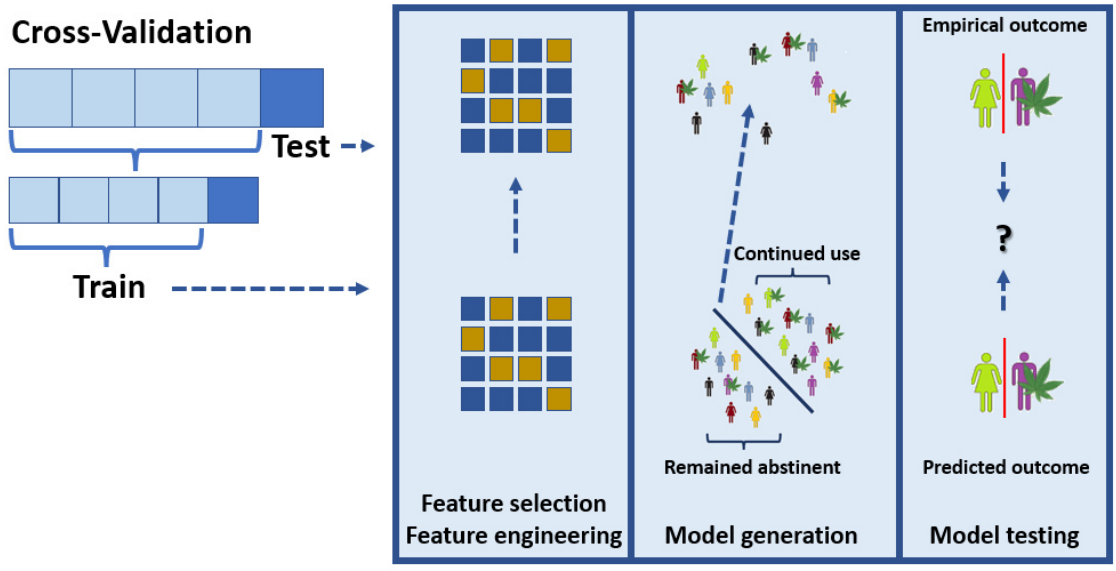

Figure 3: Generalizability assessment in machine learning analysis.Machine learning constitutes a technique that can simulate real-world scenarios in that individuals present in clinical facilities for the first time. By assessing model generalizability in terms of e.g., cross-validation the predictive accuracies are tested in completely unseen datasets. Thereby, it is important that each step of model fitting, such as feature selection, feature engineering and hyperparameter definition is optimized only on the training dataset and then applied without any changes to the testing dataset.

In paper II we employ ML strategies previously successfully integrated in outcome prediction [35,107–109] in the attempt to predict highest risk to continue cannabis use until nine-months follow-up.

4.4 Aim of the thesis

The current thesis aims to invest cannabis use patterns that are associated with particularly harmful effects of the substance. Therefore, we focus on cannabis use during specific time windows of vulnerability such as cannabis use initiation during adolescence

and continued cannabis use after a first episode of psychosis or first high-risk symptoms for psychosis. Preventative efforts targeting individuals with risky cannabis use require deep understanding of underlying (biological) mechanisms for public health campaigns and psychoeducation and further need reliable identification of individuals at highest risk for cannabis use despite known harmful effects for targeted interventions. Given that previous studies mainly investigated specific cannabis use patterns in the general population we addressed our question in a sample of individuals with ROP and CHR accounting for the particular vulnerability to the harmful effects of cannabis use in these populations. Further, the use of ML techniques allowed us to consider the complex multifaceted impact of cannabis use on psychosis risk trajectories.

1.) The main focus of the first paper included in this thesis (paper I) was on understanding underlying (biological) mechanisms for the effect of cannabis use initiation during adolescence on psychosis risk in individuals particularly prone to decremental effects of cannabis, i.e., ROP with concurrent clinically meaningful cannabis use. Here, we tested for associations between cannabis use initiation age and GMV covariance considering several possible confounding factors.

2.) The second study included in this thesis (paper II) aimed to further understand the multidimensional mechanisms contributing to continued cannabis use in individuals with ROP and CHR. Besides cannabis use initiation age and several other environmental risk factors, symptoms and cognition we further investigated the possible impact of potentially abnormal GMV covariance on continued cannabis use. Here, we expanded our research from mere understanding of associations to testing the predictive power of all modalities for generalizing to unseen cases, a pre-condition for model implementation in clinical practice.

5. Paper I: Summary

In the first presented work (paper I) we attempted to characterise underlying GMV abnormalities associated with early initiation of cannabis use in particularly vulnerable individuals for the harmful effects of cannabis use, i.e., individuals with ROP with clinically meaningful cannabis use. For this aim we included N = 102 individuals with ROP from the PRONIA and the CIP study. The two studies used harmonized protocols for all data modalities employed in this study. Age of cannabis use initiation was defined as the self-reported first cannabis use in lifetime. After standard pre-processing of the GMV images we employed Gig-ICA with four reference components [102], which have previously been associated with SCZ and were reproducible across sites. To correct also for study-specific site effects we removed all voxels that were only associated with site based on a map derived from travelling subjects. The participants' loading coefficients of the four structural brain networks that were optimized for closeness to the reference components and independency entered separate linear mixed effects models as independent variables. Cannabis use initiation age and the dummy-coded variable site entered the model as fixed and random effects, respectively. Then, we used a network-based approach to test for associations between the brain networks, cannabis use initiation age, duration of cannabis use, and positive psychotic symptoms. Our result linked long-lasting structural abnormalities manifesting in significantly higher GMV in the cerebellar network with an earlier consumption of cannabis. This network of higher GMV was further associated with lower GMV in the superior-inferior temporal network that has previously shown to be the most severely affected brain structure in SCZ compared with healthy controls. An earlier initiation of cannabis use was also associated with more severe positive psychotic symptoms. Taken together, our findings might be cautiously attributed to an interference of cannabis use with typical brain development when consumed during critical periods and thus emphasizes the importance of further investigations of the effects of cannabis during critical time windows.

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Association between age of cannabis initiation and gray matter covariance networks in recent onset psychosis

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Cannabis use during adolescence is associated with an increased risk of developing psychosis. According to a current hypothesis, this results from detrimental effects of early cannabis use on brain maturation during this vulnerable period. However, studies investigating the interaction between early cannabis use and brain structural alterations hitherto reported inconclusive findings. We investigated effects of age of cannabis initiation on psychosis using data from the multicentric Personalized Prognostic Tools for Early Psychosis Management (PRONIA) and the Cannabis Induced Psychosis (CIP) studies, yielding a total sample of 102 clinically-relevant cannabis users with recent onset psychosis. GM covariance underlies shared maturational processes. Therefore, we performed source-based morphometry analysis with spatial constraints on structural brain networks showing significant alterations in schizophrenia in a previous multisite study, thus testing associations of these networks with the age of cannabis initiation and with confounding factors. Earlier cannabis initiation was associated with more severe positive symptoms in our cohort. Greater gray matter volume (GMV) in the previously identified cerebellar schizophrenia-related network had a significant association with early cannabis use, independent of several possibly confounding factors. Moreover, GMV in the cerebellar network was associated with lower volume in another network previously associated with schizophrenia, comprising the insula, superior temporal, and inferior frontal gyrus. These findings are in line with previous investigations in healthy cannabis users, and suggest that early initiation of cannabis perturbs the developmental trajectory of certain structural brain networks in a manner imparting risk for psychosis later in life.

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INTRODUCTION

Schizophrenia (SZ) is viewed as a neurodevelopmental disorder wherein disruptions in the typical trajectory of brain development interact with environmental factors to precipitate psychosis [1]. In this scenario, adolescence is an important time window for the early identification of risk and timely intervention [2], as the adolescent brain undergoes ongoing maturational processes, which include synaptic pruning [3] and maturation of neurotransmitter systems, including the endogenous cannabinoid system [3]. Exposure to environmental stressors during this critical maturation stage might interfere with the normal developmental trajectory of gray and white matter (GM, WM), thereby increasing the risk for developing SZ [1, 4]. One of the most important environmental risk factors for SZ is heavy cannabis use [5, 6]. Given recent international changes in the legality of cannabis use, the investigation of possible harmful effects of the substance on risk groups assumes a new relevance [7]. Cannabis use is associated with structural GM changes in brain regions

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consistently associated with psychosis [8, 9], including the hippocampus, amygdala, as well as striatal, prefrontal cortical, and cerebellar regions [5, 10]. These GM alterations can be discerned in cannabis-using patients with psychosis [11], prodromal individuals [12] and in healthy individuals who use cannabis regularly [13].

Previous studies indicate that the effect of cannabis on brain structure might be moderated by the age at initiation of heavy use [14]. Healthy cannabis users who had begun to consume cannabis before 16–17 years of age show GM volume (GMV) reductions in the frontal lobe and the parahippocampal gyrus [5, 14, 15] and GMV increases in the cerebellum [13].

Despite this background, other studies of cannabis use in adolescents [16, 17] and retrospective studies investigating the structural-anatomic effects of age of cannabis initiation in adults [18] do not report alterations in GMV. Thus, results focusing on the impact of age of cannabis initiation on brain structure remain inconclusive and focus on the effects of age of initiation in healthy individuals, thereby not considering possible specific effects of the age of cannabis initiation on the earlier trajectory of brain development in psychotic individuals [19]. To date, such studies in psychosis have only investigated the general impact of cannabis use on brain structure. Previous investigations have used univariate approaches, such as region-of-interest analysis or voxel-based morphometry (VBM) [20], thereby neglecting from consideration the highly interconnected nature of the brain [21, 22]. Especially in terms of brain maturation, this interconnectivity plays an important role, since the covariance between brain voxels is thought to reflect shared maturational processes and functional specialization, which might be disrupted in parallel in the face of environmental stressors [23–25]. Multivariate, data-driven approaches such as source-based morphometry (SBM) represent a well-established alternative approach that accommodates the covariance between brain voxels [26, 27]. In SBM, an independent component analysis (ICA) identifies brain networks characterized by covariation in GMV [26, 27]. The approach thus enables the comparison of independent structural brain networks between different groups [26, 27]. By maximizing the independence of isolated brain networks, SBM is a powerful technique for separating scanner noise (e.g., often reported site-effects) from true signals [28], and is thought to unify structural regions that have comparable maturational trajectories. The recently introduced semi-blind ICA algorithms, such as group information guided ICA (GIG-ICA), incorporate prior information in the form of spatial constraints [29, 30], thus exploiting the advantages of data-driven approaches, while focusing the analysis on networks of interest [29].

In the current study, we aimed to investigate the effect of the age of cannabis initiation among patients with recent onset psychosis (ROP) on structural networks that are already reliably associated with SZ and thus are of relevance for the pathology of the disease. Due to the compilation of data from multiple sites, we concentrated our analyses on networks that are robustly associated with alterations in patients with SZ across sites. A recent study by Gupta et al. [9] merged data from nine different studies and identified four structural components of abnormal GMV covariation with high reproducibility. We hypothesized that the age of cannabis use initiation in ROP patients is associated with alterations in SZ-related GM networks, including brain regions previously associated with early initiation of cannabis use in healthy individuals (e.g., frontal areas and cerebellum). We aimed to advance the present knowledge of cannabis effects on the four components reported for SZ patients: (i) superior temporal gyrus, inferior frontal gyrus and insula, (ii) superior frontal gyrus, middle frontal, and medial frontal gyrus, (iii) brainstem, and (iv) inferior semilunar lobule and cerebellar tonsils. Previous work indicated that GM concentration was reduced in the frontal, temporal, and cerebellar components (i, ii, iv) and increased in the brainstem component, (iii) in SZ patients compared to controls [9]. Further, we adopt a network-based perspective to explore the associations of the age of cannabis initiation on the psycho- and neuropathology of psychosis. We predicted that this approach might reveal potential pathways whereby cannabis use patterns might propagate to positive psychotic symptoms and/or development of neurostructural perturbations [31].

MATERIALS AND METHODS

Study design and population

We analyzed data of 102 patients with ROP aged 15–40 years from two studies, the multisite longitudinal PRONIA study (www.pronia.eu, German Clinical Trials Register identifier DRKS00005042 [32]) and the ongoing, monocentric, longitudinal Cannabis Induced Psychosis (CIP) study, after harmonizing the study protocols (Supplementary Fig. 1). CIP patients were recruited at the Department of Psychiatry at the Ludwig Maximilian's University of Munich, while ROP cases included in PRONIA were recruited at eight European sites (see [32]). ROP experienced an affective or non-affective psychotic episode within the past 24 months and present within the 3 months preceding study entry. Psychiatric diagnoses were obtained by trained clinical raters, based on the Structured Clinical Interview for DSM-IV disorders [33]. To focus our analysis on ROP patients who had a clinically-relevant comorbid cannabis use, we imposed additional inclusion criteria, defined by (i) cannabis use preceding the onset of psychotic symptoms by no more than 2 weeks as defined in the International Classification of Diseases, 10th Revision, criteria for substance-induced psychosis [34], and/or (ii) a lifetime cannabis abuse or dependence [33]. Participants were only included when their age of cannabis initiation was recorded (Supplementary Information for detailed inclusion and exclusion criteria, Supplementary Fig. 5). Fourteen subjects from the PRONIA study had to be excluded due to the lack of this information. Subjects with missing data for age of cannabis initiation had significantly more severe symptoms, were more likely to have cannabis abuse or dependency use, and there was an interaction with site (Supplementary Table 3).

All individuals from PRONIA underwent baseline assessment between 2014 and 2019 and were followed for up to 36 months. The CIP recruitment took place from December 2016 until May 2019 and the follow-up period was 9 months. Most assessments overlapped between the two studies in that both studies included multimodal imaging, a neuropsychological assessment and a clinical protocol (assessments are listed in Supplementary Table 1).

Prior to their inclusion in the study, all participants provided written informed consent (either personally or through a legal guardian if below the age of 18). Studies were approved at their respective sites by the local research ethics committees.

Assessment of cannabis consumption

The age of initiation and other cannabis intake measures were assessed in a clinical interview. Initiation age entered all models as a continuous variable (Supplementary Fig. 3 for distribution of age of cannabis initiation). For the purpose of tabular presentation, we divided the study sample into early- and late-onset users, based on the median of 17 years (Supplementary Table 4 for age of cannabis initiation as continuous variable) [15].

Acquisition protocol and preprocessing pipeline of structural MRI

A harmonized protocol for the acquisition of structural MRI data was used at all sites. For preprocessing, we used the open-source CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), which is an extension of SPM12 running in MATLAB 2018a. First, all images were segmented into GM, WM, and cerebrospinal fluid, normalized to stereotactic space of Montreal

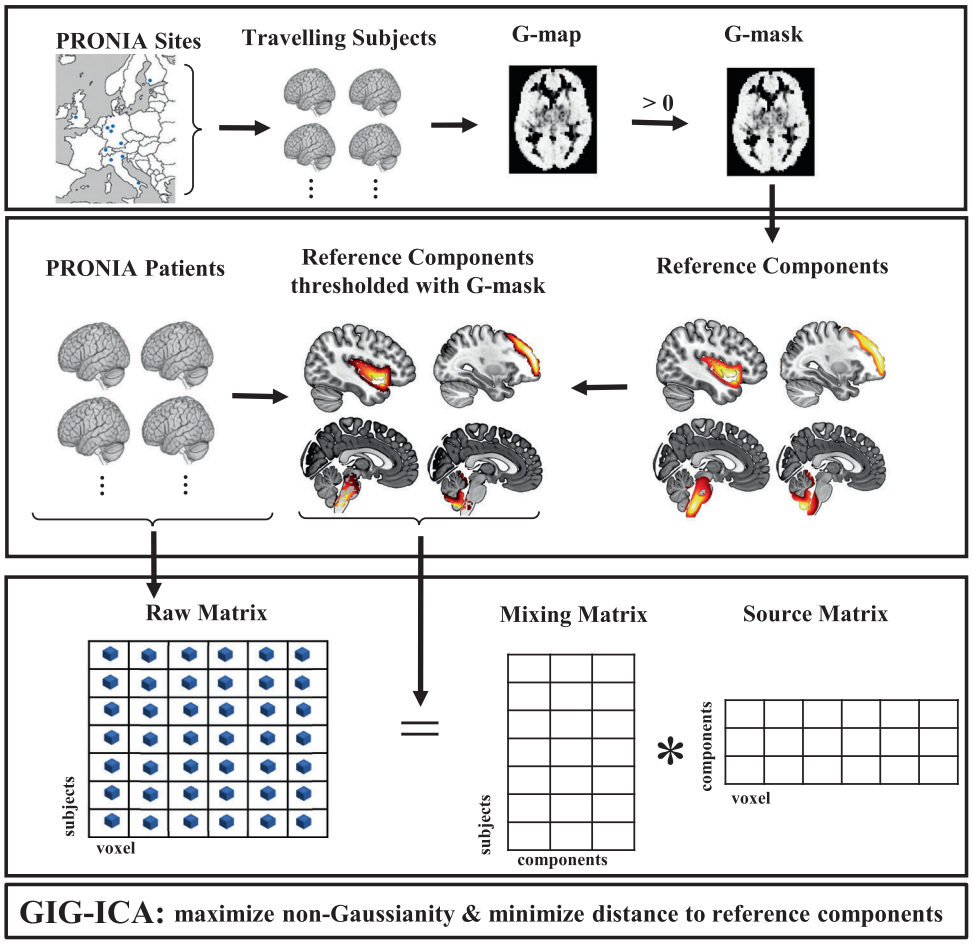

Fig. 1 For the analysis pipeline based on GIG-ICA four components from a previous study of SCZ [9] were selected as reference components and thresholded using the G-theory mask (derived from six healthy traveling subjects) to correct for scanner-specific effects. We extracted components using GIG-ICA by maximizing the non-Gaussianity and simultaneously minimizing the distance to the reference components.

Neurological Institute (MNI-152) and multiplied with the Jacobian determinants obtained during registration to derive the final GMV maps. After quality control (Supplementary Information), we regressed age and sex effects voxel-wise, as previous studies have shown that regressing for such effects prior to SBM analysis increases sensitivity to group differences [28]. Subsequently, images were realigned to a two mm voxel resolution and smoothed with a ten mm (full-width at half maximum) Gaussian kernel [9] (Supplementary Table 5).

Source-based morphometry

SBM analysis was conducted by applying GIG-ICA to sMRI data using the GIFT toolbox (http://mialab.mrn.org/software/gift/) in MATLAB 2020. Here, GIG-ICA was optimized to identify four independent components with maximum similarity to the four reference components (RCs) that had previously been associated with SZ, with high reproducibility between sites [9]. To account for study-specific scanner effects, we used a strategy based on G-theory for voxel selection of the RCs [32], employing a threshold of >0 to exclude voxels showing only between-site but no inter-subject-variation [35] (Fig. 1, Supplementary Information).

In the first step, GM images were converted to one-dimensional row vectors and concatenated across participants. After excluding outliers with extremely high source variability that might otherwise drive spurious significant results (Supplementary Information), we derived a 102-by-175,000 GMV voxel matrix. This matrix was decomposed into a source matrix and a mixing matrix. The mixing matrix represents loadings, i.e., the weights of individual participants on each component. The source matrix, represents the relationship between each voxel and the components (Fig. 1). This decomposition simultaneously maximizes the correspondence to the RCs and the independence of the components from each other such that each row in the source matrix is maximally independent from the others. To match the components derived from this study with the established RCs and to test their validity, we used a stepwise procedure as described previously [36] (Supplementary Information). Based on that previous literature [36], components from the current study (COIs) with a correlation $r > 0.5$ with a RC were included in subsequent analyses. Additionally, we utilized GIG-ICA on a subsample restricted to cases of schizophrenia spectrum disorder (SSD) to enhance comparability with the sample in which the RCs were generated and to further reduce heterogeneity in terms of severity of symptoms and diagnoses. To test for sex-specific effects of cannabis use initiation on brain structure we recalculated the components based on male subjects only. Due to the lower sample size, this analysis was not possible in females.

Voxel-based morphometry. To maximize comparability with previous studies, we performed an additional VBM analysis (Supplementary Information).

Table 1. Demographics and clinical data.

	Early (<17)	Late (17+)	df	$T/Z/X^2$	*p* value
Samples and study variables					
Sample sizes	58	44			
CIP (%)	29 (49.2)	15 (34.1)	1	1.970	0.160
Age [mean (SD) years]	24.1 (4.1)	23.4 (4.0)	94	0.820	0.413
Sex [F (%)]	11 (19.0)	12 (27.3)	1	0.571	0.450
Sample size per site			7	22.690	0.002
Munich (%)	45 (77.6)	25 (56.8)			
Milan Niguarda (%)	0 (0)	6 (13.6)			
Basel (%)	8 (13.8)	3 (6.8)			
Cologne (%)	2 (3.4)	3 (6.8)			
Birmingham (%)	3 (5.2)	0 (0)			
Turku (%)	0 (0)	5 (11.4)			
Udine (%)	0 (0)	1 (2.3)			
Düsseldorf (%)	0 (0)	1 (2.3)			
Cannabis use					
Lifetime history of DSM-IV cannabis use disorder [*N* (%)]			2	1.030	0.597
Cannabis abuse (%)	24 (41.4)	23 (22.5)			
Cannabis dependency (%)	25 (24.5)	16 (15.7)			
Initiation age [mean (SD) years]	14.9 (1.2)	19.8 (3.2)	51.400	−9.61	<0.001
Cumulative months lifetime [mean (SD) months]	58.1 (40. 5)	25.2 (24.9)	55.990	3.831	<0.001
Duration of heaviest use [mean (SD) days]	822.2 (873.6)	389.7 (379.1)	70.637	3.197	0.006
Level of use in the heaviest use period (%)			2	2.889	0.236
>10 times per month/dependency	49 (48.0)	35 (34.3)			
<10 times per month	5 (5.9)	6 (5.9)			
Only once	3 (2.9)	0 (0)			
Duration since last use [mean (SD) days]	369.1 (1151.8)	276.6 (661.6)	87.127	0.489	0.626
Level of use in the last 3 months—cumulative frequency (%)			7	3.106	0.875
0 times	16 (15.7)	16 (15.7)			
1–5 times	3 (2.9)	4 (3.9)			
6–10 times	4 (3.9)	2 (2.0)			
11–15 times	3 (2.9)	2 (2.0)			
16–20 times	2 (2.0)	2 (2.0)			
21–30 times	2 (2.0)	1 (1.0)			
>30 times	14 (13.7)	6 (5.9)			
Psychopathology [mean (SD)]					
Positive and negative syndrome scale—positive	20.7 (5.3)	17.8 (6.9)	72.541	2.293	0.025
Positive and negative syndrome scale—negative	14.7 (5.47)	14.4 (5.8)	83.919	1.031	0.306
Positive and negative syndrome scale—general	35.0 (8.3)	33.2 (8.3)	81.319	0.231	0.818
Onset age of psychotic disorder	23.6 (4.2)	23.3 (3.8)	93.776	0.399	0.691
Years between first cannabis use initiation and attenuated psychotic symptoms—years [mean (SD)]	7.5 (4.6)	3.3 (4.0)	66.025	4.175	<0.001
Years between initiation of heaviest cannabis use and attenuated psychotic symptoms—years [mean (SD)]	2.6 (3.9)	1.4 (2.6)	70.393	1.524	0.132
Medication [mean (SD)]					
Currently treated (%)	37 (63.8)	28 (63.6)	1	<0.001	1
Chlorpromazine equivalent (cumulative lifetime)	4764.1 (7445.2)	4903.0 (7872.9)	87.852	−0.089	0.929

Statistical analysis

We performed all further statistical analyses using R language for statistical computing, version 3.6.2 [37]. To analyse differences in GMV covariation due to age of cannabis initiation, we investigated participants' loading coefficients, employing a linear mixed effects model in the R-package "ImerTest" [38] with loading coefficients as dependent variables. Age of cannabis initiation was modeled as a fixed effect, while the factor "site" was modeled as a random effect. In our analysis of ICA components, larger loading coefficients indicate a stronger weighting of the spatial pattern in the individuals [9, 26]. Higher loading coefficients, coupled with a positive spatial component, shall be interpreted as greater GMV in this component [9]. Effect sizes in terms of R^2 were calculated with the R-package "r2glmm" as proposed recently [39]. To assess

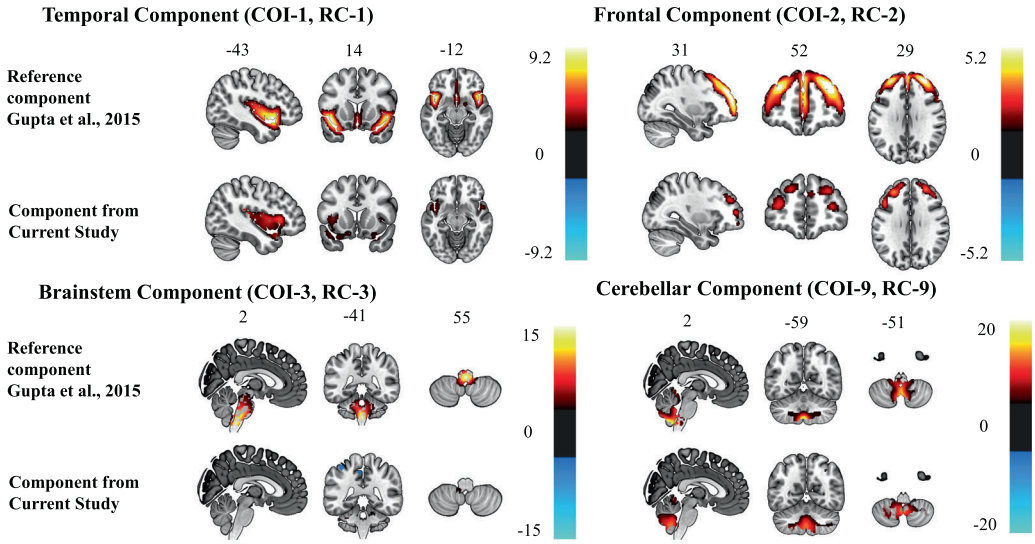

Fig. 2 Cerebral mapping of the reference components and the four components from the current study, all thresholded at |z| > 2.5. The reference components are thresholded with the G-theory mask.

the possible impact of certain confounding factors typically reported to effect GMV, we estimated the same model with addition of the duration of heaviest use, the chlorpromazine equivalent cumulative in lifetime, current medication use (yes/no) [40, 41], alcohol abuse (yes/no) [42] and the duration of illness [43] (all variables modeled as fixed factors). All p values were corrected for multiple testing using the false discovery rate (FDR) with a threshold of $p_{FDR} < 0.05$ [44]. Associations between age of cannabis use initiation and COI loadings were tested independently with cognition (Supplementary Information).

Exploratory network analysis

We fitted a network in the form of a Gaussian Graphical Model (using the R-package "qraph", version 1.6. 3 [45]), including all COI loadings passing the inclusion threshold, initiation age, duration of use, and positive psychotic symptoms in the last 7 days measured by the Positive and Negative Syndrome scale (PANSS) [46]. In such a network, undirected connections between two variables represent pairwise partial correlations after conditioning on all other variables [47]. These connections are interpreted as predictive effects between two variables, which cannot be explained by any other variable in the network. We determined the optimal network model by using stepwise, unregularized model selection and tested robustness and stability (Supplementary Information).

RESULTS

Study population

ROP patients with early (<17 years) and late (≥17 years) cannabis use initiation showed no differences in sociodemographic variables (Table 1 and Supplementary Table 2). Early users had a significantly longer mean duration of cannabis use compared to late users, had more severe positive psychotic symptoms and significantly longer duration between the cannabis use initiation and first attenuated psychotic symptoms measured by Standardized Interview for the assessment of Prodromal Symptoms (modified version 5.0) (any SIPS-P item ≥3) [48]. Patients with early- and late-initiation of cannabis did not differ for cumulative frequency of cannabis use in the previous 3 months, prevalence of a SCID lifetime diagnosis of cannabis abuse or dependency, prevalence of lifetime alcohol abuse, other drugs taken or in the cumulative dose or current intake of antipsychotics.

Creation of the components of interest (COIs)

SMRI data of 102 ROP patients with history of clinically-relevant cannabis use were decomposed into four components based on independence and correspondence to the RCs [9]. Brain regions of all four COIs were identified from the Talairach Daemon (http://www.talairach.org/daemon.html) and visualized with the MRIcroGL software (McCausland Center for Brain Imaging, University of South Carolina; https://www.nitrc.org/projects/mricrogl/). A minimum z-threshold was set to |>2.5| and a maximum z-threshold was derived from [9] for each component independently (Fig. 2).

Three of the four COIs passed the threshold of $r > 0.5$ for correspondence to the RCs and were included in further analyses, while COI-3, which comprises mainly the brainstem, was excluded ($r = 0.38$, $p < 0.001$).

COI-2 had the highest correlation with RC-2 and encompassed mainly the superior, medial, and middle frontal gyrus ($r = 0.712$, $p < 0.001$, Table 2). The next highest correlation was between COI-1 and RC-1 ($r = 0.671$, $p < 0.001$). COI-1 comprised mainly the superior temporal, precentral, frontal and parahippocampal gyrus and insula (Table 2). COI-9 had a moderate correlation with RC-9 ($r = 0.59$, $p < 0.001$), although many voxels had to be excluded from RC-9 due to study-specific scanner effects (41%). This component mainly comprised cerebellar regions (Table 2). The assignment between COIs and RCs remained similar in our control subanalyses restricted to the male and SSD groups, except that the correlation coefficient was lower (Supplementary Information).

Relationship between the components and cannabis use patterns

We found that higher loading coefficients for COI-9 were significantly associated with earlier cannabis initiation, after correcting for site ($t_{102} = -2.762$, $p_{FDR} = 0.02$). In combination with the predominantly positive component, this implies that increased GMV in cerebellar regions is associated with an earlier initiation of cannabis use. Adding several hypothesized confounding covariates had slight effects on the results, significantly higher loading coefficients were still associated with an earlier initiation ($t_{80} = -3.00$, $p_{FDR} = 0.01$), with the difference that the random effect "site" became significant in this model ($t_{80} = 2.62$, $p_{FDR} = 0.03$). No other covariates significantly correlated with the loading coefficients of any of the components. Age of cannabis initiation explained 7.9% of the 10% of the variance explained in the full model. Initiation age did not show any significant effect on the

Table 2. Statistical measures and brain coordinates of the identified brain region components.

Component	Reference component (Pearson r^2)	Loadings direction	LME (initiation age)			Brain region label	*L/R* Volume in cm^3	Brodmann area	L/R Max z-value (MNI coordinates)
			t (df)	p_{FDR}	R^2/R^2 whole model				
COI-1	Temporal (0.68)	Early > late	−0.474 (96)	0.64	0.002/0.019	Insula	8.4/7.6	13, 40	5.4 (−38, 8, 4)/4.3 (44, −28, 18)
						Inferior frontal gyrus	5.2/3.4	13, 44, 45, 47	5.4 (−40, 22, 2)/3.6 (26, 14, −24)
						Extra nuclear	1.5/0.4	13, 47	5.0 (−36, 20, 0)/3.2 (36, 0, 10)
						Precentral gyrus	0.6/1.0	6, 13, 44	4.4 (−40, 8, 8)/3.5 (48, −6, 6)
						Superior temporal gyrus	7.2/6.6	13, 21, 22, 38, 41	3.9 (−42, 14, −22)/3.9 (30, 14, −26)
						Parahippocampal gyrus	1.0/0.3	28, 34	3.3 (−20, −6, −20)/2.8 (20, −8, −18)
COI-2	Frontal (0.72)	Late > early	0.656 (93)	0.64	0.016/0.047	Superior frontal gyrus	6.3/6.0	6, 8, 9, 10, 11	4.3 (−26, 40, 34)/3.8 (26, 44, 32)
						Middle frontal gyrus	8.0/4.0	8, 9, 10, 46, 47	4.0 (−30, 40, 32)/3.6 (30, 44, 30)
						Medial frontal gyrus	1.1/0.8	9, 10	3.6 (−24, 36, 32)/2.9 (6, 54, 24)
COI-3	Brainstem (0.38)	Early > late	–	–	–	*Uncus*	*1.5/1.2*	*20, 28, 36, 38*	*5.9 (−28, 0, −42)/4.0 (26, −6, −36)*
						Middle temporal gyrus	*1.5/0.4*	*21*	*5.0 (−32, 8, −42)/3.2 (44, −70, 16)*
						Superior temporal gyrus	*1.3/0.1*	*22, 38*	*4.6 (−24, 8, −40)/2.6 (52, 14, −18)*
						Inferior parietal lobule	*1.5/0.0*	*40*	*3.8 (−38, −44, 58)/NA (0, 0, 0)*
COI-9	Cerebellum (0.59)	Early > late	−2.758 (100)	0.02	0.079/0.100	Cerebellar tonsil	4.0/3.8	–	12.2 (0, −56, −46)/10.5 (4, −56, −46)
						Inferior semilunar lobule	3.1/1.2	–	11.7 (−4, −58, −50)/10.9 (4, −58, −50)
						Nodule	0.8/1.2	–	8.5 (−4, −56, −38)/9.0 (0, −54, −38)
						Uvula	1.3/1.7	–	7.7 (−4, −64, −42)/7.2 (0, −62, −38)
						Culmen	1.0/1.2	–	4.3 (−2, −50, −6)/4.6 (2, −50, −6)

Bold italic refers to negative component regions.
LME linear mixed effects model.

other components (Fig. 3). Cognitive performance was neither associated with the age of cannabis initiation nor with the cerebellar loadings (Supplementary Information). Subsequent control analyses, in the SSD and the male subgroups showed comparable effects (Supplementary Information).

Complementary network analysis

The network (Fig. 3) illustrates the connections between the overall severity of positive symptoms at time of assessment measured by PANSS, age of cannabis initiation, duration of use, and COI-2, COI-1, and COI-9. From 15 possible edges, only four remained in the unregularized model selection procedure. Age of cannabis initiation was negatively associated with positive symptoms measured by the PANSS, age of initiation was negatively associated with the duration of cannabis use, age of initiation was negatively associated with COI-9, whereas COI-9 was negatively associated with COI-1. These associations are specific, i.e., they remain after all other associations have been taken into account. Bootstrapping analyses showed that edges retained in the final model were also present in the majority of bootstrapped networks (Supplementary Fig. 6). However, when testing case subsetting, the edges were not stable (Supplementary Fig. 7).

Voxel-based morphometry. We did not find any significant volume difference associated with the age of cannabis initiation at the proposed threshold of FWE—$p < 0.05$. However, at an uncorrected threshold ($p < 0.005$, $k = 5$) the direction of our VBM analyses was in line with our findings in SBM (Supplementary Table 10 and Supplementary Fig. 8).

DISCUSSION

To the best of our knowledge, this is the first study investigating the effects of the age of cannabis use initiation on GMV in patients with ROP. Moreover, for the first time, we employed a GIG-ICA to investigate cannabis use history on structural brain networks previously identified in SZ [9]. Our results link the initiation of cannabis use during adolescence to long-lasting structural effects, manifesting in the present finding of greater GMV in patients with an earlier age of cannabis initiation. Notably, this effect was specific for the age of initiation, and was robust to several possible confounding factors often discussed in the literature [14, 49]. Furthermore, we provide evidence that an earlier age of initiation is specifically associated with more severe positive psychotic symptoms in ROP. The presence of greater volume in the cerebellar network was associated with reduced GMV in COI-1, a network mainly comprising the insula, superior temporal, and inferior frontal gyrus, which has previously been shown to best discriminate between HC and SZ [9].

The positive association between greater GMV in the cerebellum and earlier cannabis use initiation is in line with previous structural imaging studies comparing cannabis-using and non-using healthy adolescents [50, 51] and young adults [14, 50–53]. In recent decades the cerebellum has been increasingly associated with higher cognitive functions, such as emotion regulation, working memory, and language [54], all of which undergo substantial evolution during adolescence. Notably, in the current study, cognition was not associated neither with cerebellar GMV, nor with age of cannabis initiation. Previous literature has indicated an impact of cannabis on cognitive performance, however our findings are in line with meta-analytic evidence showing the absence of a mediating effect of age of initiation [55]. Surprisingly, there was no association between the cerebellar network and cognitive performance [54]. These unexpectedly negative findings might be due particulars of our selection of cognitive domains. The cerebellum is amongst the latest brain structures to mature. It has an inverted U-shaped

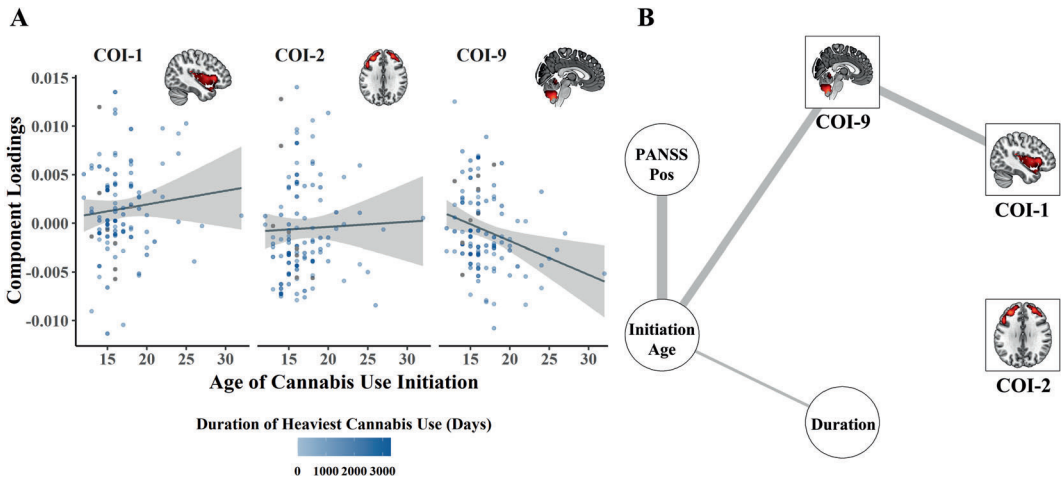

Fig. 3 Association between components of interest (COIs), cannabis, and clinical measures. Age of cannabis use initiation, duration of heaviest use and components (**A**). Network of identified components, cannabis measures and PANSS positive scale (**B**). Edges represent partial correlations between the nodes. Each edge is corrected for all other edges in the network and the scaling of edges in width and color saturation were adjusted by setting the cut-argument in qgraph to 0.2 [35]. All correlations in the network are negative.

neurodevelopmental trajectory, attaining a GMV peak in adolescence, which then declines in early adulthood [54]. A finding of increased cerebellar volume persisting into adulthood has therefore been interpreted to indicate a disturbance of typical brain maturation, such as failure of synaptic pruning [13, 14, 51]. Remarkably, a twin study of healthy brain development indicates weaker genetic effects on cerebellar GMV development as compared to all other brain structures [56]. Hence, it might be hypothesized that environmental factors play an important role in shaping cerebellar structure. Cumulative evidence suggests that these effects might be sex-specific due to a more protracted and hence more vulnerable cerebellar development in men [54], thus explaining the increased likelihood for cannabis psychosis in male (male:female, 4:1) [57]. However, due to the limited sample size, we cannot exclude that a comparable effect may also be present in females.

While previous studies often neglected the cerebellum or found a cerebellar decrease in SZ [58, 59], a recent meta-analytic study indicates that psychotic patients had greater cerebellar brain volume as compared to HC [8]. Similarly, individuals at clinical high risk for psychosis exhibit greater volume in cerebellar regions compared to HC [32]. Moreover, alterations in these regions contribute to a brain network predictive for poor psychosocial functioning [32]. Hence, we suggest that present findings might indicate an anatomic signature of psychosis either initiated or exacerbated by early cannabis use.

Surprisingly, we did not find associations between GMV of frontal networks (COI-2) and the age of cannabis use initiation. Volumetric decreases in frontal regions and the parahippocampal gyrus have been associated with an earlier initiation of cannabis use in healthy individuals [14, 15], and in cannabis-using adolescents compared to their abstinent peers [18]. The explanation for our negative result for COI-2 might be threefold. First, we specifically test for an effect of age of cannabis *initiation* in ROP patients, in contrast to previous studies potentially detecting general effects of cannabis use in psychosis. Second, specific effects of cannabis use during adolescent brain maturation might differ in vulnerable individuals later presenting with ROP, due to genetic vulnerability or additional early environmental risk factors [60]. Third, the use of univariate statistics in previous studies hindered exploring the highly interconnected nature of the brain. Despite our negative univariate results, our findings in GMV covariation, which is thought to reflect shared maturational processes [23–25], might suggest that this measure is a particularly important marker of neurodevelopmental perturbations.

The exploratory network analysis revealed a pathway in which the cerebellar network bridges the association between the network that comprises the insula, superior temporal and inferior frontal gyrus and age of cannabis initiation. Interestingly, greater GMV in the cerebellar network associated with earlier age of initiation was in turn associated with decreased GMV in the insula, superior temporal, and inferior frontal network (COI-1). This latter network was the most predictive of SZ and includes brain regions consistently implicated in psychosis [8]. Present findings are consistent with a model that cannabis consumption during adolescence causes an excursion from the typical brain maturational process, thereby increasing vulnerability to develop psychosis later in life. However, causal inferences are fraught, since it cannot be excluded from cross-sectional studies that specific GMV patterns may predispose an earlier cannabis consumption [14], although there is some evidence to the contrary [50]. Interestingly, stronger positive symptoms were associated only with an earlier age of initiation, irrespective of GMV in any brain network, or the duration of the heaviest use. This finding adds to previous studies showing that adolescent cannabis use increases the risk of more severe psychotic symptoms [61, 62]. Moreover, our observation that cannabis use precedes the onset of attenuated psychotic symptoms indicates that this effect is directed, as likewise reported elsewhere [63].

We note some limitations of our study. Although we corrected for inter-scanner effects, some results might yet have been influenced by differing MRI machines and protocols. This possibility might be excluded in future studies by balancing between different sites which would also allow for additional statistical power in support of methods to correct for any site-effects [64]. In the network analysis, final edges were included across most bootstrapped networks, but the resultant network structure was unstable under subsetting of cases. This instability could be due to the marginal sample size ($N = 102$) relative to the number of nodes analysed ($N = 6$). Further, network approaches are typically applied for investigating specific symptoms, such as PANSS subscores. Again, our sample size calls for some reduction of variables. All our analyses are cross-sectional, which limits causal inferences. A longitudinal study design could enable the investigation of directionality of the neuroanatomic effects of cannabis use in psychosis, although requiring a logistically difficult study beginning in early adolescence. Follow-up studies might

then investigate the possibly mediating and interacting detrimental effects of other risk factors, such as childhood adversity [65] or inattention-hyperactivity symptoms [66]. Importantly, our study lacks a control condition of healthy cannabis users. Future studies might test whether the effects found in the current study are specific to psychotic patients or represent general effects of cannabis on the developing brain.

Our GIG-ICA approach indicates that earlier age of cannabis use initiation among patients with ROP is specifically associated with increased volume in the same cerebellar network previously identified in SZ patients. We cautiously attribute this increase in cerebellar GMV to interference with the trajectory of typical brain maturation. Additionally, we found evidence that earlier initiation of cannabis use is associated with more severe psychotic symptoms in our ROP group. This result calls for more detailed examination of the interaction between early cannabis use, neurodevelopment perturbation, and risk of psychosis. Since the legalization of cannabis products in many countries shall have unpredictable effects on cannabis consumption in adolescents, it becomes a matter of vital interest to establish the contribution of cannabis use to the burden of risk factors for psychosis.

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AUTHOR CONTRIBUTIONS

Conceived and/or designed work: NP, LAA, OP, PC, BBQ, OH, PF, RU, AB, SB, PB, EM, LK-I, SR, RKRS, CP, SJW, NK, and JK. *Acquired data:* NP, LAA, LTB, RS, JW, RU, AB, SB, PB, RL, EM, MR, TH, LK-I, SR, RKRS, CP, SJW, NK, and JK. *Interpreting the results:* NP, LAA, LB, JK. *Drafting:* NP, LAA, LB, RS, JW, and JK. All authors have contributed to the critical revision of the paper and approved the final version.

ADDITIONAL INFORMATION

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THE PRONIA CONSORTIUM

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Supplementary materials for “Association between Age of Cannabis Initiation and Gray Matter Covariance Networks in Recent Onset Psychosis”

Table of Content

1. *Inclusion/Exclusion criteria for participants with recent-onset psychosis (ROP) in the PRONIA and CIP study.*

ROP had to meet a DSM-IV diagnoses for an affective or non-affective psychotic episode in the last three months and no previous psychotic episode more than 24 months ago. For both studies, trained clinical raters made the PRONIA and CIP diagnoses based on SCID-1 interviews for DSM-IV disorders[1]. Additional medical records were consulted to aid the diagnostic process. All diagnoses were confirmed in weekly meetings with the principal investigators at each site. In the current study, we applied an additional inclusion criteria that ROP patients should have clinically relevant comorbid cannabis use, defined by a close temporal association between the onset of psychotic symptoms and initiation of cannabis use; i.e. cannabis use preceding the onset of psychotic symptoms by no more than two weeks, and/or by a lifetime cannabis abuse or dependency[1]. In the current analysis, participants were only included when the initiation age of the first cannabis use had been assessed. Participants from both studies were excluded if they had taken antipsychotic medication for more than 90 cumulative days at or above the minimum dosage indicated for first episode psychosis as specified in the DGPPN S3 Guidelines (guideline manual is available in https://www.dgppn.de/_Resources/Persistent/43ca38d4b003b8150b856df48211df68e412d9c9/038-009k_S3_Schizophrenie_2019-03.pdf).

Further exclusion criteria were any traumatic head injury with loss of consciousness for more than five minutes, any contraindication for MRI, any neurological or somatic disease affecting the brain, a lifetime diagnoses of alcohol dependency, or inadequate language proficiency in English or the national language at the respective site.

2. *Acquisition and preprocessing of sMRI*

Data was acquired with isotropic or nearly isotropic voxel size, with a preferred voxel size of 1 mm^3. The parameters of the field of view had to ensure full 3D coverage of the entire brain including the cerebellum, and other imaging parameters had to maximize the contrast between white matter and cortical ribbon as well as obtaining an optimal signal-to-noise ratio.

For pre-processing, we used the open-source CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), an extension of SPM12 running in MATLAB 2018a. As a first step, all images were segmented into GM, WM and cerebrospinal fluid maps and normalized to stereotactic space of Montreal Neurological Institute (MNI-152 space). To derive GM volume maps, images were multiplied with the Jacobian determinants obtained during registration. *Post-hoc* quality checks were performed by correlating each slice across all subjects. Three scans deviated by more than two standard deviations (SD) of the mean, and were consequently re-examined visually. Due to artifacts, one image had to be excluded from the subsequent analysis, whereas the other two passed (sFigure 5 and 5 Sanity Checks). In a next step, we regressed age and sex effects voxel-wise, as these factors have an impact on GM, and previous studies have shown that regressing for their effects prior to SBM analysis makes the components more sensitive to group differences[2]. Subsequently, images were realigned to a two mm voxel resolution and smoothed with a ten mm (full-width at half maximum) Gaussian kernel[3].

3. G-theory based voxel selection of the Reference Components

MRI data from six individuals, who agreed to be scanned at seven of the eight included PRONIA sites (Munich, Milan Niguarda, Basel, Cologne, Birmingham, Turku, Udine), were analysed voxel-wise for subject- and site-specific variation. Here, higher g-values indicate high subject- and low site-specific variation, and low g-values indicate high site-specific and low subject specific variation[4]. The RCs were thresholded with the g-mask (voxels>0) using SPM12 running in MATLAB 2020 (Main Text, Figure 1).

4. Goodness of fit and matching of COIs and RCs.

To match the COIs derived from the current study with the RCs, we used a stepwise procedure as described previously[5]. To this end, we calculated the Pearson correlation coefficients (r) between all the RCs and all the COIs to derive a similarity matrix (sFigure 4). Based on this matrix, we defined the two components with the highest correlation as the first match. Next, we excluded the components of the first match, and correlated all remaining RCs and all remaining COIs with each other, where the RC and the COI with the highest correlation was considered as the second match. This procedure was repeated until all COIs were matched with the RCs, which was satisfied when four matched pairs of RCs and COIs were found. Based on previous study criteria[5], we considered as reliable a threshold of $r > 0.5$ between RCs and COIs.

5. Sanity checks - Outlier detection

5.1 MRI-based outlier detection

Originally, we included 105 ROP cases from the PRONIA and CIP studies. We tested the validity of the sMRI in a stepwise procedure (see Flow diagram sFigure 5). We performed a

three-step check to investigate for the presence of outliers based both on first-level and source-based MRI information. As a first step, we used the Computational Anatomy Toolbox[6] to get the volume-wise correlation of the unsmoothed sMRI images between all subjects. As a second step, we checked whether individuals with a high deviation from the average volume-wise correlation (defined as ± 2 SDs) presented any visual artifacts. Here, we inspected the raw images for presence of technical artifacts (e.g. blurring, ringing, wrapping, or incomplete head coverage). For segmented images we checked for general image quality (e.g. excessive noise, poor image contrast and poor boundaries). Scans from three individuals had a volume-wise correlation deviation by more than 2 SDs from the mean volume-wise correlation (r = 0.877). Following the instructions of the manual of the Computational Anatomy toolbox[7] these subjects were not simply removed from the analyses but were carefully checked. Of these, two scans (r = 0.865, r = 0.864) had no visual artefacts, while one scan (r = 0.857) had a scanner-related artefact, and was thus removed from all further analyses.

As a third step, to avoid single outliers with extremely high source variability that might otherwise drive spurious significant results, we also checked for outliers after the application of the GIG-ICA algorithm to the images smoothed with a 10-mm kernel. Hence, after creating the components of interest (COIs) in 104 individuals, we performed an additional component-wise quality control check employing Grubb's test[8]. No outlier was found for COI-1 and COI-2 at a significance level of alpha = 0.05 (COI-1 (mean [SD]) = 0.0015 [0.0047], COI-2 (mean [SD]) = -0.0005 [0.0051]). One subject in COI-3 and one subject in COI-9 had significantly higher source variability (alpha <0.05). The outlier in COI-3 had a loading coefficient of -0.0249 (z = 3.673), which was significantly higher than the critical z-value (3.397) (COI-3 (mean [SD]) = -0.0064 [0.0050]). The outlier in COI-9 had a loading coefficient of 0.0219 (z = 4.7116), which was significantly higher than the critical z-value (3.397) (COI-9 (mean [SD]) = -0.0008 [0.0048]). We removed the two subjects with loading coefficients that

deviated more than 2 SD from the mean. Subsequently, SBM was repeated and further analyses were calculated on this edited sample (n = 102).

5.2 Clinical based outlier detection

To check the distribution of clinical data across the remaining 102 individuals, we investigated the potential presence of significant outliers for the factors *age of cannabis use initiation* and for the *duration of heaviest cannabis use*. After rechecking our data for typographic errors, we repeated our analyses with exclusion of significant outliers in age of cannabis initiation and duration of heaviest cannabis use. Results revealed that these outliers did not drive the significance of our findings, and furthermore their values were plausible (clinically speaking). Hence, all results in the paper are reported with inclusion of the outliers; here, we also present corresponding results with removal of all outliers.

Of the 102 remaining subjects, seven subjects were excluded because they were significant outliers with respect to age of initiation (> 26 years; N = 2), and duration of heaviest cannabis use (> 2390 days; N = 5), and another eight subjects were excluded due to missing data on duration of heaviest use. We repeated our analysis of differences in GMV covariation due to age of cannabis initiation employing a linear mixed effects model with the decreased sample size (N = 87). As before, loading coefficients entered the model as dependent variables, age of cannabis use initiation was used as a fixed effect, and site was a dummy-coded random effect. This analyses with a sample without outliers yielded comparable results to our original analysis. Significantly higher loading coefficient for COI-9 retained its association with an earlier initiation of cannabis use after correcting for site (t_{84} = -2.762, p_{FDR}= 0.02). Adding several possible confounding factors (duration of heaviest use, chlorpromazine equivalent dosage cumulative lifetime, current antipsychotic intake (yes/no), alcohol abuse (yes/no), duration of illness) as additional fixed effect only slightly affected the results. Still,

significantly higher loading coefficients in COI-9 were found to be associated with an earlier initiation (t_{84} = -2.89, p_{FDR}= 0.02), while the with the difference that the random effect 'site' became significant in this model (t_{80} = 2.585, p_{FDR} = 0.04). No other components showed any significant effects with the initiation age. All *p*-values were corrected for multiple testing using the false discovery (FDR) with a threshold of p_{FDR}<.05[9].

6. Exploratory Network Analysis - Stability Analyses

As recommended in current literature[10,11], we performed several robustness and stability analyses using bootstrapping from the R-package 'bootnet' version 1.3[11]. First, we bootstrapped our network 1000 times to derive 95 % bootstrapped confidence intervals for the edge weights. Additionally, we evaluated the number of bootstrapped networks in which each edge was set to zero, i.e. was not included in the network (sFigure 6). Furthermore, we tested the stability of our results by calculating the network with subsamples, dropping cases gradually, and correlated the resulting networks calculated for the subsamples with the original network (sFigure 7). The bootstrapped results indicating that the edges found in our network are relatively stable, but that decreasing the sample size does have some impact on our results.

7. Analyses restricted to patients with a schizophrenia spectrum disorder

To improve comparability between the sample from which the RCs were derived (Gupta et al., 2015[3]) and further reduce heterogeneity due to variety in diagnoses and severity of symptoms we repeated our analyses in individuals with DSM-IV diagnoses of schizophrenia spectrum; i.e. schizophrenia, schizophreniform disorder and schizoaffective disorder. Hence, we performed initial GIG-ICA on 47 subjects.

7.1 MRI-based outlier detection - SBM

Following our approach to control for extremely high source variability (Supplement 5.1), by a component-wise quality control check employing Grubb's test[8] we included 44 subjects in our final analyses. Originally, we have performed the SBM analyses on 47 subjects. At a significance level of alpha = 0.05 no outlier was found for COI-2 and COI-9 (COI-2 (mean [SD]) = 0.0017 [0.0061], COI-9 (mean [SD]) = -0.0024 [0.0062]). One subject in COI-1 and 2 subjects in COI-3 had significantly higher or lower source variability (alpha <0.05). The outlier in COI-1 had a loading coefficient of 0.0176 (z = 3.1803), which was significantly higher than the critical z-value (z = 2.936) (COI-1 (mean [SD] = -0.0003 [0.0056]). In COI-3 the two outliers had a loading coefficient of -0.0334 (z = -3.5755) and -0.0305 (z = -3.5880), respectively. Both were lower than the critical z-value for COI-3 (z = -2.936). These outliers were removed from our sample and SBM and all subsequent analyses were performed on the remaining subjects (n = 44). See sTable 8 for demographic, substance use and clinical information of the subsample restricted to SSD divided in early (<17 years) and late (≥ 17 years) users.

7.2 Correspondence with reference components

While the assignment of our components between COIs and the RCs remained comparable to the original analyses including all subjects, the correlation between them dropped for all 4 components, which is most likely explained by the reduced sample size (only 46 % of the original subjects were included). For COI-9 (the cerebellar component) the correlation with RC-9 (r = .455, p<0.001) was now slightly below our original inclusion threshold (r > .5). However, we decided to include this component in the subsequent analyses as the correlation dropped only slightly below the threshold and further, the main goal of this comparison was to test whether the effect in this particular component (COI-9) would hold for SSD. COI-1 and COI-2 were also included in our analyses as they passed the threshold with r = .522 (p < 0.001)

and r = .587 (p <0.001), respectively. COI-3 again did not pass our threshold r =.250 (p<0.001) and was thus excluded from all subsequent analyses.

7.3 Association between age of cannabis initiation and cerebellar components

Using the same model as in the whole sample, higher loading coefficients for COI-9 were again significantly associated with an earlier initiation age of cannabis use after correcting for multiple comparisons (t_{44}=-2.543, p_{FDR}=0.04). Like in the whole sample, in patients restricted to schizophrenia spectrum disorder (SSD) neither a significant effect of the initiation age of cannabis use was found for COI-1 (t_{44}=-0.239, p_{FDR}=0.98) nor for COI-2 (t_{44}=-0.804, p_{FDR}=0.38).

8. Analyses in sample restricted to male

The developmental trajectories of the cerebellum in males are protracted in comparison with females up to 5 years. Notably, disorders associated with cerebellar abnormalities, such as autism spectrum disorder[12] and attention-deficit/hyperactivity disorder[13] more likely occur in men. It has been hypothesized that this might partially be explained by the protracted and hence more vulnerable cerebellar development in male[14]. A study about admissions to National Health Service hospitals in England has found that the likelihood to develop psychosis is higher in men compared with women and that this phenomenon is even more pronounced in cannabis psychosis (male:female, 4:1)[15]. Following the reasoning, that later development of a brain area makes it more prone to harmful effects, this sexual dimorphism could at least be partially explained by cerebellar maturational differences. To test for a sex-specific association between the initiation of cannabis use and GMV we have repeated our analyses in the male subjects only.

8.1 MRI-based outlier detection – SBM – male only

Following our approach to control for extremely high source variability (Supplement 5.1), by a component-wise quality control check employing Grubb's test [8] we included 79 subjects in our final analyses. Originally, we have performed the SBM analyses on 81 subjects. At a significance level of alpha = 0.05 no outlier were found for COI-2 and COI-4 (COI-2 (mean [SD]) = 0.00005 [0.0055], COI-4 (mean [SD]) = 0.0021 [0.0052]). One subject in COI-9 and 1 subject in COI-3 had significantly higher or lower source variability (alpha <0.05). The outlier in COI-9 had a loading coefficient of 0.0225 (z = 4.3488), which was significantly higher than the critical z-value (3.3106) (COI-9 (mean [SD] = -0.0007 [0.0053]). In COI-3 the outlier had a loading coefficient of -0.0245 (z = 3.5399) that was higher than the critical z-value (z = 3.3106) (COI-3 (mean [SD] = 0.0021 [0.0052]). These outliers were removed from our sample and SBM and all subsequent analyses were performed on the remaining subjects (n = 79). See sTable 9 for demographic, substance use and clinical information of the subsample restricted to male divided in early (<17 years) and late (≥ 17 years) users.

8.2 Correspondence with reference components - male only

The assignment of our components between COIs and the RCs remained similar to the original analyses including all subjects. A slightly lower correlation is most likely explained by the reduced sample size (only 77 % of the original subjects were included). As in the original analysis COI-9, COI-1 and COI-2 were included in our analyses, with correlations of r =.530 (p<0.001), r =.642 (p<0.001) and r =.664 (p<0.001), respectively. COI-3 again did not pass our threshold r =.332 (p<0.001) and was thus excluded from all subsequent analyses.

8.3 Association between age of cannabis initiation and the cerebellar component - male only

Using the same model as in the whole sample, higher loading coefficients for COI-9 were again significantly associated with an earlier initiation age of cannabis use after correcting for multiple comparisons (t_{77}=2.336, p_{FDR}=0.02). Like in the whole sample, in the male subjects alone neither a significant effect of the age of cannabis initiation was found for COI-1 (t_{31}=-0.057, p_{FDR}=0.75) nor for COI-2 (t_{26}=-0.396, p_{FDR}=0.43).

Unfortunately, our limited sample size of female subjects (N = 23) did not allow to test our model in a subsample restricted to female subjects.

9. Neurocognition

We further tested for associations between the age of cannabis use initiation and the neurocognitive performance, as previous literature indicates drug-related cognitive disturbances[16]. Additionally, we examined whether our finding of altered grey matter volume in the cerebellum might also be associated with cognitive disturbances as the cerebellum has recently been associated with higher cognitive functions, that evolve during adolescence[17].

9.1 Test battery

The same test battery was administered in PRONIA and CIP (see sTable 1).

9.2 Harmonization of RAVLT and HVLT-R (verbal learning)

While verbal learning in CIP as well as in most individuals from the PRONIA cohort was measured with the Rey auditory verbal learning test (RAVLT)[18], in one research site (Turku, N = 5) the Hopkins verbal learning test-revised HVLT-R[19] was used. These two

tests assess the same concepts of verbal learning but for combining their results they have to be harmonized first. Thereby, it needs to be taken into account that they administer (i) a different number of items, 12 and 15 for HVLT-R and RAVLT, respectively, (ii) a different number of trials (3 for HVLT-R, 5 for RAVLT) and (iii) that the HVLT-R includes a subgrouping of semantic.

For the purpose of harmonization, 36 healthy controls from the PRONIA study at 5 different sites (Munich, Milan, Udine, Cologne and Birmingham) performed both tests, HVLT-R and RAVLT. Their mean age was 23.17 (SD 6.22) and 22 of them were male (61.1 %). All individuals performed the tests within at least 2 hours and the order of the tests was such that half of the subjects started with HVLT-R and the other half with RAVLT to account for habituation effects.

Based on the performance of these subjects, the following linear regression model was used to transform the HVLT-R data from participants from Turku to the RAVLT's 5 repetitions:

$$\text{RAVLT-sum5} = a * \text{HVLT-Rsum3} + b$$

With a = 25.51264904

b = 1.191092045

9.3 Construction of the cognitive domains

Based on our cognitive test battery (see sTable 1 and sTable 6) we have built 6 of the 7 cognitive domains from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS [20,21]) recommendations; i.e. social cognition, working memory, speed of processing, verbal learning, reasoning and attention (see [22]). Verbal learning, one of the original cognitive domains from the MATRICS, could not be included in our analyses as neither the PRONIA nor the CIP study assessed a test comparable to the ones from the original MATRICS. While for some domains we have assessed the identical tests in

the PRONIA/CIP neurocognitive battery as in the original MATRICS for other domains we had to replace them by comparable tests measuring the same construct (see sTable 6)

9.4 Correlation with age of cannabis initiation and cerebellar component (COI-9)

To test whether there was an association between age of cannabis use initiation or COI-9 with one of the cognitive domains we have correlated them with each other. However, all correlations were non-significant (see sTable 7). Hence, the initiation age of cannabis use initiation seemingly had no impact on the cognitive performance in recent onset psychosis with clinically relevant cannabis consumption.

10 Voxel-based morphometry:

10.1 Voxel-based morphometry: Methods

We performed a univariate VBM analysis to test for GMV correlations with the age of initiation of cannabis use. Our smoothed images were regressed voxel-wise for age and sex effects as well as for total intracranial volume. In the general linear model, age of cannabis use initiation was the independent variable and site was integrated as a dummy-coded covariate. Results were thresholded with FWE-corrected $p < 0.05$.

10.2 Voxel-based morphometry: Results

We did not find any significant volume difference associated with the age of initiation of cannabis use at the proposed threshold of FWE-$p<0.05$. At an uncorrected threshold ($p < 0.005$, $k = 5$) two clusters were significantly correlated with age of cannabis use initiation. The direction of this effect was the same as for the SBM analysis, i.e. more GM volume in the cerebellum was associated with an earlier initiation of cannabis use (sTable10 and sFigure8).

Supplementary - Tables

sTable 1 Assessments of CIP and PRONIA - Table is adapted from [4]

Instrument	Form	Baseline		IV3	IV6	T1		IV12	IV15	T2
		ROP	CIP	ROP	ROP	ROP	CIP	ROP	ROP	ROP
General data	OR	X	X			X	X			
Reasons for referral	OR	X	X							
Treatment documentation	OR	X	X	X	X	X	X	X	X	X
Somatic state and health history	OR	X	X			X	X			X
SPI-A COGDIS/ COPER[23]	OR	X		X	X	X		X	X	X
SIPS positive symptoms[24]	OR	X	X	X	X	X	X	X	X	X
CAARMS[25]	OR	X	X	X	X	X	X	X	X	X
GAF[26]	OR	X	X	X	X	X	X	X	X	X
UHR - Schizotypy, genetic risk	OR	X	X	X		X	X			X
CHR criteria	OR	X				X				X
SCID-IV screening[1]	OR	X	X			X	X			X
SCID-IV summary[1]	OR	X	X			X	X			X
Demographic and biographic data	OR	X	X			X	X			X
PAS[27]	OR	X	X			X	X			X
SPI-A[23]	OR	X				X		X	X	X
SIPS negative, disorganized and general symptoms[24]	OR	X	X			X	X			X
PANSS[28]	OR	X	X	X	X	X	X	X	X	X
SANS[29]	OR	X	X			X	X			X
Chart of life events	OR	X	X	X	X	X	X	X	X	X
FROGS[30]	OR	X	X			X	X			X
GF: Social & role[31]	OR	X	X	X	X	X	X	X	X	X
Prognostic evaluation	OR	X	X			X	X			X
Substance use questionnaire	OR	X	X	X	X	X	X	X	X	X
MSPSS[32]	SR	X	X			X	X			X
RSA[33]	SR	X	X			X	X			X
CISS 24[34]	SR	X	X			X	X			X
SPIN[35]	SR	X	X			X	X			X
BDI-II[36]	SR	X	X	X	X	X	X	X	X	X
WHO-QOL-BREF[37]	SR	X	X			X	X			X
EHI-SR[38]	SR	X	X							
LEE[39]	SR	X	X			X	X			X

Wisconsin scales[40]	**SR**	**X**	**X**							
EDS[41]	**SR**	**X**	**X**							
Bullying scale [42]	**SR**	**X**	**X**							
CTQ[43]	**SR**	**X**	**X**							
NEO-FFI[44]	**SR**	**X**	**X**							
Substance use	**SR**		**X**							
Cannabis experience questionnaire (CEQ)	**SR**		**X**							
Severity of dependency scale (SES)	**SR**		**X**							
DS backward (BACS)	**NPT**	**X**	**X**			**X**				
DS forward (BACS)	**NPT**	**X**	**X**			**X**				
CPT-IP (BACS)[45]	**NPT**	**X**	**X**			**X**				
DANVA[46]	**NPT**	**X**	**X**			**X**				
DSST	**NPT**	**X**	**X**			**X**				
RAVLT*[18]	**NPT**	**X**	**X**			**X**				
ROCF[47]	**NPT**	**X**	**X**			**X**				
SAT[48]	**NPT**	**X**	**X**			**X**				
SOPT[49]	**NPT**	**X**	**X**			**X**				
TMT-A[50]	**NPT**	**X**	**X**			**X**				
TMT-B[50]	**NPT**	**X**	**X**			**X**				
VF phonetic	**NPT**	**X**	**X**			**X**				
VF semantic	**NPT**	**X**	**X**			**X**				
WAIS-III[51]	**NPT**	**X**	**X**			**X**				
sMRI	**MRI**	**X**	**X**			**X**				
rs-fMRI	**MRI**	**X**	**X**			**X**				
DWI	**MRI**	**X**	**X**			**X**				
blood sample	**bio**	**X**				**X**				
hair sample	**THC**		**X**							
Urine sample	**THC**		**X**							
EEG	**EEG**		**X**							

Abbreviation: IV3 = interval three months after baseline, IV6 = interval six months after baseline, T1 = interval nine months after baseline, IV12 = interval 12 months after baseline, IV15 = interval 15 months after baseline, T2 = interval 18 months after baseline, OR = Observer-based-rating instrument, SR = Self-rating-based instrument, NPT = Neuropsychological Test, MRI = Magnetic Resonance Imaging, sMRI = structural Magnetic Resonance Imaging, rs-fMRI = resting-state functional Magnetic Resonance Imaging, DWI = Diffusion Weighted Imaging, bio = biological test, THC = Cannabis-related test, EEG = Electro Encephalography, SPI-A COGDIS/COPER = Schizophrenia Proneness Instrument - Cognitive disturbances / Cognitive-Perceptual disturbances, CAARMS =

Comprehensive Assessment of the At-Risk Mental States, CHR Criteria, SIPS = Standardized Interview for the assessment of Prodromal Symptoms (modified version 5.0), GAF = Global Assessment of Functioning, UHR – Schizotypy, genetic risk = Genetic Risk Interview for the Assessment of Schizotypal personality traits, and familial risk for psychosis, CHR criteria = Clinical High-Risk criteria summary questionnaire, SCID-IV Screening/Summary = Structured Clinical Interview for DSM-IV, PAS = Premorbid Adjustment Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, FROGS = Functional Remission in General Schizophrenia, GF: Social/Role = Global Functioning: Social/Role, MSPSS = the Multidimensional Scale for Perceived Social Support, RSA = Resilience Scale for Adults, CISS 24 = Coping Inventory for Stressful Situations – 24 items, SPIN = Social Phobia Inventory, BDI-II = Beck Depression Inventory II, WHO-QOL-BREF = WHO Quality of Life Questionnaire – Brief Version, EHI-SR = Edinburgh Handedness Inventory – Short Version, LEE = Level of Expressed Emotions, Wisconsin scales = , EDS = Everyday Discrimination Scale – Modified Version, CTQ = Childhood Trauma Questionnaire, NEO-FFI = NEO Five Factor Inventory of Personality Traits, DS = Auditory Digit Span (Forward/Backward) adapted from the PEBL battery, CPT-IP (BACS) = Continuous-Performance Test – Identical Pairs (adapted tablet version), DANVA = Diagnostic Analysis of
Non-Verbal Accuracy 2 (adapted tablet version), DSST = Digit-Symbol-Substitution Test from the BACS battery, RAVLT = , ROCF = Rey-Osterrieth complex figure, SAT = Salience Attribution Task (adapted version), SOPT = self-ordered pointing task (adapted version), TMT-A/-B = Trail-Making Test A and B, VF phonetic/semantic = verbal fluency test, WAIS-III = Wechsler Adult Intelligence Scale (3rd edition)

*** in one of the research sites (Turku) the revised version of the Hopkins Verbal Learning Test (HVLT-R) was included instead of the RAVLT that was not available in Finnish. See the description of the two scales in 8. Neurocognition.**

sTable 2 DSM-IV Diagnoses

Variables	Early (< 17)	Late (17 +)	df	T/Z/x^2	p-value
Samples and study variables					
Sample sizes	58	44			
Substance use disorder					
Lifetime history of DSM-IV alcohol use disorder [N (%)]			1	0.002	0.967
Alcohol abuse (%)	13 (22.41)	9 (20.45)			
Alcohol dependency (%)	0 (0)	0 (0)			
Lifetime history of DSM-IV sedative-hypnotic-anxiolytic use disorder [N (%)]			0	0	1
Sedative-hypnotic-anxiolytic abuse (%)	1 (0)	1 (0)			
Sedative-hypnotic-anxiolytic dependency (%)	0 (0)	0 (0)			
Lifetime history of DSM-IV stimulants use disorder [N (%)]			1	1.002	0.293
Stimulants abuse (%)	7 (12.07)	2 (4.55)			
Stimulants dependency (%)	0 (0)	0 (0)			
Lifetime history of DSM-IV opoid use disorder [N (%)]			1	0	1
Opoid abuse (%)	2 (3.45)	1 (2.27)			
Opoid dependency (%)	0 (0)	0 (0)			
Lifetime history of DSM-IV cocaine use disorder [N (%)]			2	0.784	0.676
Cocaine abuse (%)	4 (6.90)	3 (6.82)			
Cocaine dependency (%)	1 (1.72)	0 (0)			
Lifetime history of DSM-IV hallucinogenes use disorder [N (%)]			1	0	0.991
Hallucinogenes abuse (%)	4 (6.90)	4 (9.09)			
Hallucinogenes dependency (%)	0 (0)	0 (0)			
Psychotic disorder					
Lifetime history of DSM-IV psychotic disorder [N (%)]			8	12.05	0.115
Schizophrenia	16 (15.7)	11 (25)			
Schizophreniform disorder	7 (12.1)	5 (8.6)			
Brief psychotic disorder	6 (10.3)	2 (4.5)			
Schizoaffective disorder	5 (8.6)	2 (4.5)			
Delusional disorder	4 (6.9)	2 (4.5)			
Substance-induced psychotic disorder	17 (29.3)	13 (29.6)			
Psychotic disorder not otherwise specified	0 (0)	7 (15.9)			
Major depressive disorder with psychotic symptoms	2 (3.5)	2 (4.5)			
Bipolar disorder with psychotic symptoms	1 (1.7)	0 (0)			

sTable 3 Comparison between included and excluded ROP based on missing age of cannabis use initiation

	Missing	Not Missing	df	T/Z/X²	p-value
Samples and Study Variables					
Sample sizes	14	105			
CIP (%)	0 (0)	46 (43.8)	1	8.236	0.004
Age [mean (SD) years]	23.8 (5.1)	23.4 (4.2)	15.44	-0.282	0.782
Sex [F (%)]	3 (21.4)	23 (21.9)	1		1
Sample Size per Site			18		<0.001
Munich (%)	1 (7.1)	72 (68.6)			
Milan Niguarda (%)	0 (0)	6 (5.7)			
Basel (%)	2 (14.3)	0 (0)			
Cologne (%)	7 (50)	5 (4.8)			
Birmingham (%)	0 (0)	3 (2.9)			
Turku (%)	0 (0)	5 (4.8)			
Udine (%)	0 (0)	1 (1.0)			
Düsseldorf (%)	0 (0)	2 (1.9)			
Bari (%)	2 (14.3)	0 (0)			
Cannabis Use					
Lifetime History of DSM-IV Cannabis Use Disorder [N (%)]			6		0.047
Cannabis abuse (%)	12 (85.7)	48 (45.7)			
Cannabis dependency (%)	2 (14.3)	42 (40.0)			
Cumulative months lifetime [mean (SD) months]	24.5 (33.2)	46.9 (38.7)	1.09	-0.933	0.511
Duration of heaviest use [mean (SD) days]	401.7 (693.7)	620.7 (715.5)	3.272	-0.618	0.577
Level of Use in the Heaviest Use Period (%)			2	5.922	0.052
> 10 times per month / dependency	7 (50.0)	86 (82.9)			
< 10 times per month	3 (21.4)	11 (10.5)			
Only once	2 (14.3)	4 (3.8)			
Duration since last use [mean (SD) days]	1889.8 (2514.2)	315.5 (959.0)	5.088	1.496	0.194
Level of Use in the Last 3 Months – Cumulative Frequency (%)			7	7.110	0.418
0 times	5 (35.7)	33 (31.4)			
1-5 times	0 (0)	8 (7.2)			
6-10 times	0 (0)	6 (5.7)			
11-15 times	0 (0)	5 (4.8)			
16-20 times	0 (0)	4 (3.8)			
21-30 times	0 (0)	3 (2.9)			
> 30 times	0 (0)	21 (20.0)			
Psychopathology [mean (SD)]					
Positive and Negative Syndrome Scale - Positive	23.5 (5.1)	19.37 (6.2)	18.841	2.754	0.013
Positive and Negative Syndrome Scale - Negative	21.6 (7.5)	14.5 (5.5)	15.098	3.440	0.004
Positive and Negative Syndrome Scale - General	44.8 (12.3)	34.2 (8.2)	14.745	3.138	0.007
Onset Age of Psychotic Disorder	23.2 (5.2)	23.5 (4.2)	12.742	-0.227	0.824
Medication [mean (SD)]					
Currently treated (%)	6 (42.9)	66 (62.9)	4	-	0.154
Chlorpromazine equivalent (cumulative lifetime)	5289.5 (7497.4)	4728.9 (7548.6)	12.315	0.235	0.818

sTable 4 Demographics and Clinical Data correlated with the age of cannabis initiation

	Mean (SD)	df	correlation [confidence interval]	p-value
Age (years)	23.8 (4.1)	100	0.090 [-0.107, 0.279]	0.369
Cumulative months lifetime (months)	45.6 (38.6)	56	-0.359 [-0.565, -0.111]	0.006
Duration of heaviest use (days)	624.3 (722.6)	92	-0.250 [-0.430, -0.050]	0.015
Duration since last use (days)	330.3 (973.3)	91	-0.076 [-0.276, 0.129]	0.468
Level of Use in the Last 3 Months – Cumulative Frequency (%)	-		-0.014	0.907
Level of Use in the Last 3 Months – Average Frequency	-		0.140	0.255
Positive and Negative Syndrome Scale - Positive	19.5 (6.2)	93	-0.223 [-0.406, -0.023]	0.030
Positive and Negative Syndrome Scale - Negative	14.5 (5.6)	92	0.039 [-0.165, 0.240]	0.712
Positive and Negative Syndrome Scale - General	34.2 (8.3)	91	-0.121 [-0.317, 0.085]	0.248
Onset Age of Psychotic Disorder	23.5 (4.0)	96	0.137 [-0.063, 0.327]	0.178
Chlorpromazine equivalent (cumulative lifetime)	4824.4 (7594.6)	97	0.186 [-0.012, 0.370]	0.065

sTable 5 sMRI protocol per Site

PRONIA Site	Model	Field Strength	Flip Angle	TR (ms)	TE (ms)	Voxel size [mm]	FOV	Slice Number
Munich	Philips Ingenia	3T	8	Shortest (9.4)	Shortest (5.5)	0.97 x 0.97 x 1.0	250 x 250	190
Milan Niguarda	Philips Achieva Intera	1.5T	12	Shortest (8.1)	Shortest (3.7)	0.94 x 0.94 x 1.0	240 x 240	170
Basel	SIEMENS Verio / Prisma	3T	8	2000	3.4	1.0 x 1.0 x 1.0	256 x 256	176
Cologne	Philips Achieva	3T	8	9.5	5.5	0.97 x 0.97 x 1.0	250 x 250	190 / 165
Birming-ham	Philips Achieva	3T	8	8.4	3.8	1.0 x 1.0 x 1.0	288 x 288	175
Turku	Philips Ingenuity	3T	7	8.1	3.7	1.0 x 1.0 x 1.0	256 x 256	176
Udine	Philips Achieva	3T	12	Shortest (8.1)	Shortest (3.7)	0.93 x 0.93 x 1.0	240 x 240	170
Düsseldorf	SIEMENS TrioTim	3T	8	2000	3.4	1.0 x 1.0 x 1.0	256 x 256	176

sTable 6 Cognitive Test Battery (PRONIA and CIP) - Table adapted from [22]

Neurocognitive domain	**Cognitive test**	**Description part of the test parts relevant for our analyses**	**Measure of interest**
Social cognition	Diagnostic Analysis of Nonverbal Accuracy -2	Participants are presented with 24 faces on a tablet showing 4 different emotions; happy, neutral, angry, sad and have to decide which emotion is represented.	number of correct responses
Speed of processing	1. Trail Making Test (TMT): Part A 2. Verbal Fluency: semantic Wechsler Adult Intelligence Scale, 3rd ed., 3. digit symbol coding task	1. participants have to combine numbers in ascendent order (paper-pencil) 2. participants had 1 minute to produce as many words as possible from the semantic category *animals*. 3. Participants were presented with 9 symbols each corresponding to a number from 1-9 on the top of a sheet of paper. Then, they had to write the corresponding number under as many symbols as possible in 1 minute on the same sheet of paper. (paper-pencil)	1. time of execution 2. correct words 3. number of correctly matched symbols
Working memory	Wechsler Memory Scale, 3rd ed., spatial span subtest	Participants have to repeat sequences of numbers with increasing difficulties (one number added in each sequence) first forward then backward.	sum of number of correct trials
Verbal learning	Rey Auditory Verbal Learning Test (RAVLT) and for Turku harmonized HVLT-R (see harmonization description in 8.3)	Participants have to immediately recall as many words as possible from a list of 12 words that is audio-played to them.	sum of correctly recalled words
Reasoning	Wechsler Adult Intelligence Scale, 4th ed., Matrix Reasoning	Participants are presented with a matrix showing a sequence of abstract pictures. The participants have to decide which picture of a number of possible options would complete the sequence best.	sum of correct responses
Attention	Continuous Performance Task – Identical Pairs (CPT-IP)	Participants were presented with 300 four-digit numbers on a tablet-screen with a rate of one per second and had to click as fast as possible on a computer-mouse in case of identical repeating numbers.	difference between standardized z-scores of correct and false alarm
Global cognition	Composite across all cognitive measures included above (average z-score)	The scores from all included domains were standardized to z-scores.	Sum of all standardized z-scores.

sTable 7 averaged z-scores of all 6 cognitive domains and the composite score correlated with the age of cannabis use initiation and the cerebellar component (COI-9)

	df	correlation [confidence interval]	p-value
Age of cannabis use initiation			
Social cognition	94	0.043 [-0.159, 0.241]	0.680
Speed of processing	91	-0.096 [-0.294, 0.110]	0.359
Working memory	94	-0.109 [0.302, 0.094]	0.292
Verbal learning	94	-0.057 [-0.255, 0.145]	0.580
Reasoning	90	-0.087 [-0.287, 0.120]	0.410
Attention	94	0.014 [-0.187, 0.214]	0.890
Global cognition	88	-0.094 [-0.295, 0.115]	0.378
Loadings of cerebellar component (COI-9)			
Social cognition	94	-0.028 [-0.228, 0.173]	0.783
Speed of processing	91	0.048 [-0.157, 0.249]	0.647
Working memory	94	0.046 [-0.156, 0.244]	0.655
Verbal learning	94	0.072 [-0.131, 0.268]	0.488
Reasoning	90	-0.089 [-0.289, 0.118]	0.398
Attention	94	0.074 [-0.128, 0.271]	0.472
Global cognition	88	0.057 [-0.152, 0.261]	0.594

sTable 8 Demographic and Clinical Data in the sample restricted to schizophrenia spectrum disorder (SSD)

	Early (< 17)	Late (17 +)	df	T/Z/X²	p-value
Samples and Study Variables					
Sample sizes	27	17			
CIP (%)	8 (29.6)	2 (11.8)	1	1.015	0.314
Age [mean (SD) years]	24.5 (4.7)	24.0 (4.2)	37.3	0.314	0.755
Sex [F (%)]	6 (22.2)	5 (29.4)	4	-	0.724
Sample Size per Site			12	-	0.1953
Munich (%)	19 (70.4)	10 (58.8)			
Milan Niguarda (%)	0 (0)	0 (0)			
Basel (%)	6 (22.2)	2 (11.8)			
Cologne (%)	1 (3.7)	3 (17.6)			
Birmingham (%)	1 (3.7)	0 (0)			
Turku (%)	0 (0)	1 (5.9)			
Udine (%)	0 (0)	1 (5.9)			
Düsseldorf (%)	0 (0)	0 (0)			
Cannabis Use					
Lifetime History of DSM-IV Cannabis Use Disorder [N (%)]			6	-	0.703
Cannabis abuse (%)	17 (63.0)	13 (76.5)			
Cannabis dependency (%)	7 (25.9)	3 (17.6)			
Initiation Age [mean (SD) years]	14.2 (1.2)	20.8 (4.1)	17.921	-6.126	<0.001
Cumulative months lifetime [mean (SD) months]	50 (34.5)	19 (24.1)	13.346	2.338	0.036
Duration of heaviest use [mean (SD) days]	589.1 (754.5)	438.6 (484.7)	35.960	0.755	0.455
Level of Use in the Heaviest Use Period (%)			2	2.053	0.358
> 10 times per month / dependency	22 (81.5)	13 (76.5)			
< 10 times per month	2 (7.4)	2 (11.8)			
Only once	3 (11.1)	0 (0)			
Duration since last use [mean (SD) days]	582.6 (1499.3)	523.7 (989.0)	38.933	0.151	0.880
Level of Use in the Last 3 Months – Cumulative Frequency (%)			12	-	0.709
0 times	11 (40.7)	7 (41.2)			
1-5 times	2 (7.4)	3 (17.6)			
6-10 times	1 (3.7)	1 (5.9)			
11-15 times	0 (0)	0 (0)			
16-20 times	1 (3.7)	0 (0)			
21-30 times	5 (18.5)	1 (5.9)			
> 30 times	1 (3.7)	2 (11.8)			
Psychopathology [mean (SD)]					
Positive and Negative Syndrome Scale - Positive	20.2 (5.6)	17.4 (8.1)	23.760	1.214	0.237
Positive and Negative Syndrome Scale - Negative	16.1 (5.5)	15.9 (5.7)	28.228	0.115	0.909
Positive and Negative Syndrome Scale - General	36.3 (7.8)	33.5 (8.1)	28.520	1.082	0.288
Onset Age of Psychotic Disorder	24.0 (4.9)	23.8 (4.0)	38.771	0.148	0.883
Years between first cannabis use initiation and attenuated psychotic symptoms – years [mean (SD)]	8.7 (5.5)	4.4 (3.2)	24.828	2.655	0.014
Years between initiation of heaviest cannabis use and attenuated psychotic symptoms – years [mean (SD)]	3.6 (5.0)	2.0 (3.1)	30.395	1.149	0.260

Medication [mean (SD)]					
Currently treated (%)	20 (74.1)	9 (52.9)	1	0.755	0.385
Chlorpromazine equivalent (cumulative lifetime)	4060.0 (5961.3)	5656.8 (9130.1)	22.698	-0.625	0.538

sTable 9 Demographic and Clinical Data in the sample restricted to male

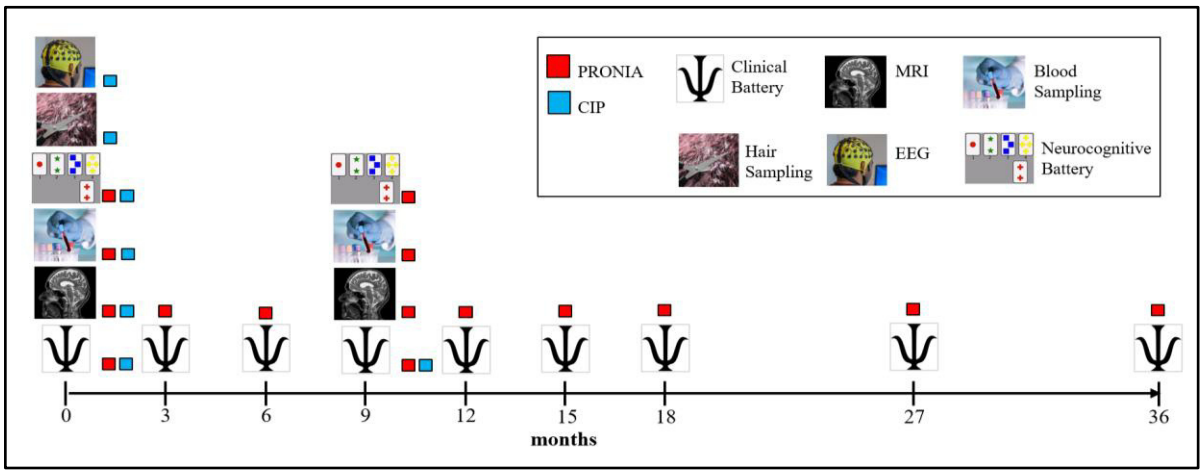
	Early (< 17)	**Late (17 +)**	**df**	**T/Z/X²**	**p-value**
Samples and Study Variables					
Sample sizes	47	32			
CIP (%)	24 (51.2)	13 (40.6)	1	0.467	0.495
Age [mean (SD) years]	23.5 (3.5)	23.4 (4.3)	57.124	0.121	0.904
Sample Size per Site			16	-	0.112
Munich (%)	35 (74.5)	20 (62.5)			
Milan Niguarda (%)	0 (0)	3 (9.4)			
Basel (%)	7 (14.9)	2 (6.3)			
Cologne (%)	2 (4.3)	2 (6.3)			
Birmingham (%)	3 (6.4)	0 (0)			
Turku (%)	0 (0)	3 (9.4)			
Udine (%)	0 (0)	1 (3.1)			
Düsseldorf (%)	0 (0)	1 (3.1)			
Cannabis Use					
Lifetime History of DSM-IV Cannabis Use Disorder [N (%)]			6	-	0.519
Cannabis abuse (%)	19 (40.4)	16 (50.0)			
Cannabis dependency (%)	22 (46.8)	11 (34.4)			
Initiation Age [mean (SD) years]	14.9 (1.1)	17.8 (3.5)	35.339	-7.615	<0.001
Cumulative months lifetime [mean (SD) months]	60.8 (39.6)	25.4 (26.9)	41.218	3.588	<0.001
Duration of heaviest use [mean (SD) days]	847.5 (901.1)	402.4 (428.9)	65.403	2.850	0.006
Level of Use in the Heaviest Use Period (%)			2	0.687	0.709
> 10 times per month / dependency	41 (87.2)	27 (84.4)			
< 10 times per month	4 (8.5)	3 (9.4)			
Only once	1 (2.1)	0 (0)			
Duration since last use [mean (SD) days]	275.0 (752.2)	257.9 (729.8)	59.092	0.096	0.924
Level of Use in the Last 3 Months – Cumulative Frequency (%)			16	-	0.870
0 times	12 (25.5)	9 (28.1)			
1-5 times	2 (4.3)	3 (9.4)			
6-10 times	4 (8.5)	1 (3.1)			
11-15 times	3 (6.4)	2 (6.3)			
16-20 times	1 (2.1)	2 (6.3)			
21-30 times	2 (4.3)	1 (3.1)			
> 30 times	11 (23.4)	5 (15.6)			
Psychopathology [mean (SD)]					
Positive and Negative Syndrome Scale - Positive	20.7 (5.5)	18.3 (7.0)	54.830	1.597	0.116
Positive and Negative Syndrome Scale - Negative	14.6 (5.5)	14.9 (5.5)	62.032	-0.237	0.814
Positive and Negative Syndrome Scale - General	35.0 (8.2)	33.0 (6.0)	71.438	1.216	0.228
Onset Age of Psychotic Disorder	23.0 (3.6)	23.3 (4.1)	58.594	-0.262	0.794

Years between first cannabis use initiation and attenuated psychotic symptoms – years [mean (SD)]	6.9 (3.8)	3.6 (4.4)	33.676	2.911	0.006
Years between initiation of heaviest cannabis use and attenuated psychotic symptoms – years [mean (SD)]	2.3 (3.2)	1.4 (2.8)	55.378	1.090	0.280
Medication [mean (SD)]					
Currently treated (%)	28 (59.6)	20 (62.5)	1	0.040	0.841
Chlorpromazine equivalent (cumulative lifetime)	4276.4 (7196.8)	4894.2 (8469.3)	57.558	-0.332	0.741

sTable 10 Voxel based morphometry Analysis Results

Brain region	**MNI coordinates**			t_{max}	z_{max}	**Cluster size (voxels)**
	x	**y**	**z**			
Cerebellum anterior lobe, Culmen, Vermis 4/5	0	-50	-2	3.11	3.02	54
Cerebellum posterior lobe, Uvula	28	-80	-36	2.93	2.86	37

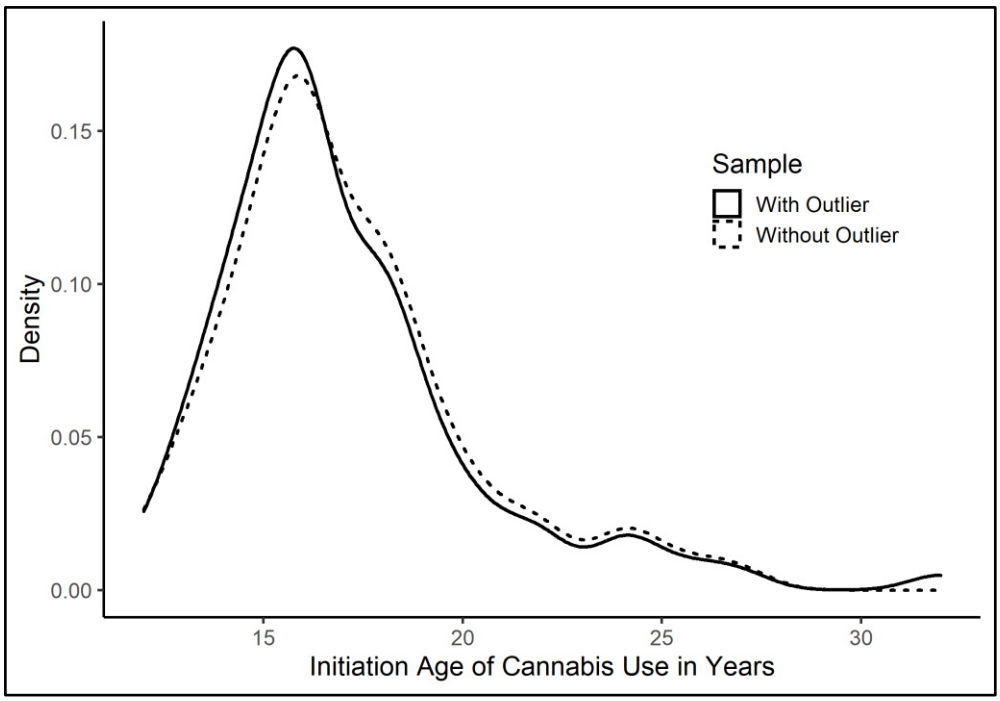
Supplementary - Figures



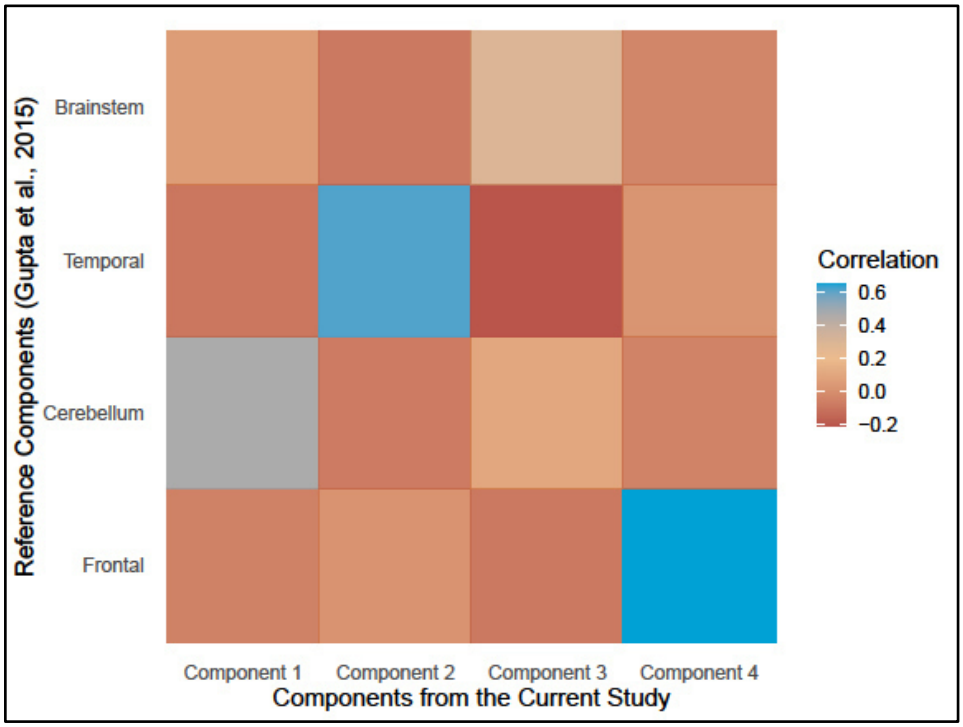
sFigure 1 Design of PRONIA and CIP studies (Figure adapted from [12]) The colored boxes indicate the study containing each assessment.

SUBSTANCE USE (dd-mm-yyyy)	___-___-_____	
Cannabis lifetime *(follow-up: since the last assessment)*	0 = No 1 = Yes	Date of onset: Date of offset: (ongoing: 66-66-6666)
Cumulative number of months:		
Daily/weekly frequency of use (average) during the last 3 months *(follow-up: since the last visit)*	1 = daily 2 = > 3 days a week 3 = <= 3 days a week 4 = less than weekly 5 = never	
Cannabis - cumulative frequency of use during the last 3 months (follow-up: since the last visit)	1 = 1-5 times 2 = 6-10 times 3 = 11-15 times 4 = 16-20 times 5 = 21-30 times 6 = > 30 times 7 = not applicable	
Last consumption (dd-mm-yyyy)	___-___-_____	
Other substances lifetime *(follow-up: since the last visit)*	1 = hallucinogens 2 = cocaine 3 = amphetamine-type stimulants incl. MDMA 4 = inhalants 5 = opioids 6 = PCP or similar type 7 = other designer drugs 8 = sedative-yypnotic- anxiolytic 9 = none	
Other substances – daily/weekly frequency of use (average) during the last 3 months *(follow-up: since the last visit)*	1 = daily 2 = > 3 days a week 3 = <= 3 days a week 4 = less than weekly 5 = never	
Other substances - cumulative frequency of use during the last 3 months (different drugs can be added) *(follow-up: since the last visit)*	1 = 1-5 times 2 = 6-10 times 3 = 11-15 times 4 = 16-20 times 5 = 21-30 times 6 = > 30 times 7 = not applicable	
Last consumption (dd-mm-yyyy)	___-___-_____	

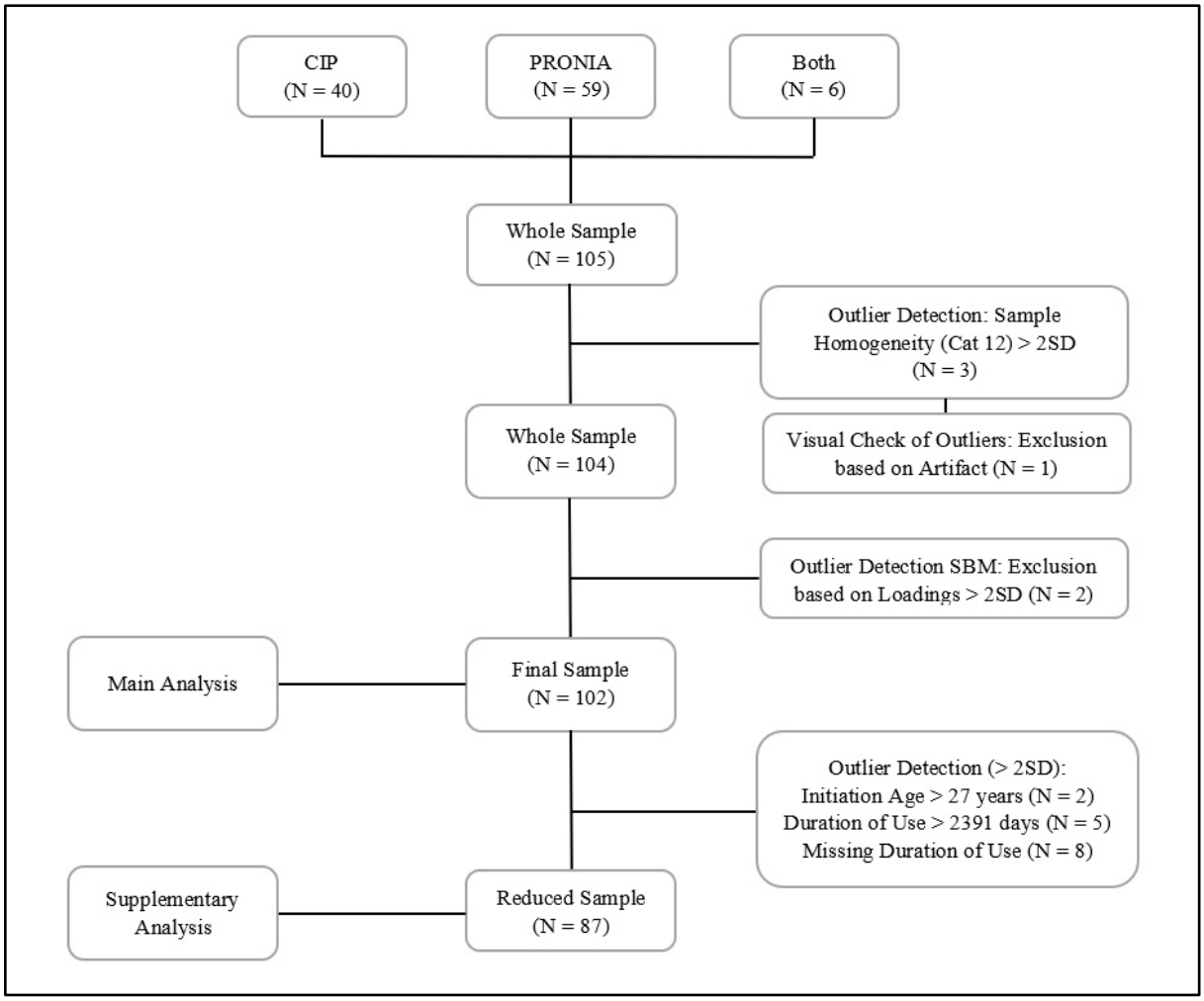
sFigure 2 Substance Use Questionnaire



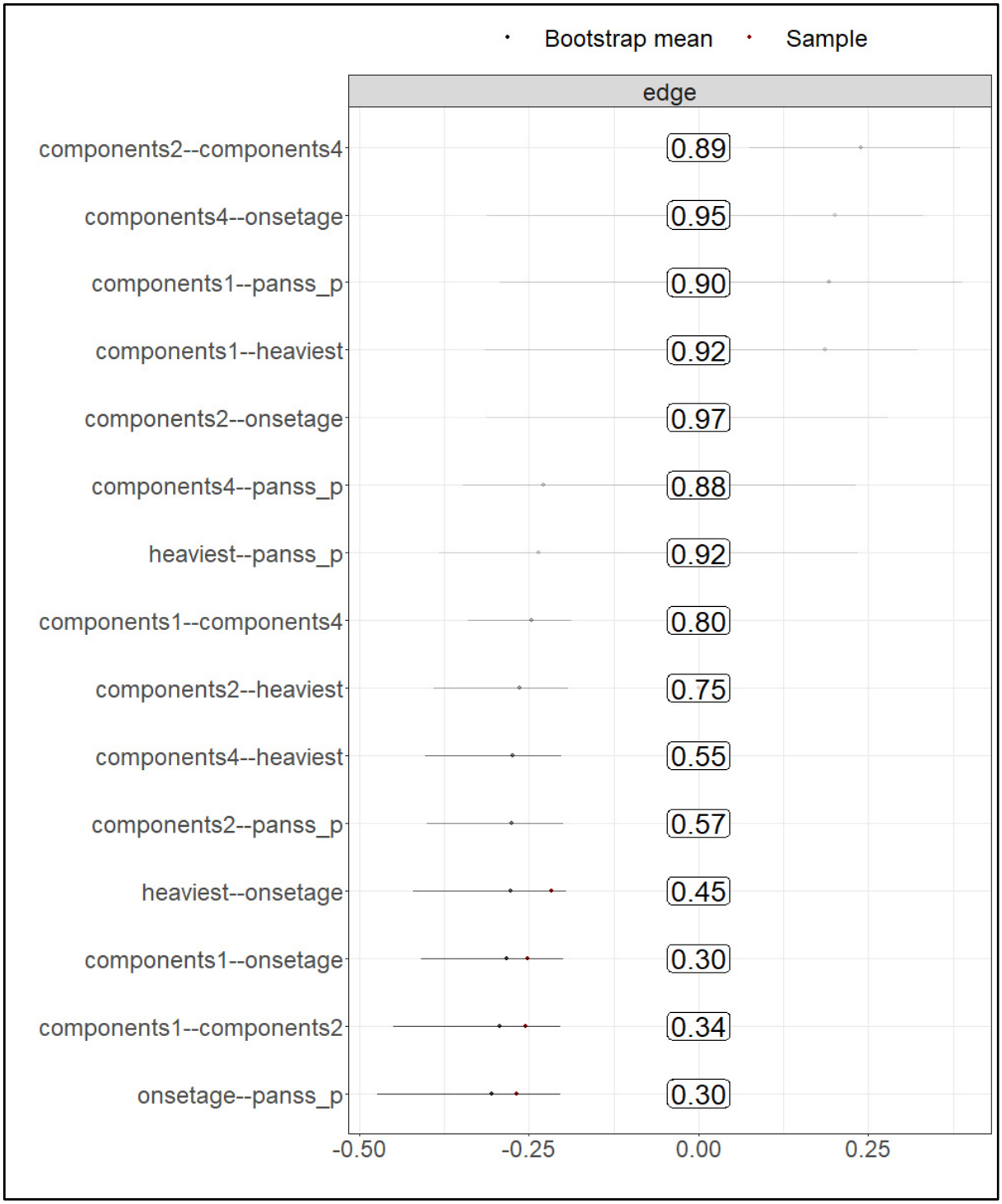
sFigure 3 Distribution of age of initiation. The distribution of age of cannabis use initiation is shown for the whole sample, with (n = 102) and without (n = 95) inclusion of significant outliers in initiation age and duration of heaviest use.



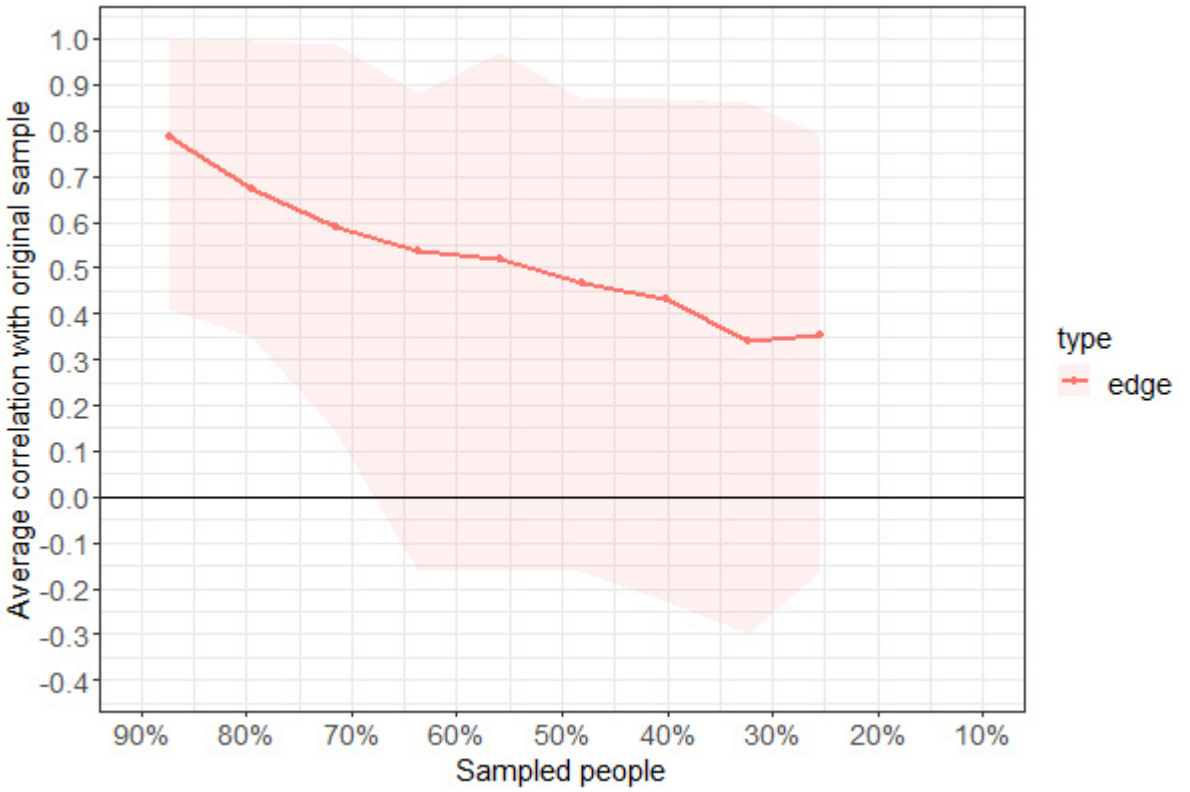
sFigure 4 Correlation between the components from the current study and the reference components - The heatmap represents the pairwise correlation between the components. Thereby, all non-zero voxels were correlated with each other.



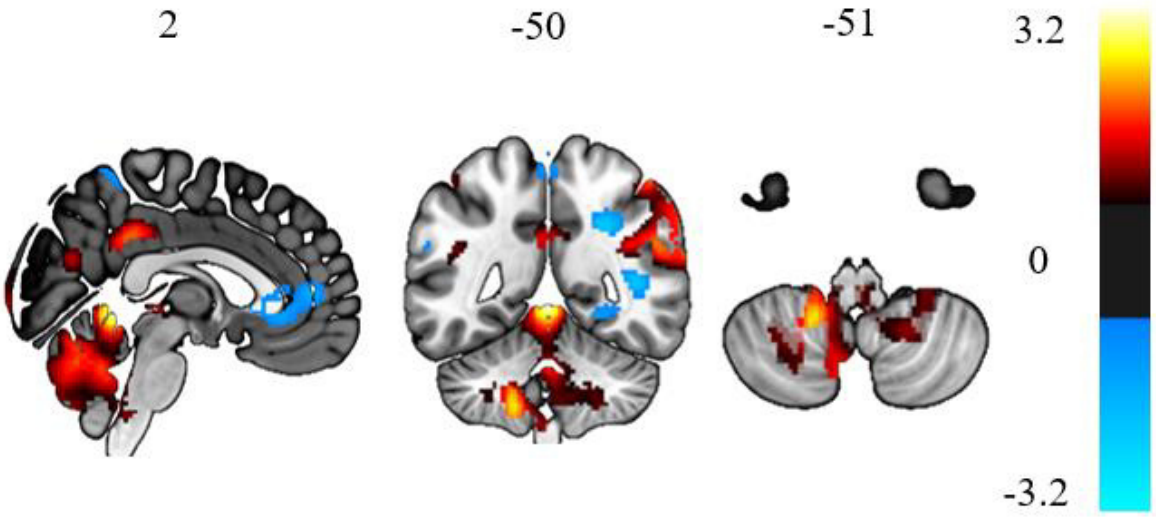
sFigure 5 Flow Diagram - Inclusion based on Outlier



sFigure 6 Results of bootstrapping the network 1000 times. Numbers in squares represent how often an edge was set to zero, i.e., not included in the network. This output shows that the edges retained in our final model were also included in the majority of bootstrapped networks.



sFigure 7 Stability of edge weights testing by case dropping subset bootstrapping for the six-item network. The x-axis depicts the percentage of cases of the original sample used at each step. The y-axis depicts the average of correlations between the edge weights from the original network with the edge weights from the networks that emerged after dropping x-percentage of cases. The maximum proportion of observations that could be dropped while confidently (95%) retaining results of high correlation (r > .7) with centrality estimates in the original sample was 0 %, indicating low stability.



sFigure 8 Results of the VBM analysis – Correlation between age of cannabis initiation and GM volume; voxels threshold at |Z| > 1.5 are shown.

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6. Paper II: Summary

Previously, continued cannabis use after a first-episode of psychosis has consistently been associated with elevated risk for poor long term clinical-outcome. Further, in individuals with CHR only one study examined continued cannabis use and found an elevated risk for the transition to psychosis. Notably, individuals with first episode of psychosis who discontinued cannabis use after a first admission to the hospital presented with a comparable long term clinical outcome like individuals who never used the substance. However, treatments that aim to support abstinence have variable outcomes in cannabis users and, so far, it is not well understood who would continue to use the substance. Thus, in the second presented work (paper II) we aimed at developing a predictor of continued cannabis use nine months after baseline assessment in individuals with ROP and CHR. We included N = 109 individuals with ROP (N = 54 with continued cannabis use) in our discovery sample from the PRONIA and the CIP study, and further tested it in N = 73 individuals with CHR (N = 36 with continued cannabis use) from the PRONIA study. To this aim, we trained models in a repeated nested cross-validation based on three different modalities, i.e., interview-based variables, cognitive variables and GMV as well as superordinate models via stacking. The clinical predictor provided clinically useful and significant results, classifying about 73 % of individuals with ROP and 59 % individuals with CHR correctly. Adding any of the other modalities did not improve the predictive accuracies. Especially specific substance use patterns, lower global functioning, a lack of coping strategies and urbanicity were reliably contributing to the prediction of continued cannabis use, emphasizing their relevance for possible treatment efforts. Future studies are required to test our predictor in independent samples of individuals with ROP to disentangle whether the drop in predictive accuracy when applied to individuals with CHR is best explained by low generalizability to other samples or differences between the groups in terms of symptom severity and specific cannabis use patterns.

Schizophrenia

ARTICLE OPEN

Pattern of predictive features of continued cannabis use in patients with recent-onset psychosis and clinical high-risk for psychosis

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Continued cannabis use (CCu) is an important predictor for poor long-term outcomes in psychosis and clinically high-risk patients, but no generalizable model has hitherto been tested for its ability to predict CCu in these vulnerable patient groups. In the current study, we investigated how structured clinical and cognitive assessments and structural magnetic resonance imaging (sMRI) contributed to the prediction of CCu in a group of 109 patients with recent-onset psychosis (ROP). We tested the generalizability of our predictors in 73 patients at clinical high-risk for psychosis (CHR). Here, CCu was defined as any cannabis consumption between baseline and 9-month follow-up, as assessed in structured interviews. All patients reported lifetime cannabis use at baseline. Data from clinical assessment alone correctly classified 73% ($p < 0.001$) of ROP and 59 % of CHR patients. The classifications of CCu based on sMRI and cognition were non-significant (ps > 0.093), and their addition to the interview-based predictor via stacking did not improve prediction significantly, either in the ROP or CHR groups (ps > 0.065). Lower functioning, specific substance use patterns, urbanicity and a lack of other coping strategies contributed reliably to the prediction of CCu and might thus represent important factors for guiding preventative efforts. Our results suggest that it may be possible to identify by clinical measures those psychosis-spectrum patients at high risk for CCu, potentially allowing to improve clinical care through targeted interventions. However, our model needs further testing in larger samples including more diverse clinical populations before being transferred into clinical practice.

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INTRODUCTION

Cannabis use has a prominent role in the development of psychosis[1,2], and exacerbates the course of the full-blown psychotic disorder[3,4]. Indeed, patients with psychosis who are habitual cannabis users have distinctly worse long-term outcome compared to those without concurrent cannabis use in terms of re-hospitalization, the severity of psychotic symptoms and general functioning[5]. In first episodes of psychosis, cannabis use is reportedly among the most powerful predictors of relapse to psychosis[6]. Likewise, in patients at clinical high-risk for psychosis (CHR) reporting lifetime cannabis use, continued cannabis use (CCu) after experiencing attenuated psychotic symptoms increased the risk of transition[7]. However, the number of individuals with cannabis use disorder has increased worldwide in recent years[8], with correspondingly high rates of cannabis use disorder reported in early psychosis patients[9]. The vulnerability to

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CCu remains even after treatment to encourage cannabis abstinence[10], and the response to abstinence interventions varies greatly between individuals[11].

This body of evidence suggests that detecting individuals at risk for CCu as well as investigating and understanding the factors and mechanisms associated with CCu is from a preventive perspective important to improve the prospects for a good long-term outcome in CHR and recent-onset psychosis (ROP) patients[12]. In cannabis users drawn from community-based samples, sociodemographic factors such as young age, male sex, low income, higher body mass index (BMI) and substance use patterns each predicted relapse of cannabis use[13,14]. Further, the transition from irregular cannabis use to cannabis use disorder—a form of CCu that persists despite distress or impairment caused by the substance[15]—can be predicted by the pattern of substance use, as well as by mental health problems, history of traumatic events, schizotypal personality and living in an urban area[16–18]. Moreover, among clinically dependent cannabis users, poor current functioning predicts relapse of cannabis use[19,20]. Only one study[20] has hitherto investigated predictors of cannabis relapse in psychotic patients ($N = 66$), wherein psychotic symptoms proved to be most predictive of relapse of cannabis use. However, a review of self-reported reasons for cannabis consumption by patients with psychosis[21] concluded that present psychotic symptoms and self-medication are rarely reported as reasons for cannabis consumption. Instead, groups of psychotic patients[21] and CHR patients[22] both reported mood enhancement and social motives as their primary motivations for use. Cognitive deficits have been linked with relapse for several substances[23], although the link with cognition is less consistently reported for cannabis compared to other substances[24]. Meta-analytic evidence of cognitive deficits attributable to cannabis use is complex, showing negative effects of cannabis on cognition in non-psychotic individuals, but also better preserved cognitive functions in psychotic patients with concurrent cannabis use[25]. Notably, the environmental risk factors for CCu, and the presence of cognitive deficits have also been individually associated with cannabis use in general, and with an increased risk for psychosis[26,27].

Whether addiction—that is to say, a substance use disorder—should properly be called a "brain disease" remains a matter of debate[28]. Nonetheless, drug-seeking and relapse in the use of diverse substances, such as alcohol[29,30] and cocaine[31], have consistently been associated with underlying neurobiological alterations[32,33]. Interestingly, there is a substantial overlap between brain regions that are associated with drug-seeking in general, cannabis use disorder and psychosis[32–35]. Decreased grey matter volume (GMV) in the frontal cortex, hippocampus, insula and temporal lobe and increased volume in the cerebellar cortex, are common to all three conditions[32,34–37]. Further, effects of cannabis use on brain structure were more pronounced in psychotic individuals and individuals at clinical high-risk for developing psychosis compared to the effects in healthy individuals, potentially indicating a particular sensitivity to cannabis exposure[38].

Several studies have investigated the association between these risk factors and cannabis relapse[13,20] or the development of a cannabis use disorder[16–18]. Nevertheless, their power for predicting CCu in psychotic patients and their generalizability to other clinical cases—a precondition for model implementation into clinical practice[39]—have not yet been tested. Moreover, most studies have analyzed risk factors in isolation, without considering their potentially interconnected nature[40]. Progress in the field of predictive medicine using multivariable approaches has demonstrated that models enabling the simultaneous investigation of several risk factors and multiple data modalities can often outperform unimodal predictors for conversion to psychosis[41,42], diagnostic approaches[43] and functional outcome[37].

In the current study, we (1) investigated multiple data modalities using machine learning[39] to assess their power to predict CCu in patients with ROP. More specifically, we generated three predictive models of CCu based on single data modalities (*unimodal*); namely (i) clinical, (ii) cognitive and (iii) structural magnetic resonance imaging (sMRI)-based predictors. Next, we combined these models for super-ordinate prediction, to test whether combinations of unimodal predictors would improve the predictive performance of the algorithm. Then, (2) we applied the predictors to CHR individuals, aiming to assess the predictors' generalizability to patients less severely affected in terms of psychotic symptoms and cannabis use. Finally, (3) we assessed how CCu is associated with several aspects of long-term clinical outcome to confirm previously published clinical relevance of CCu in ROP and CHR[4,5,7]. We hypothesized that there should emerge a pattern of interview-based variables at baseline that would predict CCu in our ROP sample above chance level and that, due to overlapping reasons for cannabis use between ROP and CHR patients[22], this model would generalize well to a separate CHR population. Further, we hypothesized that including cognition and sMRI results would improve the algorithm's predictive performance. In line with previous publications[4,5] we expected that CCu would be associated with a worse long-term clinical outcome in ROP and CHR patients, thus highlighting the clinical relevance of the prediction.

RESULTS

Sample characteristics

Overall, we included 182 patients (mean [SD] age, 23.8 [4.7] years and female = 68 [36.8%]) (Table 1) who all reported lifetime cannabis use at baseline. Eighty-seven patients (47%) had a CCu within a nine-month follow-up period, i.e. at least one cannabis consumption between baseline and follow-up. All other patients remained abstinent until at least nine months after baseline assessment and were labelled discontinued cannabis use *(DCu)*. Follow-up data for DCu patients was available on average for a mean (SD) of 597 (254) days from the baseline assessment. In this time period, only $N = 8$ (8.7%) subjects labelled as DCu had a relapse in cannabis use after the nine-month follow-up. On average, patients with CCu resumed cannabis consumption after a mean (SD) of 94 (100) days from the baseline assessment. The time between baseline and renewed cannabis use did not significantly differ between CHR and ROP groups (mean [SD], 87 [100] days for CHR and 97 [102] days for ROP; $t_{32} = -0.33$, $p = 0.744$). We trained and tested our model in repeated nested cross-validation strictly separating training and testing folds on $N = 109$ patients of age 15–40 years with ROP and tested our model in a separate group of $N = 73$ CHR patients.

In the ROP and CHR groups, CCu was significantly associated with more recent cannabis consumption at baseline. CHR patients with CCu were more likely to be male than those with DCu ($\chi^2_1 = -6.11$, $p = 0.013$). ROP patients with CCu had significantly lower lifetime highest role functioning ($t_{105} = -2.67$, $p = 0.009$), more severe Positive and Negative Syndrome Scale (PANSS)[44]—general scores ($t_{103} = 2.66$, $p = 0.009$), as well as a higher number of SCID-IV diagnoses for cannabis use disorder compared with ROP patients with DCu ($\chi^2_2 = -9.61$, $p = 0.010$; Table 1). Due to missing information or inadequate MR image quality, our samples differed slightly for the predictors based on cognition ($N_{ROP} = 105$, $N_{CHR} = 73$) and sMRI ($N_{ROP} = 101$, $N_{CHR} = 61$) (Supplementary Fig. 7).

Prediction of continued cannabis use

Only the unimodal predictor based exclusively on clinical predictors yielded significant prediction of CCu in ROP patients (balanced accuracy (BAC) = 73.3%, $p = 0.001$). Further, this model had an acceptable Area Under the Curve (AUC = 0.75) as defined previously (AUC ≥ 0.7[45]). Applied to the CHR group, the BAC dropped significantly by 14.2% points ($p < 0.001$, Supplementary Fig. 8) but still provided a correct prediction in 58.7% of the CHR

Table 1. Demographic information of patients with recent-onset psychosis and patients with clinical high-risk for psychosis.

	CCu	DCu	Statistical analysis	*p*	CCu	DCu	Statistical analysis	*p*
Discovery sample (ROP; $N = 109$)					Validation sample (CHR; $N = 73$)			
Sample Size [*N* (%)]	54 (49.5)	55 (50.5)			36 (49.3)	37 (50.7)		
Sample Size per Study Site [*N* (%)]:								
Munich (%)	29 (53.7)	25 (45.5)	$\chi^2_9 = 11.90$	0.156	12 (33.3)	15 (40.5)	$\chi^2_9 = -8.81$	0.455
Milan (%)	4 (7.4)	3 (5.5)			2 (5.6)	2 (5.4)		
Basel (%)	9 (16.7)	3 (5.5)			4 (11.1)	1 (2.7)		
Cologne (%)	2 (3.7)	9 (16.4)			6 (16.7)	10 (27.0)		
Birmingham (%)	3 (5.6)	3 (5.5)			0 (0.0)	2 (5.4)		
Turku (%)	4 (7.4)	7 (12.7)			3 (8.3)	2 (5.4)		
Udine (%)	0 (0.0)	0 (0.0)			1 (2.8)	0 (0.0)		
Bari (%)	0 (0.0)	2 (3.6)			0 (0.0)	1 (2.8)		
Duesseldorf (%)	0 (0.0)	1 (1.8)			3 (8.3)	2 (5.4)		
Muenster (%)	3 (5.6)	2 (3.6)			5 (13.9)	2 (5.4)		
Time of Relapse [mean (SD) days after Baseline]	97.4 (102.0)	–			87 (100.1)	–		
Age [mean (SD) years]	23.8 (4.3)	25.1 (5.2)	$t_{104} = -1.45$	0.151	22.0 (3.7)	23.8 (5.2)	$t_{65} = -1.80$	0.076
Sex [Female (%)]	15 (27.8)	19 (34.5)	$\chi^2_1 = 0.31$	0.578	**11 (30.6)**	**23 (62.2)**	$\mathbf{\chi^2_1 = -6.11}$	**0.013**
Race/ethnicity [*N* (%)]								
White (%)	43 (79.6)	42 (76.4)	$\chi^2_5 = -3.06$	0.691	28 (77.8)	35 (94.6)	$\chi^2_3 = -5.64$	0.131
Asian (%)	4 (7.4)	5 (9.1)			2 (5.6)	0 (0)		
African (%)	1 (1.9)	1 (1.8)			2 (5.6)	1 (2.7)		
Mixed (%)	4 (7.4)	3 (5.5)			0 (0)	0 (0)		
Other (%)	1 (1.9)	4 (7.3)			4 (11.1)	1 (2.7)		
BMI [mean (SD)]	23.1 (4.1)	22.9 (4.0)	$t_{97} = -0.30$	0.763	23.5 (4.4)	22.0 (2.9)	$t_{59} = 1.71$	0.092
Education [mean (SD) years]	13.3 (2.7)	13.9 (2.7)	$t_{105} = -1.12$	0.268	13.1 (2.6)	14.2 (2.7)	$t_{70} = -1.64$	0.106
Educational problems [mean (SD) years repeated]	0.7 (1.8)	0.4 (0.7)	$t_{67} = 1.08$	0.282	0.8 (2.2)	0.9 (2.5)	$t_{68} = -0.21$	0.837
GF-Social: highest lifetime	7.8 (0.8)	8.0 (0.8)	$t_{106} = -1.36$	0.177	7.7 (0.9)	8.1 (0.8)	$t_{68} = -1.64$	0.107
GF-Social: baseline	5.6 (1.5)	5.9 (1.5)	$t_{106} = -0.94$	0.352	5.9 (1.4)	6.6 (1.5)	$t_{71} = -1.93$	0.058
GF-Role: highest lifetime	**7.4 (0.9)**	**7.9 (0.9)**	$\mathbf{t_{105} = -2.67}$	**0.009**	7.9 (0.9)	7.9 (0.8)	$t_{69} = -0.16$	0.877
GF-Role: baseline	4.6 (1.7)	5.3 (1.9)	$t_{106} = -1.96$	0.052	5.4 (1.9)	6.0 (1.4)	$t_{64} = -1.60$	0.114
GAF Disability/Impairment Highest Lifetime	77.5 (8.8)	78.5 (9.0)	$t_{104} = -0.58$	0.561	76.6 (8.6)	79.0 (8.3)	$t_{71} = -1.22$	0.227
GAF Disability/Impairment Highest Past Month	**41.3 (10.4)**	**49.0 (16.6)**	$\mathbf{t_{91} = -2.92}$	**0.004**	48.3 (11.3)	53.0 (11.2)	$t_{70} = -0.52$	0.607
GAF Symptoms Highest Lifetime	77.7 (8.5)	79.6 (9.6)	$t_{106} = -1.07$	0.286	78.0 (9.9)	79.1 (8.8)	$t_{71} = -1.78$	0.079
GAF Symptoms Highest Past Month	40 (12.4)	43.4 (16.4)	$t_{100} = -1.21$	0.230	47.0 (10.2)	51.8 (11.8)	$t_{70} = -1.86$	0.067
Positive and Negative Syndrome Scale—Positive [mean (SD)]	20.0 (5.9)	19.2 (6.0)	$t_{105} = 0.69$	0.491	11.2 (3.5)	11.5 (3.1)	$t_{67} = -0.36$	0.718
Positive and Negative Syndrome Scale—Negative [mean (SD)]	15.2 (5.9)	14.2 (6.5)	$t_{104} = 0.87$	0.388	13.8 (6.8)	13.9 (6.0)	$t_{67} = -0.07$	0.941
Positive and Negative Syndrome Scale—General [mean (SD)]	**37.0 (10.8)**	**31.8 (9.5)**	$\mathbf{t_{103} = 2.66}$	**0.009**	30.8 (7.7)	29.5 (7.6)	$t_{68} = 0.72$	0.474
Becks Depression Inventory [mean (SD)]	22.9 (14.2)	19.1 (11.5)	$t_{93} = 1.44$	0.152	27.9 (11.5)	27.5 (10.4)	$t_{65} = 0.14$	0.891
Lifetime history of DSM-IV Cannabis use disorder [*N* (%)]								
Cannabis abuse (%)	**21 (38.9)**	**19 (34.5)**	$\mathbf{\chi^2_2 = -9.61}$	**0.008**	16 (44.4)	12 (32.4)	$\chi^2_2 = -1.14$	0.566
Cannabis dependence (%)	**17 (31.5)**	**6 (10.9)**			1 (2.8)	1 (2.7)		
Time since last Cannabis Use at Baseline [mean (SD) months]	**8.7 (25.3)**	**33.4 (60.9)**	$\mathbf{t_{66} = -2.52}$	**0.010**	**10.6 (29.2)**	**33.6 (53.8)**	$\mathbf{t_{50} = -2.14}$	**0.038**
Duration Lifetime Cannabis Use [mean (SD) months]	63.7 (50.0)	51.8 (43.9)	$t_{90} = 1.22$	0.227	52.9 (64.4)	33.7 (43.4)	$t_{45} = 1.31$	0.195
Age at Cannabis Initiation [mean (SD) years]	16.5 (2.6)	17.5 (3.7)	$t_{86} = -1.55$	0.126	17.1 (2.2)	17.5 (2.7)	$t_{56} = -0.64$	0.526
Average Number of cigarettes smoked per day [mean (SD)]	8.0 (7.4)	7.2 (7.6)	$t_{100} = 0.60$	0.553	7.7 (8.6)	4.6 (6.1)	$t_{63} = 1.71$	0.093
Average Units of alcohol consumed per day [mean (SD)]	4.4 (4.2)	5.4 (6.1)	$t_{75} = -0.92$	0.360	4.2 (5.6)	4.0 (3.3)	$t_{46} = 0.24$	0.811

Bold: significant at $p < 0.05$.
DCu discontinued cannabis use, *CCu* continued cannabis use, *BMI* body mass index, *ROP* recent-onset psychosis, *CHR* clinical high-risk for psychosis, *GAF* Global Assessment of functioning, *GF* global functioning, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition, *SD* standard deviation.

patients. The sMRI predictor performed with a BAC of 55.7% ($p = 0.093$) in the ROP and of 54.6% in the CHR group. The cognitive predictor performed below chance level in both groups (ROP: BAC = 45.6%; CHR: BAC = 49.7%). The clinical prediction accuracies could not be better explained by confounding effects (Supplementary 4), but sensitivity and specificity differed significantly depending on whether the criterion of cannabis use disorder in a lifetime was fulfilled (Supplementary 6). Stacking our significant clinical predictor with the sMRI-, the cognitive- or both predictors did not improve performance in the ROP group (BAC = 66.0–67.8%). The stacked predictors including sMRI yielded similar results as the clinical predictor when applied to the CHR group (BAC = 58.7%) (Table 2). Likewise, combining the clinical with the cognitive predictor did not significantly improve the prediction when applied to CHR compared with the unimodal clinical predictor (BAC = 60.0%, $p = 0.065$, Supplementary Fig. 8).

Predictive patterns of the clinical classifier

Features from different categories contributed reliably to the clinical classifier (Fig. 1). The significant and most reliable features predicting CCu were a higher number of substances from other substance classes tried in a lifetime and a lower lifetime highest role functioning. Further reliable predictors of CCu were a higher number of lifetime diagnoses of cannabis dependence and a lower number of units of alcohol consumption at drinking occasions, as well as lower functional disability scores of the split version of the Global Assessment of Functioning (GAF-F)[46,47] score in the past month. A higher population density of place of living, higher physical anhedonia, less frequent use of favourite food as a coping strategy and more severe mannerisms and posturing were also reliable predictors of CCu. Further, an increased likelihood of being currently unable to work because of long-term physical illness was one of the top ten most predictive features of DCu. However, this variable might be spurious, as only one ROP patient with DCu replied to this query with "yes", while all other CCu and DCu patients replied with "no" or did not respond to this question (16.5% missing answer, Supplementary Table 2 for %-missing of features and Supplementary Table 8 for univariate comparisons between CCu and DCu for all clinical variables included in the prediction).

Exploration: Continued cannabis use and long-term clinical outcome

Following investigation of long-term effects of CCu by employing linear-mixed effects models (Fig. 2, Supplementary Table 10 for further details on all models calculated), our results showed that, on average, clinical measures improved in ROP patients over the 18 months follow-up period (all $p_{FDR} < 0.007$). In the ROP group, CCu was significantly associated with lower GAF-F ($t_{136} = -3.15$, $p_{FDR} = 0.006$), lower current symptoms of the GAF Symptoms (GAF-S) ($t_{167} = -2.46$, $p_{FDR} = 0.030$), higher PANSS-general scores ($t_{168} = 3.75$, $p_{FDR} = 0.001$) and higher PANSS-positive score ($t_{205} = 2.22$, $p_{FDR} = 0.042$), while CCu did not significantly predict the sum score of the Becks Depression and Inventory-II (BDI-II)[48] ($t_{122} = 1.15$, $p_{FDR} > 0.303$). There were no significant interaction effects between time and CCu in ROP patients (all $p_{FDR} > 0.060$). In the CHR patients, all clinical measures besides BDI-II improved over the 18 months follow-up period (all $p_{FDR} < 0.001$). There was a significant time-by-group interaction for BDI-II (linear: $t_{195} = -4.46$, $p_{FDR} < 0.001$, quadratic: $t_{199} = 3.89$, $p_{FDR} < 0.001$, cubic: $t_{199} = -3.35$ $p_{FDR} < 0.003$), but no significant main effect of CCu on any of the clinical outcomes (all $p_{FDR} > 0.220$).

DISCUSSION

This is the first multivariable study examining the predictability of CCu in individuals with ROP and CHR based on unimodal and multimodal data domains. Our study adds to previous investigations by indicating (1) a potentially generalizable predictor for risk of CCu in a sample of patients who are particularly vulnerable to the harmful effects of cannabis consumption[4], and (2) by revealing a pattern of factors that might be further investigated to ultimately inform the design of tailored preventive strategies.

Table 2. Prediction results of unimodal and multimodal predictors.

	TP	TN	FP	FN	Sens%	Spec%	BAC%	PPV	NPV	PSI	NLR	PLR	AUC	*p*-value
Clinical predictor														
ROP ($N = 109$)	38	42	13	16	70.4	76.4	73.4	74.5	72.4	46.9	0.4	3.0	0.75	<0.001
Applied to CHR ($N = 73$)	15	28	9	21	41.7	75.7	58.7	62.5	57.1	19.6	0.8	1.7	0.65	NA
Cognitive predictor														
ROP ($N = 106$)	36	14	38	17	67.9	26.9	47.4	48.6	45.2	-6.2	1.2	0.9	0.41	0.763
Applied to CHR ($N = 73$)	26	12	25	10	72.2	32.4	52.3	51.0	54.5	5.5	0.9	1.1	0.48	NA
sMRI predictor														
ROP ($N = 101$)	39	17	34	11	78.0	33.3	55.7	53.4	60.7	14.1	0.7	1.2	0.56	0.093
Applied to CHR ($N = 61$)	25	8	25	5	83.3	25.8	54.6	52.1	61.5	13.6	0.6	1.1	0.68	NA
Stacked predictor (clinical and sMRI)														
ROP ($N = 109$)	34	40	15	20	63.0	72.7	67.8	69.4	66.7	36.1	0.5	2.3	0.73	0.001
Applied to CHR ($N = 73$)	15	28	9	21	41.7	75.7	58.7	62.5	57.1	19.6	0.8	1.7	0.67	NA
Stacked predictor (clinical and cognition)														
ROP ($N = 109$)	34	39	16	20	63.0	70.9	66.9	68.0	66.1	34.1	0.5	2.2	0.71	0.005
Applied to CHR ($N = 73$)	15	29	8	21	41.7	78.4	60.0	65.2	58.0	23.2	0.7	1.9	0.65	NA
Stacked predictor (clinical and sMRI and cognition)														
ROP ($N = 109$)	35	37	18	19	64.8	67.3	66.0	66.0	66.1	32.1	0.5	2.0	0.71	0.004
Applied to CHR ($N = 73$)	15	28	9	21	41.7	75.7	58.7	62.5	57.1	19.6	0.8	1.7	0.68	NA

ROP recent-onset psychosis, *CHR* clinical high-risk for psychosis, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *Sens* sensitivity, *Spec* specificity, *BAC* balanced accuracy, *PPV* positive predictive value, *NPV* negative predictive value, *PSI* prognostic summary index, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio, *AUC* area under the curve.

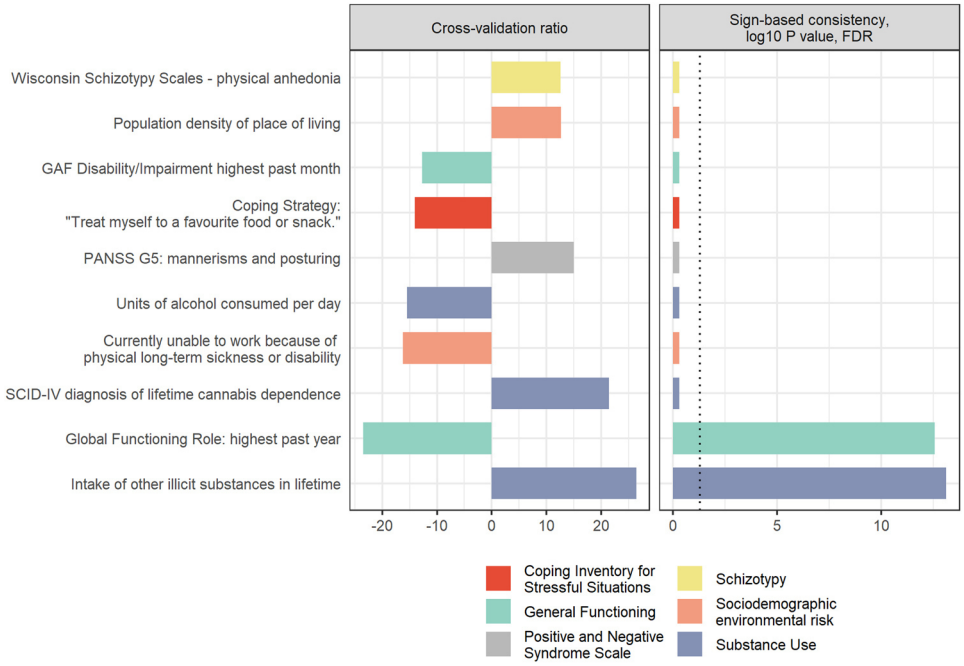

Fig. 1 Feature importance. Top ten most predictive clinical variables differentiating between continued and discontinued cannabis use until nine-month follow-up in terms of cross-validation ratio (left-side) and significant predictive features measured in terms of sign-based consistency (right-side). GAF Global Assessment of Functioning, FDR false discovery rate, PANSS G Positive and Negative Syndrome Scale—General symptoms, SCID Structured Clinical Interview for DSM Disorders.

We found evidence supporting the feasibility of generalizable and significant prediction, correctly predicting CCu and DCu within nine months after baseline in 73.3% of ROP patients, based solely on their baseline clinical data. This model generalized to CHR patients only slightly above chance (BAC = 58.7%). The most important predictors of CCu were lower lifetime best role functioning and the lifetime number of illicit substances consumed other than cannabis. Predictive performance was not improved by augmenting the model with cognitive or GMV data. Further, we found that CCu was significantly associated with worse clinical outcomes in psychotic patients, and interacted with longitudinal depressive symptoms in at-risk individuals, thus confirming the importance of timely efforts to discourage CCu in these clinical groups.

Baseline clinical predictors of continued cannabis use

Our finding that the predictive power of interview-based variables outperforms other data modalities is in line with earlier results in CHR and ROP samples presenting predictive models of other clinical outcomes, such as treatment outcome after a first episode[40], transition to psychosis[41,49–51] or global functioning[37].

We confirmed the importance of global functioning as an important predictor of CCu[52,53] and extended previous literature in two ways. First, we assessed the model's subject-specific predictive power and generalizability to at-risk individuals and investigated its effect by considering diverse factors simultaneously. Furthermore, our results reemphasize the importance of investigating broad aspects of global functioning in patients with psychosis[37,49,54]. Interestingly, CCu was mainly associated with lower levels of highest functioning. Assuming that the suboptimal functioning was also in part subjectively experienced, the lack of subjective well-functioning in several domains over a longer time period might lead to lower self-expectations, which are known to undermine abstinence[55]. The predictive power of lifetime diagnosis of cannabis dependence was expected because the diagnostic criteria of cannabis use disorder inherently entail an elevated likelihood to CCu[8,56]. The importance of the number of lifetime illicit substances is also in line with the literature[13,17,18]. Conversely, lower average alcohol consumption at drinking occasions predicted CCu. This is an interesting novel finding, as the literature has so far been inconclusive whether alcohol is typically used as a substitution or complementary to cannabis use[57]. Our finding would rather support the substitution hypothesis for alcohol use, which is in line with a previous study[58] reporting changes in alcohol consumption patterns during cannabis abstinence. In line with that evidence, we found that patients with CCu were less likely to use food or snacks as a coping strategy in stressful life situations. Additionally, the CCu patients presented with higher physical anhedonia, a decreased ability to experience pleasure, which might reflect a general lack of coping strategies against relapse to cannabis use. Importantly, this conjecture is supported by studies showing that mood enhancement and social factors are the primary motivations for cannabis consumption in patients with psychosis[21] and CHR patients[22]. Further, we replicated earlier findings on the importance of higher population density of place of living[18] as a predictive risk factor of CCu. The population density was previously shown not only to be predictive of cannabis relapse, but also of lifetime cannabis use and psychosis[26,59], suggesting that urbanicity and cannabis use may interact to increase the risk for psychosis[60,61]. Future studies should disentangle the specific impact of these two factors on psychosis.

Validation of the clinical predictor in clinical high-risk patients

Our clinical predictor performed only slightly above the chance level when applied to CHR patients. Indeed, univariate statistics (Supplementary Table 8) show that several of the most important clinical predictors did not significantly differ between CCu and DCu among CHR patients. Importantly, the CHR group had a lower proportion of subjects with cannabis use disorder compared with the ROP group, which might indicate that even the CCu individuals among CHR patients are less heavy cannabis users. As our predictor seems to be more sensitive to patients with cannabis use disorder (Supplementary 6), further investigations and testing in more diverse clinical populations are warranted.

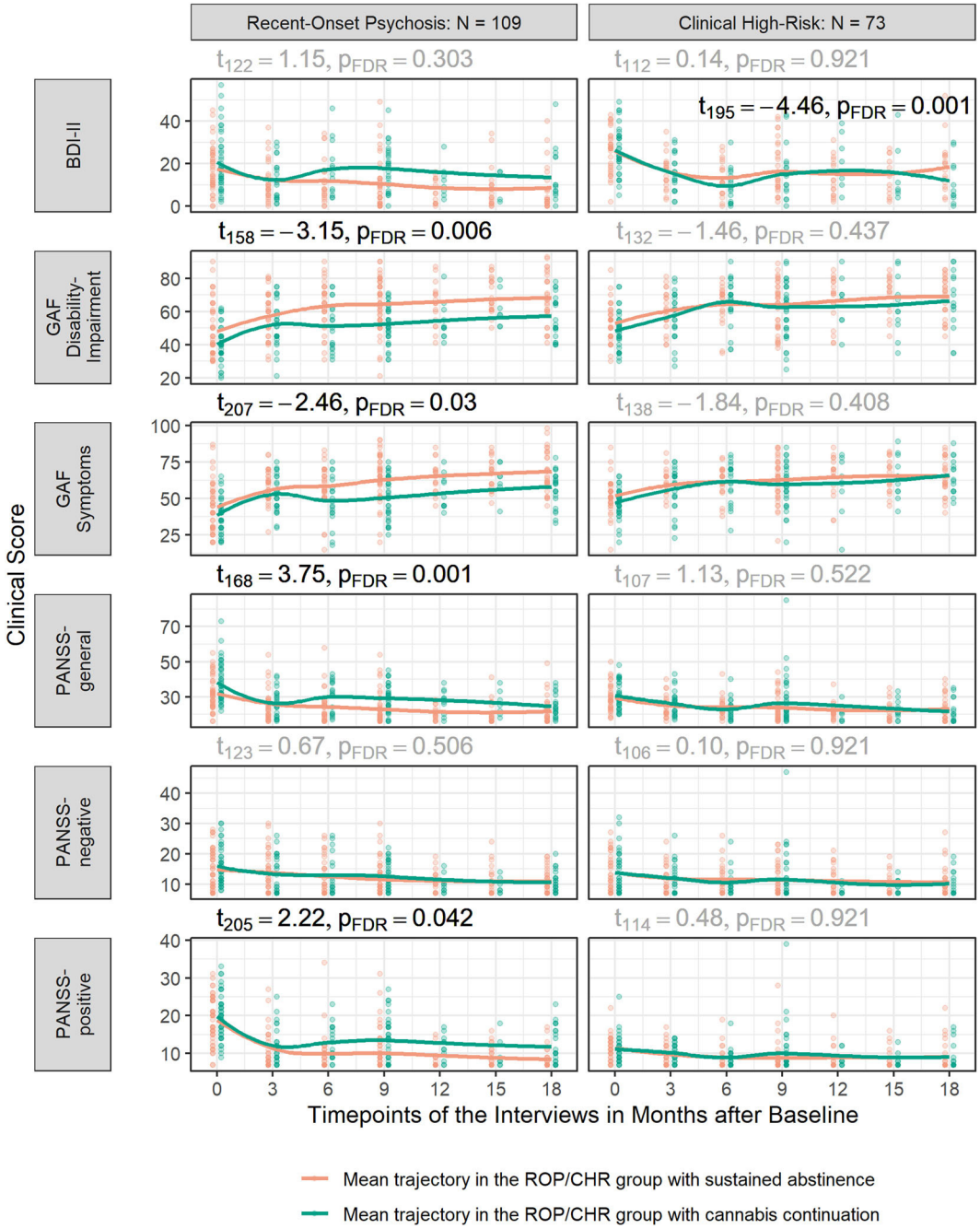

Fig. 2 Association of continued cannabis use and long-term clinical outcomes. Association of continued cannabis use with the long-term course of several clinical outcomes from baseline till 18 months follow-up. Linear-mixed models were calculated modelling the clinical outcome as dependent variable and group (continued cannabis use/discontinued cannabis use), time since baseline, linear trends, quadratic trends and trend interactions as independent variable. Subject entered as random effect. Significant group effects are marked in black above and significant interactions effects are marked in black within the graphs. False-discovery rate correction was performed to control for the number of comparisons for each fixed effect across the clinical outcome variables. Of note: For graphical depiction, time from baseline is presented as ordinal variable, however, in the model calculation the time from baseline entered as a continuous variable. Further, as the model fit for the optimal complexity varied by outcome the regression-line in the plot is modelled with the 'LOESS' nonparametric function. PANSS Positive and Negative Syndrome Scale, GAF Global Assessment of Functioning, BDI-II Beck's Depression Inventory-II, ROP recent-onset psychosis, CHR clinical high-risk for psychosis.

Applying our predictor to CHR patients with concurrent cannabis use disorder, to ROP patients with and without cannabis use disorder, as well as non-psychotic individuals with cannabis use disorder might disentangle the coupling between psychotic symptoms and cannabis use.

sMRI predictor of continued cannabis use

Contrary to expectation, our sMRI predictor did not perform significantly better than chance. This might be related to the study-specific outcome: CCu was defined as any cannabis consumption between baseline and nine-month follow-up. Most

previous studies have instead investigated associations between more severe forms of cannabis use and GMV[32]. One study[62] attempted to predict future cannabis use in 14-year-old abstinent adolescents, defined as at least ten instances of cannabis use during two years follow-up, with the finding that GMV differences did not precede cannabis use. Although general use in predictive models of additional and costly sMRI would not be justified, it still merits testing in future studies including larger samples to see if sMRI might help to predict more severe forms of CCu. Notably, although we carefully corrected for site-specific MR variation (Supplementary), the unbalanced sample sizes across sites might nonetheless have impacted the predictive accuracy of sMRI.

Cognitive predictor of continued cannabis use

Cognition did not predict CCu above chance level, which was surprising since schizophrenia is characterized by severe impairments in cognition[43,63], as is likewise heavy cannabis use[64]. On the other hand, a previous meta-analysis has shown that the evidence is inconclusive for an association between cannabis dependence and cognitive impairments[24]. This inconsistency might be explained by differences in the cognitive tests analyzed, as some performance deficits have been shown to be task-specific[65]. Moreover, other evidence shows that cognition is better preserved in cannabis-using psychotic individuals than in patients without concurrent cannabis use[25,66], and hence cognition might be a less important factor for predicting CCu in this particular patient group. Furthermore, a recent review on acute and residual effects of cannabis on cognition[67] concluded that the association between cognition and cannabis is likely explained by genetic and environmental factors that predispose certain individuals both to cannabis use and cognitive deficits, and to a lesser degree by actual neurotoxic effects. Future studies are warranted to disentangle whether these negative results reflect our use of tests that are insensitive to particular cognitive changes predicting CCu, or whether cognitive disturbances are indeed not predictive of CCu in psychotic and at-risk patients.

Effect of continued cannabis use on long-term clinical outcome

Our longitudinal analyses partially support the notion that CCu increases the risk for a poor long-term outcome in ROP and CHR individuals. Even though we found significant differences between CCu and DCu for almost all clinical outcome measures in the ROP group, we found a significant interaction between time and CCu only with depression in the CHR group. Depressive symptoms are a common comorbidity in patients with recent-onset psychosis[68]. However, our finding was unexpected since other studies investigating the impact of altered cannabis use on depressive symptoms have been so far inconclusive[52,69]. In the ROP group, we found a trending interaction effect of CCu with general symptoms over time, which would be in line with the previous literature[52]. There are several possible explanations for these non-significant interaction effects: First, patients with DCu have been longer abstinent than CCu patients, and thus they might already have recovered from the detrimental effects of the cannabis consumption. Second, our analyses might have been less sensitive to time-dependent effects due to the attrition rate in our study, leading to missing data and a relatively small sample size. Third, some of the patients with CCu have reported only one cannabis use at follow-up. Previous studies have shown that even a decreased CCu might improve the long-term clinical outcome[4]. Future studies might investigate further baseline measures to disentangle the main effects of CCu versus general cannabis use.

Limitations

Among the important limitations of our study, we note that missing assessments in several subjects for some timepoints hindered analysis of time-to-event data, which might otherwise have improved accuracy by disentangling further subjects' risk[42]. Additionally, the patient population of our study is difficult to contact and typically present a high attrition rate[4]. Thus, the follow-up period was only nine months, and our final sample was relatively small and unbalanced across sites, which might well have influenced results—especially in the imaging domain. Even though we carefully corrected for site effects, future studies are needed to investigate thoroughly and replicate our findings in larger samples and across sites. This would also be important to validate the speculation, as might arise from our findings, that MRI and cognitive measures are not of pivotal importance for predicting continued cannabis use. Even though most individuals who remained abstinent during the nine-month follow-up remained abstinent thereafter, further studies are warranted specifically to investigate the long-term prediction of continued cannabis use. Furthermore, our relatively small sample size hindered a further stratification of the critical outcome "continued cannabis use". Future studies might also assess the predictability of different severities of CCu. Indeed, any reduction in cannabis use improves psychosis outcome[5], and may be a more realistic harm reduction aim in therapy than complete abstinence[52]. As such, it would be useful to predict the relevant amount of cannabis use as distinct from complete abstinence. Most critically, our study lacks an external validation of the prediction of CCu in ROP. Thus, it cannot be inferred whether the drop in the accuracy of our predictor is better explained by low generalizability or by the differences of our samples in terms of severity of clinical symptoms and substance use. Hence, future tests of generalizability in ROP samples with similar substance use profiles are called for. Moreover, our study lacks some variables with known associations with cannabis use disorder, such as the individual's motivation to quit cannabis use[53] or specific substance-related cognitive tests[65], the inclusion of which might improve accuracy in future studies. Importantly, cannabis use was assessed via self-report, which might suffer from recall- and social desirability bias. Ideally, future studies should confirm cannabis use and ascertain cannabis abstinence by biological measurements, preferably via hair toxicology, given its long detection window[70].

CONCLUSION

This is the first multimodal examination of prognostication of CCu in ROP patients, along with generalizability testing in CHR patients. We found that the best predictor was based solely on clinical variables, reliably showing a contribution of global functioning, especially lower highest lifetime functioning, specific patterns of substance use, urbanicity and a lack of coping strategies. This predictor might be improved in future studies by adding specific cannabis-related questionnaires or additional data modalities such as cortical thickness, genetics or functional MRI, aiming to improve its clinical utility. Importantly, the ultimate aim to identify better those patients with ROP or CHR who are most likely to continue cannabis use, enabling tailored interventions and thus improve their clinical outcome, calls for testing and improvement of the model in larger and more diverse clinical samples.

METHODS

Study design and population

As part of the multisite 'Personalized Prognostic Tools for Early Psychosis Management' study (PRONIA [www.pronia.eu, German Clinical Trials Register identifier DRKS00005042[37]]) $N = 80$ patients of age 15–40 years with ROP and $N = 73$ CHR patients were included. A further $N = 29$ patients of age 18–40 years with ROP were recruited within the monocentric,

longitudinal cannabis-induced psychosis study (CIP)[71]. The ROP group included via PRONIA had experienced an affective or non-affective psychotic episode within the past 24 months that was present within the past three months prior to study entry. The ROP group included in CIP had a psychosis diagnosis originally associated with cannabis use that preceded the onset of psychotic symptoms by no more than two weeks in the last 24 months, as defined in the International Classification of Diseases, 10th Revision, criteria for substance-induced psychosis[72]. CHR individuals needed to fulfil (1) the basic symptom criterion "Cognitive Disturbances" assessed by the Schizophrenia Proneness Instrument[73]; and/or (2) a slightly adapted version of the ultra-high-risk criteria according to the Structured Interview for Psychosis-Risk Syndromes[74].

ROP patients included in CIP were recruited at the Department of Psychiatry of Ludwig-Maximilian-University in Munich, while both PRONIA samples were recruited at ten different European sites (see ref. [41]). Diagnoses were based on internationally established criteria and given by trained clinical raters[37,71]. Current or past alcohol dependence and polysubstance dependence within the past six months were exclusion criteria (Supplementary 1 for general exclusion criteria). Further, ROP and CHR patients included via PRONIA had to be abstinent from cannabis in the four weeks prior to inclusion. We imposed an additional inclusion criterion, only admitting patients with lifetime cannabis use prior to baseline.

All patients from PRONIA underwent baseline assessment between 2014 and 2019 and were followed for up to 36 months. The CIP recruitment took place from December 2016 until May 2019, and the follow-up period was nine months. The study protocols were largely harmonized (detailed assessments are listed in Supplementary Table 1).

Prior to inclusion, all patients provided written, informed consent (either personally or through a legal guardian if below the age of 18). Studies were approved at their respective sites by the local research ethics committees.

Outcome target

Substance use was assessed in a semi-structured interview at each visit[71] (Supplementary Fig. 1). At the baseline interview, clinical raters asked the patient about his/her history of cannabis use and subsequently if he/she had used cannabis since the previous examination. We defined *CCu* as any cannabis consumption between baseline and nine month follow-up. Conversely, we labelled each patient who remained abstinent until at least nine months after baseline assessment as discontinued cannabis use *(DCu)*.

Definition of the predictors

We trained three unimodal classifiers: (i) clinical, (ii) cognitive and (iii) sMRI (Supplementary Table 2 for the full list of variables). Predictors for the clinical domain were selected based on their prior association with cannabis use, consisting of: (1) substance use-related items[56,71], (2) environmental risk-factors[16], (3) clinical symptoms[8,19,20], (4) global functioning[75], (5) stress and coping strategies information[76], (6) demographic data and (7) the BMI[14]. The cognitive predictor variables were selected from subscores of the cognitive domains of the MATRICS Consensus Cognitive Battery[77], following the previous approaches[41]. The sMRI classifier was based on whole-brain GMV. A harmonized protocol for the acquisition of sMRI data was used at all sites[37]. For pre-processing, we used the open-source CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), which is an extension of SPM12 running in MATLAB 2018a (Supplementary 2 and Supplementary Table 3 for details of sMRI acquisition and pre-processing). We employed group information guided–independent component analysis (GIG-ICA)[78], which simultaneously takes into account the covariance between brain voxels and their similarity to reference components (RCs) of interest[71,79]. We chose nine RCs[34] previously shown to be linked with schizophrenia[34], which included several regions that have also been associated with cannabis use disorder, namely the prefrontal cortex, insula and cerebellum[32] (Supplementary Fig. 2 for RCs).

Machine learning strategy

We generated and tested our predictors on the total sample of ROP patients ($N = 109$). Next, we tested if our predictors would generalize to CHR patients ($N = 73$). Our machine learning pipeline was implemented in NeuroMiner version 1.1 (www.pronia.eu/neurominer) running in MATLAB R2019. To build the set of predictors, we strictly separated the training and test phases in repeated nested cross-validation (CV) with ten folds and five permutations both at the outer (CV_2) and inner cycles (CV_1). All features of the (i) clinical and (ii) cognitive predictors were standardized based on the median, with imputation of missing values by Seven-Nearest Neighbour imputation, and pruning of non-informative features (zero-variance, infinity). Subsequently, all features were scaled from zero to one. To find a set of optimally predicting features, we employed a wrapper-based feature selection using linear support vector machines (SVM; LIBSVM 3.12[80]; http://www.csie.ntu.edu.tw/~cjlin/libsvm). Following a previous approach[41], we trained the models on the CV_1 training data and picked the best-performing models based on the average SVMs (BAC) at the CV_1 training and testing data. More specifically, we performed a greedy sequential forward search[81] across the range of the SVM *C* regularization parameters ($2^{[-4_{\in}\mathbb{Z}\rightarrow+4]}$[41]), adding one feature at a time until the top ten percent most predictive features were selected.

For the (iii) sMRI-based predictor, we accounted for site-specific heterogeneity in two steps. First, we used the so-called g-theory mask[37,41] to exclude all voxels showing only between-site but no inter-subject variation[71,82]. Second, we adjusted the remaining voxels for site effects using ComBat[83,84], a harmonization method based on an empirical Bayesian approach, frequently used to remove non-biological variation related to differences between MRI scanners. To preserve the biological variation of interest (CCu), we used ComBat on a subsample of healthy individuals from PRONIA that was matched for age and sex between sites (Supplementary Fig. 3, and Supplementary Table 4 for age and sex distribution of matched healthy control sample, Supplementary Fig. 4, and Supplementary Table 5 for pre/post comparisons). This model was then applied independently to our discovery (ROP) and validation samples (CHR) (Supplementary Fig. 5, Supplementary Table 6). Finally, the thresholded and site-corrected sMRI images entered our machine learning pipeline. Strictly separating between CV_1 and CV_2, we first scaled total intracranial volume proportionally from each voxel. We then corrected for sex and age effects based on betas computed in our healthy control subsample and employed GIG-ICA to reduce feature dimensionality. Next, the components were scaled between zero and one. Again, we employed an SVM[80] with optimization of the *C*-parameter within a range from $2^{[-4_{\in}\mathbb{Z}\rightarrow+4]}$[41]. See Supplementary 3 for a detailed description of sMRI processing and Supplementary Fig. 2 for an overview of all steps.

Multimodal prediction models

To combine our best-performing unimodal (i) clinical predictor with the other unimodal predictors we used a stacked generalization procedure[37]. Here, the CV_1-test decision scores from unimodal predictors served as features within the same CV structure and were scaled from zero to one, with the imputation of any missing sMRI and cognitive data using Seven-Nearest Neighbour imputation. Again, we optimized the *C*-parameter within a range of $2^{[-4_{\in}\mathbb{Z}\rightarrow+4]}$.

We assessed the significance of all classifiers via permutation testing[85,86] with 1000 permutations and $\alpha = 0.05$. Further, we compared differences between all predictors' performances in ROP using the nonparametric Quade-test[87] at the omnibus level followed by post-hoc pairwise comparisons using the t-distribution[88]. Between the ROP and CHR groups we compared the performance of our best predictor (clinical) using the nonparametric and unpaired Wilcoxon rank-sum test, whereas in CHR we compared the best unimodal predictor (clinical) with the best multimodal (clinical-cognitive) predictor. Additionally, we assessed whether our clinical and sMRI-based unimodal predictions were biased by confounding effects such as age, site, sex or level of functioning (Supplementary 4). To assess whether the imbalanced group assignment of the clinical predictor in CHR patients was associated with differences in substance use severity between ROP and CHR groups, we compared the sensitivity and specificity of these models separately for subjects with and without cannabis use disorder (Supplementary 6).

Feature importance

To understand which features were most reliably contributing to the prediction of CCu, we computed the CV ratio[37,85]. The significance of features for predictors that included wrapper-based feature selection (clinical and cognition) was calculated by sign-based consistency following previous approaches[41] (Supplementary 5).

Exploration: effect of continued cannabis use on long-term clinical outcome

To explore the clinical relevance of CCu-prediction, we examined the impact of CCu on long-term clinical outcome employing linear-mixed

effects models using the package 'lmerTest'[89] in R language for statistical computing, version 3.6.3[90] separately in ROP and CHR groups. Clinical outcomes, specifically the sum score of positive, negative and general symptoms from the PANSS[91], the sum score of BDI-II[48], current symptoms of the GAF-S[46,47] and current functional disability of the GAF-F until 18 months follow-up entered the model as dependent variables. Following the approach in a previous study[92] we tested the main fixed effects "group" (CCu vs. DCu), time since baseline, linear, quadratic and cubic trends and trend interactions with the outcome. Patients were modelled as a random effect. We assessed model complexity for both groups (ROP and CHR) and each outcome individually employing the parametric bootstrap method for the Likelihood Ratio Test (*R* package *PBmoDCuomp*[93]) with 200 iterations. We deleted missing data for each case per visit.

DATA AVAILABILITY

The data are not publicly available due to Institutional Review Board restrictions—since the participants did not consent to their data being publicly available.

CODE AVAILABILITY

The NeuroMiner software available on github (https://github.com/neurominer-git/NeuroMiner-1) was used for the data analysis.

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AUTHOR CONTRIBUTIONS

N.P., R.S., L.T.B., O.P., P.C., B.B.Q., O.H., P.F., R.U., S.B., P.B., E.M., L.K.I., S.R., R.K.R.S, C.P., S.J.W., N.K. and J.K. conceptualized the analysis. N.P., L.T.B., L.A.A. and J.K. drafted the manuscript. N.P., J.K. and N.K. had full access to the data in the study and conducted the data analysis. N.P., R.S., L.A.A., L.T.B., D.D., A.R., R.U., S.B., P.B., R.L., E.M., F.S.L., M.R., T.L., L.K.I., S.R., R.K.R.S., C.P., S.J.W., G.P., A.B., N.K. and J.K. were involved in acquisition of data. R.U., S.B., P.B., E.M., L.K.I., S.R., R.K.R.S., C.P., S.J.W., A.B., G.P., N.K. and J.K. were involved in obtaining funding. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors are accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

ADDITIONAL INFORMATION

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THE PRONIA CONSORTIUM

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Supplementary: Pattern of predictive features of continued cannabis use in patients with recent-onset psychosis and clinical high-risk for psychosis

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Content

1.) Exclusion criteria for patients with recent-onset psychosis and clinical high-risk for psychosis

Patients with recent-onset psychosis (ROP) were excluded if they had taken antipsychotic medication for more than 90 cumulative days, at or above the minimum dosage indicated for first episode psychosis as specified in the DGPPN S3 Guidelines (guideline manual is available in https://www.dgppn.de/_Resources/Persistent/43ca38d4b003b8150b856df48211df68e412d9c9/038-009k_S3_Schizophrenie_2019-03.pdf). Patients with CHR were excluded if they had taken antipsychotic medication for more than 30 cumulative days or if they had received antipsychotic medication at the minimum recommended dosage for first episode psychosis in the past three months prior to baseline assessment.

Further exclusion criteria were any traumatic head injury with loss of consciousness for more than five minutes, any contraindication for magnetic resonance imaging (MRI), any neurological or somatic disease affecting the brain, a lifetime diagnosis of alcohol dependence, current or within-past-six-months polysubstance dependence or inadequate language proficiency in English or the national language at the respective site.

2.) Acquisition and pre-processing of structural magnetic resonance imaging

Data was acquired with isotropic or nearly isotropic voxel size, with a preferred voxel size of one mm^3. The parameters of the field of view had to ensure full 3D coverage of the entire brain including the cerebellum, and other imaging parameters had to maximize the contrast between white matter and cortical ribbon as well as obtaining an optimal signal-to-noise ratio.

For pre-processing, we used the open-source CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), an extension of SPM12 running in MATLAB 2018a. As a first step, all images were segmented into grey matter (GM), white matter and cerebrospinal fluid maps and normalized to stereotactic space of Montreal Neurological Institute (MNI-152

space). To derive GM volume maps, images were multiplied with the Jacobian determinants obtained during registration. *Post-hoc* quality checks were performed by correlating each slice across all subjects. Four scans from patients with ROP and one scan from a CHR patient deviated by more than two standard deviations (SD) of the mean, and were consequently re-examined visually. Due to artifacts, one scan from a patient with ROP and one image from a patient with CHR had to be excluded from the subsequent analysis, whereas the other images passed inspection (sFigure 6). Subsequently, images were realigned to a two mm voxel resolution and smoothed with a ten mm (full-width at half maximum) Gaussian kernel [1].

3.) Design of Machine learning analysis performed on structural magnetic resonance imaging

3.1 Healthy individuals used for harmonization between sites and regression of age- and sex specific effects

To build a reliable classifier of continued cannabis use (CCu) based on structural magnetic resonance imaging (sMRI) data, we had first to remove the effect of several well-known confounders, i.e., age-, sex- and site-specific variation. To remove variation related to differences between these factors and simultaneously preserve the effect of interest (CCu) we used a subset of the healthy individuals (HC) from the 'Personalized Prognostic Tools for Early Psychosis Management' study (PRONIA) to define the age, sex, and site-specific variation and then remove these effects individually from our patient groups (ROP, CHR) individually. HC from the seven sites included in the sMRI classifier were matched for age and sex between sites (see sFigure 3 for age and sex distribution by site, statistics in sTable 4) and used as a target for harmonization.

3.2 G-theory based mask correction for site-specific variation

As a first step, following previous publications from our group we used the so-called g-theory based mask to correct for site-specific scanner variation [2–4]. In short, MRI data from six

individuals, who agreed to be scanned at six of the seven included PRONIA sites (Munich, Milan Niguarda, Basel, Cologne, Birmingham, Turku), were analysed voxel-wise for subject- and site-specific variation. Here, higher g-values indicate high subject- and low site-specific variation, and low g-values indicate high site- and low-subject specific variation [5]. The reference components (RCs) and all images from the patient groups and HCs used for harmonization between sites and regression of age- and sex specific effects, were thresholded with the g-mask (voxels>0) using SPM12 running in MATLAB 2020 (sFigure 2) to exclude voxels showing only between-site but no inter-subject-variation [2,6].

3.3 Harmonization between sites using the ComBat-algorithm

Second, we applied on the remaining voxels the ComBat algorithm [7], which is a harmonization method removing non-biological variation related to differences between MRI scanners. To preserve the biological variation of interest (predicting CCu), we trained the ComBat algorithm on our matched HCs. Before applying the learned rule from the ComBat-algorithm trained on HCs to the patient data we first compared the uncorrected sMRI data with the corrected data. Here, we used group information-guided independent components analysis (GIG-ICA) pre- and post-harmonization to find nine components of interest (COIs) in HCs that were optimized for similarity with our nine RCs and for independence between each other. Then, we tested for site-specific effects on the COIs by conducting an analysis of variance with loadings serving as the independent factor, and site as a dummy-coded variable serving as the dependent factor. Further, we investigated the pattern of sex- and age-specific variation in the COIs pre- and post-harmonization by visualizing their pattern (sFigure 3). Pronounced site-specific effects that were present pre-harmonization were removed post-harmonization in all COIs while preserving age- and sex-specific variations (see sTable 5, sFigure 3).

We then applied our model to the discovery (ROP) and replication sample (CHR) independently, and retested whether site-specific variation had indeed been removed from the

COIs. This time we investigated whether the biological signature of interest was preserved despite the harmonization process. To this end, we calculated the effect sizes of CCu on COIs pre- and post- harmonization as Cohen's d. Even though some significant site-specific variation remained the effects were reduced (sTable5), while the effect sizes of the effect of interest (CCu) in all COIs and sites were preserved (sFigure 6).

3.4 Machine learning pipeline of structural magnetic resonance imaging predictor

Finally, the thresholded and site-corrected sMRI images were entered into our machine learning pipeline. We first corrected for sex and age effects using betas computed in our HC subsample. To strictly separate training from testing, we implemented GIG-ICA from the GIFT toolbox (http://mialab.mrn.org/software/gift/) in NeuroMiner to reduce dimensionality. GIG-ICA was optimized to identify nine independent components with maximum similarity to nine RCs that had previously been associated with schizophrenia [1]. In each inner cross-validation (CV)-fold, GM images were converted to one-dimensional row vectors and concatenated across patients deriving a $N_{patients}$-by-205,075 grey matter volume voxel matrix. This matrix was decomposed into a source matrix and a mixing matrix. The mixing matrix represents loadings, i.e., the weights of individual patients on each COI. The source matrix represents the relationship between each voxel and the COI. This decomposition simultaneously maximizes the correspondence to the RCs and the independence of the components from each other such that each row in the source matrix is maximally independent from the others. Next, the components were scaled between zero and one. As in the other modalities, we employed a linear support vector machine (SVM) [8] with an optimization of the C-parameter within a range from $2^{[-4 \in \mathbb{Z} \rightarrow +4]}$ [3]. For a graphical depiction of the entire sMRI machine learning pipeline see sFigure 3.

4.) Assessment of potential confounds in the clinical and structural magnetic resonance imaging predictors

We are aware that several well-known confounding factors might have biased our predictive accuracies in the clinical- and sMRI-predictors. For sMRI, site-, age- and sex-effects might be particularly relevant. Further, level of functioning was associated with CCu in follow-up (see "Results Section" of the main manuscript Figure 1) and was one of the most important patterns of our clinical predictor of CCu (see "Results Section" of the main manuscript Figure 2). Therefore, we performed a validation analysis to explore the specificity of our prediction for CCu. We used patients with ROP (ROP-artificial) that had been excluded from the main study due to missing cannabis information (N = 73) or non-user status at baseline (N = 36). We assigned artificial "continued cannabis use (CCu)" and "discontinued cannabis use (DCu)" labels to the ROP-artificial patients. Group membership (CCu/DCu) was defined by matching subjects for age-, sex-, site- and highest functioning in past month measured with the Global Assessment of Functioning scale to our original ROP patients (see sTable 7). Then, we used the identical machine learning pipeline for the clinical- and sMRI predictor that we had employed in the main part of the study for the prediction of CCu. Results of this prediction are presented in sTable 8. Both predictors provided non-significant predictions, leading us to conclude that our results are unlikely to be biased by age, sex, site, or functioning.

5.) Visualization of feature importance

To understand which features were most reliably contributing to the prediction of CCu, we computed the CV ratio ($CVR = \frac{mean(w)}{SE_{(w)}}$) [4,9]. Here, w represents the normalized weights under Euclidian assumptions of the linear SVM generated in our repeated nested CV scheme. A positive CVR indicates that an increase of a feature predicts CCu, while a negative CVR means that any decrease in the respective feature predicts CCu. Significance of features for predictors

that included wrapper-based feature selection (clinical and cognition) was calculated by sign-based consistency

$$(I_j = \frac{|\sum_{i=1}^{n} \hat{w}_j^i > 0 - \sum_{i=1}^{n} \hat{w}_j^i < 0|}{n} * (1 - \frac{|\sum_{i=1}^{n} \hat{w}_j^i = 0}{n})\ ^{3}.$$

Here, I_j represents the importance of the j^{th} feature and $\hat{w}_j^i$ represents the normalized weights under Euclidian assumptions of the linear SVM for the j^{th} feature. In the first term of the equation (left-hand side), the consistency of the weights assigned by SVM to given features are calculated. This consistency is reduced by the second term of the equation (right-hand side), which measures the fraction of SVMs that de-selected the particular feature. Significance threshold was defined based on z-statistic, defined as $(z_j = \frac{I_j}{\sqrt{var\{I_j\}}})$ and p-values were corrected for the false-discovery rate (FDR) following previous approaches[3].

6.) Investigation of different results in patients with SCID-IV diagnoses of cannabis use disorder

ROP patients had more lifetime cannabis use disorder than patients with CHR. As substance use patterns were an important predictor for CCu and patients with CHR were more likely classified as having DCu (low sensitivity of the predictor) we further investigated whether the sensitivity and specificity differed between individuals with cannabis use disorder at baseline. Thus, we calculated the overall sensitivity and specificity as well as for the individual median for the five permutations of the outer CV2-folds for patients with and without cannabis use disorder in ROP and CHR patients, separately. We then employed unpaired two-sample Wilcoxon-rank-sum test to compare sensitivity and specificity between patients with cannabis use disorder and without for ROP and CHR patients. The metrics differed significantly in both patient groups (sTable 11). Therefore, the moderate generalizability of the classifier might at

least partially be explained by the differences in severity of substance use between ROP and CHR patients.

7.) Supplementary Tables

sTable 1 Assessments of the cannabis induced psychosis and the 'Personalized Prognostic Tools for Early Psychosis Management' studies - Table from [2], originally adapted from [5]

Instrument	Form	Baseline		IV3	IV6	T1		IV12	IV15	T2
		ROP	CIP	ROP	ROP	ROP	CIP	ROP	ROP	ROP
General data	OR	X	X			X	X			
Reasons for referral	OR	X	X							
Treatment documentation	OR	X	X	X	X	X	X	X	X	X
Somatic state and health history	OR	X	X			X	X			X
SPI-A COGDIS/ COPER[10]	OR	X		X	X	X		X	X	X
SIPS positive symptoms[11]	OR	X	X	X	X	X	X	X	X	X
CAARMS[12]	OR	X	X	X	X	X	X	X	X	X
GAF[13]	OR	X	X	X	X	X	X	X	X	X
UHR - Schizotypy, genetic risk	OR	X	X	X		X	X			X
CHR criteria	OR	X				X				X
SCID-IV screening[14]	OR	X	X			X	X			X
SCID-IV summary[14]	OR	X	X			X	X			X
Demographic and biographic data	OR	X	X			X	X			X
PAS[15]	OR	X	X			X	X			X
SPI-A[10]	OR	X				X		X	X	X
SIPS negative, disorganized and general symptoms[11]	OR	X	X			X	X			X
PANSS[16]	OR	X	X	X	X	X	X	X	X	X
SANS[17]	OR	X	X			X	X			X
Chart of life events	OR	X	X	X	X	X	X	X	X	X
FROGS[18]	OR	X	X			X	X			X
GF: Social & role[19]	OR	X	X	X	X	X	X	X	X	X
Prognostic evaluation	OR	X	X			X	X			X
Substance use questionnaire	OR	X	X	X	X	X	X	X	X	X
MSPSS[20]	SR	X	X			X	X			X
RSA[21]	SR	X	X			X	X			X
CISS 24[22]	SR	X	X			X	X			X
SPIN[23]	SR	X	X			X	X			X
BDI-II[24]	SR	X	X	X	X	X	X	X	X	X
WHO-QOL-BREF[25]	SR	X	X			X	X			X
EHI-SR[26]	SR	X	X							

LEE[27]	**SR**	**X**	**X**			**X**	**X**			**X**
Wisconsin scales[28]	**SR**	**X**	**X**							
EDS[29]	**SR**	**X**	**X**							
Bullying scale [30]	**SR**	**X**	**X**							
CTQ[31]	**SR**	**X**	**X**							
NEO-FFI[32]	**SR**	**X**	**X**							
Substance use	**SR**		**X**							
Cannabis experience questionnaire (CEQ)	**SR**		**X**							
Severity of dependency scale (SES)	**SR**		**X**							
DS backward (BACS)	**NPT**	**X**	**X**			**X**				
DS forward (BACS)	**NPT**	**X**	**X**			**X**				
CPT-IP (BACS)[33]	**NPT**	**X**	**X**			**X**				
DANVA[34]	**NPT**	**X**	**X**			**X**				
DSST	**NPT**	**X**	**X**			**X**				
RAVLT*[35]	**NPT**	**X**	**X**			**X**				
ROCF[36]	**NPT**	**X**	**X**			**X**				
SAT[37]	**NPT**	**X**	**X**			**X**				
SOPT[38]	**NPT**	**X**	**X**			**X**				
TMT-A[39]	**NPT**	**X**	**X**			**X**				
TMT-B[39]	**NPT**	**X**	**X**			**X**				
VF phonetic	**NPT**	**X**	**X**			**X**				
VF semantic	**NPT**	**X**	**X**			**X**				
WAIS-III[40]	**NPT**	**X**	**X**			**X**				
sMRI	**MRI**	**X**	**X**			**X**				
rs-fMRI	**MRI**	**X**	**X**			**X**				
DWI	**MRI**	**X**	**X**			**X**				
blood sample	**bio**	**X**				**X**				
hair sample	**THC**		**X**							
Urine sample	**THC**		**X**							
EEG	**EEG**		**X**							

Abbreviation: IV3 = interval three months after baseline, IV6 = interval six months after baseline, T1 = interval nine months after baseline, IV12 = interval 12 months after baseline, IV15 = interval 15 months after baseline, T2 = interval 18 months after baseline, OR = Observer-based-rating instrument, SR = Self-rating-based instrument, NPT =

Neuropsychological Test, MRI = Magnetic Resonance Imaging, sMRI = structural Magnetic Resonance Imaging, rs-fMRI = resting-state functional Magnetic Resonance Imaging, DWI = Diffusion Weighted Imaging, bio = biological test, THC = Cannabis-related test, EEG = Electro Encephalography, SPI-A COGDIS/COPER = Schizophrenia Proneness Instrument - Cognitive disturbances / Cognitive-Perceptual disturbances, CAARMS = Comprehensive Assessment of the At-Risk Mental States, CHR Criteria, SIPS = Standardized Interview for the assessment of Prodromal Symptoms (modified version 5.0), GAF = Global Assessment of Functioning, UHR – Schizotypy, genetic risk = Genetic Risk Interview for the Assessment of Schizotypal personality traits, and familial risk for psychosis, CHR criteria = Clinical High-Risk criteria summary questionnaire, SCID-IV Screening/Summary = Structured Clinical Interview for DSM-IV, PAS = Premorbid Adjustment Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, FROGS = Functional Remission in General Schizophrenia, GF: Social/Role = Global Functioning: Social/Role, MSPSS = the Multidimensional Scale for Perceived Social Support, RSA = Resilience Scale for Adults, CISS 24 = Coping Inventory for Stressful Situations – 24 items, SPIN = Social Phobia Inventory, BDI-II = Beck Depression Inventory II, WHO-QOL-BREF = WHO Quality of Life Questionnaire – Brief Version, EHI-SR = Edinburgh Handedness Inventory – Short Version, LEE = Level of Expressed Emotions, Wisconsin scales = , EDS = Everyday Discrimination Scale – Modified Version, CTQ = Childhood Trauma Questionnaire, NEO-FFI = NEO Five Factor Inventory of Personality Traits, DS = Auditory Digit Span (Forward/Backward) adapted from the PEBL battery, CPT-IP (BACS) = Continuous-Performance Test – Identical Pairs (adapted tablet version), DANVA = Diagnostic Analysis of Non-Verbal Accuracy 2 (adapted tablet version), DSST = Digit-Symbol-Substitution Test from the BACS battery, RAVLT = Rey Auditory Verbal test, ROCF = Rey-Osterrieth complex figure, SAT = Salience Attribution Task (adapted version), SOPT = self-ordered pointing task (adapted version), TMT-A/-B = Trail-Making Test A and B, VF phonetic/semantic = verbal fluency test, WAIS-III = Wechsler Adult Intelligence Scale (3rd edition), ROP = recent-onset psychosis via the 'Personalized Prognostic Tools for Early Psychosis Management', CIP = recent-onset psychosis patients included via the cannabis induced psychosis study, CHR = clinical high-risk for psychosis

***In one of the research sites (Turku) the revised version of the Hopkins Verbal Learning Test (HVLT-R) was included instead of the RAVLT that was not available in Finnish.**

sTable 2 Features of clinical and cognitive predictors

Category	Feature	Percent missing in Discovery sample (ROP)	Percent missing in Replication sample (CHR)
Substance Use related items	Number of Other Substances besides Cannabis tried in Lifetime	22.0	24.7
Substance Use related items	DSM-IV Lifetime Diagnosis of Cannabis Abuse	0.0	1.4
Substance Use related items	DSM-IV Lifetime Diagnosis of Cannabis Dependency	0.0	1.4
Substance Use related items	Average Number of cigarettes per day	7.3	2.7
Substance Use related items	Average Units of alcohol consumed per day	22.9	23.3
Substance Use related items	Cumulative Frequency of Cannabis used in the last 3 months	26.6	26
Substance Use related items	Cumulative Frequency of Other Substances besides Cannabis used in the last 3 months	39.4	53.4
Substance Use related items	Age of cannabis use initiation	10.1	20.5
Substance Use related items	Cumulative time of Cannabis Use in Lifetime (months)	14.7	20.5
Substance Use related items	Time since last Cannabis Use before Baseline (months)	10.1	13.7
Environmental risk factors	Sum of experienced burden of Recent Life Events (last year)	2.8	0.0
Environmental risk factors	CTQ (emotional abuse)	14.7	6.8
Environmental risk factors	CTQ (emotional neglect)	13.8	5.5
Environmental risk factors	CTQ (physical abuse)	12.8	6.8
Environmental risk factors	CTQ (physical neglect)	13.8	8.2
Environmental risk factors	CTQ (sexual abuse)	15.6	8.2
Environmental risk factors	WSS (magical ideation)	15.6	11.0
Environmental risk factors	WSS (perceptual aberration)	12.8	8.2
Environmental risk factors	WSS (physical anhedonia)	16.5	8.2
Environmental risk factors	WSS (social anhedonia)	16.5	9.6
Symptoms	BDI-II 1 – Sadness	8.3	5.5
Symptoms	BDI-II 2 - Pessimism	9.2	4.1
Symptoms	BDI-II 3 – Past failures	9.2	4.1
Symptoms	BDI-II 4 – Loss of Pleasure	9.2	4.1
Symptoms	BDI-II 5 – Guilt Feelings	9.2	4.1
Symptoms	BDI-II 6 – Punishment Feelings	9.2	4.1
Symptoms	BDI-II 7 – Self Dislike	9.2	4.1
Symptoms	BDI-II 8 – Self Criticalness	9.2	4.1
Symptoms	BDI-II 9 – Suicidal thoughts or wishes	9.2	4.1
Symptoms	BDI-II 10 – Crying	9.2	5.5

Symptoms	BDI-II 11 – Agitation	9.2	4.1
Symptoms	BDI-II 12 – Loss of Interest	9.2	5.5
Symptoms	BDI-II 13 – Indecisiveness	9.2	4.1
Symptoms	BDI-II 14 – Worthlessness	9.2	4.1
Symptoms	BDI-II 15 – Loss of Energy	9.2	4.1
Symptoms	BDI-II 16 – Changes in Sleeping Pattern	9.2	5.5
Symptoms	BDI-II 17 – Irritability	9.2	4.1
Symptoms	BDI-II 18 – Changes in Appetite	9.2	5.5
Symptoms	BDI-II 19 – Concentration Difficulty	9.2	5.5
Symptoms	BDI-II 20 – Tiredness or Fatigue	9.2	5.5
Symptoms	BDI-II 21 – Loss of Interest in Sex	11	4.1
Symptoms	PANSS G1 – Somatic concern	1.8	4.1
Symptoms	PANSS G2 – Anxiety	1.8	4.1
Symptoms	PANSS G3 – Guilt feelings	1.8	4.1
Symptoms	PANSS G4 – Tension	1.8	4.1
Symptoms	PANSS G5 – Mannerisms and posturing	1.8	4.1
Symptoms	PANSS G6 – Depression	1.8	4.1
Symptoms	PANSS G7 – Motor retardation	1.8	4.1
Symptoms	PANSS G8 – Uncooperativeness	1.8	4.1
Symptoms	PANSS G9 – Unusual thought content	1.8	4.1
Symptoms	PANSS G10 – Disorientation	1.8	4.1
Symptoms	PANSS G11 – Poor attention	1.8	4.1
Symptoms	PANSS G12 – Lack of judgement and insight	1.8	4.1
Symptoms	PANSS G13 – Disturbance of volition	1.8	4.1
Symptoms	PANSS G14 – Poor impulse control	1.8	4.1
Symptoms	PANSS G15 – Preoccupation	1.8	4.1
Symptoms	PANSS G16 – Active social avoidance	1.8	4.1
Symptoms	PANSS N1 – Blunted affect	1.8	4.1
Symptoms	PANSS N2 – Emotional withdrawal	1.8	4.1
Symptoms	PANSS N3 – Poor Rapport	1.8	4.1
Symptoms	PANSS N4 – Passive/apathetic social withdrawal	1.8	4.1
Symptoms	PANSS N5 – Difficulty in abstract thinking	1.8	4.1
Symptoms	PANSS N6 – Lack of spontaneity and flow of conversation	1.8	4.1
Symptoms	PANSS N7 – Stereotyped thinking	1.8	4.1

Symptoms	PANSS P1 – Delusions	1.8	4.1
Symptoms	PANSS P2 – Conceptual disorganization	1.8	4.1
Symptoms	PANSS P3 – Hallucinatory behavior	1.8	4.1
Symptoms	PANSS P4 – Excitement	1.8	4.1
Symptoms	PANSS P5 – Grandiosity	1.8	4.1
Symptoms	PANSS P6 – Suspiciousness/persecution	1.8	4.1
Symptoms	PANSS P7 – Hostility	1.8	4.1
Global Functioning	GAF Disability/Impairment Lifetime	0.9	0.0
Global Functioning	GAF Disability/Impairment Past Month	0.0	0.0
Global Functioning	GAF Disability Impairment Past Year	0.0	0.0
Global Functioning	GAF Symptoms Lifeimte	0.9	0.0
Global Functioning	GAF Symptoms Past Month	0.0	0.0
Global Functioning	GAF Symptoms Past Year	0.0	0.0
Global Functioning	GF: Role Current	0.9	0.0
Global Functioning	GF: Role Lowest Past Year	0.9	0.0
Global Functioning	GF: Role Highest Past Year	0.9	0.0
Global Functioning	GF: Role Highest Lifetime	1.8	0.0
Global Functioning	GF: Social Current	0.9	0.0
Global Functioning	GF: Social Lowest Past Year	0.9	0.0
Global Functioning	GF: Social Highest Past Year	0.9	0.0
Global Functioning	GF: Social Highest Lifetime	0.9	0.0
CISS 24	CISS 1 „Try to be with other people.”	10.1	8.2
CISS 24	CISS 2 „Blame myself for putting things off.”	11.0	5.5
CISS 24	CISS 3 „Blame myself for having gotten into this situation.”	10.1	6.8
CISS 24	CISS 4 „Window shop.“	10.1	6.8
CISS 24	CISS 5 „Outline my priorities.“	10.1	6.8
CISS 24	CISS 6 „Treat myself to a favorite food or snack.”	11.0	6.8
CISS 24	CISS 7 „Feel anxious about not being able to cope.”	10.1	6.8
CISS 24	CISS 8 „Become very tense.“	10.1	6.8
CISS 24	CISS 9 „Think about how I solved similar problems.“	10.1	6.8
CISS 24	CISS 10 „Go out for a snack or meal.”	10.1	6.8
CISS 24	CISS 11 „Become very upset.“	10.1	6.8
CISS 24	CISS 12 „Determine a course of action and follow it.”	11.0	8.2
CISS 24	CISS 13 „Blame myself for not knowing what to do.”	10.1	6.8

CISS 24	CISS 14 „Work to understand the situation.”	10.1	6.8
CISS 24	CISS 15 „Think about the event and learn from my mistakes.”	11.0	6.8
CISS 24	CISS 16 „Wish that I could change what had happened or how I felt.”	10.1	5.5
CISS 24	CISS 17 „Visit a friend.“	11.0	6.8
CISS 24	CISS 18 „Spend time with a special person.”	10.1	6.8
CISS 24	CISS 19 „Analyse my problem before reacting.”	10.1	5.5
CISS 24	CISS 20 „Phone a friend.“	10.1	5.5
CISS 24	CISS 21 „Get angry.“	10.1	6.8
CISS 24	CISS 22 „See a movie.“	10.1	6.8
CISS 24	CISS 23 „Come up with several different solutions to the problem.”	10.1	6.8
CISS 24	CISS 24 „Try to be organised so I can be on top of the situation.”	10.1	6.8
Sociodemographic data	Age	0.0	0.0
Sociodemographic data	Population Density of place of living	0.9	0.0
Sociodemographic data	Population Density of Place of birth	4.6	5.5
Sociodemographic data	Lived in a partnership for at least one year	1.8	0.0
Sociodemographic data	Number of people living with	2.8	1.4
Sociodemographic data	Years of education	1.8	1.4
Sociodemographic data	Type of current work: Home work (looking after family or home)	0.0	0.0
Sociodemographic data	Type of current work: in full time education	22.9	13.7
Sociodemographic data	Type of current work: unemployed but available for work (with regard to health)	22.9	13.7
Sociodemographic data	Type of current work: unable to work because of physical long-term sickness or disability	16.5	13.7
Sociodemographic data	Type of current work: unable to work because of mental long-term sickness or disability	22.9	13.7
Sociodemographic data	Type of current work: other	16.5	13.7
Sociodemographic data	Sex	0.0	0.0
Body Mass Index	Body Mass Index	0.9	8.3
Cognition (CPT)	Number correct responses overall (True positives)	0.0	4.1
Cognition (CPT)	Number errors distracting stimuli overall (False positives)	0.0	4.1
Cognition (CPT)	Reaction time correct responses overall	0.0	4.1
Cognition (RAVLT)	1. immediate repetition list A	10.5	9.6
Cognition (RAVLT)	2. immediate repetition list A	10.5	9.6
Cognition (RAVLT)	3. immediate repetition list A	10.5	8.2
Cognition (RAVLT)	4. immediate repetition list A	10.5	8.2
Cognition (RAVLT)	5. immediate repetition list A	10.5	8.2

Cognition (BDS)	Number of correct trials auditory digit span backward	0.0	0.0
Cognition (DANVA)	Number of correctly recognized faces	0.0	0.0
Cognition (DSST)	Number of correctly matched symbols – Number of incorrectly matched symbols	1.9	4.1
Cognition (FDS)	Number of correctly remembered digit strings	0.0	0.0
Cognition (PVF)	Number of correct words from a phonetic category in 60 seconds	0.0	1.4
Cognition (PVF)	Number of incorrect words from a phonetic category in 60 seconds	0.0	1.4
Cognition (PVF)	Number of repeated words from a phonetic category in 60 seconds	0.0	1.4
Cognition (SVF)	Number of correct words from a semantic category in 60 seconds	0.0	1.4
Cognition (SVF)	Number of incorrect words from a semantic category in 60 seconds	1.0	1.4
Cognition (SVF)	Number of repeated words from a semantic category in 60 seconds	1.0	1.4
Cognition (ROCF)	Accuracy: sum score of all elements – phase 2 (drawing from memory immediately after copying)	1.9	4.1
Cognition (ROCF)	Accuracy: sum score of all elements – phase 3 (drawing from memory 30 minutes after copying)	1.9	4.1
Cognition (ROCF)	Placement: sum score of all elements – phase 1 (drawing from figure)	1.9	4.1
Cognition (ROCF)	Placement: sum score of all elements – phase 2 (drawing from memory immediately after copying)	1.9	4.1
Cognition (ROCF)	Placement: sum score of all elements – phase 3 (drawing from memory 30 minutes after copying)	1.9	4.1
Cognition (ROCF)	Time of execution: phase 1 (drawing from figure)	2.9	4.1
Cognition (ROCF)	Time of execution: phase 2 (drawing from memory immediately after copying)	5.7	4.1
Cognition (ROCF)	Time of execution: phase 3 (drawing from memory 30 minutes after copying)	5.7	4.1
Cognition (GTMA)	Time of execution TMT-A	3.8	8.2
Cognition (GTMB)	Time of execution TMT-B	3.8	8.2
Cognition (SOPT)	Maximum correct responses before error by 4 elements – trial 1	0.0	1.4
Cognition (SOPT)	Maximum correct responses before error by 4 elements – trial 2	0.0	1.4
Cognition (SOPT)	Maximum correct responses before error by 4 elements – trial 3	0.0	1.4
Cognition (SOPT)	Maximum correct responses before error by 6 elements – trial 1	1.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 6 elements – trial 2	1.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 6 elements – trial 3	1.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 8 elements – trial 1	0.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 8 elements – trial 2	0.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 8 elements – trial 3	0.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 10 elements – trial 1	0.0	4.1
Cognition (SOPT)	Maximum correct responses before error by 10 elements – trial 2	0.0	4.1

Cognition (SOPT)	Maximum correct responses before error by 10 elements – trial 3	1.0	4.1
Cognition (WAIS)	Matrices test-raw score	4.8	5.5
Cognition (WAIS)	Matrices test–standard score	5.7	5.5
Cognition (WAIS)	Vocabulary test-raw score	4.8	1.4
Cognition (WAIS)	Vocabulary test-standard score	6.7	1.4

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, ROP = recent-onset psychosis, CHR = clinical high-risk for psychosis, CTQ = Childhood Trauma Questionnaire, WSS = Wisconsin Schizotypy scales, BDI-II = Beck Depression Inventory II, PANSS = Positive and Negative Syndrome Scale, GAF = Global Assessment of Functioning, GF: Social/Role = Global Functioning: Social/Role, CISS 24 = Coping Inventory for Stressful Situations – 24 items, CPT-IP (BACS) = Continuous-Performance Test – Identical Pairs (adapted tablet version), RAVLT = Rey Auditory Verbal Learning test, DANVA = Diagnostic Analysis of Non-Verbal Accuracy 2 (adapted tablet version), DSST = Digit-Symbol-Substitution Test from the BACS battery, DS (F/B) = Auditory Digit Span (Forward/Backward) adapted from the PEBL battery, PVF = phonetic verbal fluency test, SVF = semantic verbal fluency test, ROCF = Rey-Osterrieth complex figure, TMT-A/-B = Trail-Making Test A and B, SOPT = self-ordered pointing task (adapted version), WAIS-III = Wechsler Adult Intelligence Scale (3rd edition)

***In one of the research sites (Turku) the revised version of the Hopkins Verbal Learning Test (HVLT-R) was included instead of the RAVLT, which is not available in Finnish language. Due to this inconsistency, these values were changed to "missing", and imputed during feature engineering in the cross-validation scheme for all subjects that had performed the HVLT-R.**

sTable 3 sMRI protocol per Site

PRONIA Site	Model	Field Strength	Flip Angle	TR (ms)	TE (ms)	Voxel size [mm]	FOV	Slice Number
Munich	Philips Ingenia	3T	8	Shortest (9.4)	Shortest (5.5)	0.97 x 0.97 x 1.0	250 x 250	190
Milan Niguarda	Philips Achieva Intera	1.5T	12	Shortest (8.1)	Shortest (3.7)	0.94 x 0.94 x 1.0	240 x 240	170
Basel	SIEMENS Verio / Prisma	3T	8	2000	3.4	1.0 x 1.0 x 1.0	256 x 256	176
Cologne	Philips Achieva	3T	8	9.5	5.5	0.97 x 0.97 x 1.0	250 x 250	190 / 165
Birming-ham	Philips Achieva	3T	8	8.4	3.8	1.0 x 1.0 x 1.0	288 x 288	175
Turku	Philips Ingenuity	3T	7	8.1	3.7	1.0 x 1.0 x 1.0	256 x 256	176
Muenster	SIEMENS Prisma^{fit}	3T	8	2130	2.3	1.0 x 1.0 x 1.0	256 x 256	192

Abbreviations: T = tesla, TR = repetition time, TE = echo time, ms = milliseconds, mm = millimeter, FOV = field of view

sTable 4 Healthy individuals used for harmonization between sites and regression of age- and sex specific effects

Institute	Sample Size	Sex [Female (%)]	Statistical Analysis	*p-values*	Age [mean (SD) years]	Statistical Analysis	*p-values*
Munich	22	12 (55.5)	$\chi^2_6 = 0.24$	1.000	26.9 (4.8)	$F_6 = 0.57$	.751
Milan	22	12 (55.5)			27.0 (4.9)		
Basel	22	12 (55.5)			26.4 (4.3)		
Cologne	22	12 (55.5)			27.0 (5.2)		
Birmingham	22	11 (50.0)			25.5 (6.1)		
Turku	22	12 (55.5)			27.2 (5.2)		
Muenster	12	7 (58.3)			24.7 (4.1)		

Abbreviations: df = degrees of freedom, SD = standard deviation

sTable 5 Association between component-loadings derived with group information-guided independent component analysis and site before and after ComBat-harmonization in healthy individuals

Component	Before ComBat				After ComBat			
	Sum of Squares	df	F	*p-values*	Sum of Squares	df	F	*p-values*
COI – 1	0.000	6, 137	1.15	.345	0.000	6, 137	0.29	.940
COI – 2	0.000	6, 137	1.39	.224	0.000	6, 137	0.69	.657
COI – 3	0.001	6, 137	8.81	<.001	0.000	6, 137	0.71	.644
COI – 4	0.001	6, 137	7.41	<.001	0.000	6, 137	0.31	.932
COI – 5	0.001	6, 137	1.78	.108	0.000	6, 137	0.21	.975
COI – 6	0.002	6, 137	3.39	.004	0.000	6, 137	0.47	.830
COI – 7	0.000	6, 137	1.07	.384	0.000	6, 137	0.07	.999
COI – 8	0.001	6, 137	8.10	<.001	0.000	6, 137	1.79	.107
COI – 9	0.001	6, 137	2.53	.024	0.000	6, 137	0.67	.669

Abbreviations: df = degrees of freedom, COI = component of interest

sTable 6 Associations between site and component-loadings derived with group information-guided independent component analysis before and after application of ComBat-harmonization estimates learned in healthy individuals applied to patients with recent-onset psychosis and clinical high-risk for psychosis patients

patients with recent-onset psychosis								
Component	**Before ComBat**				**After ComBat**			
	Sum of Squares	**df**	**F**	***p-values***	**Sum of Squares**	**df**	**F**	***p-values***
COI – 1	0.000	6, 94	0.44	.848	0.000	6, 94	0.36	.903
COI – 2	**0.001**	**6, 94**	**2.95**	**.011**	**0.001**	**6, 94**	**2.54**	**.025**
COI – 3	0.000	6, 94	1.33	.254	**0.000**	**6, 94**	**2.26**	**.044**
COI – 4	**0.002**	**6, 94**	**9.32**	**<.001**	0.000	6, 94	0.96	.455
COI – 5	0.001	6, 94	1.45	.206	0.001	6, 94	0.93	.481
COI – 6	0.000	6, 94	0.92	.482	0.000	6, 94	0.49	.818
COI – 7	0.000	6, 94	2.01	.071	**0.001**	**6, 94**	**2.22**	**.048**
COI – 8	**0.000**	**6, 94**	**2.48**	**.028**	**0.001**	**6, 94**	**2.34**	**.038**
COI – 9	0.000	6, 94	1.05	.401	**0.001**	**6, 94**	**2.64**	**.021**
patients with clinical high-risk for psychosis								
Component	**Before ComBat**				**After ComBat**			
	Sum of Squares	**df**	**F**	***p-values***	**Sum of Squares**	**df**	**F**	***p-values***
COI – 1	**0.001**	**6, 54**	**3.09**	**.011**	**0.001**	**6, 54**	**2.74**	**.021**
COI – 2	**0.001**	**6, 54**	**3.01**	**.013**	**0.001**	**6, 54**	**2.70**	**.023**
COI – 3	0.000	6, 54	1.35	.250	**0.001**	**6, 54**	**2.76**	**.021**
COI – 4	**0.001**	**6, 54**	**3.36**	**.007**	0.000	6, 54	0.99	.440
COI – 5	0.001	6, 54	1.45	.214	0.002	6, 54	2.11	.068
COI – 6	0.001	6, 54	1.20	.323	0.001	6, 54	1.35	.253
COI – 7	**0.001**	**6, 54**	**3.12**	**.011**	**0.001**	**6, 54**	**2.57**	**.029**
COI – 8	0.000	6, 54	1.68	.145	0.001	6, 54	1.22	.313
COI – 9	**0.001**	**6, 54**	**2.58**	**.028**	0.001	6, 54	1.70	.138

Abbreviations: df = degrees of freedom, COI = component of interest

sTable 7 Matched recent-onset psychosis sample based on age, sex, site and scores of the Global Assessment of Functioning (functional disability) to the original sample

	"Artificial CCu"	"Artificial DCu"	Statistical Analysis	*p-values*
Patients with recent-onset psychosis not included in original sample (N = 109)				
Sample Size [N]	54	55		
Munich (%)	29 (53.7)	25 (45.5)	$\chi^2_9 = 11.90$	.156
Milan (%)	4 (7.4)	3 (5.5)		
Basel (%)	9 (16.7)	3 (5.5)		
Cologne (%)	2 (3.7)	9 (16.4)		
Birmingham (%)	3 (5.6)	3 (5.5)		
Turku (%)	4 (7.4)	7 (12.7)		
Udine (%)	0 (0.0)	0 (0.0)		
Bari (%)	0 (0.0)	2 (3.6)		
Duesseldorf (%)	1 (1.9)	0 (0.0)		
Muenster (%)	3 (5.6)	2 (3.6)		
Age [mean (SD) years]	24.6 (5.5)	25.7 (6.3)	$t_{105} = -0.96$	.338
Sex [Female (%)]	23 (42.6)	25 (45.5)	$\chi^2_1 = 0.309$	.578
GF-Social: Highest Lifetime	7.6 (1.1)	7.8 (0.8)	$t_{98} = -1.15$	.255
GF-Social: Baseline	**5.5 (1.6)**	**6.1 (1.1)**	**$t_{95} = -2.09$**	**.040**
GF-Role: Highest Lifetime	7.7 (1.2)	7.9 (1.0)	$t_{103} = -0.60$	.551
GF-Role: Baseline	4.9 (2.0)	5.4 (1.7)	$t_{104} = -1.55$	.125
GAF Disability/Impairment Highest Lifetime	78.0 (8.1)	77.7 (13.3)	$t_{87} = 0.14$	.889
GAF Disability/Impairment Highest Past Month	41.8 (12.6)	45.3 (13.7)	$t_{106} = -1.41$	.163
GAF Symptoms Highest Lifetime	78.7 (9.9)	77.9 (14.3)	$t_{94} = 0.33$	.741
GAF Symptoms Highest Past Month	40.4 (14.7)	39.8 (15.1)	$t_{107} = 0.21$	.833
Positive and Negative Syndrome Scale – Positive [mean (SD)]	18.9 (5.6)	17.8 (6.6)	$t_{97} = 0.85$	.397
Positive and Negative Syndrome Scale – Negative [mean (SD)]	16.8 (8.8)	14.5 (5.7)	$t_{92} = 1.64$	.104
Positive and Negative Syndrome Scale – General [mean (SD)]	35.9 (10.0)	33.5 (10.2)	$t_{101} = 1.21$	.228
No Cannabis User Baseline (%)	19 (35.2)	17 (30.9)	$t_{90} = 1.22$	.227

Abbreviations: df = degrees of freedom, GAF = Global Assessment of Functioning, GF: Social/Role = Global Functioning: Social/Role, CCu = continued cannabis use, DCu = discontinued cannabis use

sTable 8 Differences between patients with continued and discontinued cannabis use

	CCu	**DCu**	**Statistical Analysis**	***p-values***	**CCu**	**DCu**	**Statistical Analysis**	***p-values***
	Discovery Sample (ROP; N=109)				**Validation Sample (CHR; N=73)**			
Sample Size [N (%)]	54 (49.5)	55 (50.5)			36 (49.3)	37 (50.7)		
Number of Other Substances besides Cannabis tried in Lifetime [mean (SD)]	**1.7 (1.7)**	**0.6 (1.1)**	**t_{62} = 3.6**	**<.001**	0.6 (1.2)	0.7 (0.9)	t_{43} = -0.31	.756
Lifetime History of DSM-IV Cannabis Use Disorder [N (%)]								
Cannabis Abuse (%)	**21 (38.9)**	**19 (34.5)**	**χ^2_2 = -9.61**	**.008**	16 (44.4)	12 (32.4)	χ^2_2 = -1.14	.566
Cannabis Dependency (%)	**17 (31.5)**	**6 (10.9)**			1 (2.8)	1 (2.7)		
Average Number of cigarettes per day [mean (SD)]	8.0 (7.4)	7.2 (7.6)	t_{100} = 0.60	.553	7.7 (8.6)	4.6 (6.1)	t_{63} = 1.71	.093
Average Units of alcohol consumed per day [mean (SD)]	4.4 (4.2)	5.4 (6.1)	t_{75} = -0.92	.360	4.2 (5.6)	4.0 (3.3)	t_{46} = 0.24	.811
Level of Cannabis Use in the Last 3 Months – Cumulative Frequency (%)								
0 times	11 (20)	22 (40)	χ^2_6 = 5.52	.479	**9 (25)**	**23 (62)**	**χ^2_4 = 11.22**	**.024**
1-5 times	7 (13)	7 (13)			**8 (22)**	**6 (16)**		
6-10 times	4 (7)	3 (5)			**2 (6)**	**0 (0)**		
11-15 times	4 (7)	1 (2)			**2 (6)**	**1 (3)**		
16-20 times	1 (2)	1 (2)			**0 (0)**	**0 (0)**		
21-30 times	2 (4)	1 (2)			**0 (0)**	**0 (0)**		
> 30 times	8 (15)	8 (15)			**3 (8)**	**0 (0)**		
Level of Use of Other Substances in the Last 3 Months – Cumulative Frequency (%)								
0 times	17 (31)	29 (53)	χ^2_5 = 5.55	.353	15 (42)	11 (30)	χ^2_2 = 2.90	.234
1-5 times	7 (13)	3 (5)			2 (6)	5 (14)		
6-10 times	2 (4)	1 (2)			0 (0)	1 (3)		
11-15 times	1 (2)	1 (2)			0 (0)	0 (0)		
16-20 times	0 (0)	0 (0)			0 (0)	0 (0)		
21-30 times	1 (2)	0 (0)			0 (0)	0 (0)		
> 30 times	1 (2)	1 (2)			0 (0)	0 (0)		
Age at Cannabis Initiation [mean (SD) years]	16.5 (2.6)	17.5 (3.7)	t_{86} = -1.55	.126	17.1 (2.2)	17.5 (2.7)	t_{56} = -0.64	.526
Duration Lifetime Cannabis Use [mean (SD) months]	63.7 (50.0)	51.8 (43.9)	t_{90} = 1.22	.227	52.9 (64.4)	33.7 (43.4)	t_{45} = 1.31	.195
Time since last Cannabis Use at Baseline [mean (SD) months]	**8.7 (25.3)**	**33.4 (60.9)**	**t_{66} = -2.52**	**.010**	**10.6 (29.2)**	**33.6 (53.8)**	**t_{50} = -2.14**	**.038**
Sum of experienced burden of Recent Life Events (last year) [mean (SD)]	9.3 (10.9)	12.3 (11.4)	t_{104} = -1.40	.164	15.1 (10.4)	13.8 (9.9)	t_{71} = 0.53	.595
CTQ (emotional abuse) [mean (SD)]	12.3 (3.3)	11.4 (3.1)	t_{91} = 1.31	.193	**13.3 (3.2)**	**11.5 (2.3)**	**t_{61} = 2.67**	**.010**
CTQ (emotional neglect) [mean (SD)]	10.9 (4.2)	10.6 (4.8)	t_{86} = 0.35	.727	**12.7 (4.4)**	**10.6 (4.0)**	**t_{66} = 2.08**	**.041**
CTQ (physical abuse) [mean (SD)]	7.0 (3.8)	6.4 (3.4)	t_{93} = 0.79	.433	**7.7 (3.6)**	**5.8 (2.1)**	**t_{56} = 2.66**	**.010**
CTQ (physical neglect) [mean (SD)]	7.8 (3.1)	6.8 (2.0)	t_{83} = 1.87	.064	7.9 (2.6)	6.8 (2.4)	t_{64} = 1.88	.064
CTQ (sexual abuse) [mean (SD)]	5.7 (2.0)	6.0 (2.0)	t_{89} = -0.73	.468	5.8 (1.9)	6.6 (3.4)	t_{51} = -1.21	.232
WSS (magical ideation) [mean (SD)]	**4.9 (3.3)**	**3.3 (3.7)**	**t_{89} = 2.60**	**.011**	3.3 (2.9)	2.9 (2.7)	t_{62} = 0.58	.564
WSS (perceptual aberration) [mean (SD)]	**3.5 (4.3)**	**1.7 (2.8)**	**t_{87} = 2.53**	**.013**	2.1 (2.3)	3.1 (3.2)	t_{60} = -1.38	.172
WSS (physical anhedonia) [mean (SD)]	4.3 (3.2)	3.3 (2.7)	t_{88} = 1.62	.109	3.8 (2.9)	2.6 (2.4)	t_{64} = 1.83	.072
WSS (social anhedonia) [mean (SD)]	**4.8 (3.0)**	**3.4 (3.1)**	**t_{89} = 2.19**	**.031**	6.0 (3.5)	4.6 (2.9)	t_{62} = 1.79	.079
Becks Depression Inventary – II [mean (SD)]								
BDI-II 1 - Sadness	0.9 (0.9)	0.7 (0.6)	t_{90} = 1.27	.209	1.4 (0.8)	1.3 (0.8)	t_{67} = 0.39	.696
BDI-II 2 - Pessimism	0.9 (0.9)	0.7 (0.8)	t_{97} = 1.10	.273	1.3 (0.9)	1.1 (0.9	t_{68} = 0.66	.513
BDI-II 3 – Past failures	1.2 (1.0)	0.9 (0.8)	t_{96} = 1.49	.140	1.8 (1.0)	1.4 (1.0)	t_{68} = 1.57	.121
BDI-II 4 – Loss of Pleasure	1.0 (0.9)	0.9 (0.8)	t_{96} = 0.72	.473	1.4 (8.5)	1.5 (0.8)	t_{68} = -0.59	.559
BDI-II 5 – Guilt Feelings	0.9 (0.8)	0.7 (0.8)	t_{97} = 1.08	.284	1.2 (1.0)	1.0 (0.8)	t_{65} = 0.82	.418
BDI-II 6 – Punishment Feelings	1.0 (1.0)	0.8 (1.0)	t_{97} = 1.31	.192	1.0 (1.1)	0.8 (1.0)	t_{68} = 0.68	.497
BDI-II 7 – Self Dislike	1.0 (1.0)	0.9 (0.9)	t_{96} = 0.55	.582	1.3 (0.9)	1.4 (1.0)	t_{67} = -0.13	.901
BDI-II 8 – Self Criticalness	1.2 (1.1)	0.9 (0.8)	t_{94} = 1.63	.106	1.3 (1.1)	1.3 (0.9)	t_{65} = 0.00	1.000
BDI-II 9 – Suicidal thoughts or wishes	0.5 (0.7)	0.5 (0.6)	t_{96} = 0.70	.485	1.1 (0.7)	0.8 (0.6)	t_{67} = 1.79	.078

BDI-II 10 – Crying	0.7 (1.1)	0.6 (0.9)	$t_{96} = 0.58$	.561	1.2 (1.2)	1.2 (1.2)	$t_{67} = -0.18$	.858
BDI-II 11 - Agitation	1.0 (0.9)	0.8 (0.7)	$t_{95} = 1.35$	.179	1.1 (0.9)	1.1 (0.7)	$t_{64} = 0.28$	.779
BDI-II 12 – Loss of Interest	1.1 (1.0)	1.0 (1.1)	$t_{96} = 0.66$	.513	1.2 (1.0)	1.3 (1.0)	$t_{67} = -0.22$	.830
BDI-II 13 – Indecisiveness	1.2 (1.1)	1.0 (1.0)	$t_{97} = 0.83$	.406	1.6 (1.2)	1.7 (1.0)	$t_{67} = -0.22$	.827
BDI-II 14 – Worthlessness	0.9 (1.0)	0.8 (0.8)	$t_{96} = 0.73$	.469	1.1 (0.8)	1.3 (1.0)	$t_{67} = -0.53$	.597
BDI-II 15 – Loss of Energy	1.0 (0.8)	0.9 (0.8)	$t_{97} = 0.39$	.695	1.2 (0.8)	1.4 (0.7)	$t_{67} = -1.28$	.206
BDI-II 16 – Changes in Sleeping Pattern	2.3 (1.9)	1.8 (1.8)	$t_{97} = 1.13$	.260	2.5 (1.8)	2.4 (1.9)	$t_{67} = 0.22$	.824
BDI-II 17 – Irritability	0.9 (1.0)	0.6 (0.7)	$t_{91} = 1.96$	.053	1.2 (1.1)	0.9 (0.8)	$t_{62} = 1.36$	.177
BDI-II 18 – Changes in Appetite	1.8 (1.7)	1.2 (1.5)	$t_{97} = 1.87$	.064	1.3 (1.6)	1.6 (1.7)	$t_{67} = -0.92$	.360
BDI-II 19 – Concentration Difficulty	1.4 (1.0)	1.2 (0.8)	$t_{96} = 0.92$	.362	1.6 (0.8)	1.8 (0.7)	$t_{66} = -1.07$	.287
BDI-II 20 – Tiredness or Fatigue	1.1 (0.8)	1.0 (0.8)	$t_{97} = 0.37$	.713	1.4 (0.9)	1.6 (0.7)	$t_{65} = -0.85$	.397
BDI-II 21 – Loss of Interest in Sex	0.8 (1.0)	0.9 (1.0)	$t_{95} = -0.76$	.451	0.8 (0.9)	0.8 (1.0)	$t_{68} = 0.13$	.901
Positive and Negative Syndrome Scale [mean (SD)]								
PANSS general 1 - Somatic concern	2.2 (1.7)	1.8 (1.6)	$t_{104} = 1.33$	.186	1.7 (1.0)	1.8 (1.3)	$t_{65} = -0.52$	.606
PANSS general 2 - Anxiety	2.9 (1.6)	2.8 (1.6)	$t_{105} = 0.53$	.596	2.7 (1.1)	2.7 (1.4)	$t_{63} = 0.00$	1.000
PANSS general 3 - Guilt feelings	2.1 (1.6)	2.3 (1.6)	$t_{105} = -0.65$	.516	2.1 (1.5)	1.7 (1.2)	$t_{65} = 1.42$	.161
PANSS general 4 - Tension	2.6 (1.4)	2.2 (1.3)	$t_{104} = 1.22$	.225	1.9 (0.8)	1.9 (1.1)	$t_{63} = -0.12$	.903
PANSS general 5 - Mannerisms and posturing	**1.5 (1.0)**	**1.2 (0.5)**	**$t_{78} = 2.41$**	**.018**	1.2 (0.4)	1.1 (0.4)	$t_{68} = 0.95$	.346
PANSS general 6 – Depression	3.4 (1.6)	2.8 (1.6)	$t_{105} = 1.85$	.067	3.9 (1.3)	3.8 (1.3)	$t_{68} = 0.38$	.707
PANSS general 7 - Motor retardation	1.6 (1.1)	1.5 (1.0)	$t_{103} = 0.41$	.684	1.4 (0.9)	1.1 (0.4)	$t_{49} = 1.98$	.054
PANSS general 8 - Uncooperativeness	1.5 (1.3)	1.3 (0.6)	$t_{75} = 1.30$	.199	1.1 (0.5)	1.1 (0.4)	$t_{61} = 0.26$	.795
PANSS general 9 - Unusual thought content	**3.5 (2.0)**	**2.6 (1.7)**	**$t_{102} = 2.46$**	**.015**	1.8 (1.1)	1.7 (1.1)	$t_{68} = 0.34$	.738
PANSS general 10 – Disorientation	1.5 (early0.8)	1.3 (0.9)	$t_{105} = 0.95$	.344	1.2 (0.9)	1.3 (0.8)	$t_{67} = -0.14$	.886
PANSS general 11 - Poor attention	2.5 (1.3)	2.2 (1.2)	$t_{105} = 1.33$	.188	2.0 (1.1)	2.4 (1.1)	$t_{68} = -1.52$	.133
PANSS general 12 - Lack of judgement and insight	2.9 (1.5)	2.4 (1.5)	$t_{105} = 1.65$	.103	1.4 (0.9)	1.3 (0.6)	$t_{61} = 0.63$	.533
PANSS general 13 - Disturbance of volition	2.1 (1.2)	2.0 (1.5)	$t_{103} = 0.72$	.474	2.4 (1.6)	1.8 (1.2)	$t_{63} = 1.72$	.089
PANSS general 14 - Poor impulse control	1.7 (1.0)	1.6 (1.3)	$t_{101} = 0.39$	.695	1.4 (0.7)	1.4 (0.8)	$t_{67} = 0.31$	.758
PANSS general 15 – Preoccupation	**2.2 (1.4)**	**1.7 (1.1)**	**$t_{100} = 2.12$**	**.036**	1.8 (1.1)	1.7 (1.0)	$t_{68} = 0.23$	.821
PANSS general 16 - Active social avoidance	**2.8 (1.6)**	**2.1 (1.3)**	**$t_{99} = 2.25$**	**.027**	2.6 (1.6)	2.6 (1.6)	$t_{68} = 0.00$	1.000
PANSS N1 – Blunted affect	2.3 (1.5)	2.2 (1.4)	$t_{104} = 0.22$	.825	2.1 (1.2)	2.3 (1.4)	$t_{67} = -0.36$	.717
PANSS N2 - Emotional withdrawal	2.6 (1.2)	2.4 (1.4)	$t_{104} = 1.07$	.285	2.4 (1.4)	2.6 (1.6)	$t_{67} = -0.57$	.574
PANSS N3 – Poor Rapport	2.0 (1.3)	1.9 (1.2)	$t_{104} = 0.23$	.822	1.9 (1.2)	2.1 (1.3)	$t_{68} = -0.57$	.570
PANSS N4 – Passive/apathetic social withdrawal	2.6 (1.8)	2.5 (1.4)	$t_{102} = 0.44$	.657	2.7 (1.5)	2.6 (1.4)	$t_{67} = 0.33$	.745
PANSS N5 – Difficulty in abstract thinking	1.8 (1.6)	1.5 (0.8)	$t_{100} = 1.53$	.130	1.3 (0.8)	1.5 (1.0)	$t_{65} = -0.51$	.614
PANSS N6 – Lack of spontaneity and flow of conversation	1.9 (1.0)	1.8 (1.2)	$t_{101} = 0.24$	.808	1.8 (1.2)	1.6 (0.9)	$t_{64} = 0.76$	.449
PANSS N7 – Stereotyped thinking	2.0 (1.3)	1.8 (1.3)	$t_{105} = 0.67$	.507	1.5 (1.1)	1.3 (0.6)	$t_{51} = 0.81$	.424
PANSS P1 – Delusions	4.5 (2.0)	4.5 (1.9)	$t_{104} = -0.17$	.863	1.9 (1.8)	2.1 (1.2)	$t_{68} = -0.91$	.368
PANSS P2 - Conceptual disorganization	2.3 (1.5)	2.1 (1.4)	$t_{104} = 1.03$	.307	1.6 (0.8)	1.7 (1.0)	$t_{65} = -0.39$	.699
PANSS P3 – Hallucinatory behavior	2.8 (1.9)	3.0 (1.9)	$t_{105} = -0.57$	.573	1.8 (1.0)	2.1 (1.3)	$t_{64} = -1.33$	.187
PANSS P4 – Excitement	2.0 (1.3)	2.0 (1.4)	$t_{105} = 0.00$	1.00	1.1 (0.4)	1.3 (0.6)	$t_{59} = -1.51$	.138
PANSS P5 – Grandiosity	2.5 (1.9)	2.0 (1.8)	$t_{104} = 1.30$	.196	1.3 (0.8)	1.2 (0.7)	$t_{67} = 0.15$	.878
PANSS P6 – Suspiciousness/persecution	4.1 (2.1)	4.0 (2.2)	$t_{105} = 0.36$	.718	2.3 (1.2)	1.8 (.10)	$t_{66} = 1.80$	.077
PANSS P7 - Hostility	1.8 (1.3)	1.7 (1.2)	$t_{103} = 0.67$	.503	1.3 (0.7)	1.2 (0.7)	$t_{68} = 0.53$	.601
Global Functioning [mean (SD)]								
GAF Disability/Impairment Highest Lifetime	77.5 (8.8)	78.5 (9.0)	$t_{104} = -0.58$	.561	76.6 (8.6)	79.0 (8.3)	$t_{71} = -1.22$	.227

GAF Disability/Impairment Highest Past Year	**59.4 (14.1)**	**66.5 (14.6)**	**$t_{107} = -2.61$**	**.010**	62.5 (12.3)	66.1 (13.4)	$t_{71} = -1.21$	.234
GAF Disability/Impairment Highest Past Month	**41.3 (10.4)**	**49.0 (16.6)**	**$t_{91} = -2.92$**	**.004**	48.3 (11.3)	53.0 (11.2)	$t_{70} = -0.52$	.607
GAF Symptoms Highest Lifetime	77.7 (8.5)	79.6 (9.6)	$t_{106} = -1.07$	.286	78.0 (9.9)	79.1 (8.8)	$t_{71} = -1.78$	.079
GAF Symptoms Highest Past Year	**56.6 (15.8)**	**64.7 (16.5)**	**$t_{107} = -2.65$**	**.009**	61.9 (11.8)	65.3 (11.3)	$t_{71} = -1.24$	.220
GAF Symptoms Highest Past Month	40 (12.4)	43.4 (16.4)	$t_{100} = -1.21$	.230	47.0 (10.2)	51.8 (11.8)	$t_{70} = -1.86$	.067
GF-Social: Highest Lifetime	7.8 (0.8)	8.0 (0.8)	$t_{106} = -1.36$	.177	7.7 (0.9)	8.1 (0.8)	$t_{68} = -1.64$	.107
GF-Social: Lowest Past Year	5.2 (1.6)	5.3 (1.6)	$t_{106} = -0.33$	.740	5.7 (1.2)	6.0 (1.5)	$t_{70} = -1.05$	.299
GF-Social: Highest Past Year	**6.5 (1.2)**	**7.2 (1.3)**	**$t_{106} = -2.7$**	**.008**	**6.8 (1.2)**	**7.4 (0.9)**	**$t_{69} = -2.37$**	**.020**
GF-Social: Baseline	5.6 (1.5)	5.9 (1.5)	$t_{106} = -0.94$	.352	5.9 (1.4)	6.6 (1.5)	$t_{71} = -1.93$	.058
GF-Role: Highest Lifetime	**7.4 (0.9)**	**7.9 (0.9)**	**$t_{105} = -2.67$**	**.009**	7.9 (0.9)	7.9 (0.8)	$t_{69} = -0.16$	.877
GF-Role: Lowest Past Year	4.3 (1.7)	4.9 (1.9)	$t_{105} = -1.7$	.094	5.2 (1.9)	5.6 (1.3)	$t_{63} = -1.19$	.239
GF-Role: Highest Past Year	**6.0 (1.8)**	**7.2 (1.2)**	**$t_{93} = -3.9$**	**<.001**	**6.9 (1.2)**	**7.4 (0.9)**	**$t_{66} = -2.06$**	**.043**
GF-Role: Baseline	4.6 (1.7)	5.3 (1.9)	$t_{106} = -1.96$	.052	5.4 (1.9)	6.0 (1.4)	$t_{64} = -1.60$	.114
CISS 1 „Try to be with other people.“	3.0 (1.2)	3.1 (1.2)	$t_{96} = -0.62$	.540	2.6 (1.0)	2.9 (1.0)	$t_{64} = -1.13$	.264
CISS 2 „Blame myself for putting things off.“	3.8 (1.1)	3.4 (1.2)	$t_{92} = 1.61$	.112	3.7 (1.1)	4.0 (0.)	$t_{65} = -0.93$	.356
CISS 3 „Blame myself for having gotten into this situation.“	3.6 (1.3)	3.2 (1.2)	$t_{96} = 1.30$	.197	3.8 (1.2)	3.7 (1.0)	$t_{65} = 0.22$	.823
CISS 4 „Window shop.“	2.1 (1.3)	2.4 (1.2)	$t_{96} = -1.22$	.226	2.1 (1.3)	2.4 (1.1)	$t_{65} = -1.25$	.218
CISS 5 „Outline my priorities.“	3.2 (1.2)	3.3 (0.9)	$t_{92} = -0.87$	.387	2.9 (1.0)	2.9 (1.1)	$t_{66} = -0.23$	.818
CISS 6 „Treat myself to a favorite food or snack.“	3.3 (1.2)	3.7 (1.2)	$t_{94} = -1.59$	.115	3.3 (1.2)	3.4 (1.2)	$t_{66} = -0.40$	.692
CISS 7 „Feel anxious about not being able to cope.“	3.4 (1.2)	3.3 (1.2)	$t_{96} = 0.31$	.758	3.9 (1.0)	3.9 (1.1)	$t_{66} = 0.11$	.910
CISS 8 „Become very tense.“	3.6 (1.2)	3.1 (1.3)	$t_{94} = 1.71$	.091	4.3 (0.8)	4.1 (1.0)	$t_{63} = 0.91$	.368
CISS 9 „Think about how I solved similar problems.“	3.1 (1.1)	3.3 (1.2)	$t_{94} = -0.94$	.347	3.0 (1.2)	2.9 (1.1)	$t_{66} = 0.21$	.832
CISS 10 „Go out for a snack or meal.“	2.7 (1.4)	2.9 (1.3)	$t_{96} = -0.55$	.587	2.9 (1.2)	2.7 (1.0)	$t_{64} = 0.64$	.523
CISS 11 „Become very upset.“	2.9 (1.3)	2.6 (1.1)	$t_{95} = 1.06$	.291	3.3 (1.1)	3.2 (1.2)	$t_{66} = 0.31$	.758
CISS 12 „Determine a course of action and follow it.“	2.9 (1.3)	3.2 (1.2)	$t_{95} = -1.23$	.223	2.5 (0.9)	2.5 (0.8)	$t_{65} = -0.35$	.729
CISS 13 „Blame myself for not knowing what to do.“	**3.5 (1.2)**	**2.9 (1.4)**	**$t_{92} = 2.28$**	**.025**	3.8 (1.0)	3.6 (1.0)	$t_{66} = 0.61$	.544
CISS 14 „Work to understand the situation.“	3.9 (1.1)	4.0 (0.8)	$t_{92} = -0.48$	.631	4.1 (1.0)	3.8 (.8)	$t_{60} = 1.06$	.291
CISS 15 „Think about the event and learn from my mistakes.“	3.6 (1.2)	3.8 (1.1)	$t_{95} = -0.85$	.396	3.6 (1.2)	36 (1.1)	$t_{65} = -0.11$	.916
CISS 16 „Wish that I could change what had happened or how I felt.“	3.7 (1.4)	3.5 (1.3)	$t_{96} = 0.79$	.431	4.1 (1.1)	4.0 (1.1)	$t_{67} = 0.43$	.672
CISS 17 „Visit a friend.“	2.9 (1.2)	3.2 (1.2)	$t_{94} = -0.97$	.334	3.0 (1.3)	2.9 (1.1)	$t_{65} = 0.20$	.844
CISS 18 „Spend time with a special person.“	3.2 (1.1)	3.4 (1.1)	$t_{95} = -0.84$	.403	3.3 (1.3)	3.2 (1.3)	$t_{66} = 0.37$	.710
CISS 19 „Analyse my problem before reacting.“	3.2 (1.2)	3.3 (1.2)	$t_{95} = -0.43$	.667	3.7 (1.0)	3.5 (1.0)	$t_{67} = 0.77$	.446
CISS 20 „Phone a friend.“	2.6 (1.2)	3.0 (1.2)	$t_{95} = -1.78$	.079	2.5 (1.3)	2.5 (1.3)	$t_{67} = 0.05$	.964
CISS 21 „Get angry.“	**3.3 (1.2)**	**2.6 (1.4)**	**$t_{91} = 2.34$**	**.021**	3.4 (1.2)	2.9 (1.3)	$t_{66} = 1.75$	.085
CISS 22 „See a movie.“	3.0 (1.4)	2.8 (1.4)	$t_{95} = 0.77$	.445	3.3 (1.2)	3.2 (1.4)	$t_{65} = 0.28$	.782
CISS 23 „Come up with several different solutions to the problem.“	3.1 (1.2)	3.1 (1.1)	$t_{96} = -0.30$	.762	3.1 (1.1)	2.7 (1.0)	$t_{65} = 1.48$	.145
CISS 24 „Try to be organised so I can be on top of the situation.“	3.1 (1.2)	3.6 (1.2)	$t_{96} = -2.11$	.037	2.6 (1.2)	2.9 (1.2)	$t_{66} = -0.94$	.349
Age [mean (SD) years]	23.8 (4.3)	25.1 (5.2)	$t_{104} = -1.45$	.151	21.96 (3.65)	23.8 (5.2)	$t_{65} = -1.80$	.076
Population density of place of living [mean (SD)]	3146 (2479)	2851 (2208)	$t_{104} = 0.65$	.517	2830 (2476)	2625 (1970)	$t_{67} = 0.39$	.698
Population density of place of birth [mean (SD)]	3889 (6315)	2976 (4534)	$t_{88} = 0.84$	.402	3056 (3997)	2032 (1905)	$t_{43} = 1.33$	.192
Lived in a partnership for at least one year [yes (%)]	24 (44)	29 (53)	$\chi^2_1 = 0.24$	.627	**11 (31)**	**23 (62)**	**$\chi^2_1 = 6.11$**	**.013**
Number of people living with [mean (SD)]	6.5 (27.8)	2.5 (2.6)	$t_{51} = 1.01$	.318	3.4 (3.0)	2.5 (1.7)	$t_{56} = 1.51$	.138

Education [mean (SD) years]	13.3 (2.7)	13.9 (2.7)	$t_{105} = -1.12$	.268	13.1 (2.6)	14.2 (2.7)	$t_{70} = -1.64$	.106
Type of current work [N (%)]								
Home work (looking after family or home)	0 (0)	0 (0)	$\chi^2_4 = 7.16$	.128	**0 (0)**	**0 (0)**	**$\chi^2_3 = 8.16$**	**.043**
in full time education	14 (26)	21 (38)			**16 (44)**	**22 (59)**		
unemployed but available for work (with regard to health)	9 (17)	7 (13)			**1 (3)**	**5 (14)**		
unable to work because of physical long-term sickness or disability	0 (0)	1 (2)			**0 (0)**	**0 (0)**		
unable to work because of mental long-term sickness or disability	21 (39)	10 (18)			**13 (36)**	**5 (16)**		
other	1 (2)	0 (0)			**1 (3)**	**0 (0)**		
Sex [Female (%)]	15 (27.8)	19 (34.5)	$\chi^2_1 = 0.31$	.578	**11 (30.6)**	**23 (62.2)**	**$\chi^2_1 = -6.11$**	**.013**
Body Mass Index [mean (SD)]	23.1 (4.1)	22.9 (4.0)	$t_{97} = -0.30$	.763	23.5 (4.4)	22.0 (2.9)	$t_{59} = 1.71$	.092

*bold: significant at p<.05

Abbreviations: CCu = continued cannabis use, DCu = discontinued cannabis use, ROP = recent-onset psychosis, CHR = clinical high-risk for psychosis, GAF = Global Assessment of functioning, GF = Global Functioning, WSS = Wisconsin Schizotypyp Scale, PANSS G= Positive and Negative Syndrome Scale general, PANSS P= Positive and Negative Syndrome Scale positive, PANSS N= Positive and Negative Syndrome Scale negative, CISS = Coping Inventory of Stressful Situations, BDI-II = Beck's Depression Inventory – II, SD = standard deviation

sTable 9 Prediction results in recent-onset psychosis matched based on age, sex, site and scores from the Global Assessment of Functioning (functional disability) to original sample

	TP	TN	FP	FN	Sens %	Spec %	BAC %	PPV	NPV	PSI	NLR	PLR	AUC	p-value
Clinical predictor														
ROP (N = 109)	30	32	22	25	54.5	59.3	56.9	57.5	56.1	13.8	0.8	1.3	0.62	.083
sMRI predictor														
ROP (N = 101)	18	25	26	32	36.0	49.0	42.5	40.9	43.9	-15.2	1.3	0.7	0.43	.989

Abbreviations: TP = true positive, TN = true negative, FP = false positive, FN = false negativ e, Sens % = Sensitivity, BAC = balanced accuracy, PPV = positive predictive value, NPV = n egative predictive value, PSI = prognostic summary index, NLR = negative likelihood ratio, P LR = positive likelihood ratio, AUC = area under the curve, ROP = recent-onset psychosis

sTable 10 Results of Mixed-model analysis of illness course

The degrees of freedom were approximated using Satterthwaite method (lmerTest). Parametric permutation-based Likelihood Ratio Tests (LRT) were conducted with 200 permutations to determine significant benefits of adding additional predictors ($Time^2$, $Outcome:Time^2$; $Time^3$, $Outcome:Time^3$) in comparison with the linear model. We present here the comparison of the model providing the best fit based on LRT (quadratic/polynomial) with the linear fit. In case that the linear model provided the best fit we present the LRT-test result in comparison with the quadratic model.

	Recent-Onset Psychosis					**Clinical High-Risk for Psychosis**				
Positive and Negative Syndrome Scale – Positive										
Term	**df**	**t-value**	**p_{FDR}**	**LRT $\chi^2_{(df)}$**	**LRT $p_{(FDR)}$**	**df**	**t-value**	**p_{FDR}**	**LRT $\chi^2_{(df)}$**	**LRT $p_{(FDR)}$**
Group	205	2.22	.042	53.66_4	<.001	114	0.48	.759	3.37_2	.186
Time (linear)	306	-5.73	<.001			261	-3.72	<.001		
Time (quadratic)	312	2.76	.010			-	-	-		
Time (polynomial)	316	-1.64	.110			-	-	-		
Time x Group	315	-1.38	.420			261	0.38	.779		
$Time^2$ x Group	318	1.55	.420			-	-	-		
$Time^3$ x Group	320	-1.34	.420			-	-	-		
Positive and Negative Syndrome Scale – General										
Group	168	3.75	.001	43.30_4	<.001	106	1.13	.392	4.56_2	.102
Time (linear)	297	-3.96	<.001			257	-4.57	<.001		
Time (quadratic)	302	1.65	.110			-	-	-		
Time (polynomial)	305	-0.68	.500			-	-	-		
Time x Group	306	2.62	.060			258	-0.59	.697		
$Time^2$ x Group	308	-2.62	.060			-	-	-		
$Time^3$ x Group	309	2.50	.060			-	-	-		
Positive and Negative Syndrome Scale – Negative										
Group	145	0.77	.444	9.50_2	<.009	106	0.10	.921	5.07_2	.079
Time (linear)	302	-3.41	.002			258	-3.67	<.001		
Time (quadratic)	306	1.94	.074			-	-	-		
Time (polynomial)	-	-	-			-	-	-		
Time x Group	307	-0.02	.991			259	-0.05	.962		
$Time^2$ x Group	309	0.06	.991			-	-	-		
$Time^3$ x Group	-	-	-			-	-	-		
Beck's Depression Inventory – II										
Group	122	1.15	.303	8.31_2	.016	198	-1.29	.293	29.41_4	<.001
Time (linear)	219	-2.98	.006			131	1.46	.250		
Time (quadratic)	219	1.72	.110			193	-0.54	.588		
Time (polynomial)	-	-	-			193	1.07	.320		
Time x Group	226	-0.01	.991			195	-4.46	<.001		
$Time^2$ x Group	227	0.31	.991			199	3.89	<.001		
$Time^3$ x Group	-	-	-			199	-3.35	.003		
Global Assessment of Functioning – functional disability										
Group	158	-3.15	.006	23.77_2	<.001	159	-1.80	.220	15.35_2	<.001
Time (linear)	308	6.00	<.001			279	4.32	<.001		
Time (quadratic)	313	-3.37	.002			283	-2.38	.030		
Time (polynomial)	-	-	-			-	-	-		
Time x Group	313	-0.44	.991			266	1.34	.362		
$Time^2$ x Group	315	0.25	.991			268	-1.36	.362		
$Time^3$ x Group	-	-	-			-	-	-		
Global Assessment of Functioning – Symptoms										
Group	207	-2.46	.030	17.25_2	<.001	282	3.70	.220	9.42_2	.009
Time (linear)	318	5.86	<.001			168	-2.02	<.001		
Time (quadratic)	327	-3.08	.004			286	-1.95	.075		

Time (polynomial)	-	-	-			-	-	-		
Time x Group	325	-0.81	.837			268	1.18	.399		
Time^2 x Group	329	0.53	.991			270	-0.96	.482		
Time^3 x Group	-	-	-			-	-	-		

Abbreviations: LRT = Likelihood Ratio Tests

sTable 11 Results of the clinical predictor for patients with and without cannabis use disorder separately

	Cannabis use disorder fulfilled	No Cannabis use disorder fulfilled	Wilcoxon-test: Z-statistic	Wilcoxon-test: p-value
Patients with recent-onset psychosis				
True positives	30	8	-	-
True negatives	16	26	-	-
False positives	9	4	-	-
False negatives	8	9	-	-
Sensitivity (min-max)	78.9 (69.4 – 81.6)	50.0 (37.5 – 56.2)	2.66	.008
Specificity (min-max)	64.0 (56.0 – 66.7)	86.7 (80.0 – 86.7)	-2.52	.012
balanced accuracy	71.4	68.3	-	-
Patients at clinical high-risk for psychosis				
True positives	8	7	-	-
True negatives	8	20	-	-
False positives	5	4	-	-
False negatives	9	12	-	-
Sensitivity (min-max)	47.1 (47.1 – 47.1)	36.8 (36.8 – 42.1)	2.77	.006
Specificity (min-max)	61.5 (53.8 – 61.5)	86.9 (83.3 – 83.3)	-2.77	.006
balanced accuracy	54.3	61.9	-	-

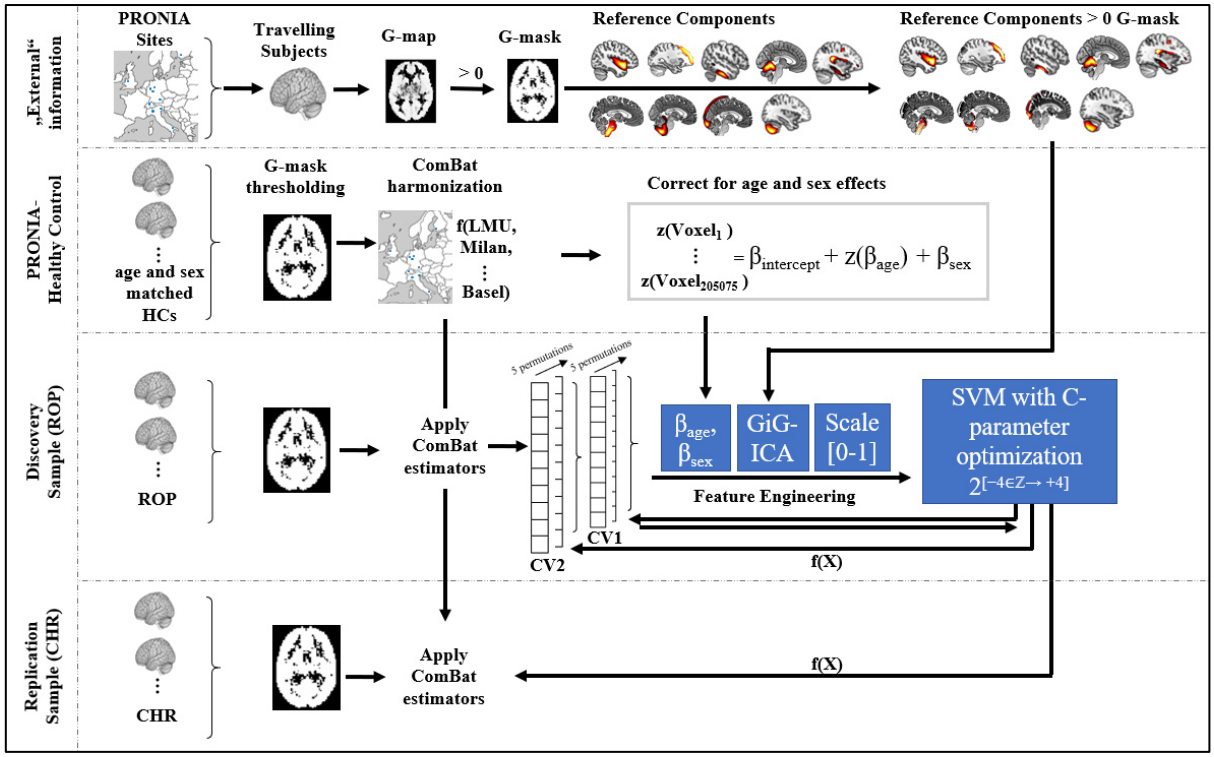
Abbreviations: min/max = lowest/highest sensitivity/specificity across permutations at the outer cross-validation folds.

8.) Supplementary Figures

SUBSTANCE USE (dd-mm-yyyy)	___-___-_____	
Cannabis lifetime *(follow-up: since the last assessment)*	0 = No 1 = Yes	Date of onset: Date of offset: (ongoing: 66-66-6666)
Cumulative number of months:		
Daily/weekly frequency of use (average) during the last 3 months *(follow-up: since the last visit)*	1 = daily 2 = > 3 days a week 3 = <= 3 days a week 4 = less than weekly 5 = never	
Cannabis - cumulative frequency of use during the last 3 months *(follow-up: since the last visit)*	1 = 1-5 times 2 = 6-10 times 3 = 11-15 times 4 = 16-20 times 5 = 21-30 times 6 = > 30 times 7 = not applicable	
Last consumption (dd-mm-yyyy)	___-___-_____	
Other substances lifetime *(follow-up: since the last visit)*	1 = hallucinogens 2 = cocaine 3 = amphetamine-type stimulants incl. MDMA 4 = inhalants 5 = opioids 6 = PCP or similar type 7 = other designer drugs 8 = sedative-hypnotic- anxiolytic 9 = none	
Other substances – daily/weekly frequency of use (average) during the last 3 months *(follow-up: since the last visit)*	1 = daily 2 = > 3 days a week 3 = <= 3 days a week 4 = less than weekly 5 = never	
Other substances - cumulative frequency of use during the last 3 months (different drugs can be added) *(follow-up: since the last visit)*	1 = 1-5 times 2 = 6-10 times 3 = 11-15 times 4 = 16-20 times 5 = 21-30 times 6 = > 30 times 7 = not applicable	
Last consumption (dd-mm-yyyy)	___-___-_____	

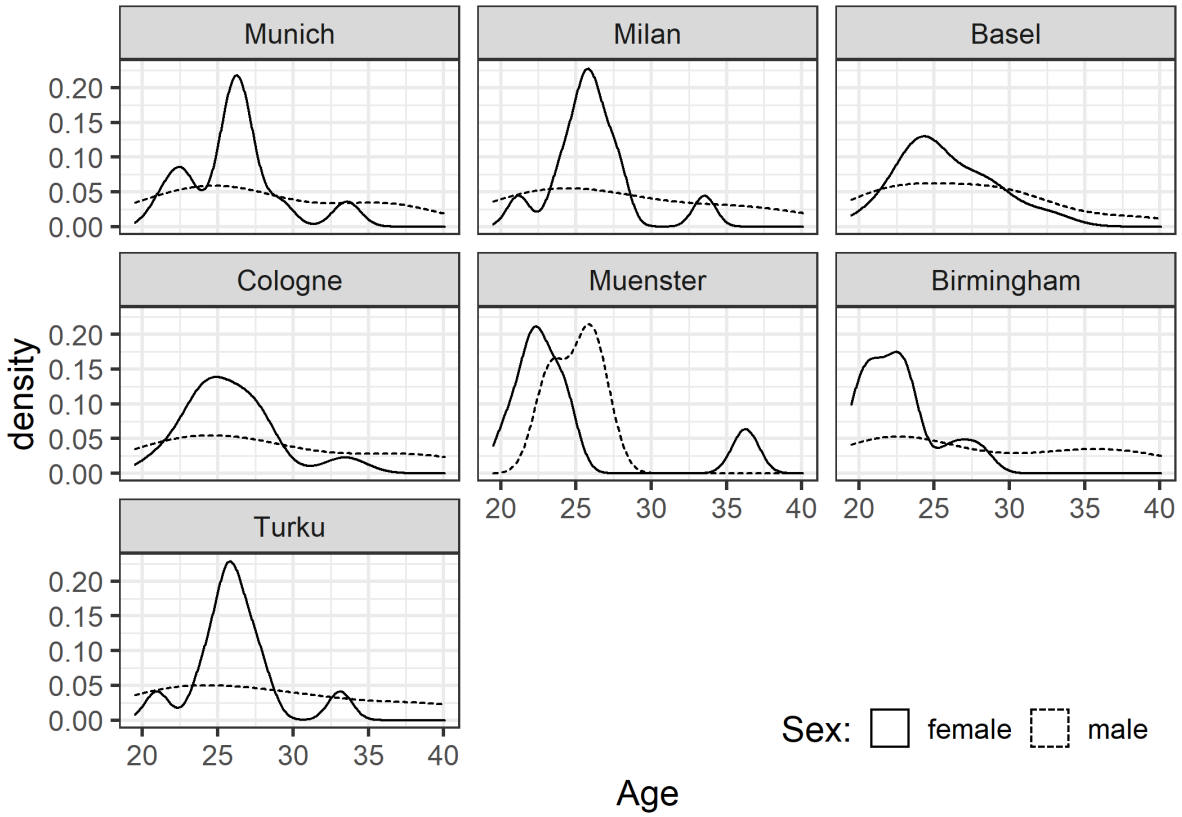
sFigure 1 Substance Use Questionnaire

Abbreviations: MDMA = methylenedioxy-N-methylamphetamine, PCP = phencyclidine

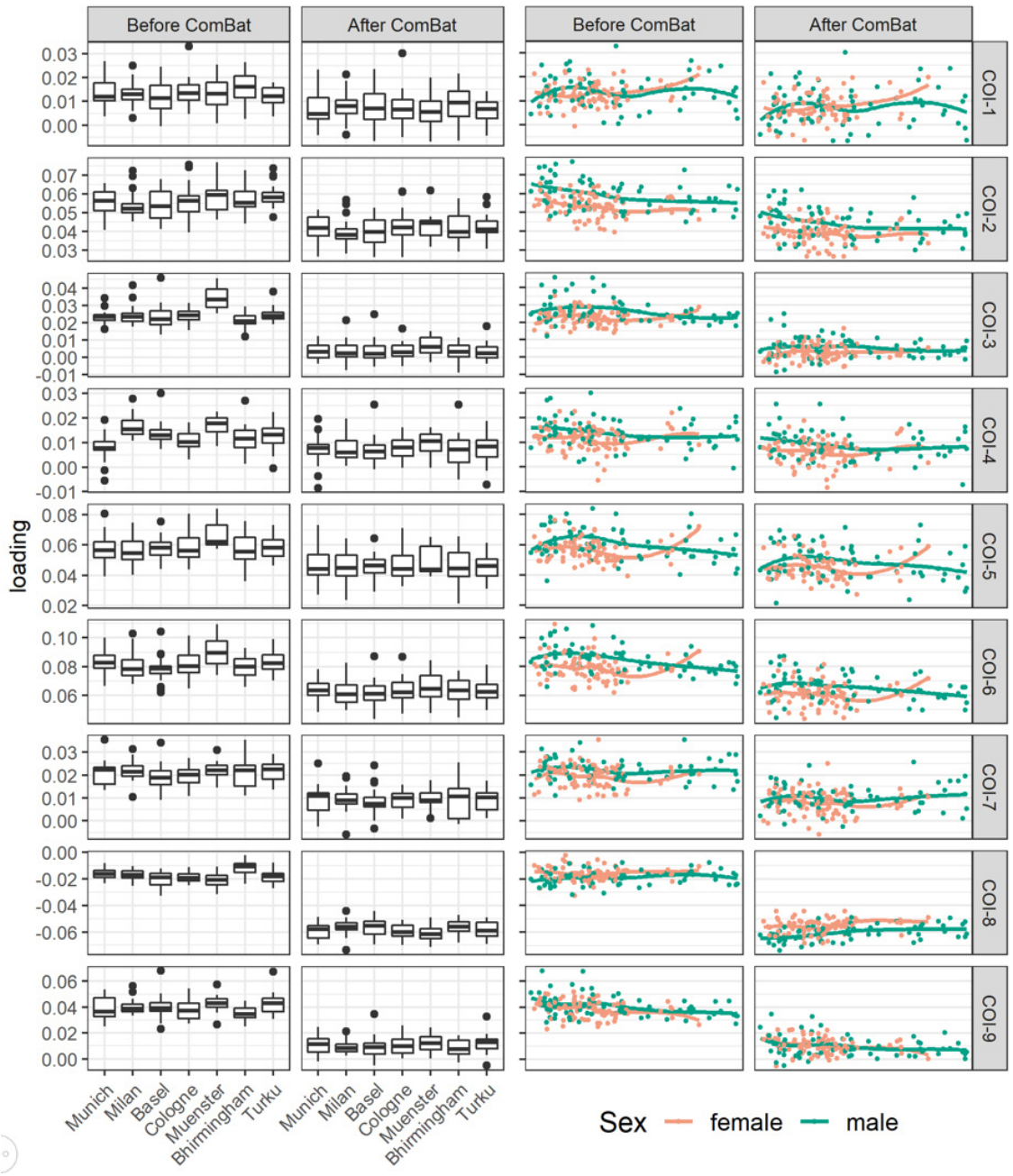


sFigure 2 Machine learning pipeline of structural Magnetic Resonance Imaging (sMRI)

In our machine learning pipeline, we used "external" information to account for site-specific scanner differences. Six subjects were scanned at six of the seven PRONIA sites, and their images were used to build a g-theory mask. This mask was used to exclude all voxels that were only associated with site-specific differences but showed no subject specific variation from the reference components (RCs) and all subjects. Then, the ComBat-algorithm was used to adjust for site specific-effects in a group of matched healthy individuals (HC), and the estimators were then used to remove site-specific effects independently from each ROP and CHR patient. Additionally, sex- and age- specific effects were regressed linearly from HC-sMRI images and the betas were used to remove these effects from independently from ROP and CHR patients in the machine learning pipeline. Finally, we trained and tested our machine learning model in ROP and applied the model to the completely held-out CHR. *Abbreviations:* CHR = clinical high-risk for psychosis, ROP = recent-onset psychosis, GiG-ICA = group information guided–independent component analysis, SVM = support vector machine.

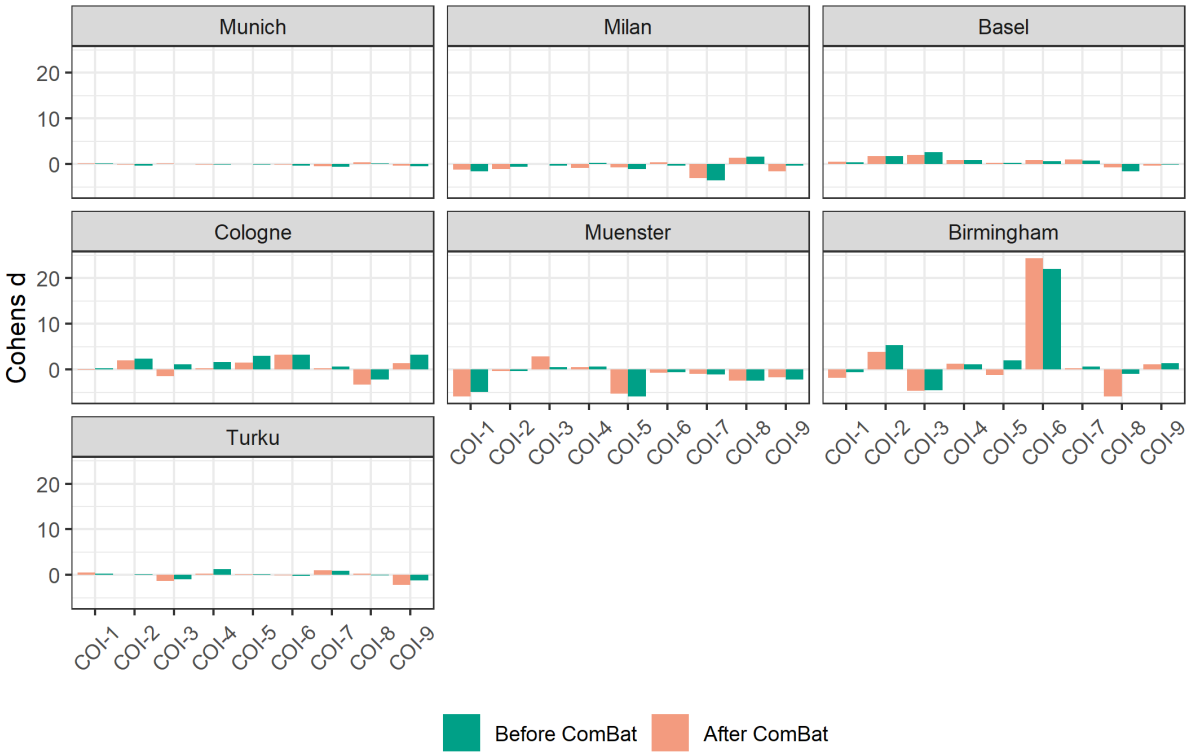


sFigure 3 Age and sex distribution of healthy individuals used for harmonization between sites and regression of age- and sex specific effects



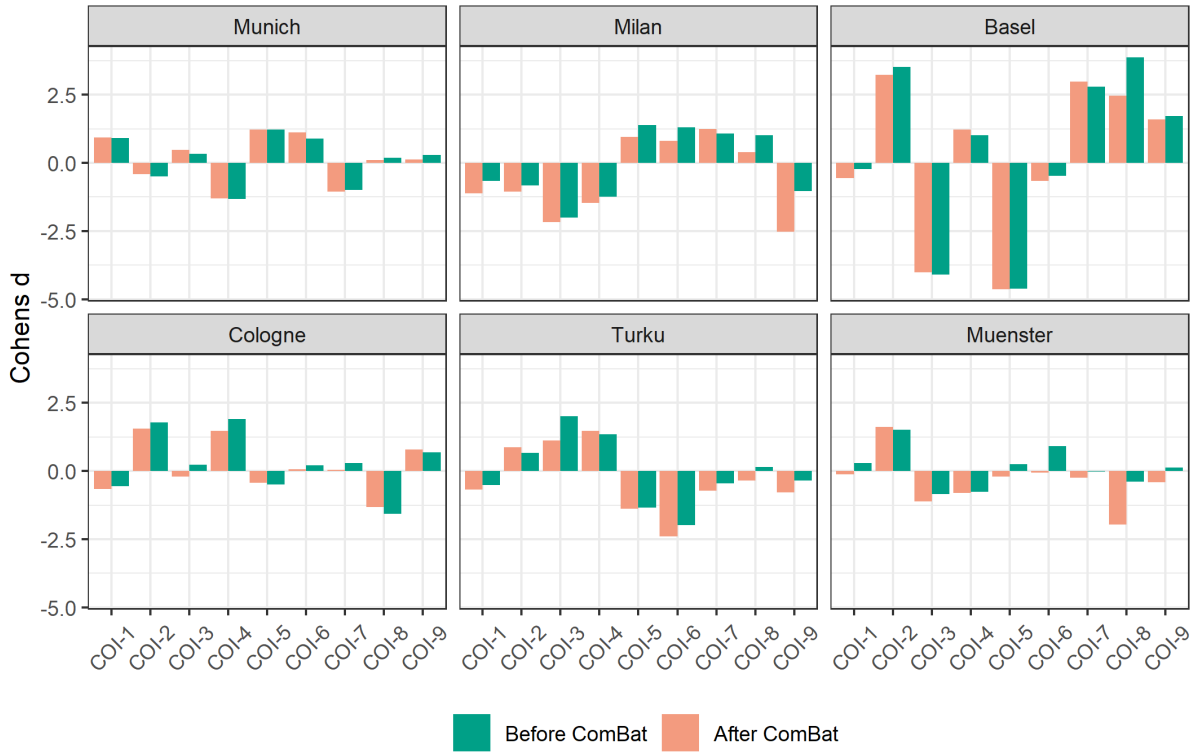
sFigure 4 Components derived by group information-guided independent component analysis in healthy individuals used for harmonization between sites and regression of age- and sex specific effects before and after ComBat-harmonization

Differences between sites (left). Associations between loadings and age and sex (right). *Abbreviations:* COI = component of interest



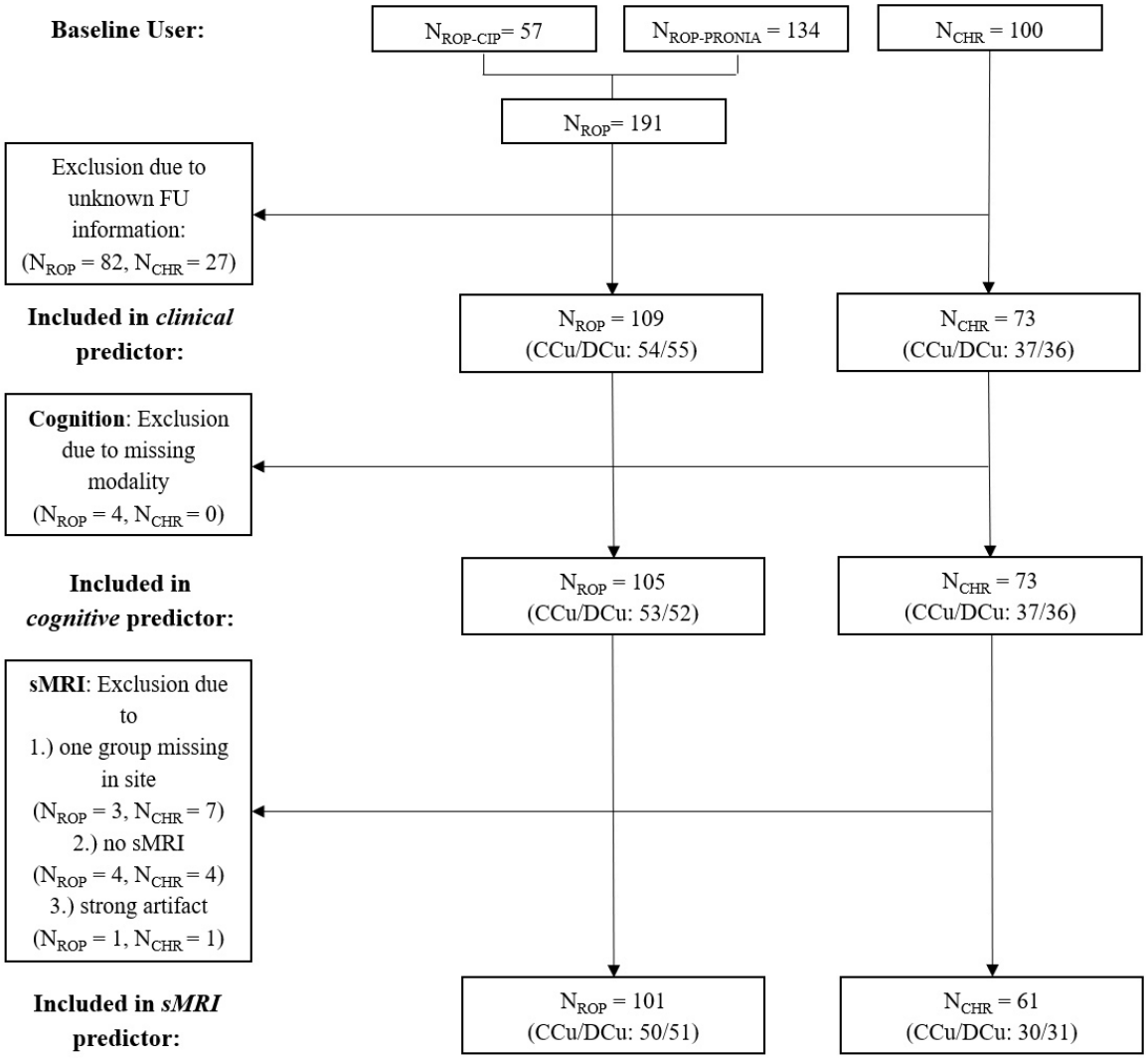
sFigure 5 Effect sizes between patients with continued/discontinued cannabis use in recent-onset psychosis before and after harmonization

The effect sizes (Cohen's d) between patients with continued cannabis use and discontinued cannabis use before and after harmonization (ComBat) for each site and each component of interest in recent-onset psychosis. *Note that the effect sizes are maintained. *Abbreviations:* COI = component of interest.



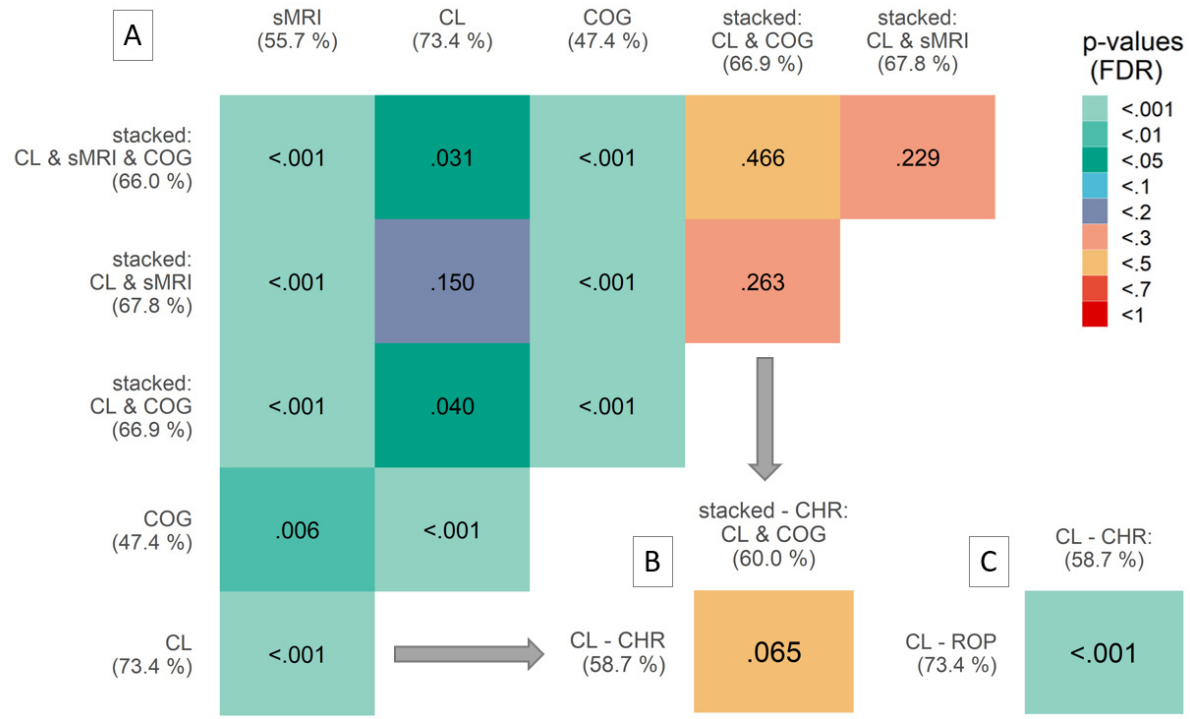
sFigure 6 Effect sizes between patients with continued/discontinued cannabis use in clinical high-risk for psychosis before and after harmonization

The effect sizes (Cohen's d) between patients with continued cannabis use and discontinued cannabis use before and after harmonization (ComBat) for each site and each component of interest in clinical high-risk for psychosis. *From Birmingham only subjects with discontinued cannabis use were included, thus no effect sizes could be calculated. Note that the effect sizes are maintained. *Abbreviations:* COI = component of interest.



sFigure 7 Flow Diagram of inclusion/exclusion for the three different predictors

Abbreviations: ROP = recent-onset psychosis, ROP-CIP = recent-onset psychosis patients included via the cannabis induced psychosis study, ROP-PRONIA = recent-onset psychosis patients included via the Personalized Prognostic Tools for Early Psychosis Management study, CHR = clinical high-risk for psychosis, sMRI = structural magnetic resonance imaging, CCu = continued cannabis use, DCu = discontinued cannabis use



sFigure 8 Comparison between different predictor performances

We compared the predictors' median balanced accuracy (BAC) across all outer cross-validation (CV2) folds test data partitions between all unimodal and multimodal predictors (A). As we found a significant difference between all discovery models in our omnibus test ($F_{5, 245}$ = 7.9, p < .001), we calculated pairwise comparisons between all predictors using the t-distribution approximation. P-values were false discovery rate (FDR) corrected. Further, we compared the median BAC from our replication data using the Wilcoxon test between our best performing uni- and multimodal predictors (B). Finally, we compared the best predictor (clinical) between the replication (recent-onset psychosis) and the discovery sample (clinical high-risk for psychosis) using the unpaired Wilcoxon test based on the respective median BACs across all CV2-folds (C). Numbers in the rectangles are respective p_{FDR}-values between the two corresponding tests. Numbers in brackets indicate the BAC of the respective predictor. *Abbreviations:* sMRI = structural magnetic resonance imaging predictor, CL = clinical predictor, COG = cognitive predictor, ROP = recent-onset psychosis, CHR = clinical high-risk for psychosis, FDR = false discovery rate.

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