Universität Basel
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Prediction of Social Psychiatric and Treatment Related Outcomes in the Spectrum of Psychotic Disorders

Inaugural Dissertation submitted in fulfillment of the requirements for the degree of Doctor of Philosophy to the Department of Psychology of the University of Basel by

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Declaration of Authorship

I, Letizia Brändli-Leanza (born June 5, 1991), hereby declare that I have contributed independently and substantially to this dissertation without any assistance from third parties who are not indicated. I have used only the resources indicated and have cited all references. Published manuscripts were prepared in cooperation with coauthors and have not been submitted elsewhere for review or consideration, nor have they been published elsewhere. This dissertation includes the following three manuscripts:

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Abbreviations

APS	Attenuated psychotic symptoms
ARMS	At-risk mental state
BLIPS	Brief limited intermittent psychotic symptoms
BPRS-E	Brief Psychiatric Rating Scale Expanded Version
BS	Basic symptoms
BSIP	Basel Screening Instrument for Psychosis
CAARMS	Comprehensive Assessment of At-Risk Mental States
CBT	Cognitive Behavioral Therapy
CHR-P	Clinical high risk state for psychosis
CHR-P-NT	Clinical high risk state for psychosis without later psychotic transition
CIC	Cumulative incidence curve
FEP	First episode psychosis
FePsy	Basel Projekt zur Früherkennung von Psychosen
GRD	Genetic risk and deterioration syndrome
JTC	Jumping-to-conclusions
MCT	Metacognitive Training for Psychosis (group setting)
MCT+	Individualized Metacognitive Training for Psychosis
NICE	National Institute for Health and Care Excellence
PANSS	Positive and Negative Syndrome Scale
SANS	Scale for the Assessment of Negative Symptoms
SIPS	Structured Interview for Prodromal Symptoms
UHR	Ultra-high risk
UPS	Unspecified prodromal symptoms

Abstract

Psychotic disorders are severe and potentially disabling mental disorders which rank among the world's top 10 causes of chronic disability and produce high healthcare costs. First-line treatment with antipsychotic medication is associated with only medium effect sizes for positive symptoms and several limitations. Research has thus increasingly embraced new and complementary treatment approaches, namely the early detection and intervention research and the development of psychological interventions. This thesis aimed to address unresolved research questions in these areas. Article 1 and 2 focused on the early detection and intervention of psychotic disorders and investigated predictors of study drop-out, service disengagement, and long-term clinical and functional outcome in patients at clinical high risk for psychosis (CHR-P). Article 3 analyzed moderators of individualized Metacognitive Training (MCT+), a theory-driven intervention designed to improve delusional symptom severity. In Article 1, 36% of CHR-P patients dropped out and/or disengaged within 5 years. A late study inclusion period, associated with more frequent follow-ups and higher participation burden, was predictive for higher risk of drop-out and disengagement. In Article 2, remission from CHR-P status after 10 years was estimated as 51%. Better baseline psychosocial functioning was associated with a higher rate of remission. However, only a minority of patients fully recovered clinically and functionally. In Article 3, the occurrence of the jumping-to-conclusions bias and low self-esteem were associated with larger improvements over time in MCT+ compared to an active control intervention. Article 1 and 2 underline the importance of individually tailored treatment planning and call for the right balance between too high-frequency assessments on one hand, and a lack of treatment care for patients experiencing long-term clinical symptoms and functional impairments on the other. The findings of Article 3 provide useful criteria for selecting patients who might particularly benefit from MCT+.

Introduction

Psychotic disorders such as schizophrenia are severe mental disorders which encompass positive symptoms such as hallucinations, delusions or disorganized speech, and negative symptoms such as alogia, anhedonia, and avolition (American Psychiatric Association, 2013). Recent findings from epidemiological studies suggest that the median lifetime prevalence of schizophrenia in the general population is approximately 0.3-0.7% (American Psychiatric Association, 2013; McGrath, Saha, Chant, & Welham, 2008). Schizophrenia typically emerges in adolescence or early adulthood (Häfner, Riecher-Rössler, Maurer, Fätkenheuer, & Löffler, 1992), a time in life characterized by important psychosocial developments (McGorry & Goldstone, 2016). It has been reported that schizophrenia occupies the eighth-largest share of disability-adjusted life years in European adults (Klosterkötter, 2016; Wittchen et al., 2011). Additionally, the disorder has been associated with high premature mortality rates leading to about 15 years of potential life lost and increased rates of multiple somatic disorders (Hjorthøj, Stürup, McGrath, & Nordentoft, 2017; Laursen, 2019). Numerous studies have reported that schizophrenia and other psychotic disorders are associated with impairments in social, occupational, vocational, and cognitive functioning (Gold, 2004; Harvey & Strassnig, 2012; Velthorst et al., 2017). Further, the burden of psychotic disorders caused by stigma and discrimination is amongst the highest of mental disorders (Rössler, Salize, van Os, & Riecher-Rössler, 2005; Schultze-Lutter et al., 2015). Psychotic disorders share high lifetime comorbidity rates with other mental disorders such as substance use disorders, anxiety disorders, and affective disorders (Buckley, Miller, Lehrer, & Castle, 2009; Siu, Chong, & Lo, 2018; Tsai & Rosenheck, 2013). Importantly, the period over which a psychosis remains untreated is associated with more severe psychopathology, delayed and incomplete symptom remission, as well as greater relapse risk (Boonstra et al., 2012; Hill et al., 2012; Oliver et al., 2018; Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014).

According to the Clinical Practice Guidelines and the guidelines of the National Institute for Health and Care Excellence (NICE), psychotic disorders are treated with antipsychotic medication, often considered as the first-line treatment (American Psychiatric Association, 2019; National Institute for Health and Care Excellence, 2014). Pharmacotherapy with antipsychotic medication has been shown to reduce both positive symptoms of psychotic disorders as well as the risk of relapse (Haddad & Correll, 2018). However, treatment with antipsychotic medication has been associated with several limitations such as only medium effect sizes on positive symptoms (Haddad & Correll, 2018; Leucht et al., 2017), considerable side effects, and high treatment nonadherence (Garcia et al., 2016; Lally & MacCabe, 2015; Leucht et al., 2017).

The growing realization of these limitations has led to increased efforts to develop new approaches for the treatment of psychotic disorders. One of these promising approaches represents the early detection and intervention of psychotic disorders, which has been a highly productive research area over the last two decades. A second approach is the development of complementary psychological interventions for the treatment of positive symptoms, which resulted in the development of a theory-driven intervention, namely the individualized Metacognitive Training for psychosis (MCT+). This thesis aimed to investigate social psychiatric and treatment related outcomes in the psychosis spectrum within the context of these two approaches.

Theoretical Background

Early Detection and Intervention in Psychosis

During the past 20 years, various international clinical and research programs focusing on the early detection and intervention of psychosis have been established (McGorry, Edwards, Mihalopoulos, Harrigan, & Jackson, 1996; Miller et al., 1999; Riecher-Rössler et al., 2007; Yung et al., 1996). Most first episodes of psychotic disorders (FEP) are preceded by an extended period of functional impairment and nonspecific symptoms. Typically, these are

followed by subthreshold psychotic symptoms, which emerge prior to the development of frank psychosis. On average, this period lasts around 2-5 years and can retrospectively be referred to as the prodrome of the disorder (Häfner et al., 1998; Riecher-Rössler et al., 2006). Help-seeking patients who are at risk of developing a psychotic disorder are referred to as clinical high risk for psychosis (CHR-P) or at-risk mental state (ARMS) patients. In line with the suggestion of Fusar-Poli (2017), the term CHR-P will be used throughout this thesis. CHR-P patients can be identified using a set of operationalized criteria known as the ultra-high risk (UHR) criteria, which require the presence of one or more of the following criteria: Attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), genetic risk and deterioration syndrome (GRD) or unspecified prodromal symptoms (UPS). Furthermore, the Basic Symptom (BS) criteria can as well be used for identification of CHR-P patients (Fusar-Poli et al., 2013). BS are subtle, subclinical and self-experienced disturbances in stress tolerance, affect, thinking, speech, perception or drive (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). As BS criteria were not used in this thesis, they will not be further elaborated here. A full model of psychosis onset suggested by Fusar-Poli et al. (2013) according to the UHR criteria, as well as further explanations of the criteria, can be found in Appendix A.

To determine whether patients meet the above mentioned UHR criteria, different instruments have been developed, such as the Basel Screening Instrument for Psychosis (BSIP; Peralta et al., 2019; Riecher-Rössler et al., 2008), the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005), and the Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2003). Definitions of the UHR criteria slightly differ depending on the instrument used. Detailed UHR and FEP criteria according to the BSIP (Riecher-Rössler et al., 2008), which was used in this thesis can be found in Appendix B. Numerous studies have investigated the predictive accuracy of the UHR criteria. A meta-analysis reported a cumulative mean risk for transition to psychosis of 10% after 6 months,

17% after 1 year, 20% after 2 years and 25% after 3 years (Fusar-Poli et al., 2016). Thus, independently from the psychometric instrument used, less than one third of patients identified as being at-risk for psychosis develop frank psychosis during follow-up. The currently used interviews have been shown to have a high sensitivity (meta-analytical finding = 0.96) but a rather low specificity (meta-analytical finding = 0.47) when used in clinical samples of help-seeking patients (Fusar-Poli et al., 2015).

There is a clear rationale for the early detection and intervention in psychosis. It has been shown that interventions in CHR-P patients are associated with symptom reduction, improvement of social and vocational outcomes and a reduction of the risk of transition to frank psychosis (McGorry, Hartmann, Spooner, & Nelson, 2018; Schmidt et al., 2015; Schultze-Lutter et al., 2015; van der Gaag et al., 2013). The growing adoption of the CHR-P concept has recently led to the inclusion of the 'Attenuated Psychosis Syndrome' into the Diagnostic and Statistical Manual-5 appendix as a condition for further study (American Psychiatric Association, 2013; Riecher-Rössler & Studerus, 2017).

Study drop-out and service disengagement in CHR-P patients. For many years, the prediction of psychosis marked the paramount goal of early detection research. However, many studies focusing on psychosis prediction reported relatively high attrition rates ranging from 13% at 6-9 month follow-up (Lencz et al., 2006), 26% at 18 months (Ruhrmann et al., 2010), 21-36% at 2 years (Stowkowy et al., 2018; Ziermans, Schothorst, Sprong, & van Engeland, 2011), and up to 53-68% at 3 years (Hengartner et al., 2017; Morrison et al., 2007). At the same time, many CHR-P patients access research participation via treatment, and besides dropping out of studies, often also disengage from clinical services. Currently, the reasons for study drop-out and service disengagement in CHR-P patients are largely unknown, and it is not yet clear whether CHR-P patients show symptom worsening or improvement before study drop-out and service disengagement. As follow-up information from these patients is missing, transition to FEP cannot be entirely ruled out, especially as

transition to psychosis can occur in the long-term, up to 10 years after initial referral (Nelson et al., 2013). In case of a systematic drop-out, i.e. due to symptom remission or worsening, the estimation of risk prediction models might be biased. In CHR-P patients with a subsequent transition to psychosis, study drop-out and service disengagement might be particularly hindering, as symptom progression might further hamper help-seeking and service engagement.

A number of studies have investigated study drop-out and service disengagement in FEP patients and found associations with substance abuse or dependence, poor medication compliance, history of self-harm or suicidal attempts, lack of insight, lower symptom severity at baseline, missing support or involvement of a family member, as well as having milder psychopathology and being employed or a student (for systematic review see Doyle et al., 2014). There are only few prior studies which addressed study drop-out and service disengagement in CHR-P patients. While one study could not detect any clinical, functional or demographic variables associated with study drop-out (Stowkowy et al., 2018), another study reported that higher baseline negative symptoms predicted later study drop-out (Hengartner et al., 2017). Stowkowy et al. (2018) additionally assessed a change in symptoms over time and reported that both study completers and drop-out patients demonstrated significant symptomatic improvement over time. However, this finding has not yet been replicated by other studies and it remains unclear whether symptomatic change might occur immediately before study drop-out and/or service disengagement. Thus, insight into possible predictors and reasons for study drop-out and service disengagement might provide helpful information to ensure appropriate treatment and prevent adverse outcomes.

Clinical and functional long-term outcome of CHR-P patients. As only a minority of patients who fulfill UHR criteria later develop frank psychosis (Fusar-Poli et al., 2016), it is necessary to assess outcomes of CHR-P patients without a later transition (CHR-P-NT). However, as the cumulative risk of transitioning to psychosis tends to plateau after the third

year of initial identification (Kempton, Bonoldi, Valmaggia, McGuire, & Fusar-Poli, 2015), most previous studies have followed-up patients for 2-3 years only. A recent study reported different trajectories in CHR-P patients, with 43% having favorable outcomes such as remission or recovery, and 57% having unfavorable outcomes such as transition, non-remission, or relapse within one year (Polari et al., 2018). However, only little is known about the clinical and functional long-term outcome of CHR-P-NT patients. A recently performed systematic review incorporating ten studies with follow-up durations of 2-7.5 years reported that 28-71% of CHR-P-NT patients still suffered from subthreshold psychotic symptoms and 22-82% fulfilled criteria for a non-psychotic mental disorder. The majority of patients also suffered from psychosocial impairments (Beck et al., 2019a). As only limited information on long-term outcomes in CHR-P-NT patients is available and an evaluation of the predictors of long-term clinical and functional outcome is lacking, there is a need to improve the current knowledge about the trajectories and long-term outcome of these patients.

Individualized Metacognitive Training for Psychosis (MCT+)

Delusions represent core symptoms of schizophrenia and other psychotic disorders. They are defined as erroneous beliefs that cannot be corrected despite indisputable contrary evidence (American Psychiatric Association, 2013). As previously stated, treatment with antipsychotic medication in frank psychosis is associated with only medium effect sizes (Leucht et al., 2017) and numerous side effects that can negatively affect treatment adherence and medication compliance (Garcia et al., 2016; Lally & MacCabe, 2015). Besides, earlier studies reported that antipsychotic treatment might only reduce salience and importance of delusions, but not delusional conviction (Mizrahi et al., 2006; Schneider, Jelinek, Lincoln, & Moritz, 2011).

A large body of literature investigating the nature of delusions found that cognitive biases are associated with the formation and maintenance of delusional beliefs (Garety & Freeman, 2013). Prominent cognitive biases include the jumping-to-conclusions bias (JTC),

overconfidence in false judgments, and belief inflexibility/incorrigibility (Garety & Freeman, 2013; Moritz et al., 2014; Moritz et al., 2017b). The JTC bias is a tendency to make hasty decisions and inferences based on limited evidence (Garety & Freeman, 2013), which has consistently been reported to be present in patients with delusions and psychotic disorders (Garety & Freeman, 2013; So, Siu, Wong, Chan, & Garety, 2016). JTC as well as other reasoning biases associated with delusions appear not to be influenced by antipsychotic medication (Andreou et al., 2015b; Menon, Mizrahi, & Kapur, 2008; So, Garety, Peters, & Kapur, 2010). Thus, there has been growing interest in developing psychological interventions complementing antipsychotic treatment for delusions and other positive psychotic symptoms.

MCT+ represents one of these interventions (Andreou et al., 2017; Moritz, Krieger, Bohn, & Veckenstedt, 2017a; Moritz, Veckenstedt, Randjbar, & Vitzthum, 2011). It is a manualized 12-session intervention, aiming to reduce delusional conviction by raising patients' awareness for the above described cognitive biases associated with delusions. Individualized MCT+ represents a further development of the manualized group treatment program MCT (Moritz, Veckenstedt, Randjbar, Vitzthum, & Woodward, 2011). However, in contrast to group MCT which approaches the metacognitive foundation of delusions with predominantly non-delusional scenarios, MCT+ puts a stronger emphasis on individual delusional convictions (Andreou et al., 2017) and incorporates techniques adapted from Cognitive Behavioral Therapy (CBT). Recent meta-analyses (Eichner & Berna, 2016; Liu, Tang, Hung, Tsai, & Lin, 2018; Philipp et al., 2019) of several randomized controlled trials have suggested that MCT and MCT+ are effective in the short- and long-term treatment of delusions and other positive symptoms. Detailed information on the content and learning aims of all the MCT+ modules including cognitive biases can be found in Appendix C.

Moderators of treatment efficacy in MCT+. Given the growing focus on individualized prediction of patient outcomes in psychiatry, the identification of patients who

are more likely to benefit from specialized interventions is of particular importance. Multiple studies have assessed predictors of treatment outcomes in CBT oriented interventions (O'Keeffe, Conway, & McGuire, 2017) while only one such study has been performed in group MCT (Moritz, Menon, Andersen, Woodward, & Gallinat, 2018). Results indicated that low baseline self-esteem, social anxiety, and a positive appraisal of the intervention were significantly associated with improved short- and long-term outcomes in group MCT compared to an active control intervention (Moritz et al., 2018). Moreover, low quality of life, high baseline distress and excitement, as well as a lowered decision threshold in the JTC task (only at trend-level) predicted better short-term delusional outcome in the MCT group (Moritz et al., 2018). However, the findings reported in group MCT might not necessarily generalize to individualized MCT+, and to date, no study has yet investigated moderators of treatment efficacy in MCT+. Therefore, shedding light on specific moderators of treatment efficacy in MCT+ might inform clinical practice and enable to recommend specific criteria for selecting patients which benefit most from MCT+.

Research Questions

Against this background, the aims of this thesis were 1) to investigate study drop-out and service disengagement in CHR-P patients, 2) to assess the clinical and functional long-term outcome of CHR-P patients without a later transition to psychosis and 3) to explore moderators of MCT+ efficacy in patients with psychosis. To examine these research questions, the following three original studies have been conducted and published in international peer-reviewed journals. The following specific research questions were addressed in Articles 1-3 which together constitute this thesis (see appendices D-F).

Article 1: *Predictors of study drop-out and service disengagement in patients at clinical high risk for psychosis* (Leanza et al., 2020b).

- How high is the rate of CHR-P patients who show study drop-out during follow-up and who are prone to service disengagement?

- What baseline characteristics are associated with study drop-out and service disengagement in CHR-P patients?
- Can certain baseline variables predict study drop-out and service disengagement in this population?
- Did patients show a change in symptoms immediately before study drop-out and service disengagement?

Article 2: *Clinical and functional ultra-long-term outcome of patients with a clinical high risk (CHR) for psychosis* (Beck et al., 2019b).

- What is the proportion of CHR-P patients who transition to psychosis and how many remit from their CHR-P status in the long term?
- What is the long-term clinical and functional outcome of patients who do not transition to psychosis, e.g., regarding subclinical psychotic symptoms, non-psychotic clinical symptoms, psychosocial functioning, and overall recovery?
- Are there any variables predicting clinical and functional outcome in CHR-P-NT patients at long-term follow-up?

Article 3: *Moderators of treatment efficacy in individualized metacognitive training for psychosis (MCT+)* (Leanza, Studerus, Bozikas, Moritz, & Andreou, 2020a).

- Do variables assessed at baseline moderate the treatment efficacy of MCT+ on delusional severity as well as overall positive symptoms relative to an active control intervention with no expected effect on positive symptoms?

Methods

Setting and Recruitment

The data for Articles 1 and 2 were collected within the prospective early detection and intervention in psychosis (FePsy; Früherkennung von Psychosen) study (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009), which was conducted in the specialized Center for Early Detection and Gender Research at the University of Basel Psychiatric Hospital Basel,

Switzerland, between March 2000 and September 2017. Patients suspected to be at risk for psychosis were referred to by general practitioners, parents, teachers, and mental health professionals. All CHR-P patients meeting inclusion criteria (see Riecher-Rössler et al., 2007) were included in the study after providing written informed consent. Additionally, Article 2 included data from patients recruited via the Bruderholz study. Information about sample recruitment and further details concerning the Bruderholz study can be found in Simon et al. (2012).

CHR-P patients were followed up at regular intervals for up to 5 years to examine whether transition to psychosis had occurred. From 2000 to 2008, follow-up frequency depended upon the estimated risk set. During the first year, high-risk (i.e., APS, BLIPS, GRD) patients were assessed monthly, while low-risk patients fulfilling only unspecific risk criteria were assessed at 3-month intervals. From 2009 onwards, uniform follow-up assessments were provided to all CHR-P patients, and low-risk patients were followed up monthly in the same intervals as high-risk patients during the first year. During the second and third years, all patients were assessed every 3 months and thereafter annually. During follow-up, all patients received treatment according to their needs, clinical case management, and supportive counseling. Antipsychotic medication was only initiated after transition to psychosis had occurred. In Article 2 all patients who did not transition to psychosis during the initial follow-up period were regarded as patients without initial transition and were asked to take part in the long-term follow-up assessment.

The FePsy study was approved by the ethics committee of Northwestern and Central Switzerland (EKNZ) and was conducted in accordance with the Declaration of Helsinki. Further details concerning the FePsy study design can be found elsewhere (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009).

Data for Article 3 were retrieved within the context of a monocentric, rater-blind, randomized controlled clinical trial (Andreou et al., 2017) carried out at the Department of

Psychiatry and Psychotherapy of the University Medical Center Hamburg-Eppendorf, Germany, between January 2013 and July 2015. Patients with non-affective psychotic disorders and current or past delusions were recruited among in- and outpatients treated at the Psychosis Center of the Department. All patients who met inclusion criteria (see Andreou et al., 2017) provided written informed consent before entering the trial.

In this study, patients were randomized according to a computerized randomization plan to either MCT+ or CogPack (Marker, 2003), which is an active cognitive control intervention. Treatment allocation was performed observer-blind by a person who was not involved in the assessments and intervention delivery. Assessments were carried out at baseline, at 6 weeks (T1; 12 intervention sessions completed) and 6 months later (T2). Data analyses in this study considered only baseline data and data from T1. All assessments were carried out by raters blind to treatment allocation.

The trial was approved by the Ethics Committee of the German Psychology Association. A more detailed description of the overall trial and its main findings can be found in Andreou et al. (2017).

Measures

In both the FePsy study and the MCT+ original trial, all patients underwent a broad entry examination (Andreou et al., 2017; Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009). A full description of all measures used in the studies can be found in Articles 1-3 (Appendices D-F). Here, only the main measures are described.

Psychopathological assessments. In Articles 1 and 2 of the FePsy study, all patients suspected to be at risk for psychosis were screened using the BSIP (Riecher-Rössler et al., 2008), which allows the identification of CHR-P and FEP patients (see Appendix B). The BSIP has been shown to have a high interrater reliability and predictive validity (Riecher-Rössler et al., 2008). Positive psychotic symptoms were assessed using the Brief Psychiatric Rating Scale Expanded Version (BPRS-E; Lukoff, Nuechterlein, & Ventura, 1986; Ventura,

Green, Shaner, & Liberman, 1993). Furthermore, transition to psychosis during follow-up was monitored using the four BPRS-E items suspiciousness, unusual thought content, hallucinations, and conceptual disorganization. Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989). In Article 3 (MCT+ trial), positive (primarily delusions) and negative symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). The PANSS is considered as the gold standard assessment in clinical trials (Suzuki, 2011) and has been shown to have good psychometric properties (Kay, Opler, & Lindenmayer, 1989).

Other outcome measures. In Article 1, study drop-out during follow-up was defined as the primary outcome of interest. CHR-P patients were considered as drop-out when no contact could be established for at least 1 year after several unsuccessful contact attempts (i.e. through phone calls, letters, e-mails). Patients were also considered as having dropped out when they explicitly refused to further participate in the study. In this case, drop-out reasons were assessed and documented on specific drop-out protocols. In Article 2, remission from CHR-P status was considered as one of the main outcomes and was defined as the absence of APS or BLIPS, i.e. subthreshold severity scores on all four above-mentioned positive symptom items of the BPRS-E (Ventura et al., 1993) for at least 12 consecutive months preceding the latest follow-up assessment.

In Article 3, delusional severity at T1 as measured with the PANSS (Kay et al., 1987) was defined as the outcome variable. However, the primary study aim was to assess moderators of MCT+ efficacy on delusions and other positive symptoms. The moderator variable which assessed the prominent cognitive JTC bias associated with delusions was measured with the Fish Task (Moritz, Van Quaquebeke, & Lincoln, 2012), a computerized version of the Beads Task (Garety, Hemsley, & Wessely, 1991). In this task, two lakes (A and B) containing fish in opposite color ratios are presented. Patients are successively showed 10 fish in a predetermined sequence. After each draw, patients are asked to estimate the

probability that fish originated from lake A and to indicate whether they have made a decision regarding the origin of the fish. Parallel versions were used across the testing sessions to reduce practice effects. The variables of interest were presence of the JTC bias (defined in a dichotomous fashion as decisions based on only one or two fish) and the probability threshold at decision (i.e. the minimum probability estimate at which a decision was made in favor of the respective lake; a higher probability threshold indicates more cautious inference making). Other moderator variables included in the study can be found in Article 3 (Appendix F).

Statistical analyses. All statistical analyses of Articles 1-3 were conducted using the R environment for statistical computing (R Development Core Team, 2019).

Article 1 investigated baseline predictors of study drop-out and service disengagement in CHR-P patients, while Article 2 examined baseline predictors for remission from CHR-P and transition to psychosis. Analyses in Article 2 were conducted in two different samples, namely the initial baseline sample of all CHR-P patients and the sample of CHR-P-NT patients who participated in the long-term follow-up assessment. According to the FePsy study design, follow-up assessment could be ceased due to various events, and CHR-P patients could only experience one of the event types over follow-up. Therefore, competing risk survival models were used and different competing events were defined for Article 1 and 2. In Article 1, study drop-out and transition to psychosis were considered as competing events. Univariable models were fitted for each baseline predictor variable of study drop-out. Study inclusion date (i.e. inclusion from 2000-2008 vs. inclusion from 2009-2017) was included as a binary predictor because of the previously described methodological changes in study design in 2009 concerning the frequency of follow-up intervals. To investigate whether symptoms changed immediately before study drop-out, dependent sample t-tests were applied. The rates of study drop-out and transition to full-blown psychosis over the whole course of the 5-year follow-up were assessed using cumulative incidence curves (CIC), which are the competing risks analogs of Kaplan-Meier survival curves (Kleinbaum & Klein, 2012).

CIC curves were also used in Article 2, where remission from CHR-P and transition rates over the whole 16-year follow-up period were analyzed in the initial sample. Competing risks survival analyses were again conducted to investigate baseline predictors for remission from CHR-P status and transition to psychosis, using univariable models for each predictor variable. Here, remission from CHR-P was regarded as the primary outcome of interest, while transition to psychosis was regarded as the competing event. Besides, in the second sample of CHR-P-NT patients logistic and multiple regression analyses were conducted to examine the predictive value of baseline sociodemographic and clinical variables regarding both remission from CHR-P status and psychosocial functioning at long-term follow-up.

In Article 3, linear mixed-effects models were applied to investigate potential moderators of MCT+ efficacy on delusions and other positive symptoms. For each moderator variable, one mixed-effects model was fitted that included group (MCT+ vs. CogPack), time (baseline vs. T1), and the corresponding moderator variable, as well as all possible two and three-way interactions, as fixed effects factors. Additionally, the models included an intercept that randomly varied per subject.

Detailed descriptions of all statistical analyses can be found in Articles 1-3 (Appendices D-F).

Summary of the Results

Predictors of study drop out and service disengagement in patients at clinical high risk for psychosis

Data of 200 patients were analyzed. Within 5 years, 53 patients (36%) dropped out of the study and 43 (28%) transitioned to psychosis. As nearly all patients who had dropped out also disengaged from the clinical service, study drop-out was used as a proxy for service disengagement. 41 (77.4%) of patients with study drop-out explicitly requested to discontinue the follow-up assessments. One of the main reasons identified was being annoyed by requests for study participations (19.5%). Patients with more severe baseline disorganized symptoms and a late study inclusion (2009-2017) were significantly more likely to drop out and

disengage. No other baseline sociodemographic or clinical variables significantly predicted study drop-out. Immediately before drop-out, a significant improvement in negative symptoms was observed. There were no significant differences in positive symptoms. For detailed results, see Appendix D.

Clinical and functional ultra-long-term outcome of patients with a clinical high risk for psychosis

From the original sample of 255, 60 patients transitioned to psychosis. At 5-, 10-, and 15-year follow-up, the estimated cumulative transition rates were 31%, 35%, and 38%. The proportion of patients with remission from CHR-P status within the first 2, 3, 4, and 5 years of follow-up was estimated as 24%, 33%, 36%, and 37%, respectively. Ten years after baseline, an estimated proportion of 51% had remitted, with no further remissions after that time point. Results indicated that higher baseline psychosocial functioning was associated with a higher remission rate in the original sample. Other baseline variables such as age, psychopathological symptoms, or cannabis use were not significantly associated with remission. Of the 72 CHR-P-NT patients reassessed at long-term follow-up, 60 (83%) had not transitioned to psychosis. Of these, 51 (85%) had remitted from their high risk state, 39 (65%) had no axis I diagnosis, but only 17 (28%) had fully recovered clinically and functionally. No significant associations between baseline variables and remission from CHR-P status at long-term follow-up were found. See Appendix E for more information on results.

Moderators of treatment efficacy in individualized metacognitive training for psychosis

In MCT+ relative to CogPack (active control intervention) the presence of the jumping-to-conclusions bias, a lowered decision threshold in the Fish Task, and low baseline self-esteem were associated with larger improvements in delusional severity and/or overall positive symptoms over time. Other moderator variables such as subjective attitudes towards psychosis, cognitive insight, quality of life, or selective attention, did not moderate the

treatment efficacy of MCT+ relative to CogPack. For a detailed description of the results, see Appendix F.

Discussion

Suffering from a CHR-P status or a full-blown psychotic disorder often has a significant impact on a person's life. Psychotic symptoms in both patient groups are often accompanied by functional deterioration and high burden. To improve the outlook and maximize the chances of remission for those affected, both early detection and intervention research, as well as the development of new treatment approaches are indispensable. This dissertation therefore aimed to address several unresolved and scarcely investigated research questions regarding social psychiatric and treatment related outcomes in the spectrum of psychotic disorders.

Findings of the early detection and intervention studies

In Article 1, patients with more severe baseline disorganized symptoms and a late study inclusion (2009-2017) were significantly more likely to drop out. A significant improvement of negative symptoms was observed immediately before study drop-out and service disengagement. In Article 2, 51% of patients remitted from the CHR-P status within 15 years. In patients with a long-term follow-up assessment, the remission rate was 85%, but only 28% showed full clinical and functional recovery. Higher baseline psychosocial functioning was associated with a greater likelihood of remission from CHR-P status during follow-up.

Compared to other studies which reported study drop-out rates in CHR-P patients (Hengartner et al., 2017; Stowkowy et al., 2018), the rather low drop-out and disengagement rate of 36% reported in Article 1 might be attributed to methodological differences regarding its operationalization. To date, a clear consensus on the definition of service disengagement is still lacking and a dynamic, multidimensional approach incorporating different dimensions of engagement and disengagement is warranted (Tindall, Francey, & Hamilton, 2015).

The association between study inclusion date with drop-out and disengagement might be attributed to changes in the study design applied in 2009 described above (see Methods). Due to the long recruitment span in the FePsy study, confounding factors might have impacted this result. For example, in 2011 a weekly e-mail reminder system was implemented to facilitate the management of follow-up time points for caregivers. Besides, from 2011 onwards, patients were asked to participate in further multicenter studies in addition to the FePsy project. Both might have resulted in patients being contacted more often and in shorter intervals. Thus, contacting patients too often or burdening them with too many assessments might have led to unintended effects, such as patients being annoyed and therefore disengaging from the clinical service and dropping out of study assessments. In line with this, some patients did indeed declare being annoyed by requests for study participations.

Overall, the findings of Article 1 indicate that patients who drop out and disengage from the clinical service do not suffer from more severe psychopathological symptoms. This is in line with Stowkowy et al. (2018), who reported symptomatic improvements in patients with drop-out over time. As positive symptoms did not significantly worsen immediately before drop-out, it appears unlikely that patients who discontinue study follow-up and leave clinical service do so because of increased positive symptoms or transition to psychosis. The reported improvement of negative symptoms immediately before drop-out and disengagement might rather be associated with better psychosocial functioning, which might have lowered the need for treatment and increased the likelihood of dropping out. Hence, it may be suggested that the follow-up duration and the proposed 5-year model of care might have been too long and overly pathologizing for patients experiencing symptomatic improvements. Thus, some patients might no longer require clinical service treatment and might be discharged to other models of care depending on their symptomatology. However, positive symptoms remained relatively stable between the second-last and last assessment, suggesting that some patients might still suffer from subthreshold psychotic symptoms at the time of

drop-out and disengagement. The findings in Article 2 demonstrated that some patients still transition to psychosis in the long-term and that only a minority of CHR-P-NT patients had fully recovered clinically and functionally at long-term follow-up. This leads to the question of how to possibly adapt the clinical care to individual patient needs in order to strike the balance between capturing late transitions and not imposing a burden on patients. Hence, it might be prudent to individually tailor the frequency and length of follow-ups according to the symptom severity. Individualized risk calculators (Cannon et al., 2016; Fusar-Poli et al., 2017; Malda et al., 2019) implementing multivariable risk factors may facilitate treatment planning accordingly. However, until now the implementation of these tools into clinical practice is still lacking. Finally, creating a greater incentive for patients to further participate in follow-up assessments might minimize study drop-out. Offering follow-up assessments via telephone, video calls, or online questionnaires, and reducing questions to transition-relevant items might facilitate participation for patients. Further, highlighting the value of study participation and offering a small reimbursement (e.g. vouchers) might increase patients' motivation for follow-up assessments.

The FePsy study has examined a variety of clinical and sociodemographic variables. Yet, in both Articles 1 and 2 only little evidence of predictors for study drop-out, service disengagement, and remission was found. On one hand, the rather modest sample sizes of patients with study drop-out (n = 53 vs. 147 without drop-out) and patients without remission in the long-term follow-up sample (n = 9 vs. 51 with remission), might have reduced the power to detect small effects. On the other hand, factors associated with transition might play a less important role with regard to these specific outcomes. Eventually, other factors not assessed in the FePsy study might play a greater role concerning study drop-out, service disengagement, and remission. A good therapeutic relationship and working alliance with the caregiver has earlier been described as a common factor for symptom reduction and improvements in quality of life within the frame of psychotherapy (Wampold & Budge,

2012). Thus, a therapeutic bond that is characterized through trust, feelings of empathy, and belongingness may enhance engagement of patients needing clinical care and may further be associated with remission from CHR-P status. Moreover, expectations of success and self-efficacy or feelings of disempowerment and dissatisfaction with the service, reported to influence engagement in FEP patients, might influence service disengagement in CHR-P patients as well (Lal & Malla, 2015; Tindall et al., 2015). Alternatively, remission from CHR-P status might rather be associated with protective rather than risk factors. Patients with better baseline psychosocial functioning may be more resilient and feature more internal and external protective resources such as supportive relationships and a stable educational or work environment. However, it might be difficult to predict study drop-out, service disengagement, and remission based on information obtained at service entry only. Models incorporating information obtained during follow-up might be needed to predict these outcomes with sufficient accuracy. Thus, further studies are needed to comprehend which factors and mechanisms might contribute to study drop-out, service disengagement, and remission.

Findings of the MCT+ study trial

In Article 3, patients who were prone to the jumping-to-conclusions bias at baseline showed a stronger decrease of delusional symptoms and positive symptoms after 6 weeks following MCT+ than CogPack. The only available study that explicitly assessed moderators of treatment efficacy in group MCT (Moritz et al., 2018) could not demonstrate this association. However, this contrasting finding may be attributed to differences in the follow-up duration between the studies (6-week follow up vs. 6-month and 3-year follow-up) as well as setting related differences in the delivery of the intervention (individualized vs. group format). Additionally, a lower decision threshold, as well as low baseline self-esteem, were associated with larger improvements in the MCT+ compared to the CogPack intervention. These results are in line with Moritz et al. (2018), who found that low baseline self-esteem predicted improved outcomes in group MCT relative to CogPack and that a lowered decision

threshold moderated treatment efficacy in patients participating in group MCT for delusional severity at a trend level.

The reported results in Article 3 are consistent with the aim of MCT+ to improve delusions as well as positive symptoms by improving cognitive biases. It has previously been demonstrated that jumping-to-conclusions can be reduced by improving neurocognitive performance following a cognitive remediation intervention such as CogPack (Andreou et al., 2015a). However, this does not necessarily translate into a decline in delusional severity. Andreou et al. (2015a) reported that both patients partaking in group MCT and CogPack showed improvement in jumping-to-conclusions over time. However, improvements in jumping-to-conclusions were only associated with a reduction in delusion severity in the MCT group. Thus, the specific mechanism of action concerning delusional improvement in MCT and MCT+ might be attributed to its core element, namely the explicit education on cognitive biases and on the importance of adequate evidence gathering before reaching a conclusion.

As patients prone to the jumping-to-conclusions bias displayed the greatest improvements in delusions and positive symptoms, it would be valuable to analyze whether other cognitive biases associated with delusions such as the bias against disconfirmatory evidence (Eisenacher & Zink, 2017; McLean, Mattiske, & Balzan, 2017; Woodward, Moritz, Cuttler, & Whitman, 2006) or overconfidence in false memories and errors (Balzan, Woodward, Delfabbro, & Moritz, 2016; Moritz et al., 2009; Moritz & Woodward, 2006) might as well moderate treatment efficacy of MCT+. Also, other factors such as treatment satisfaction or, as proposed by Moritz et al. (2018), self-efficacy and motivation to change might possibly impact treatment efficacy of MCT+. However, as this was the very first study investigating moderators of individualized MCT+, further studies are needed to draw firm conclusions on which patients might maximally benefit from MCT+.

Previous cognitive models have assigned a major role to cognitive biases in the pathogenesis of psychosis, contributing to delusion formation and persistence (Garety & Freeman, 2013). Especially the jumping-to-conclusions bias seems to be an early cognitive marker of emerging psychosis, which has been found to be present in CHR-P patients (Rausch et al., 2016). Thus, CHR-P patients who present with the jumping-to-conclusion bias suffering from APS or BLIPS might benefit from the content of group MCT and/or individualized MCT+ similarly as patients with psychosis. However, the effects of MCT on subthreshold psychotic symptoms have not yet been investigated. Unfortunately, a pilot study planned and organized at the University of Basel Psychiatric Hospital on the effects of MCT in a mixed group of CHR-P and FEP patients had to be terminated due to recruitment issues and high study drop-out.

Strengths and Limitations

To the best of knowledge, this thesis assessed predictors of study drop-out and service disengagement in CHR-P patients as well as predictors of clinical and functional long-term outcome in CHR-P patients without transition to psychosis for the first time. Also, the assessment of moderators of individualized MCT+ is so far unique. Strengths of this thesis were: (1) The longitudinal study design and the very long observation period of up to 16 years used in Articles 1 and 2, which allowed to investigate outcomes and predictors thereof in the long-term; (2) the application of competing risks survival models in Articles 1 and 2, which allowed to take into account both the primary outcome of interest (i.e. study drop-out, remission), the time to event as well as the competing event (i.e. transition to psychosis); (3) the assessment of CHR-P patients with the BSIP, which has been shown to have a high reliability and validity; (4) the randomized controlled trial design of Article 3, which is regarded as the gold standard of efficacy evaluations and allowed to control for potentially confounding variables; (5) the assessment of full-blown psychotic symptomatology with the reliable and valid PANSS.

Some limitations should be considered regarding this thesis: (1) In Articles 1, 2 and 3 analyses were not controlled for multiple testing, which might have led to chance effects and false-positive findings, possibly impacting internal and external validity. However, as analyses were of exploratory nature, correction for multiple testing might have increased type II errors limiting the capacity to detect important predictors and moderators; (2) the samples of Articles 1, 2 and 3 consisted of patients who were mostly referred to the clinical service, which might have led to a selection bias possibly affecting the external validity of the results. Assumptions for patients who never reached clinical service, such as for example homeless people at-risk for psychosis or with a full-blown psychotic episode, cannot be made; (3) the rather modest number of patients with study drop-out in Article 1 or without remission in Article 2 might have limited the statistical power to detect significant outcome predictors.

Outlook

To further explore predictors of study drop-out, service disengagement and long-term outcome in CHR-P patients, multivariable predictor models encompassing multiple domains should be considered. In addition, predictor models might include protective factors such as therapeutic alliance or feelings of self-efficacy and not solely focus on variables associated with transition to psychosis. Further studies on the validation of individual risk prediction tools are needed to implement these tools into clinical practice and ensure individual treatment planning. Additional studies assessing moderators of treatment efficacy in group MCT and individualized MCT+ are warranted to provide specific criteria for selecting patients for whom the intervention is most appropriate. At the same time, further investigations are needed to clarify whether the implementation of an MCT based intervention in CHR-P patients might be an effective treatment method in emerging psychosis.

Conclusions

In conclusion, this thesis provides new insights on important research questions regarding social psychiatric and treatment related outcomes in the spectrum of psychotic

disorders. The findings underline the importance of individualized risk assessment and treatment care in CHR-P patients and suggest that the question concerning predictors of study drop-out, service disengagement, and remission are not yet sufficiently answered. Thus, future studies should replicate and extend the current findings to investigate whether other predictor variables might be associated with these outcomes. Additionally, this dissertation points out that those patients with psychosis who are prone to the jumping-to-conclusions bias and have low self-esteem particularly benefit from the theory-driven MCT+ intervention. This could be considered as a starting point for future research on which patients might particularly benefit from MCT+.

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Appendix A

Model of Psychosis Onset from the Clinical High Risk State

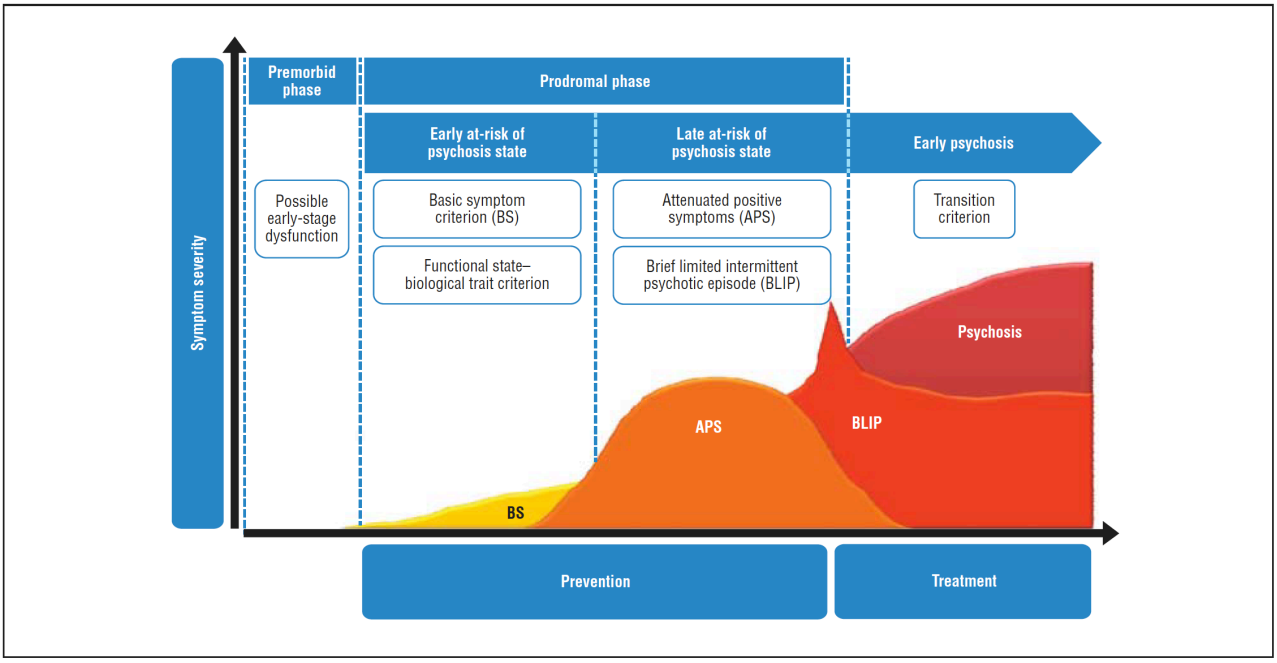

Figure A1. Assumed natural history of the high risk state and model of psychosis onset suggested by Fusar-Poli et al. (2013). The higher the line on the y-axis, the higher the symptom severity.

Basic symptom criterion: Subtle and subclinical disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action. The disturbances are self-experienced by the patient, with full insight into their abnormal nature (Schultze-Lutter et al., 2007).

Functional state - biological trait criterion: Family history of psychosis (first-degree relatives) and/or presence of schizotypal personality disorder, combined with a significant functional decline.

Attenuated positive symptoms: Subthreshold positive symptoms, often subthreshold in either intensity and/or frequency persisting over 1 week.

Brief limited intermittent psychotic episode: Transient, full-blown psychotic symptoms which last no longer than 1 week with spontaneous remission.

Definition of the different risk categories vary slightly depending on the instrument used for risk assessment (see Fusar-Poli et al., 2013 for further details).

Appendix B

Ultra-High Risk and First-Episode Psychosis Criteria According to the Basel Screening Instrument for Psychosis Used in the Basel FePsy Study

Table B1
Inclusion Criteria for Clinical High Risk for Psychosis and First-Episode Psychosis Patients

Clinical High Risk for Psychosis (CHR-P)	**a) Attenuated Psychotic Symptoms (APS)** Current (now or in the last 14 days) attenuated psychotic (pre-psychotic) symptoms, defined by a score of - 3 - 4 on the BPRS "Suspiciousness" scale or - 2 - 3 on the BPRS "Hallucinations" scale or - 3 - 4 on the BPRS "Unusual Thought Content" scale - appearance at least several times per week - in total persisting for > 1 week **and / or** **b) Brief Limited Intermittent Psychotic Symptoms (BLIPS)** Previous (more than 14 days ago) shown transient isolated psychotic symptoms, at least one of the following symptoms, defined by a score of - 4 or more on the BPRS "Hallucinations" scale or - 5 or more on the BPRS "Unusual Thought Content" or - 5 or more on the BPRS "Suspiciousness" scale or - 5 or more on the BPRS "Conceptual Disorganization" scale - in total persisting < 1 week - spontaneous remission **and / or** **c) Genetic Risk Category Combined with Potential Prodromes** - Psychosis in first-degree relative plus at least 2 or more risk factors from the BSIP (Items 1-18) or - Suspected psychosis in first-degree relative or confirmed psychosis in second-degree relative plus at least 1 highly specific and at least 2 or more risk factors **and / or** **d) Unspecific Risk Category** At least 2 highly specific risk factors plus at least 2 further risk factors
First-Episode Psychosis (FEP)	**Current psychotic transition, at least one of the following symptoms** - 4 or more on the BPRS "Hallucinations" scale or - 5 or more on the BPRS "Unusual Thought Content" or - 5 or more on the BPRS "Suspiciousness" scale or - 5 or more on the BPRS "Conceptual Disorganization" scale - appear more than once a week, for > 1 week

Note. BPRS = Brief Psychiatric Rating Scale. In the Basel Screening Instrument for Psychosis, CHR-P patients are synonymously referred to as at-risk mental state patients (ARMS). Highly specific risk factors: Items 1-18 of the instrument indicated with an asterisk. A highly specific risk factor can be replaced by 2 unspecific risk factors (Items 1-18 without asterisk). See Peralta et al. (2019) for an English version of the instrument with all items.

Appendix C

Individualized Metacognitive Training for Psychosis

Content and Learning Aims

Table C1
Individualized Metacognitive Training (MCT+)

Therapy Unit	Content	Learning Aims
1	Building a meaningful therapeutic relationship, assessment of case history.	- Assessment of current and past symptoms and illness course - Clarification of motivational aspects
2	Introduction to the MCT+ program.	- Basic introduction - Definition "Metacognition" - Goal assessment
3	Elaboration of an individual case formulation.	- Development of a vulnerability-stress model
4*	**Attributional style, monocausal inferences** In patients with psychosis, a tendency to make one-sided explanations for the occurrence of a specific situation has been observed. For example, making external attributions (blaming others) for negative events or failures.	- Illustrate that one-sided attributions might promote misinterpretations possibly leading to interpersonal problems or conflicts - Encourage the consideration of different factors (e.g., circumstances, others, myself), which might simultaneously contribute to the outcome of an event
5*	**Jumping-to-conclusions and decision making** Patients with psychosis tend to make hasty decisions without enough background information.	- Demonstrate associations between jumping-to-conclusions and anxiety, feelings of threat and avoidance behavior - Invite the patient to consider and gather as much information as possible before making a decision
6*	**Uncorrectable beliefs, bias against disconfirmatory evidence** A tendency to continue to cling to an opinion or belief, even when confronted with information that speaks against it.	- Tunnel vision can lead to interpersonal problems and may obstruct a realistic appraisal of a situation - Discuss possible consequences of tunnel vision together with the patient - Work on cognitive flexibility, encourage an exchange with trustworthy friends or family
7*	**Theory of mind and empathizing** Deficits in Theory of Mind have been observed in patients with psychosis, e.g., difficulties in detecting and evaluating facial expressions of others, or inferring motives of others from their ongoing behavior.	- Evaluation on how to make more reliable interpretations in social situations - Exercise emotion recognition - Discuss implicit social laws (courtesy, dress codes, manners) - Remind the patient to draw firm conclusions about another person only if the person is well-known
8*	**Memory and overconfidence in false memories** Patients with psychosis suffer from memory deficits. Patients are more confident in their false memories, but confidence in true memories can be decreased.	- Discussion of possibly reduced ability to differentiate between true and false memories - Presentation of heuristics to discriminate true from false memories (e.g., true memories are often more vivid)

9	**Depression and thinking** Patients may suffer from thinking biases that might promote comorbid depressive symptoms.	- Illustrate important association between thoughts, feelings and behavior - Sensibilization for depressive thinking biases and thoughts and behavioral consequences like social withdrawal, feelings of loneliness and depression - Support in planning mood-enhancing activities, - Tips to improve and stabilize mood, dealing with ruminating thoughts
10	**Self-esteem** Psychotic symptomatology may have long-term negative consequences on patients' self-esteem.	- Discussion of positive and negative effects of psychosis on self-esteem - Observable and not directly observable characteristics of a healthy self-esteem - Communication of specific strategies to improve self-esteem and application to everyday life
11	**Living with psychosis and relapse prevention** How to deal with the diagnosis and stigmatization, which might be associated with the disorder. Prepare an individual plan for relapse prevention.	- Learning how to communicate the disorder to others - Explanation of symptoms and of how to correct false information or stereotypes about the disorder - Importance of stress reduction concerning relapse prevention - Individual list with early warning signs and emergency plan
12	**Hearing voices (optional)** Education and information about hearing voices.	- Analyze own voice hearing, investigate possible triggers and maintaining factors - Assessment of own (problematic) thoughts about hearing voices and analyze whether these might reinforce voice hearing due to stress and burden - Encourage to try out different strategies to deal with hearing voices

Note. Therapy units marked with an asterisk focus on prominent cognitive biases associated with the formation and maintenance of delusional beliefs. For more detailed information see Moritz et al. (2017a). All therapy units contain various exercises to make the content more tangible to the patient. All the slides can be found on https://clinical-neuropsychology.de/metacognitive-therapy-psychosis-english/

Appendix D (Article 1)

Predictors of study drop-out and service disengagement in patients at clinical high risk for psychosis

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ORIGINAL PAPER

Predictors of study drop-out and service disengagement in patients at clinical high risk for psychosis

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Abstract

Purpose Study drop-out during follow-up and service disengagement frequently occur in patients at clinical high risk for psychosis (CHR-P). However, little is known about their predictors. Therefore, we aimed to analyze the rate and reasons for drop-out and service disengagement in CHR-P patients and investigate their sociodemographic and clinical predictors.

Methods Data from 200 patients of the prospective Früherkennung von Psychosen (FePsy) study were analyzed with competing risks survival models, considering drop-out and transition to psychosis as competing events. To investigate whether symptoms changed immediately before drop-out, *t* tests were applied.

Results Thirty-six percent of patients dropped out within 5 years. Almost all drop-outs also disengaged from our service. Hence, study drop-out was used as a proxy for service disengagement. Patients with more severe baseline disorganized symptoms and a late inclusion into the study were significantly more likely to disengage. Immediately before disengagement, there was significant improvement in negative symptoms only.

Conclusion A considerable proportion of CHR-P patients disengaged from our clinical study and service. Patients who were included during a later study period with more assessments disengaged more often, which might have been due to more frequent invitations to follow-up assessments and thereby increasing participation burden. Hence, our study provides a cautionary note on high-frequency follow-up assessments. Larger-scale studies evaluating predictors on multiple domains would help to further elucidate drop-out and disengagement.

Keywords Attrition · Service use · Clinical service · At-risk mental state · Early intervention

Introduction

Psychotic disorders such as schizophrenia are serious mental disorders, which occupy the sixth largest share of disability-adjusted life years (DALYs) in European adults [1, 2]. Schizophrenia is associated with high premature mortality rates leading to about 15 years of potential life lost and increased rates of multiple somatic disorders [3, 4]. In the last decades, there has been growing interest in the early detection and intervention regarding psychotic disorders, as it has been shown that early treatment can improve outcomes in those affected [2, 5]. Even patients at clinical high risk for psychosis (CHR-P) may suffer from a high symptomatic burden and functional decline [for meta-analysis, see 6]. The establishment of CHR-P services has shown that early detection and intervention is beneficial to this patient group in many respects. Specifically, it has been associated with symptom reduction, improvement of functional outcomes

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and a reduction of the risk of transition to frank psychosis [2, 5, 7].

However, an unresolved issue in studying CHR-P patients is that a considerable proportion of these patients drop out during the study follow-up. Recent studies reported drop-out rates ranging from 36% at 2 years of follow-up [8] to 68% at 3 years [9]. Only few studies investigated predictors of study drop-out and those existing reported inconsistent results. While one study reported that higher baseline negative symptoms significantly predicted later study drop-out [9], another study could not detect any significant relationship between baseline clinical variables and later study drop-out [8]. However, in both studies, sociodemographic and clinical variables such as age, gender, marital status, ethnicity, positive psychotic or depressive symptoms, social and role functioning, antipsychotic or antidepressant medication, as well as years of education were not associated with study drop-out [8, 9].

At the same time, many CHR-P patients disengage from clinical early intervention services. It has previously been described that service disengagement may be associated with poorer outcomes and higher health care costs across mental health services [10, 11]. To our knowledge, only one study has explicitly focused on service disengagement in CHR-P patients [12]. In this study, data on patients referred to the Outreach and Support in South London (OASIS) were collected indirectly from clients' general practitioners and electronic patient files. It was found that over one-fifth (21.2%) of referred patients did not attend or engage with the service. Furthermore, those who did not engage with the clinical service were more often unemployed at the time of referral than engagers [12]. No differences with regard to ethnicity, age, gender, or marital status were found.

While only few studies have investigated predictors of service disengagement and study drop-out in CHR-P patients, a number of studies have been performed in first episode psychosis (FEP) patients [for systematic review, see 13], which might provide further indications for potential predictors in CHR-P patients. Studies analyzing service disengagement in FEP patients found that disengagement was significantly predicted by substance abuse or dependence [13–15], poor medication compliance [14, 16], history of self-harm or suicidal attempts [14], lack of insight [13], lower symptom severity at baseline [13, 15], missing support or involvement of a family member [13], as well as having milder psychopathology, and being employed or a student [15]. Conflicting findings have been reported regarding duration of untreated psychosis (DUP), since shorter as well as longer DUP [13, 14] has been associated with service disengagement.

There are still several open questions regarding service disengagement and/or study drop-out in CHR-P patients. So far, it is not clear if some of the factors associated with service disengagement in FEP patients (e.g., substance abuse/dependence or lack of illness insight) are also associated with service disengagement in CHR-P patients. Furthermore, it is unknown whether patients who disengage from services show symptom worsening or improvement immediately before service disengagement and/or study drop-out.

Thus, the present study aimed to analyze the rate, self-reported reasons and predictors for service disengagement and/or study drop-out in CHR-P patients. Due to our study design, we were able to analyze predictors of both service disengagement and study drop-out at the same time, as these two outcomes were highly correlated in our study. Specifically, we aimed to replicate previous findings and examine additional predictors of service disengagement which have previously not been analyzed in this patient group. Based on previous studies in FEP patients, we hypothesized that lack of insight and cannabis use would significantly predict service disengagement in CHR-P patients. Additionally, we hypothesized that clinical variables would possibly predict service disengagement. We especially tested if service disengagement is associated with recent change in symptoms.

Materials and methods

Setting and recruitment

Study participants were recruited between March 1, 2000 and May 31, 2017 within the prospective "Früherkennung von Psychosen" (FePsy; early detection of psychosis) study. A detailed description of the overall study design can be found elsewhere [17, 18]. Recruitment took place via the FePsy Clinic, University of Basel Psychiatric Hospital, Switzerland, where patients suspected to be at risk for psychosis were referred to by general practitioners, parents, teachers, as well as mental health professionals. All patients referred to our service and meeting inclusion criteria (see below) were asked to participate in our prospective study. All study participants provided written informed consent. The study was approved by the ethics committee of Northwestern and Central Switzerland (EKNZ) and was conducted in accordance with the Declaration of Helsinki.

Screening

CHR-P patients were identified using the Basel Screening Instrument for Psychosis (BSIP), which is a semi-structured interview developed by Riecher-Rössler et al. [19]. The BSIP allows the identification of CHR-P or FEP patients. It is composed of the prodromal symptoms of the Diagnostic and Statistical Manual of Mental Disorders [DSM-III-R; 20], other risk factors such as young age or drug abuse derived from previous studies [19, 21], and the Personal Assessment

and Crisis Evaluation (PACE) criteria by Yung et al. [22]. Additionally, the BSIP defines an unspecific risk category (URC) for patients thought to be at lower risk because of presenting with less specific symptoms and risk factors for psychosis. The instrument has been shown to have a high reliability and predictive validity [18, 19]. A more detailed description of the BSIP as well as an English version of the instrument can be found in Peralta et al. [23].

Patients were included in this study if they met CHR-P criteria according to the BSIP, which occurred if one of the following criteria was met: (1) attenuated psychotic symptoms (APS); (2) brief limited intermittent psychotic symptoms (BLIPS); (3) genetic risk and deterioration syndrome (GRD): genetic risk in combination with two or more other risk factors such as social decline; and (4) URC: a combination of risk factors according to the BSIP, which can be found in Peralta et al. [23]. Patients fulfilling the criteria for APS, BLIPS or GRD are considered at "high risk" because of presenting a more psychosis-related risk set; whereas, patients fulfilling the URC criteria were considered at "lower risk" because of the unspecific nature of their symptoms [17, 19, 23].

Exclusion criteria were: age < 18, insufficient knowledge of German, IQ < 70, current or previous episode of schizophrenic psychosis according to the BSIP criteria (i.e., transition criteria according to Yung et al. [22] fulfilled), antipsychotic treatment for > 3 weeks (lifetime) and/or a total amount of ≥ 2500 mg chlorpromazine equivalent, or psychotic symptomatology within a clearly diagnosed affective psychosis or borderline personality disorder [17].

Baseline assessments

Sociodemographic variables and illness insight were assessed with the Basel Interview for Psychosis [BIP; 24], a semi-structured interview designed to assess indicators of emerging psychosis and the temporal development of psychiatric symptoms over the entire life span. Illness insight in the BIP was categorically rated as "absent", "fully present", or "questionable".

Baseline negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms [SANS; 25]. The SANS total score and its five original subscales (i.e., affective flattening, alogia, avolition/apathy, asociality/anhedonia and inattention) were used for statistical analyses. Baseline psychotic symptoms were assessed with the Brief Psychiatric Rating Scale Expanded version [BPRS-E; 26], and BPRS-E subscales were calculated according to the five-factor structure (positive symptoms, negative symptoms, activation, affect and disorganization) proposed by Shafer et al. [27]. Functioning was measured with the Global Assessment of Functioning (GAF) scale [28]. To assess comorbid psychopathology, we applied the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-I; 29] and additionally applied the SCID-II for personality disorders if screening was positive [30].

Follow-up assessments

CHR-P patients were reassessed and followed up at regular intervals for up to 5–7 years to examine whether transition to psychosis had occurred. However, since only few patients had a follow-up duration of more than 5 years, these patients were treated as right-censored at the 5-year follow-up. From 2000 to 2008, follow-up frequency depended upon the estimated risk set. Specifically, during the first follow-up year, "high-risk" patients were assessed monthly, while "low-risk" patients fulfilling only the URC criteria were assessed at 3-month intervals. During the second and third follow-up years, all patients were assessed every 3 months and thereafter annually. In the year 2009, methodological changes were applied to the FePsy study. To provide uniform follow-up assessments to all CHR-P patients, "low-risk" patients were followed up in the same intervals as "high-risk" patients and were also assessed monthly during the first follow-up year. Assessment intervals during the second and third years did not change.

During follow-up, all patients received supportive counseling and clinical management. A small fraction ($n = 9$) of the included patients also participated in the Neurapro study [31, 32] and thus were treated with omega-3 fatty acids or placebo. Transition to psychosis was monitored applying the transition criteria of Yung et al. [22] using the four BPRS items "suspiciousness", "unusual thought content", "hallucinations" and "conceptual disorganization". Follow-up assessments were terminated in case of transition to psychosis, or if no transition occurred after 5–7 years.

Outcome assessment

Study drop-out during follow-up was defined as the primary outcome variable and was assessed prospectively. CHR-P patients were considered as drop-out when no contact could be established for at least 1 year after several contact attempts had not been successful. Contact attempts included phone calls, letters, e-mails, text messages or contact with family members or general practitioners and other medical professionals, if release from medical confidentiality had been provided previously. CHR-P patients were also considered as having dropped out from our study when they explicitly refused to further participate in the study. In this case, drop-out reasons were assessed and documented on specific drop-out protocols. For those patients who dropped out, the drop-out date was defined as the date of their last visit.

To test whether study drop-out could be used as a proxy for service disengagement, we additionally assessed whether

patients dropping out of our study also disengaged with our clinical service. To this end, electronical medical records of a subset of our sample were inspected.

Statistical analyses

All statistical analyses were conducted using the R environment for statistical computing [33]. Drop-out was the primary outcome measure. However, according to the FePsy study design, follow-up assessment could be ceased either due to drop-out or due to transition to psychosis. Drop-out and transition were treated as competing events, since CHR-P patients could only experience one of the two event types over follow-up.

In a first step, we investigated rates of drop-out and transition to psychosis over the whole course of follow-up using cumulative incidence curves (CIC), which are the competing risks analogs of Kaplan–Meier survival curves [34, 35].

To discriminate between CHR-P patients with and without drop-out, and to test sociodemographic and clinical predictors, we applied competing risks survival analysis. We, therefore, fitted a cause-specific Cox proportional hazard model where the competing event "transition to psychosis" was treated as a censored category. We previously checked that the proportionality-of-hazards assumption was met. Univariable models were fitted for each potential predictor. Predictor variables included sociodemographic variables (age, sex, relationship status, living situation, occupation, functioning, level of education) as well as clinical variables (Axis-I diagnoses, type of CHR-P status (any of APS, BLIPS or GRD vs. URC only), cannabis use, current intake of antidepressants, BRPS and SANS subscales and illness insight). We additionally used inclusion date (i.e., inclusion from 2000 to 2008 vs. inclusion from 2009 to 2017) as a binary predictor because of the previously described methodological changes in study design in 2009. Ten patients had been treated with antipsychotics during the follow-up, which could have altered their natural disease course, and were, therefore, considered right-censored at the time when treatment with antipsychotics started. Five patients could no longer participate because they had moved too far away and were, therefore, considered right-censored at the time of relocation. For each univariable model, likelihood ratio *p* values were estimated. Testing was two-tailed at a 5% significance level and missings were excluded pairwise.

To examine whether patients presented with increasing or decreasing symptoms immediately before drop-out, we assessed a potential change in symptoms over time. We, therefore, compared BPRS sub- and total scales of the last and second-last assessments and applied dependent sample *t* tests. For this analysis, we only included CHR-P patients with study drop-out and a maximum time difference of 120 days between the last and second-last assessment.

Results

Sample characteristics

A total of 739 patients with suspected CHR-P were screened, of whom 310 were identified as having a CHR-P, 308 met criteria for FEP, and 121 were not at-risk for psychosis. Of the 310 CHR-P patients, 277 met our inclusion criteria. Of these, 200 provided written informed consent and thus were included in this study (see Table 1 for sociodemographic and clinical sample characteristics). The 77 patients who refused to participate did not differ from the 200 included patients with regard to gender and years of education but they were significantly older ($M_{Participants} = 25.1$ years; $M_{Refusers} = 29.5$ years).

Rate and reasons of drop-out

Within 5 years, 53 patients dropped out from the study and 43 transitioned to psychosis. An inspection of medical

Table 1 Sociodemographic and clinical sample characteristics

	N	CHR-P *N* = 200
Age (years, mean ± SD)	200	25.06 ± 6.86
Gender	200	
Women		62 (31.0%)
Men		138 (69.0%)
Education (years, mean ± SD)	200	11.69 ± 2.82
Risk group	200	
APS[a]		135 (67.5%)
BLIPS[a]		15 (7.5%)
GRD[a]		48 (24.0%)
URC only		40 (20.0%)
Antipsychotics currently[b]	200	9 (4.5%)
Antidepressants currently	200	47 (23.5%)
Anxiolytics currently	200	25 (12.5%)
BRRS total score (mean ± SD)	189	39.28 ± 8.81
SANS total score (mean ± SD)	187	21.54 ± 16.09
GAF score (mean ± SD)	157	55.45 ± 10.69

N is the number of non-missing values. Values of continuous variables are stated as mean ± 1 standard deviation. All other variables are given in total numbers and percentages in parentheses

APS attenuated psychotic symptoms, *BLIPS* brief limited intermittent psychotic symptoms, *GRD* genetic risk and deterioration syndrome, *URC* unspecific risk category, *BPRS* Brief Psychiatric Rating Scale, *SANS* Scale for the Assessment of Negative Symptoms, *GAF* Global Assessment of Functioning

[a]Patients can meet criteria for more than one specific category

[b]Below a total cumulative lifetime dose of 2500 mg of chlorpromazine equivalents

records revealed that only two patients with study drop-out still remained in our clinical service. The estimated cumulative incidence curves for both drop-out and transition are displayed in Fig. 1. The risk of dropping out within 1, 2, 3, 4, and 5 years of the follow-up was estimated as 0.13, 0.20, 0.26, 0.33 and 0.36, respectively. The respective transition risk was estimated as 0.15, 0.18, 0.22, 0.24, and 0.28. The mean follow-up time of patients with later drop-out was 1.55 years and 1.23 years of patients with a subsequent transition to psychosis.

Of those with drop-out, 41 patients (77.4%) explicitly requested to discontinue follow-up assessments. The identified reasons for refusal were: symptomatic improvement, and therefore no more need for service (6 patients, 14.6%), transition to another mental health service or psychotherapist (3 patients, 7.3%), lack of time and interest (4 patients, 9.8%), being annoyed by requests for study participations (8 patients, 19.5%) and no specific reason (16 patients, 39.0%). Information was missing for 4 patients (9.8%). Twelve out of 53 patients (22.6%) could not be reached for at least 1 year after several attempts and were, therefore, considered as drop-out.

Baseline predictors of study drop-out

Results of competing risks survival analysis are presented in Table 2. Univariate cause-specific hazard models revealed that patients with a late inclusion into the service (2009–2017) were significantly more likely to drop out than patients with an early inclusion (2000–2008). Furthermore, patients with a higher baseline score in the BPRS disorganization scale were significantly more likely to drop out. Notably, no other baseline sociodemographic or clinical predictors significantly predicted study drop-out. Results of the cause-specific hazard models for transition to psychosis can be found in the supplementary material.

Change in symptoms from second-last to last assessment in patients with study drop-out

Twenty-five patients were found to have a maximum time difference of 120 days between the second-last and last assessment before study drop-out, and thus were included in this analysis. When examining a potential change in symptoms, we observed that only BPRS-negative symptoms had significantly improved over time ($M_{second\text{-}last} = 4.18$ and $SD = 1.55$; $M_{last} = 3.56$ and $SD = 1.16$; $p = 0.019$). There were no significant differences from the second-last to last assessment in BPRS total score ($M_{second\text{-}last} = 33.00$ and $SD = 8.82$; $M_{last} = 30.90$ and $SD = 6.10$; $p = 0.097$), BPRS positive symptoms ($M_{second\text{-}last} = 4.52$ and $SD = 1.71$; $M_{last} = 4.08$ and $SD = 1.55$; $p = 0.156$), BPRS activation ($M_{second\text{-}last} = 3.40$ and $SD = 0.91$; $M_{last} = 3.42$ and $SD = 0.84$; $p = 0.918$), BPRS affect ($M_{second\text{-}last} = 4.90$ and $SD = 1.85$; $M_{last} = 4.56$ and $SD = 1.47$; $p = 0.356$) and BPRS disorganization ($M_{second\text{-}last} = 3.62$ and $SD = 1.09$; $M_{last} = 3.48$ and $SD = 0.92$; $p = 0.577$). The results of the dependent sample *t* tests can be found in Fig. 2.

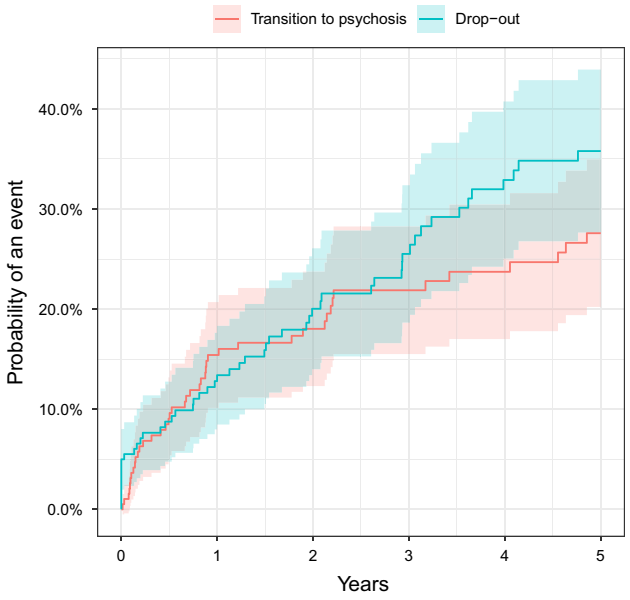

Fig. 1 Estimated cumulative incidence curves for both study drop-out and transition, which show the estimated proportion of patients with a drop-out (blue) and transition to psychosis (red) on the *y*-axis for different lengths of follow-up on the *x*-axis

Discussion

The present study is one of the first to study rates, reasons and predictors of study drop-out and service disengagement in CHR-P patients. We found that 36% of CHR-P patients dropped out from the study within 5 years and almost all of them also disengaged from our clinical service after study drop-out. Hence, in this study drop-out can be used as proxy for service disengagement. We found that study drop-out and service disengagement during follow-up were significantly associated with higher levels of baseline disorganized symptoms and with being included in the study after 2009. Moreover, we found that negative symptoms had significantly improved from the second-last to the last assessment before study drop-out, whereas positive symptoms had not changed.

The drop-out and disengagement rate of 36% after 5 years of follow-up in our study is rather low compared to previous studies, which reported drop-out rates of 36% after 2 years of follow-up [8] and 68% after 3 years [9]. Our low rate might be attributed to methodological differences regarding the operationalization of study drop-out. In our study, patients were considered as having dropped out when no contact

Table 2 Competing Risks survival analysis for study drop-out

	N	No drop-out	Drop-out	Test statistic		
		N = 147	*N* = 53	HR	CI	*p* value
Age	200	25.2 ± 7.1	24.8 ± 6.2	0.99	[0.95; 1.02]	0.479
Sex	200					0.376
Women		43 (29.3%)	19 (35.8%)	Ref.		
Men		104 (70.7%)	34 (64.2%)	0.78	[0.44; 1.36]	
Inclusion date	200					0.010*
2000–2008		63 (42.9%)	19 (35.8%)	Ref.		
2009–2017		84 (57.1%)	34 (64.2%)	2.11	[1.18; 3.77]	
Relationship status	168					0.270
In a relationship		32 (25.0%)	14 (35.0%)	Ref.		
Not in a relationship		96 (75.0%)	26 (65.0%)	0.69	[0.36; 1.33]	
Living situation	167					0.218
Alone		52 (40.6%)	20 (51.3%)	Ref.		
With partner or relatives		76 (59.4%)	19 (48.7%)	0.68	[0.36; 1.27]	
Occupational status	168					0.838
No occupation		42 (32.6%)	14 (35.9%)	Ref.		
Working or studying		87 (67.4%)	25 (64.1%)	0.93	[0.49; 1.80]	
Years of education	200	11.5 ± 2.7	12.3 ± 3.0	1.07	[0.98; 1.16]	0.115
Highest education	200					0.678
Elementary/middle school		71 (48.3%)	27 (50.9%)	Ref.		
Apprenticeship		30 (20.4%)	9 (17.0%)	0.71	[0.33; 1.51]	
High school		11 (7.5%)	5 (9.4%)	1.28	[0.49; 3.34]	
Qualification for university		28 (19.0%)	11 (20.8%)	1.07	[0.53; 2.16]	
Bachelor/Master's degree		7 (4.8%)	1 (1.9%)	0.39	[0.05; 2.89]	
Cannabis use	164	32 (25.6%)	14 (35.9%)	1.49	[0.77; 2.86]	0.235
Antidepressants currently	200	34 (23.1%)	13 (24.5%)	0.90	[0.48; 1.68]	0.735
Unspecific risk only	200	32 (21.8%)	8 (15.1%)	0.70	[0.33; 1.49]	0.359
Current affective disorder	161	44 (35.2%)	14 (38.9%)	1.12	[0.57; 2.18]	0.751
Current anxiety disorder	161	17 (13.6%)	9 (25.0%)	1.65	[0.78; 3.51]	0.189
GAF	157	55.7 ± 10.6	54.7 ± 11.0	0.98	[0.95; 1.01]	0.233
Illness insight	134					0.481
Not present/questionable		24 (22.6%)	5 (17.9%)	Ref.		
Present		82 (77.4%)	23 (82.1%)	1.41	[0.54; 3.73]	
SANS						
Total score	187	21.6 ± 15.6	21.4 ± 17.6	1.00	[0.98; 1.02]	0.993
Affective flattening	185	4.9 ± 6.2	5.3 ± 6.1	1.01	[0.96; 1.06]	0.772
Alogia	186	2.5 ± 3.7	2.9 ± 4.1	1.00	[0.94; 1.08]	0.920
Avolition/apathy	187	5.4 ± 3.1	5.0 ± 3.5	1.00	[0.91; 1.09]	0.951
Asociality/anhedonia	183	7.5 ± 5.3	7.0 ± 5.7	0.99	[0.94; 1.05]	0.703
Inattention	170	2.0 ± 2.4	1.6 ± 2.0	0.97	[0.83; 1.13]	0.665
BPRS						
Total score	189	38.8 ± 8.6	40.8 ± 9.5	1.02	[0.99; 1.05]	0.177
Positive symptoms	190	5.4 ± 2.0	5.7 ± 2.4	1.10	[0.96; 1.26]	0.171
Negative symptoms	189	5.4 ± 2.7	5.8 ± 2.9	0.99	[0.89; 1.10]	0.884
Activation	189	3.9 ± 1.7	3.6 ± 1.1	0.91	[0.73; 1.13]	0.371
Affect	188	6.7 ± 2.8	7.1 ± 3.0	1.05	[0.95; 1.15]	0.343
Disorganization	189	3.8 ± 1.3	4.2 ± 1.5	1.21	[1.01; 1.45]	0.039*

N is the number of non-missing values. Values of continuous variables are stated as mean ± 1 standard deviation. All other variables are given in total numbers and percentages in parentheses

HR hazard ratio, *CI* 95% confidence interval, *Ref* reference value, *$p \leq 0.05$, *GAF* Global Assessment of Functioning, *SANS* Scale for the Assessment of Negative Symptoms, *BPRS* Brief Psychiatric Rating Scale

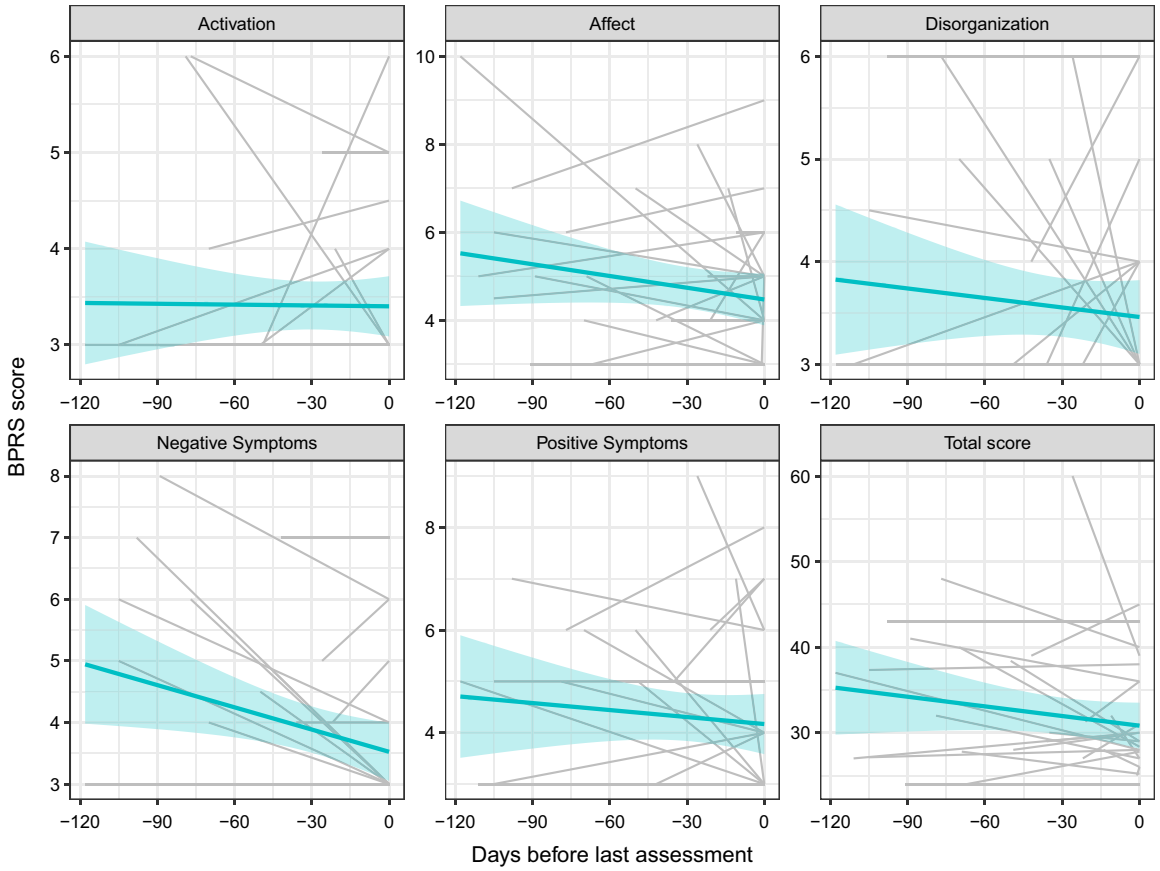

Fig. 2 Change in symptoms from second-last to last assessment in patients with study drop-out. Fine gray lines represent individual trajectories and thick blue lines represent averaged trajectories for each of the six psychopathological symptom dimensions

could be established for at least 1 year. However, clear and widely accepted definitions of study drop-out and service disengagement are lacking both for ARMS and FEP patients so far [11, 13]. Other studies have used lower [15, 16, 36, 37], as well as higher thresholds [38, 39], analyzed different follow-up durations [8, 9], or defined different types of disengagement [14]. Engagement and disengagement are often measured through attendance [11], as we did in our study. Yet, there are also studies describing service engagement and disengagement as multidimensional, multifaceted constructs comprising more than just service attendance [10, 11, 40, 41]. A multidimensional understanding of service disengagement as proposed by Tindall et al. [41], for example, could have provided further useful insights. The authors suggest understanding engagement as a process incorporating different stages. In these, circumstances can push a person towards engagement (e.g., fear of relapse or a good relationship with the case manager), or pull them from engagement (e.g., not wanting to open up, or a change in case manager).

Interestingly, we found a significant association between the study inclusion date and drop-out/service disengagement. CHR-P patients who were included between 2009 and 2017 dropped out significantly more often than those included between 2000 and 2008. This might be due to changes in the study design applied in 2009. Specifically, whereas CHR-P patients with a low risk were followed-up three-monthly in the first year when included before 2009, they were followed up monthly (i.e., treated equally as high risk patients) when included after 2009. Additionally, in 2011, we implemented an e-mail reminder system to facilitate the management of follow-up time points for care givers. Our case managers set their schedule for follow-up visits according to weekly reminder e-mails, which might have resulted in patients being contacted more often and especially in shorter intervals. Moreover, starting in 2011, patients were asked to additionally participate in two further multicenter studies on the early detection and treatment of psychosis [31, 32, 42]. We, therefore, speculate that contacting patients too often or burdening them with too many assessments might lead to unintended effects, such as patients being annoyed by it and therefore disengaging from the clinical service. In line with this, some patients even declared being annoyed by requests for study participations when asked about a specific reason for service disengagement.

Although lack of insight has been associated with service disengagement in FEP patients, we could not find any such association in CHR-P patients. One possible explanation is that illness insight in CHR-P patients is relatively intact compared to FEP patients [43]. Accordingly, in our sample only 21.6% of CHR-P patients were considered to have lacking or questionable insight according to the BIP [24]. Therefore, it seems possible that insight does not play a major role in service disengagement in the at-risk population.

Contrary to our hypotheses, we could not demonstrate any association between cannabis consumption and study drop-out/service disengagement. Substance abuse and dependence are among the most robust predictors of disengagement in FEP patients, with cannabis use in particular increasing risk of disengagement [13]. Notably, although not significant, the association between cannabis use and service disengagement in our study was in the same direction as in studies with FEP patients. It might be possible that cannabis consumption only leads to service disengagement in combination with more severe symptoms in later stages of psychotic disorders [13]. Alternatively, our non-significant finding might also be the result of low statistical power, as only 14 of 53 patients with service disengagement reported cannabis use at baseline. Further studies addressing the association between cannabis use and disengagement in larger CHR-P patient samples are warranted.

Regarding baseline clinical and sociodemographic variables, there were almost no associations with study drop-out/service disengagement. These results are largely consistent with previous studies investigating study drop-out/service disengagement in CHR-P patients [8, 9, 12]. Regarding the lacking influence of negative symptoms, our results are consistent with those of a large study by Stowkowy et al. [8] in 764 CHR-P patients, although another study did report an association with service disengagement [9]. On the other hand, our finding that higher baseline disorganized symptoms significantly elevated disengagement risk was rather unexpected. The only available study that explicitly reported findings regarding disorganized symptoms in CHR-P patients [8] could not demonstrate an association with service disengagement. Our contrasting finding may be attributed to the use of different instruments assessing disorganized symptom severity and different methods of dealing with patients with a subsequent transition in the statistical analysis.

For the first time, we investigated whether a change in symptoms had occurred immediately before study drop-out. While positive symptoms and all other subscales from the BPRS had not significantly worsened, negative symptoms had significantly improved between the second-last and last assessment. Thus, it appears unlikely that patients disengaged from the service because of increased suspiciousness or a transition to psychosis. Our results rather suggest that an improvement of negative symptoms and thus better social functioning might lower the need for treatment, and thereby increases the likelihood of dropping out. Hence, the duration of follow-up might have been too long for patients experiencing significant symptomatic improvement during the follow-up, which might have artificially increased the drop-out rate at later follow-up time points. However, it should be emphasized that in our study, positive symptoms remained relatively stable from the second-last to last appointment. This indicates that at least some patients might still suffer from subthreshold psychotic symptoms at the time of disengagement and still be at-risk for psychosis. This would be in line with our recent ultra-long-term follow-up study, which showed that some patients still transit to psychosis after many years [44]. Hence, it might be difficult to strike the right balance between capturing late transitions and not imposing a burden on patients. It might, therefore, be prudent to extend follow-up visit intervals with increasing follow-up duration, as has already been done in this study, or to flexibly adapt the frequency and length of follow-ups according to the symptom severity.

Strengths and limitations

Strengths of this study were the longitudinal design and the application of competing risk survival models, which allowed us to take transition to psychosis and the time to event into account. Furthermore, we evaluated a large number of predictor variables, including cannabis use and illness insight, regarding their association with service disengagement in this specific patient group for the first time. Additionally, to the best of our knowledge, this study is the first to investigate changes in symptoms immediately before study drop-out.

A limitation of this study is that we did not assess further potential predictors previously associated with service disengagement in FEP patients such as forensic history [13, 14, 45] or therapeutic alliance and quality of the relationship with the case manager, which have earlier been described as vital engagement reasons [11, 41].

Conclusion

In conclusion, sociodemographic and clinical baseline variables in great part did not predict study drop-out/service disengagement during follow-up in CHR-P patients. However, we observed that patients with a later inclusion into our project were at significantly greater risk for study drop-out/service disengagement, which might have occurred because the patients were burdened with increased assessments during the later time period. Hence, our study provides a cautionary note on high frequency follow-up assessments in this specific patient group. Larger-scale studies using

multidimensional assessments to evaluate predictors on multiple levels (e.g., clinical, sociodemographic, therapist) would help to further elucidate study drop-out and service disengagement in CHR-P patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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.

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Appendix E (Article 2)

Clinical and functional ultra-long-term outcome of patients with a clinical high risk (CHR) for psychosis

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Original article

Clinical and functional ultra-long-term outcome of patients with a clinical high risk (CHR) for psychosis

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ABSTRACT

Background: Few studies have followed up patients with a clinical high risk (CHR) for psychosis for more than 2–3 years. We aimed to investigate the rates and baseline predictors for remission from CHR and transition to psychosis over a follow-up period of up to 16 years. Additionally, we examined the clinical and functional long-term outcome of CHR patients who did not transition.
Methods: We analyzed the long-term course of CHR patients that had been included in the longitudinal studies "Früherkennung von Psychosen" (FePsy) or "Bruderholz" (BHS). Those patients who had not transitioned to psychosis during the initial follow-up periods (2/5 years), were invited for additional follow-ups.
Results: Originally, 255 CHR patients had been included. Of these, 47 had transitioned to psychosis during the initial follow-ups. Thus, 208 were contacted for the long-term follow-up, of which 72 (34.6%) participated. From the original sample of 255, 26%, 31%, 35%, and 38% were estimated to have transitioned after 3, 5, 10, and 16 years, respectively, and 51% had remitted from their high risk status at the latest follow-up. Better psychosocial functioning at baseline was associated with a higher rate of remission. Of the 72 CHR patients re-assessed at long-term follow-up, 60 had not transitioned, but only 28% of those were fully recovered clinically and functionally.
Conclusions: Our study shows the need for follow-ups and clinical attention longer than the usual 2–3 years as there are several CHR patients with later transitions and only a minority of CHR those without transition fully recovers.

1. Introduction

The majority of patients with schizophrenic psychoses experience a prodromal phase with first signs and symptoms, beginning on average 3–4 years before the onset of frank psychosis [1,2]. Based on this evidence, the concept of the clinical high risk (CHR) state for psychosis was developed approximately two decades ago, including specified criteria such as the presence of attenuated psychotic symptoms, short limited psychotic symptoms or genetic risk and functional decline [3].

A large body of research has since been conducted to establish and optimize early detection of the early stages of the disorder and to predict transition to frank psychosis. Current meta-analytical evidence indicates that about 20% of CHR patients develop frank psychosis [4] and about 35% remit from their CHR state [5] within two years after initial identification. The speed of psychosis progression tends to plateau from the third year on, reaching a cumulative transition risk of about 35% after 10 years [6]. Therefore, most previous studies have focused on the first 2–3 years after initial identification [7–9] and there is only little evidence on the long-term outcome of CHR patients [10–15].

Although CHR patients without later transition (CHR-NT patients) make up the majority of CHR samples [4,9], little is known about their clinical and functional long-term outcome. So

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far, there are only very few studies evaluating non-psychotic clinical and functional outcome of CHR-NT patients with follow-up durations of more than 2 years [10–12,15]. These studies indicate that even CHR patients without transition to frank psychosis experience (subclinical) psychotic symptoms, non-psychotic disorders and psychosocial impairments in the long-term [10–12,15], although most of the comorbid disorders seem to be already present at baseline [16,17].

However, the existing long-term studies on CHR-NT patients have several methodological limitations. Functional outcome was frequently assessed by the GAF in which the level of functioning is rated based on psychosocial functioning or clinical symptoms, whichever area is more impaired, leading to a conflation of both. Most studies reported rates of remission from the CHR state only for certain points in time. Furthermore, a risk estimate that takes into account the "competing" risk of transition and the usually considerable proportion of drop-outs was rarely provided.

Little is known about how many CHR patients transition to frank psychosis and how many remit from their clinical high risk state in the long term. Furthermore, limited information is available on the clinical and functional outcome of those who do not transition, e.g., regarding subclinical psychotic symptoms, non-psychotic clinical symptoms and diagnoses such as depression and anxiety, psychosocial functioning and overall recovery. Insight into the long-term outcome of CHR-NT patients could inform clinical service planning and future research on the CHR state.

In this study, we therefore thoroughly investigated the ultra-long-term course (up to 16 years) of CHR patients, evaluating transitions to psychosis over the whole follow-up period including late transitions. Furthermore, we assessed the clinical and functional outcome of those without transition, i.e., the rates of remission from the CHR state, clinical symptoms and axis I diagnoses, functional outcome, and the prevalence of full clinical and functional recovery. Moreover, we aimed to investigate predictors of clinical and functional outcome in CHR-NT patients at long-term follow-up as to the best of our knowledge this has not previously been investigated. Based on a systematic review [15], we expected that most CHR-NT patients do not recover functionally and clinically during several years of follow-up.

2. Methods

2.1. Participants and procedure

Patients with a clinical high risk (CHR) for psychosis were recruited via the prospective Früherkennung von Psychosen (FePsy) study [18,19] and the Bruderholz study (BHS) [20]. Both were prospective clinical studies of all consecutive referrals from defined catchment areas to the specialized early detection centers of the counties of Basel city (FePsy) and Basel countryside (BHS). Patients received treatment according to needs, case-management, and supportive psychotherapy during the follow-up. Antipsychotic treatment was only initiated after transition to psychosis had occurred. Further details regarding the characteristics of the studies can be found in Table 1 and in previous publications [18–20]. Both studies were approved by the Ethics Committee northwest/central Switzerland (EKNZ) and all participants provided written informed consent. If subjects were under age 18, additional written informed consent was obtained from their parents.

All CHR patients who did not transition to frank psychosis during the respective initial follow-up periods, including patients who dropped out and did not complete all planned follow-up assessments, were regarded as patients without initial transition (CHR-NT), and were asked to take part in the long-term follow-up assessment of the current study (see Supplementary Materials page 1 for detailed information on the very thorough contact procedure).

Patients who refused to participate in the extensive long-term follow-up examination were asked to participate in a shorter telephone interview instead.

2.2. Measures

2.2.1. Baseline assessment

Baseline parameters and measures are reported in Table 1.

2.2.2. Follow-up assessments

CHR status was re-evaluated at each follow-up visit using the positive symptom items of the Brief Psychiatric Rating Scale – Expanded (BPRS-E) [22,23] in the FePsy study and the Structured Interview for Prodromal Symptoms/Scale of Prodromal Symptoms (SIPS/SOPS) [24,25] in the Bruderholz study.

Remission from CHR. Remission from CHR was defined as the absence of attenuated psychotic symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS), i.e., sub-threshold severity scores on all positive symptom items of the BPRS-E (FePsy) or SOPS (BHS) for at least 12 consecutive months preceding the latest follow-up assessment. Thus, in the FePsy study, the four BPRS-E symptoms relevant for this assessment had to be constantly under the following thresholds: suspiciousness $\leq$ 2, hallucinations $\leq$ 1, unusual thought content $\leq$ 2, and formal thought disorder $\leq$ 2. In the Bruderholz study, the five positive psychotic symptom items of the SOPS had to be constantly $\leq$ 2. Both sets of criteria are similar to those used by Schlosser et al. [26]. The date of remission was defined as the date at which the APS/BLIPS-free period lasting at least 12 months started. In those CHR-NT patients who participated in the long-term follow-up assessment, the date of remission was determined retrospectively for the whole follow-up period including the initial follow-up period. In those patients who did not take part in the long-term assessment, remission was evaluated by using all BPRS-E/SOPS positive symptom ratings of the initial follow-up period.

Transition to psychosis according to the criteria by Yung and colleagues [3] was also evaluated not only at each follow-up assessment but also retrospectively for the entire follow-up period by considering all available information, including medical records.

Non-remission from CHR. In case neither remission from CHR nor transition to psychosis occurred, patients were considered non-remitted at the time point they were last seen. This was the date of the long-term follow-up visit for patients participating in the long-term follow-up, whereas for patients not participating in the long-term follow-up this was the last visit in the initial follow-up.

Psychosocial functioning in CHR-NT patients at long-term follow-up, referring to the preceding 4 weeks, was evaluated by the Personal and Social Performance scale (PSP) [27] which is based on the Social and Occupational Functioning Scale (SOFAS) [28] and has been validated in many languages, including German [29]. Functioning is assessed in four domains, i.e., occupational functioning, interpersonal relationships, self-care, and presence of disturbing/aggressive behavior. Overall functioning is expressed in a global score. For the current study a global score of $\leq$ 70 was defined as functional impairment since scores above 70 indicate no or mild dysfunction [27].

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [30,31] was used to assess *current axis I diagnoses* in CHR-NT patients at long-term follow-up.

Full clinical and functional recovery at long-term follow-up was defined as meeting all of the following criteria: no transition to frank psychosis, remission from CHR, good functional outcome

Table 1
Characteristics of the FePsy and Bruderholz studies.

	FePsy study	Bruderholz study
Inclusion period:	• 3/01/2000 – 07/31/2014	• 2003 – 2006
Initial follow-up:	• up to 5-7 years • monthly (1st year), 3-monthly (2nd and 3rd year), and annually thereafter	• up to 2 years • 3-monthly to annually
CHR criteria	Risk criteria according to BSIP: • Attenuated psychotic symptoms (APS) • Brief limited intermittent psychotic symptoms (BLIPS) • Genetic risk and combination of certain prodromal symptoms/risk factors, including deterioration in functioning (GRD) • Unspecific risk category (URC), i.e., combination of a minimum number of certain predefined prodromal symptoms/risk factors	UHR criteria according to SIPS/SOPS: • Attenuated psychotic symptoms (APS) • Brief limited intermittent psychotic symptoms (BLIPS) • Genetic risk and deterioration syndrome (GRD) Basic symptom criterion: • At least one "predictive basic symptom" [1] with a SPI-A score $\geq$ 3
Exclusion criteria	• age < 18 years • IQ < 70 • previous psychotic episode (with transition acc. to Yung et al. [3] • antipsychotic treatment for >3 weeks (lifetime) and/or total amount of • $\geq$ 2500 mg chlorpromazine equivalents • (pre-)psychotic symptoms only within a clearly diagnosed affective psychosis or borderline personality disorder • (pre-)psychotic symptoms clearly due to organic reasons or substance abuse only • insufficient knowledge of German	• age < 14 years • IQ < 70 • previous psychotic episode • traumatic brain injury, epilepsy or other known neurological disorder • other significant medical condition considered to affect cognitive performance and self-perception
Baseline measures at initial study intake		
CHR criteria	• BSIP	• SIPS/SOPS • SPI-A
Positive & negative symptoms	• BPRS-E [2]	• PANSS
Psychosocial functioning	• GAF	• GAF
Axis I diagnoses	• SCID-I for DSM-IV	• SCID-I for DSM-IV
Cannabis use	• Basel Interview for Psychosis (BIP)	• Bruderholz Demography Questionnaire (BDQ)
Transition criteria	• acc. to Yung et al [3]; BPRS-E	• acc. to Yung et al [3]; SOPS

Note: FePsy study = Früherkennung von Psychosen (Basel early detection of psychosis) study; Bruderholz study = Basel countryside early detection of psychosis study; CHR = Clinical high risk for psychosis; SIPS = Structured Interview for Prodromal Symptoms / SOPS = Scale of Prodromal Symptoms (McGlashan et al, 2001([24])); BSIP = Basel Screening Instrument for Psychosis (Riecher-Rössler et al [42]; Peralta et al (43)); SIPS = Structured Interview for Prodromal Symptoms; SOPS = Scale of Prodromal Symptoms; SPI-A = Schizophrenia Proneness Instrument, Adult version (Schultze-Lutter et al (44)); PANSS = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler (45)); BPRS-E = Brief Psychiatric Rating Scale – Expanded (Ventura et al (23)); GAF = Global Assessment of Functioning scale of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association (28)); SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders (First & Gibbon [30]; Wittchen, Gruschwitz & Zaudig (31)); BIP (Riecher-Rössler et al (46)).
[a]According to Klosterkötter et al [47]: thought interference, thought perseveration, thought pressure, thought blockages, disturbances of receptive language, decreased ability to discriminate between ideas and perception, fantasy and true memory, unstable ideas of reference, derealization, visual and acoustic perception disturbances.
[b]Positive and negative symptom subscales according to Shafer et al ([21]).

(PSP global score > 70), and the absence of any current axis I disorder in accordance with Rutigliano et al. [32].

2.3. Statistical analyses

Statistical analyses were conducted using the R environment for statistical computing [33]. Analyses were conducted in two different samples: 1) the initial baseline sample of all CHR patients and 2) the sample of CHR patients who participated in the long-term follow-up assessment of the current study and had not transitioned to frank psychosis during the whole follow-up period. To test the representativity of the second sample, we compared those who participated in the long-term follow-up assessment with those who did not regarding various socio-demographic and clinical characteristics – both at baseline and at their last visit of the initial follow-up period.

In the first sample we investigated of CHR remission and transition rates over the whole follow-up period using cumulative incidence curves (CIC) which are the competing risks analogs of Kaplan-Meier survival curves [34]. We used proportional cause-specific hazards models to investigate baseline predictors for remission from CHR and transition to psychosis, i.e., age and gender, positive symptoms, negative symptoms, psychosocial functioning, and current cannabis use.

In the second sample we conducted 1) logistic and 2) multiple regression analyses to examine the predictive value of the aforementioned baseline socio-demographic and clinical variables regarding 1) remission from CHR and 2) psychosocial functioning at the long-term follow-up assessment. For each predictor variable, a separate model was fitted that additionally included study (FePsy vs. BHS) as covariate.

3. Results

3.1. Initial baseline sample (all CHR patients)

The **initial baseline sample** consisted of 255 CHR patients. The average **follow-up duration** (mean ± SD; range) of the whole

initial sample was 3.9 ± 4.1 (range: 0–16.6), of those with later transition 2 ± 2.5 (0.01–11.21), and of those without transition 8.2 ± 4.4 (0.1–16.6) years, respectively.

3.2. Ultra-long-term follow-up sample of CHR-NT patients

Forty-seven CHR patients of the initial baseline sample had been detected to have had transitioned to frank psychosis during initial follow-up. Thus, 208 CHR patients **without initially detected transition (CHR-NT)** were contacted and invited to participate in the ultra-long-term follow-up assessment. Of these, 72 (34.6%) did participate (71 face-to-face interviews, 1 telephone interview), 28 (13.5%) refused to take part, and 108 (51.9%) could not be reached. For two further patients only medical records were available, including information on transition status. Twelve patients participating in the long-term follow-up assessment turned out to have had transitioned in the meantime. Therefore, the long-term sample of CHR-NT patients consisted of 60 participants. Further details on the study sample can be found in Fig. 1 and Table 2.

There were no significant group differences between CHR patients who participated in the long-term follow-up assessment (n = 72) and those who did not (n = 183) regarding various sociodemographic and clinical variables (all p-values > 0.05; data available upon request), indicating a high representativity of the long-term follow-up sample.

3.3. Clinical outcome of the total initial CHR sample (n = 255)

3.3.1. Rates of transition to psychosis

Overall, 60 patients had transitioned to frank psychosis. At 2-, 3-, 4-, and 5-year follow-up the estimated transition rates were 18.7%, 23.1%, 25.9%, and 30.8%, respectively. Ten and 15 years after baseline the rates were 34.9% and 38.2%, respectively (for the proportions of transitions for each year see Fig. 2 and Table S2).

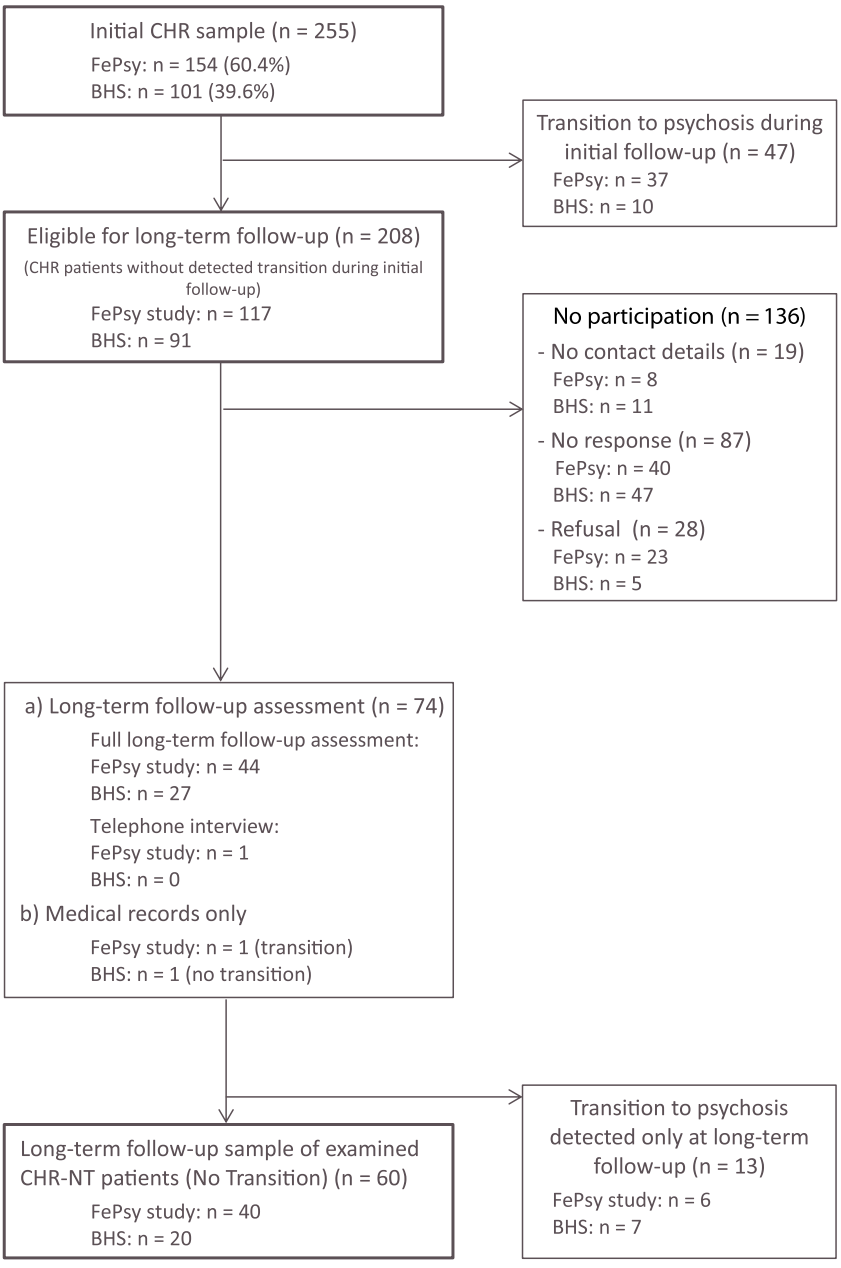

Fig. 1. Flow diagram of the study population.

Table 2
Socio-demographic and clinical characteristics of the CHR-NT patients of the long-term follow-up sample (n = 60) at baseline and long-term follow-up.

	FePsy study (n = 40)		Bruderholz study (n = 20)		Total sample (n = 60)	
	M (SD; range)	n (%)	M (SD; range)	n (%)	M (SD; range)	n (%)
Baseline						
Age, years	26 (8.7; 18.2–56.8)		20.2 (5.7; 14.4–35.6)		24.1 (8.2; 14.4–56.8)	
Gender, male		26 (65)		15 (75)		41 (68.3)
Education, years	12.4 (3; 8–19)		14.7 (3.3; 9–23)		13.1 (3.3; 8–23)	
Positive symptoms (BPRS-E/PANSS)	5.1 (2.2; 3–13)		5.5 (1.5; 3–8)		5.2 (2; 3–13)	
Negative symptoms (BPRS-E/PANSS)	5.7 (3; 3–14)		3.9 (1.6; 3–7)		5.3 (2.8; 3–14)	
Psychosocial functioning (GAF)	58.8 (10.2; 42–90)		43.8 (12.6; 0–58)		53.6 (13.1; 0–90)	
Current cannabis use (BIP), yes		7 (17.5)		1 (5)		8 (13.3)
Long-term follow-up						
Age at follow-up, years	34 (11.4; 21.3–72.4)		31.1 (6.2; 24.1–48.8)		33 (10; 21.3–72.4)	
CHR state (BPRS- E/PANSS)						
Remission		33 (82.5)		18 (90)		51 (85)
Non-remission		7 (17.5)		2 (10)		9 (15)
Psychosocial functioning (PSP)	72 (10.1; 48–90)		73 (8.1; 58-87)		72.3 (9.4; 48–90)	
Functional impairment, yes[a]		18 (45)		11 (55)		29 (48.3)
Any axis I diagnosis (SCID-I)		14 (35)		7 (35)		21 (35)
Mood disorder		2 (5)		5 (25)		7 (11.7)
Anxiety disorder		6 (15)		3 (15)		9 (15)
Substance use disorder		7 (17.5)		0 (0)		7 (11.7)
Full clinical and functional recovery[b]		11 (27.5)		6 (30)		17 (28.3)
Time to remission from CHR [years]	1.6 (2.1; 0–10)		3.9 (4; 0–9.7)		2.4 (3.1; 0–10)	

Note: CHR = Clinical high risk for psychosis; GAF = Global Assessment of Functioning scale of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, [28]); BPRS-E = Brief Psychiatric Rating Scale – Expanded (Ventura et al. [23]); PANSS = Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, [45]); PSP = Personal and Social Performance Scale; GAF = Global Assessment of Functioning scale of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association [28],); SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders (First & Gibbon, [30]; Wittchen, Gruschwitz & Zaudig, [31]); BIP (Riecher-Rössler et al [46]).

[a] Personal and Social Performance Scale (PSP) total score $\leq$ 70.

[b] Remission from CHR *and* absence of functional impairment *and* no axis I disorder.

3.3.2. Rates of remission from CHR

The proportion of patients with a remission from CHR within the first 2, 3, 4, and 5 years of follow-up was estimated with the cumulative incidence curve as 23.7%, 32.8%, 36.4%, and 37.4%, respectively. Ten years after initial baseline an estimated proportion of 51.4% had remitted, with no further remissions after that time point (for the rates of remissions at each year after initial baseline, see Fig. 2 and Table S2).

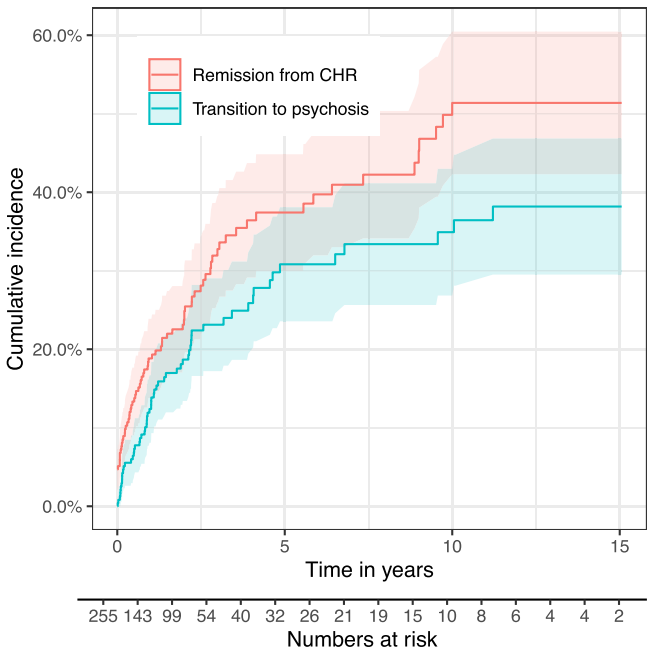

Fig. 2. Cumulative incidence curves.
Note: Estimated risks of remission from CHR and transition to frank psychosis over the whole follow-up period. Numbers at risk indicate CHR patients who are still in follow-up at this time point and neither remitted from their CHR nor transitioned.

3.3.3. Baseline predictors of remission from CHR

In the overall CHR sample, better psychosocial functioning at baseline was associated with a higher likelihood of remission from CHR during follow-up (p = 0.003). Age, sex, positive and negative symptoms as well as cannabis use were not significantly associated with remission (see Table 3).

3.4. Clinical and functional outcome of the CHR-NT long-term follow-up sample (n = 60)

The mean follow-up duration of the CHR-NT long-term follow-up sample was 8.2 ± 4.4 (range: 0.1–16.6) years. The average follow-up duration was 7.1 ± 4.3 (1.2–16.6) years of those with later remission from the CHR state and 2.5 ± 3.2 (0–15.1) years of those who neither remitted nor transitioned, respectively.

Of the 60 CHR-NT patients of the long-term follow-up sample, 51 (85%) had remitted from their high risk status (CHR), 39 (65%) had not any axis I diagnosis, 31 (51.7%) showed good psychosocial functioning. All in all, only 17 (28.3%) had fully recovered clinically *and* functionally. For further characteristics of the long-term follow-up sample see Table 2 and Fig. 3.

3.4.1. Baseline predictors of remission from CHR and psychosocial functioning at long-term follow-up (n = 60)

There were no significant associations between any of the baseline variables and remission from CHR at long-term follow-up (all p-values > 0.05; see Table S3). However, higher age (p = 0.06) and less negative symptoms (p = 0.09) at baseline were associated with better psychosocial functioning at long-term follow-up at a trend level (see Table S4).

Table 3
Baseline predictors of remission from CHR in the whole sample (n = 255).

Outcome (Competing Event)	Variable	Hazard Ratio	Confidence Interval	p-value
Remission (Transition)	Age	1	0.97–1.03	.83
	Sex	0.99	0.62–1.56	.95
	Positive symptoms	1.04	0.93–1.16	.49
	Negative symptoms	0.96	0.88–1.05	.37
	Psychosocial	1.04	1.01–1.06	.003**
	Cannabis use	0.76	0.4–1.4	.39

*p ≤ .05.
** p ≤ .01.

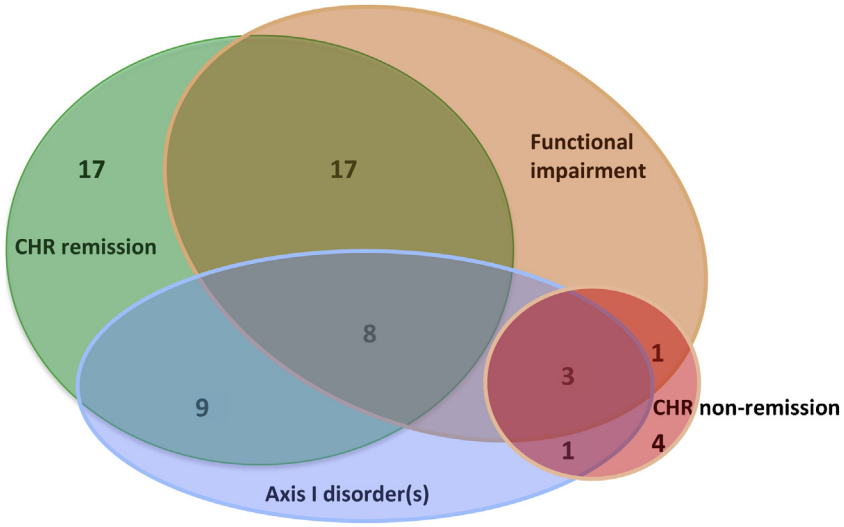

Fig. 3. Clinical and functional outcome of CHR patients without transition to frank psychosis at ultra-long-term follow-up (n = 60).

4. Discussion

We evaluated rates of transition and remission from the clinical high risk state and their predictors in a large sample of CHR patients over a follow-up period of up to 16 years. At the latest follow-up time, an estimated 38% of the overall sample of 255 patients had transitioned to frank psychosis, 51% had remitted from their CHR state, and 11% continued to experience subclinical psychotic symptoms. A higher level of psychosocial functioning at baseline was associated with a higher likelihood of remission from the CHR state during the follow-up.

Of the 60 CHR patients who participated in our direct, personal long-term follow-up assessments (i.e., at an average of 8 years after baseline) and had not transitioned to psychosis, 85% had remitted from their CHR state, 35% presented with at least one axis I diagnosis (apart from the CHR state), 48% showed poor functional outcome, and overall, only 28% had fully recovered clinically and functionally. This suggests that the majority of CHR-NT patients continue to experience clinical symptoms or functional impairments, even many years after initial identification. In this sample of CHR-NT patients, higher age and less negative symptoms at baseline were associated, at a trend level of significance, with better functional outcome at long-term follow-up.

4.1. Transition to psychosis

The present study estimated rates of transition for up to 16 years after initial referral, which – to our knowledge - is the longest time period that has ever been reported. Overall, we estimated that 26% of CHR patients had developed frank psychosis after 3 years, 31% after 5 years, 35% after 10 years, and 38% after 16 years. Our estimated transition rates in the first 4 years of the follow-up are very similar to those reported in the most recent meta-analyses [4,9]. As expected [4], most transitions occurred during the first 2–3 years of follow-up. However, several of our CHR patients had experienced a “late transition” 4 or more years after initial identification.

So far, only very few studies have estimated cumulative transitions rates for periods longer than 4 years [35,36]. In line with our results, the study by Nelson et al [35] on 416 CHR patients revealed cumulative transition rates of 28% and 35% after 4 and 10 years, respectively. In contrast, the study by Fusar-Poli et al [36] on 509 CHR patients detected only few transitions after more than 4 years. However, they might have missed some late transitions as their follow-up was limited to 10 years and they had a relatively high rate of drop-outs.

The multiple late transitions revealed in our study and that of Nelson et al [35] support the importance of follow-up durations longer than three years. This is not only important to estimate the true rates of transitions but also to evaluate the outcome of CHR patients without transition to psychosis. The fact that there is quite a number of late transitions also challenges many studies on risk prediction, as most prediction models were developed based on samples with short follow-up durations and can therefore only make accurate predictions regarding the short term.

4.2. Remission from CHR

In the whole sample of CHR patients, including those who transitioned, we estimated that 24% of CHR patients had remitted

from their CHR state after 2 years, 32% after 3 years, 36% after 5 years, and 50% after 10 and 16 years, indicating that a considerable number of CHR patients experience subclinical psychotic symptoms even many years after initial identification. The only other study that has estimated cumulative remission rates using competing risk survival analysis estimated 36% remissions after two years [26]. Our results are also similar to those of the meta-analysis of Simon et al. [5], which found a remission rate of 35% after two years.

Of the CHR patients without transition that participated in our direct long-term follow-up assessments 85% had remitted from their CHR state. This is about 10% higher than in other studies [5,10,11,37] which might be explained by the shorter average follow-up durations of most of these studies compared to the on average 8 years of follow-up in our sample.

Persistence of attenuated psychotic symptoms might indicate an ongoing risk of transition to psychosis [38]. Recurrent symptoms might also point towards a moderate disposition to react to stress with subclinical psychotic symptomatology, but not full psychosis due to, e.g., comparably low vulnerability and/or good protective factors. Subclinical psychotic symptoms might also indicate other diagnoses such as affective disorder, posttraumatic stress disorder and borderline personality disorder.

4.3. Baseline predictors for remission from CHR

In the whole sample of CHR patients we found better psychosocial functioning at baseline to be associated with a higher remission rate. Not predictive were age, sex, positive symptoms, negative symptoms, or cannabis use. A similar study of Schlosser et al [26] found not only baseline psychosocial functioning but also lower levels of negative symptoms to increase the likelihood of remission. This discrepancy might be due to the large difference in the follow-duration (up to 2 vs. 16 years) and different measures of negative symptoms (i.e., SOPS vs. BPRS/PANSS).

Poor psychosocial functioning is closely associated with (emerging) psychosis and might be a more stable marker for vulnerability to psychosis, i.e., non-remission from CHR, than positive symptoms at baseline [39]. A subgroup of CHR patients might not be predisposed to psychosis but might suffer from non-psychotic disorders associated with decreased psychosocial functioning and subclinical psychotic symptoms. CHR patients with better psychosocial functioning at baseline might have a higher resilience, including more internal and external resources such as a good social network and support, and a stable school or work environment. Those protective factors might contribute to their remission from CHR.

If only the CHR-NT patients that participated in our direct long-term follow-up assessments were considered, no significant associations between baseline predictors and remission from CHR were found. This is in line with a study of Ziermans et al [40]. However thismight also be due to a lack of statistical power as only few patients had not remitted from their CHR state (n = 9).

4.4. Clinical and functional ultra-long-term outcome of CHR-NT patients

The relatively high proportion of CHR patients without transition to psychosis diagnosed with clinical axis I diagnoses and/or showing poor psychosocial functioning at long-term follow-up is consistent with our recent review [15]. It suggests that most patients still require clinical attention and should be further examined. Despite the relatively large proportions of CHR-NT patients presenting with non-psychotic disorders at long-term follow-up, recent studies have shown that the clinical high risk state for psychosis is not predictive for non-psychotic diagnoses [17,41]. The large number of comorbidities in CHR-P patients could at least partially be due to clinicians using other diagnosis as a substitute for a CHR diagnosis as the latter is not yet included in the DSM or ICD.

4.5. Limitations

We included patients from two different studies with slightly different study designs. While the FePsy study evaluated CHR patients aged 18 years or older, the Bruderholz study also included adolescents who made up almost half of its sample. Furthermore, the FePsy study used the BSIP for assessing CHR criteria, whereas the Bruderholz study used the SIPS. In addition, the initial follow-up duration was longer in the FePsy study (5–7 years) than in the Bruderholz study (2 years). Moreover, positive and negative symptoms were assessed with the BPRS-E in the FePsy study and the PANSS in the Bruderholz study. The small number of non-remitted patients in the CHR-NT sample possibly limits the statistical power of the analyses of predictors of remission from CHR. Nevertheless, our study is one of the first to extensively evaluate outcome of CHR patients over such a long follow-up duration, using an advanced methodological approach to estimate remission and transition rates for a large sample.

4.6. Conclusions

By investigating a relatively large sample of CHR patients over a very long follow-up duration of up to 16 years, we could demonstrate that several patients still transition to psychosis after the usual time period assessed in most previous studies. We also found that only a minority of CHR-NT patients had fully functionally and clinically recovered at long-term follow-up. So far, we have obviously underestimated the rate of late transitions as well as the long-term prevalence of clinical symptoms and functional impairments in CHR patients without transition. One implication of our study is that existing prediction models, which are mostly based on samples with short follow-up duration, can predict transition to psychosis only at short-term. Our study reinforces the need for longer follow-ups of patients at clinical high risk for psychosis to provide adequate clinical care and inform future research.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eurpsy.2019.08.005.

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Appendix F (Article 3)

Moderators of treatment efficacy in individualized metacognitive training for psychosis (MCT+)

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Moderators of treatment efficacy in individualized metacognitive training for psychosis (MCT+)

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ABSTRACT

Background and objectives: Individualized Metacognitive Training (MCT+) is a manualized intervention designed to improve delusional severity by reducing delusion-associated cognitive biases such as jumping-to-conclusions. Increased interest in personalized medicine stipulates the identification of patients who are more likely to benefit from specialized interventions. The present study aimed to explore baseline moderators of MCT+ efficacy on delusions and overall positive symptoms in psychosis.

Methods: We analyzed data from a randomized rater-blind controlled trial, in which 92 patients with psychotic disorders and current or past delusions were randomly assigned to either MCT+ or CogPack®, a cognitive remediation software. Baseline moderator variables consisted of jumping-to-conclusions, cognitive insight, quality of life, self-esteem, selective attention, and patients' attitudes towards their symptoms. Linear mixed-effects models were applied to investigate specific moderators of MCT+ efficacy.

Results: In MCT+ relative to CogPack, presence of a jumping-to-conclusions bias, a lowered decision threshold, and low self-esteem were associated with larger improvements in delusional severity and/or overall positive symptoms over time. Subjective reasoning style and insight, as well as subjective attitudes towards psychosis, did not moderate the treatment efficacy of MCT+ relative to CogPack.

Limitations: Participation of both treatment groups in group MCT as a part of standard care, possibly leading to additional effects on delusional severity.

Conclusions: Patients with low self-esteem and those who are prone to jumping-to-conclusions seem to particularly benefit from MCT+. Our results can help inform clinical practice as they provide specific criteria for selecting patients for whom MCT+ is most appropriate.

1. Introduction

Delusions represent core symptoms of schizophrenia spectrum and other psychotic disorders (American Psychiatric Association, 2013). Treatment with antipsychotic medication has been associated with several limitations, specifically only medium effect sizes on positive symptoms (Haddad & Correll, 2018; Leucht et al., 2017), high treatment nonadherence (Garcia et al., 2016), and side effects (Lally & MacCabe, 2015). These limitations have led to increased efforts to develop specialized theory-driven interventions that target delusions and other positive symptoms, like Cognitive Behavior Therapy for psychosis (CBTp) (Mehl, Werner, & Lincoln, 2015) and more recently social cognition interventions (Grant, Lawrence, Preti, Wykes, & Cella, 2017).

Metacognitive Training for psychosis (MCT) represents one of these psychological interventions (Moritz, Veckenstedt, Randjbar, Vitzthum, & Woodward, 2011). MCT is a manualized group treatment program that aims to reduce delusional conviction by raising patients' awareness for cognitive biases associated with delusions (Garety & Freeman, 2013; Moritz, Andreou, et al., 2014; Moritz, Pfuhl, et al., 2017), such as jumping-to-conclusions, overconfidence in false judgments, and belief inflexibility/incorrigibility, using entertaining exercises. These aspects of MCT were further developed into an individualized intervention, MCT+, which blends elements of group MCT and CBTp (Moritz, Veckenstedt, Randjbar, & Vitzthum, 2011). Similar to group MCT, MCT+ targets reasoning biases frequently encountered in patients with delusional symptoms (Andreou et al., 2017). However, whereas group

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MCT approaches the 'metacognitive infrastructure' of delusions with predominantly non-delusional scenarios, MCT+ takes a step further and applies the learning aims to individual delusional beliefs and other core symptoms, including techniques adapted from CBT (Andreou et al., 2017).

Several randomized controlled trials (Andreou et al., 2017; Balzan, Mattiske, Delfabbro, Liu, & Galletly, 2019; Moritz, Andreou, et al., 2014; Pankowski, Kowalski, & Gaweda, 2016) as well as recent meta-analyses (Eichner & Berna, 2016; Liu, Tang, Hung, Tsai, & Lin, 2018; Philipp et al., 2019) have suggested that MCT and MCT+ are effective in the short- and long-term treatment of delusions and other positive symptoms. However, an earlier published negative meta-analysis including fewer studies suggested that MCT might not be suitable for all patients (van Oosterhout et al., 2016). Similarly, negative reviews and meta-analyses (Jauhar et al., 2014; Jauhar, Laws, & McKenna, 2019; Jones et al., 2018) have questioned the general view of CBTp as an effective treatment for all patients with psychosis. Given the recently growing focus on individualized prediction of patient outcomes in psychiatry, research on patient characteristics that may predict or moderate treatment efficacy and outcome for psychological interventions is highly relevant. Treatment that is likely to fail an individual is to be avoided for reasons of cost-effectiveness but also because of diminishing returns after each new treatment (Bücker, Schnakenberg, Karyotaki, Moritz, & Westermann, in press).

Regarding CBTp, predictors of treatment outcome have been elucidated in several studies. A recently performed systematic review reported that female gender, older age, higher clinical insight at baseline, shorter illness duration and higher educational attainment all predicted better outcome in CBT interventions (for systematic review see O'Keeffe, Conway, & McGuire, 2017). Inconsistent results were found for higher baseline symptom severity, neuropsychological functioning and cognitive flexibility (O'Keeffe et al., 2017). So far, there is only one study that has specifically analyzed moderators of treatment outcome in group MCT (Moritz, Menon, Andersen, Woodward, & Gallinat, 2018). Results showed that low baseline self-esteem, social anxiety and a positive appraisal of the intervention were consistently associated with improved short- and long-term outcomes in group MCT relative to an active control intervention (Moritz et al., 2018). Additionally, short-term delusional outcome was predicted by low quality of life, high baseline distress, and excitement, as well as a lowered decision threshold (only at trend-level) (Moritz et al., 2018). Neurocognitive measures such as processing speed, selective attention, and verbal memory did not significantly moderate treatment outcome. However, according to the authors of the study, these findings might not generalize to other forms of metacognitive training, such as individualized MCT+ for psychosis (Moritz et al., 2018).

As mentioned before, the identification of patients who are more likely to benefit from specialized interventions is of great importance. Thus, the present study aimed to explore potential predictors of MCT+ efficacy on delusions and other positive symptoms. To meet this purpose, we explored moderators of selective MCT+ efficacy using data from a randomized rater-blind controlled trial in patients with psychotic disorders, in which MCT+ was compared to an active control intervention with no expected effect on positive symptoms (computerized cognitive training). We were particularly interested in the moderating effects of reasoning style, self-esteem, quality of life and cognitive functioning that have been reported to predict response in group MCT and CBTp. Additionally, for the first time, we investigated whether patients' subjective appraisal of and attitudes toward their psychotic symptoms might moderate symptomatic outcomes following MCT+.

2. Materials and methods

2.1. Participants and setting

All data analyzed in this study were collected within the context of a monocentric, rater-blind, randomized controlled clinical trial (Andreou et al., 2017) carried out at the Department of Psychiatry and Psychotherapy of the University Medical Center Hamburg-Eppendorf (Germany). A more detailed description of the overall trial and its main findings can be found elsewhere (Andreou et al., 2017).

A total of 92 patients with non-affective psychotic disorders and current or past delusions were recruited among in- and outpatients treated at the Psychosis Center of the Department between January 2013 and July 2015. The trial was approved by the Ethics Committee of the German Psychology Association. All patients provided written informed consent before entering the trial.

Broad inclusion criteria were applied to recruit a representative clinical patient population: age 18–65 years, a DSM-IV diagnosis of a schizophrenia spectrum disorder confirmed with the Mini Neuropsychiatric Interview (Sheehan et al., 1998), and present or prior delusional ideas. Exclusion criteria were age < 18 years, a primary diagnosis of a substance use disorder, alcohol dependence in the last six months, IQ < 70, severe organic brain disorders, previous experience with group MCT or any of the experimental interventions (see below), and any ongoing CBT-oriented psychotherapy.

Patients were randomized according to a computerized randomization plan to either one of two interventions: MCT+ or CogPack® (Marker, 2003) (see 2.2 for details regarding the interventions). Treatment arm allocation was performed observer-blind by a person who was neither involved in the assessments nor intervention delivery. All patients continued to receive their usual treatment throughout study participation. Patients from both groups were allowed to take part in MCT groups during study participation.

Assessments within the randomized controlled trial were carried out at baseline, at 6 weeks (T1, corresponding to the completion of 12 intervention sessions) and 6 months later (T2). The present analysis considered only baseline data and data from the short-term follow-up (T1).

2.2. Interventions

MCT+ (Andreou et al., 2017; Moritz, Veckenstedt, Randjbar, & Vitzthum, 2011; Moritz, Veckenstedt, Randjbar, & Vitzthum, 2011) is a manualized 12-session intervention including twice-weekly individual therapy. The intervention focuses on highlighting the fallibility of cognition in general and aims to encourage patients to reflect on their thinking styles in relation to their symptoms and everyday life (Andreou et al., 2017). Therapy modules target prominent cognitive biases such as jumping-to-conclusions, overconfidence in false judgments and belief inflexibility/incorrigibility. The approach further addresses self-esteem and coping with stigma and stress, as these topics represent important treatment targets for patients (Moritz, Berna, Jaeger, Westermann, & Nagel, 2017) and may interact with positive symptoms. The MCT+ manual is freely available in several languages via http://www.uke.de/mct_plus. More detailed information on MCT+ can be found in Andreou et al. (2017) and Moritz, Veckenstedt, Randjbar, and Vitzthum (2011).

CogPack (Marker, 2003) is a computerized cognitive training program that targets cognitive dysfunctions frequently encountered in patients with psychotic disorders. The intervention as well comprised 12 consecutive sessions, which were administered on personal computers and covered a wide range of neuropsychological exercises involving memory, reasoning, selective attention and psychomotor speed. To match the two patient groups on therapeutic effort, CogPack was used as the active control intervention.

2.3. Outcome variables

The primary study aim was to assess potential moderators of MCT+ efficacy on delusions and other positive symptoms. Therefore, delusion severity at T1 was defined as the primary outcome variable and was assessed with the item P1 of the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). The PANSS is a widely used instrument considered as the gold standard assessment in clinical trials (Suzuki, 2011). It has been shown to have good psychometric properties (Kay, Opler, & Lindenmayer, 1989). Additionally, to the PANSS P1 delusion item we used the positive symptoms factor according to the five-factor model of the PANSS (positive symptoms, negative symptoms, disorganized symptoms, excitement, depression) proposed by Wallwork, Fortgang, Hashimoto, Weinberger, and Dickinson (2012).

2.4. Moderator variables

A full description of all measures used in the original trial is provided elsewhere (Andreou et al., 2017). Here, only the measures relevant to the current study are described.

A broad range of different variables was included to analyze moderators of selective MCT+ efficacy. All moderator variables were assessed pre-intervention at baseline and comprised of jumping-to-conclusions, reasoning style/cognitive insight, quality of life, self-esteem, cognition, and patients' subjective positive and negative meanings regarding their psychotic illness. We decided not to include any symptom-related moderator variables in the analyses, as this would complicate the interpretation of results because of the high correlation with the outcome variables and regression to the mean.

- The jumping-to-conclusions bias was assessed with the Fish Task (Moritz, Van Quaquebeke, & Lincoln, 2012), a computerized version of the Beads Task. The variables of interest were jumping-to-conclusions (defined in a dichotomous fashion as decisions based on only one or two fish), as well as the probability threshold at decision (i.e., the minimum probability estimate, at which a decision was made in favor of the respective lake; a higher probability threshold indicates more cautious inference making).
- Reasoning style/cognitive insight was measured with the Beck Cognitive Insight Scale (BCIS) (Beck, Baruch, Balter, Steer, & Warman, 2004), which measures the ability to distance oneself from one's ideas and reflect upon their possible fallibility. The 15-item self-report measure yields two scores corresponding to self-reflectiveness and self-certainty. It has been suggested (Beck & Warman, 2004) and confirmed in patient studies (Riggs, Grant, Perivoliotis, & Beck, 2012) that both self-reflectiveness and self-certainty represent inflexible reasoning styles that are associated with delusional beliefs. The internal consistency of the BCIS is adequate (Beck et al., 2004; Riggs et al., 2012).
- The World Health Organization Quality of Life-BREF (WHOQOL-BREF) (Murphy, Herrman, Hawthorne, Pinzone, & Evert, 2000) item 1 (overall quality of life) was used as a measure of overall life satisfaction.
- Self-esteem was assessed with the Rosenberg Self-Esteem Scale (Collani & Herzberg, 2003), a widely used 10-item self-report measure.
- The d2-test (Brickenkamp, 1978) measures selective attention and was included as a cognitive moderator variable. Higher values can be interpreted as better attentional performance.
- To investigate whether patients' subjective appraisal of and attitudes towards their psychotic symptoms might moderate MCT+ efficacy, a shortened version of the Subjective Sense in Psychosis Questionnaire (SUSE) (Klapheck, Nordmeyer, Cronjäger, Naber, & Bock, 2012) was used. The latter measures the meaning of psychoses within the five subscales biographical integration, positive (enriching) and negative (burdening) symptom experience as well as positive and negative consequences of psychosis on a 4-point Likert scale. To facilitate analyses, two mean scores were calculated reflecting positive and negative experiences and consequences of psychosis. Higher values on the positive scale reflect higher appraisal of positive symptoms, while higher values on the negative scale reflect higher negative appraisal of positive symptoms.

2.5. Statistical analyses

All statistical analyses were conducted using the R environment for statistical computing (R Development Core Team, 2019).

To investigate potential moderators of MCT+ efficacy on delusions and other positive symptoms, we applied linear mixed-effects models using the lme4 package (Bates, Maechler, Bolker, & Walker, 2014) for R (R Development Core Team, 2019). For each moderator variable, one mixed-effects model was fitted that included group (MCT+ vs. CogPack), time (baseline vs. T1), and the corresponding moderator variable, as well as all possible two and three-way interactions, as fixed effects factors. Additionally, the models included an intercept that randomly varied per subject. Continuous moderator variables were z-transformed to get fully standardized regression coefficients. Visual inspection of the model residual plots did not reveal any obvious deviations from homoscedasticity or normality. The main effects of group (reported in (Andreou et al., 2017)) and time were not of interest and will thus not be reported. We were mainly interested in the results of the three-way interactions, which allowed us to investigate specific moderators of MCT+ efficacy. In case of significant three-way interactions, two-way interactions between group and time were tested for high and low values of the moderator to determine differences in MCT+ and CogPack efficacy depending on the moderator. However, in the absence of significant three-way interaction effects, we also report significant two-way interactions between the respective moderator and time (baseline vs. T1) to indicate potential predictors of outcome irrespective of the type of treatment. Testing was two-tailed at a 5% significance level. We did not apply any correction of multiple testing because we were interested in analyzing potential treatment moderators in a rather new and unexplored area of research. Thus, we refrained from formulating directed hypotheses and analyses are considered being of exploratory nature.

Due to significant baseline differences in delusional severity and both positive and negative symptoms between MCT+ and CogPack patients, we additionally conducted all analyses on predictors of differential treatment response with subsets of the MCT+ and CogPack groups that were matched for these symptoms using the R package Matching (Sekhon, 2011).

3. Results

3.1. Sample characteristics

Compared to the MCT+ group, patients in the CogPack group showed significantly higher baseline delusional severity and positive symptoms, and significantly lower baseline negative symptoms. The two intervention groups did not differ on any of the other investigated variables at baseline (see Table 1).

3.2. Moderation: predictors of differential treatment response (MCT+ vs. CogPack)

Significant three-way interactions between group, time and baseline jumping-to-conclusions measures indicated that the improvement in delusional severity in response to MCT+ as compared to CogPack was dependent on both jumping-to-conclusions (decisions based on $\leq$ 2 fish) ($\beta = -1.71$, $SE = 0.53$, $p = 0.002$) and decision threshold in the Fish Task ($\beta = 0.74$, $SE = 0.25$, $p = 0.003$). Follow-up two-way

Table 1
Sample description and treatment characteristics.

	MCT+				CogPack					
	n	mean	SD	score range	n	mean	SD	score range	t/χ^2	p
Gender (m/f)	21/25				30/16				3.56	0.09
Age in years		36.91	12.5	18.0–63.0		35.59	13.1	19.0–67.0	0.50	0.62
Years of education		11.65	1.7	9.0–16.0		11.27	2.1	4.0–14.0	0.94	0.35
IQ		105.42	12.2	83.0–133.0		100.91	11.5	71.0–125.0	1.78	0.08
d2-Test - selective attention		153.69	50.7	17.0–292.0		147.66	39.2	38.0–223.0	−0.63	0.53
CPZ dose at T0		440.96	449.5	35.7–2375.0		420.24	349.9	50.0–1504.3	0.85	0.40
Symptoms										
PANSS										
P1 (delusions)		2.59	1.3	1–5		3.24	1.7	1–6	2.05	0.04
total score		49.78	13.0	30–88		49.35	12.8	31–86	0.16	0.87
positive		7.37	3.1	4–14		9.33	4.4	4–20	2.46	0.02
negative		10.83	4.8	6–25		8.30	2.9	6–20	3.06	0.003
disorganization		5.30	2.2	3–11		5.76	2.5	3–12	0.92	0.36
excitement		4.74	1.3	4–9		5.17	1.5	4–9	1.48	0.14
depression		6.85	3.1	3–14		5.74	2.7	3–14	1.83	0.07
Reasoning style										
Fish Task - draws to decision		4.02	2.8	1–11		3.44	2.6	1–11	1.02	0.31
Fish Task - decision threshold		79.22	19.3	10–100		78.47	22.5	20–100	0.17	0.87
BCIS self-certainty		13.84	2.8	8–20		14.74	2.9	8–21	1.48	0.14
BCIS self-reflectiveness		23.89	4.1	17–36		24.29	5.0	13–35	0.12	0.68
Quality of Life & self-esteem										
Rosenberg self-esteem scale		16.82	8.3	0–35		19.82	8.2	−1–35	1.72	0.89
WHOQOL-BREF overall quality of life		2.93	1.0	1–5		3.16	1.0	1–5	1.06	0.29
Subjective symptom appraisal										
SUSE - positive appraisal		2.54	0.78	1–4		2.65	0.67	1–4	0.71	0.48
SUSE – negative appraisal		2.40	0.56	1–4		2.26	0.61	1–4	−1.14	0.26

Note: CPZ: Chlorpromazine equivalent dosage; PANSS: Positive and Negative Syndrome Scale; BCIS: Beck Cognitive Insight Scale; WHOQOL-BREF: The World Health Organization Quality of Life-BREF; SUSE: Subjective Sense in Psychosis Questionnaire.

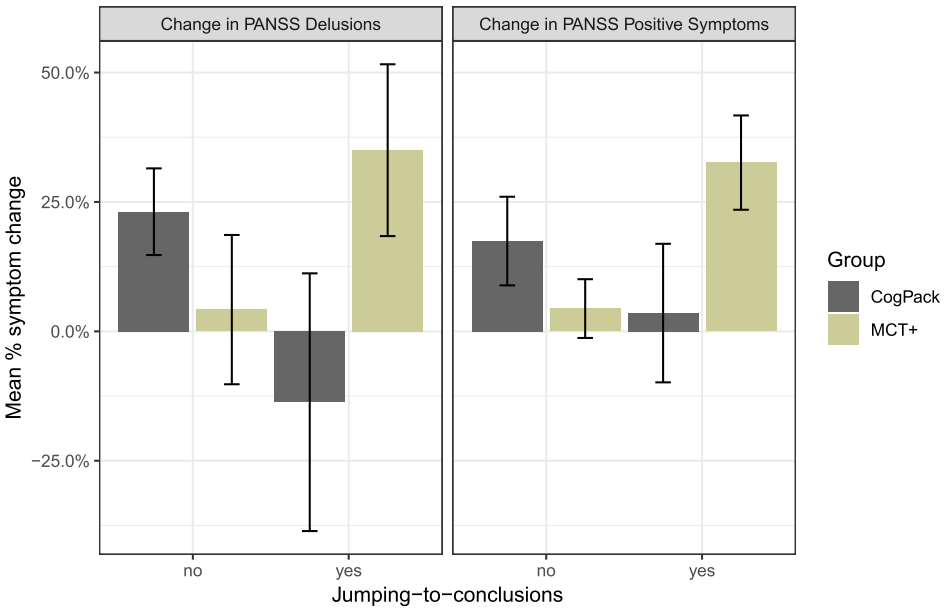

Fig. 1. Moderation of treatment response: Percentual symptom improvement in delusional severity and overall positive symptoms across treatment groups for patients with and without baseline jumping-to-conclusions. Please note that, in contrast to the statistical models described in Methods and Results, graphs do not include missing data.

analyses according to the presence or absence of jumping-to-conclusions at baseline indicated that patients with the jumping-to-conclusions bias at baseline showed significantly larger improvements in the PANSS delusion score over time following MCT+ than CogPack (group x time interaction effect $\beta = -1.18$, $SE = 0.42$, $p = 0.008$), while this was not the case in patients without the jumping-to-conclusions bias at baseline (group x time interaction effect $\beta = 0.53$, $SE = 0.32$, $p = 0.109$) (see Fig. 1). Similarly, a lowered decision threshold was associated with trend-wise larger improvements in delusional severity over time in the MCT+ relative to the CogPack group (group x time interaction effect $\beta = -0.70$, $SE = 0.40$, $p = 0.088$), compared to patients with a higher decision threshold (group x time interaction effect $\beta = 0.52$, $SE = 0.33$, $p = 0.124$) (see Fig. 2).

Additionally, significant three-way interactions between group, time and baseline self-esteem revealed that the improvement of delusional severity in response to MCT+ as compared to CogPack was dependent on self-esteem ($\beta = 0.62$, $SE = 0.26$, $p = 0.020$). As shown in Fig. 3, follow-up analyses indicated that low baseline self-esteem (group x time interaction effect $\beta = -0.29$, $SE = 0.35$, $p = 0.406$) tended to be associated with a higher delusional reduction following MCT+ than following CogPack, compared to high baseline self-esteem (group x time interaction effect $\beta = 0.20$, $SE = 0.40$, $p = 0.615$), even though no significant two-way interactions emerged.

With respect to overall positive symptoms, significant three-way

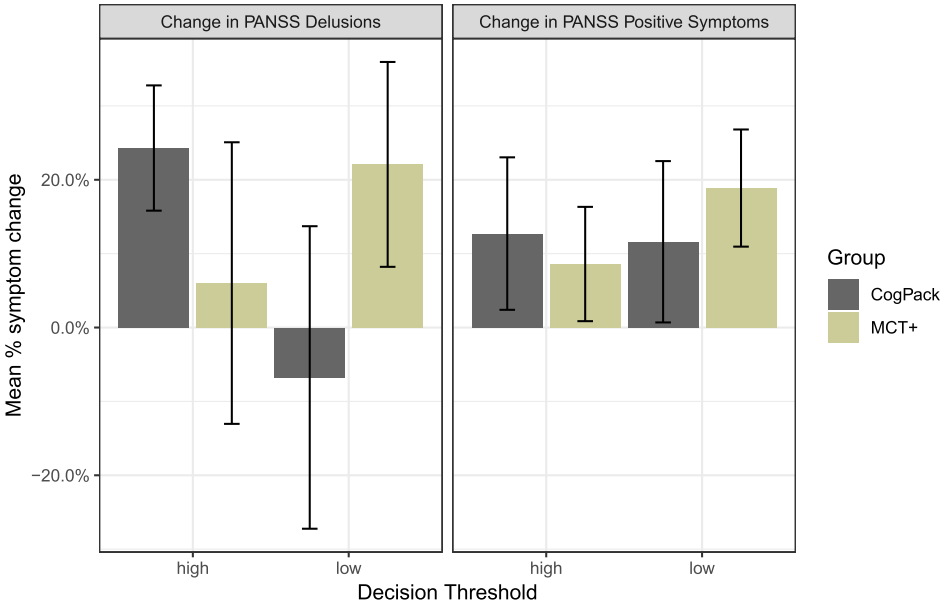

Fig. 2. Moderation of treatment response: Percentual symptom improvement in delusional severity and overall positive symptoms across treatment groups and levels of decision threshold (dichotomized along the median: decision threshold ≤ 80% = low; decision threshold > 80% = high). Please note that, in contrast to the statistical models described in Methods and Results, graphs do not include missing data.

interactions between group, time and jumping-to-conclusions measures were found. The improvement of overall positive symptoms in response to MCT+ as compared to CogPack was again dependent on both jumping-to-conclusions ($\beta = -3.91$, SE = 1.26, p = 0.003) and decision threshold in the Fish Task ($\beta = 1.46$, SE = 0.61, p = 0.019). As shown in Figs. 1 and 2, presence of baseline jumping-to-conclusions (group x time interaction effect $\beta = -2.19$, SE = 1.25, p = 0.089) and a lowered decision threshold (group x time interaction effect $\beta = -0.02$, SE = 0.99, p = 0.987) were associated with larger overall symptom improvement following MCT+ relative to CogPack, while the relative benefit of MCT+ disappeared in patients with a high decision threshold at baseline (group x time interaction effect $\beta = 0.71$, SE = 0.82, p = 0.389) and those without jumping-to-conclusions (group x time interaction effect $\beta = 1.69$, SE = 0.62, p = 0.009).

None of the other variables investigated significantly moderated treatment outcome (all $p > 0.10$).

The matching procedure resulted in MCT+ and CogPack groups each consisting of 36 patients that no longer differed in baseline psychopathology. We found that all results of the moderator analyses remained the same, except for the finding that the previously significant three-way interaction between group, time and baseline self-esteem only reached trend-wise significance (p = 0.074).

3.3. Predictors of treatment response irrespective of treatment group

A significant two-way interaction revealed that lower baseline selective attention significantly predicted higher improvement in delusional severity ($\beta = 0.31$, $SE = 0.14$, $p = 0.036$) and overall positive symptoms ($\beta = 0.99$, $SE = 0.33$, $p = 0.004$) over time independently of the intervention group.

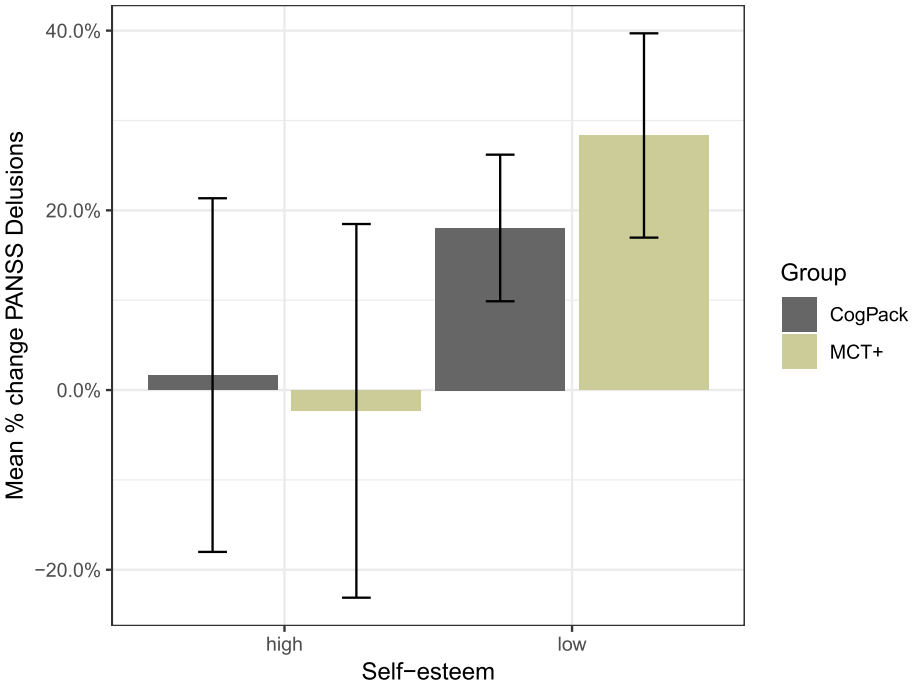

Fig. 3. Moderation of treatment response: Percentual symptom improvement in delusional severity across treatment groups and levels of self-esteem (dichotomized along the median: Rosenberg self-esteem score ≤ 18 = low; Rosenberg self-esteem score > 18 = high). Please note that, in contrast to the statistical models described in Methods and Results, graphs do not include missing data.

4. Discussion

To the best of our knowledge, this is the first study investigating moderators of individualized MCT+ efficacy on delusions and overall positive symptoms. We found that the presence of the jumping-to-conclusions bias at baseline significantly moderated treatment efficacy in the MCT+ group for both outcome measures delusional severity and overall positive symptoms. Moreover, we found that baseline self-esteem significantly moderated delusional reduction following MCT+ relative to CogPack. These results were unlikely due to significant baseline differences in psychopathology as the analyses in matched treatment groups yielded the same results, except that self-esteem moderated treatment response only on a trend-level, which however, might have been due to reduced power.

Specifically, patients who were prone to the jumping-to-conclusions bias at baseline showed a stronger decrease of delusional symptoms and positive symptoms over time following MCT+ than following CogPack. Additionally, we also found that a lower decision threshold was associated with larger improvements in delusional severity in the MCT+ compared to the CogPack intervention. The reported effects are consistent with the aim of MCT+ to improve delusions as well as positive symptoms by improving cognitive biases. The jumping-to-conclusions bias is also associated with neurocognitive deficits in verbal and working memory (Krezolek, Pionke, Banaszak, Kokoszka, & Gaweda, 2019), and thus one might expect patients with jumping-to-conclusions to also benefit from the improvement of these deficits through the control intervention (CogPack). However, improvement in jumping-to-conclusions resulting merely from better neurocognitive performance does not necessarily translate into a decline in delusion severity, as we have shown in a previous study (Andreou et al., 2015). We suggested then (Andreou et al., 2015) that the core element of MCT, i.e. explicit education on cognitive biases and on the importance of adequate evidence gathering before reaching a conclusion, is the decisive link between more cautious inference drawing and delusion improvement. Our present findings are consistent with this view, showing that patients who display the greatest improvement in delusions and positive symptoms following MCT+ are those who are prone to the jumping-to-conclusions bias at baseline.

Low self-esteem additionally predicted better treatment response to MCT+ relative to CogPack. This result is in line with Moritz et al. (2018), who found that low baseline self-esteem predicted improved outcomes in group MCT relative to CogPack. It has previously been suggested that increased self-esteem might be associated with overconfidence in errors (Hoffrage, 2004), a cognitive bias found in patients with schizophrenia, which is characterized by overconfidence in false inferences and judgments (for review see Balzan, 2016). Moreover, Moritz et al. (2015) found that the latter bias was more pronounced in patients who experienced subjective feelings of competence in a respective domain of question. It may thus be speculated that low self-esteem might be associated with reduced overconfidence in errors and/or feelings of competence (Moritz et al., 2015), making patients more amenable to question their own beliefs and therefore more open to the "seeds of doubt" that MCT+ seeks to plant. Else, MCT+ may improve negative beliefs patients hold about themselves, which have been found to be a potential risk factor for future delusional symptoms (Freeman & Garety, 2014).

Selective attention did not significantly moderate differences in treatment outcome between MCT+ and CogPack but instead reached statistical significance irrespectively of the intervention group (two-way interactions moderator and time). Unexpectedly, patients with lowered baseline selective attention showed higher improvement in delusional severity and positive symptoms over time. Our finding could be associated with greater margins for change in patients with lowered selective attention compared to patients who already presented intact selective attention at baseline. Combined with the observation of Moritz et al. (2018) that improvement of selective attention over time predicted overall symptomatic outcome following both group MCT and CogPack, it seems reasonable that larger attentional gains in patients with lower baseline selective attention were associated with better treatment response. This effect is conceivably independent of specific intervention effects, as cognitive impairments have long been identified as predictors of worse symptomatic (Andreou et al., 2013; Holthausen et al., 2007) and functional (for review see Bowie & Harvey, 2006; Christensen, 2007) outcomes in psychosis.

Some negative findings of the present analysis merit discussion. Concerning cognitive insight (as assessed by the BCIS), our results are in line with Moritz et al. (2018) who found that reasoning style and cognitive insight did not moderate treatment response in group MCT relative to cognitive remediation. This may seem counterintuitive at first, given the significant moderating effect of a cognitive bias (jumping-to-conclusions) in the present analysis. However, it has previously been shown that objective cognitive biases such as jumping-to-conclusions and subjective measures of cognitive insight are not correlated (Moritz et al., 2016). We also failed to find any effect of low baseline quality of life on MCT+ efficacy relative to CogPack, in contrast to findings by Moritz et al. (2018), who reported that low baseline quality of life predicted better outcomes in the MCT group. This contrasting finding may be setting-related, as group MCT is associated with a stronger social dimension compared to the individualized intervention. It is unlikely that the content of MCT+, the frequency of the intervention and the number of sessions might have contributed in failing to detect a significant moderating effect of life quality, as the mentioned factors are all highly comparable to group MCT. On the other hand, setting differences between the two interventions might explain this discrepancy, as group MCT is associated with a stronger social dimension compared to the individualized intervention. The delivery of MCT in a group setting might stimulate a sense of belonging, bonding and support and therefore be especially beneficial for patients with low social and global functioning, which has been found to be associated with quality of life (Nevarez-Flores et al., 2019). Finally, an interesting negative finding was the observation that positive and negative subjective appraisal of and attitudes towards psychosis did not moderate treatment response. Thus, although positive subjective appraisal and attitudes to psychotic symptoms have been reported to negatively affect antipsychotic medication compliance (Moritz, Hünsche, & Lincoln, 2014), it may be that they are less important for outcome in the context of an individualized psychological intervention. However, further studies are warranted to replicate this finding since, to the best of our knowledge, this is the very first study to analyze patient's subjective appraisal of psychotic symptoms as a moderator of the efficacy of a psychological intervention. As a last remark, the negative results regarding cognitive insight and subjective experience of psychosis speak for the broad applicability of MCT+, as they suggest that MCT+ efficacy is dependent on neither subjective insight nor attitude towards the illness.

Certain limitations should be considered regarding this study. First, not controlling for multiple comparisons might have led to chance effects, as the possibility of finding false-positive results is not controlled for. However, our analyses were of exploratory nature and correction for multiple testing might have led to type II errors limiting the capacity to detect important moderators. Second, both MCT+ and CogPack patients were allowed to take part in group MCT during the trial, as group MCT was defined as a part of the standard clinical treatment. Participation in group MCT may have had an additional effect on delusional severity and positive symptoms, which we could not control for; however, rates of MCT group participation did not differ between the two groups and thus are unlikely to have influenced the direction of results. Third, we did not test other moderators that might be relevant in the context of MCT+ efficacy, such as the bias against disconfirmatory evidence (BADE), which has been found to be associated with delusional severity (Eisenacher & Zink, 2017; McLean, Mattiske, & Balzan, 2017). Other biases, such as the BADE should be further

examined in future studies on the efficacy of MCT+.

In summary, individualized MCT+ seems to be more effective for improving delusions and positive symptoms in patients who are prone to jumping-to-conclusions and who have low self-esteem. Subjective reasoning style and insight, as well as subjective attitudes towards psychosis, do not seem to moderate the treatment efficacy of MCT+ relative to cognitive remediation, indicating that also patients with low metacognitive awareness and/or particularly positive or negative attitudes towards their psychosis might still benefit from the intervention. Our results can inform clinical practice as they provide specific criteria for selecting patients for whom MCT+ is most appropriate.

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CRediT authorship contribution statement

Letizia Leanza: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Erich Studerus:** Conceptualization, Methodology, Formal analysis, Visualization, Writing - review & editing. **Vasilis P. Bozikas:** Conceptualization, Writing - review & editing. **Steffen Moritz:** Conceptualization, Investigation, Resources, Data curation, Writing - review & editing. **Christina Andreou:** Funding acquisition, Project administration, Conceptualization, Investigation, Data curation, Supervision, Methodology, Writing - review & editing.

Declaration of competing interest

All authors declare that they have no conflict of interest in relation to the subject of this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbtep.2020.101547.

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