Risk indicators for schizophrenia across different stages of illness course

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Abstract

Schizophrenia is associated with a range of negative personal, economic and social consequences. Long duration of untreated psychosis can lead to unfavorable chronic illness courses and long-term low functioning. Hence, there is high interest in detecting vulnerable individuals early in the prodromal phase before psychotic decompensation to introduce early interventions. There are various clinical, (neuro-)physiological, or cognitive markers and risk factors discussed as being suitable for early detection of schizophrenia. The present dissertation investigated several of these risk indicators concerning their presence in vulnerable at-risk individuals and patients with manifest psychosis to gain further insights about their qualification for at-risk assessments. The three clinical samples (at-risk subjects, early, and chronic schizophrenia patients) were compared to a healthy control group.

Study (1) examined the event-related brain potential of the mismatch negativity and cognitive test performance as potential risk markers of schizophrenia. These two indices were expected to differentiate between healthy individuals and the clinical samples and as markers for illness progression they were hypothesized being further reduced in manifest psychotic patients compared to at-risk individuals. Additionally, associations of these measures with symptom severity were assessed at index assessments and at 6-month follow-up. Results yielded significantly reduced mismatch negativity in schizophrenia patients, but incon-
spicuous findings in at-risk individuals. Cognitive deficits were prevalent in all clinical samples compared to healthy individuals and they predicted higher symptom severity.

*Study (2)* investigated adverse childhood experiences and the role of cortisol concentration as risk indicators for psychosis development. Reports of childhood adversities were expected to be higher in the clinical samples, including at-risk individuals, compared to the healthy controls. High amounts of adverse childhood experiences and altered hair cortisol levels were hypothesized being associated with elevated symptom severity. Results confirmed higher childhood adversities in the clinical samples but hair cortisol concentration did not differ between groups. Adverse childhood experiences predicted symptom severity, while especially early abuse was related to lower cortisol levels and the latter predicted elevated psychotic symptoms.

*Study (3)* focused on the investigation of family history of schizophrenia, cannabis use and childhood adversities as risk factors for schizophrenia proneness and their individual contribution to symptom severity. It was hypothesized that there are higher rates of individuals with a positive family history of psychosis and more cannabis users in the clinical samples than in the healthy control group and that risk factors predict group affiliation and symptom severity. Results showed that current cannabis use and family history of psychosis were specific for manifest psychosis, while early cannabis use prior to age 16 did not differ between groups. Yet, early cannabis use together with adverse childhood experiences predicted symptom severity in the clinical population.
The present thesis showed that some of the investigated risk indicators are present in at-risk individuals and reflect non-specific psychopathology (cognitive performance and childhood adversities), while others were specific for manifest psychosis (mismatch negativity, current cannabis use, and family history of psychosis) or only predicted symptom severity (early cannabis use and hair cortisol concentration). High sample heterogeneity, small sample sizes, and the lack of long-term follow-ups clearly limit the interpretation of the present results. In conclusion, the present dissertation stresses the importance of considering a variety of different risk indicators for the identification of at-risk individuals in order to justify the future introduction of early interventions.
Zusammenfassung


Studie (1) untersuchte das ereigniskorrelierte Potenzial der Mismatch-Negativität und die kognitive Testleistung als potenzielle Risikomarker für Schizophrenie. Es wurde erwartet, dass sich diese beiden Kennwerte zwischen gesunden Individuen und den klinischen Gruppen unterscheiden, und als Marker für das Fortschreiten der Erkrankung wurde vermutet, dass sie bei Psychose-Patienten im Vergleich zu Risikoprobanden weiter reduziert sind. Darüber hinaus wurden die Zusammenhänge zwischen den beiden Maßen und der Symptom-


*Studie (3)* konzentrierte sich auf die Untersuchung der Familiengeschichte von Schizophrenie, Cannabiskonsum und nachteiligen Kindheitserfahrungen als Risikofaktoren für die Entwicklung einer Psychose sowie deren individueller Beitrag zur Schwere der Symptome. Es wurde erwartet, dass die klinischen Gruppen im Vergleich zur Kontrollgruppe mehr Personen mit einer positiven familiären Vorgeschichte sowie mehr Cannabiskonsumenten aufweisen. Außerdem wurde die Hypothese aufgestellt, dass die Risikofaktoren die Gruppenzugehörig-

Die vorliegende Arbeit zeigte, dass einige der untersuchten Risikoindikatoren bei Risikopersonen vorhanden sind und eine unspezifische Psychopathologie (kognitive Leistungsfähigkeit und negative Kindheitserfahrungen) widerspiegeln, während andere spezifisch für manifeste Psychosen waren (Mismatch-Negativität, aktueller Cannabiskonsum und Familienanamnese) oder die Symptomschwere vorhersagten (früher Cannabiskonsum und Cortisol-Konzentration im Haar). Die hohe Stichprobenheterogenität, die kleinen Stichproben sowie das Fehlen langfristiger Nachuntersuchungen beschränken eindeutig die Interpretation der vorliegenden Ergebnisse. Zusammenfassend veranschaulicht die vorliegende Dissertation die Wichtigkeit, verschiedene Risikoindikatoren für die Identifizierung von Risikopersonen zu berücksichtigen, um in Zukunft die Einführung frühzeitiger Interventionen zu rechtfertigen.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACE</td>
<td>adverse childhood experiences</td>
</tr>
<tr>
<td>APS</td>
<td>attenuated psychotic symptoms</td>
</tr>
<tr>
<td>AR(P)</td>
<td>at-risk (psychosis) individuals</td>
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<td>BLIPS</td>
<td>brief limited intermittent psychotic symptoms</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>BSIP</td>
<td>Basel Screening Instrument for Psychosis</td>
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<tr>
<td>CS</td>
<td>chronic schizophrenia patients</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
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<tr>
<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>ERP</td>
<td>event-related potential</td>
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<tr>
<td>ES</td>
<td>early schizophrenia patients</td>
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<tr>
<td>GAF</td>
<td>Global Assessment of Functioning</td>
</tr>
<tr>
<td>HC</td>
<td>healthy controls</td>
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<tr>
<td>HCC</td>
<td>hair cortisol concentration</td>
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<td>HPA</td>
<td>hypothalamus pituitary axis</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>MACE</td>
<td>Maltreatment and Abuse Chronology of Exposure</td>
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<tr>
<td>MCCB</td>
<td>MATRICS Consensus Cognitive Battery</td>
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<tr>
<td>MMN</td>
<td>Mismatch Negativity</td>
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<tr>
<td>UHR</td>
<td>ultra-high risk</td>
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Chapter 1

General introduction

In spite of its rather low median lifetime prevalence of about 0.5% (Saha, Chant, Welham, & McGrath, 2005; Simeone, Ward, Rotella, Collins, & Windisch, 2015), schizophrenia is a mental disorder with an unexpectedly high global burden of disease (Vos et al., 2016; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). Besides economic consequences (Chong et al., 2016), the personal and humanistic burden of chronic schizophrenia can also be devastating (Millier et al., 2014): low functional and cognitive status (Palmer et al., 2002), reduced quality of life (Browne et al., 2000), or a negative impact on patients’ caregivers and families (Hayes, Hawthorne, Farhall, O’Hanlon, & Harvey, 2015) have been associated with the mental disorder. Furthermore, long duration of untreated psychosis is associated with poor long-term outcomes, regarding social functioning and illness course (Penttilä, Jaaskelainen, Hirvonen, Isohanni, & Miettunen, 2014). Consequently, there is a high interest in examining the origins of psychosis\(^1\) to gain knowledge about the prevention of a potential illness onset or to alleviate chronic illness courses by early interventions.

In order to elucidate the pathogenesis of schizophrenia, Zubin and Spring (1977) postulated the well-established concept of vulnerability. Since then, many

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\(^1\) In the present thesis, the term „psychosis“ refers to psychoses that occur in the context of schizophrenia spectrum disorders.
researchers highlighted the importance of an individual’s predisposition for psychosis in combination with external stressors for schizophrenia development, i.e., the interplay between genes and environment (Henquet, Di Forti, Morrison, Kuepper, & Murray, 2008; van Os, Rutten, & Poulton, 2008). This view stresses the need for investigating a great variety of potential risk indicators of schizophrenia that include both genetic and environmental factors.

Heinz Hafner’s seminal work on onset and long-term course of schizophrenia (Hafner et al., 1992, 1995) established the gradual development of the disorder, from the emergence of early non-specific symptoms (like depression, restlessness, or anxiety) over several years, until the manifestation of the first specific positive symptoms. Awareness of the long-lasting prodromal phase with a mean duration of five years (Hafner & an der Heiden, 1999) has prompted research on early indicators, like biomarkers, risk factors, or prodromal signs, for the identification of vulnerable individuals and the facilitation of early treatments (Freedman et al., 2005; Laurens et al., 2015; Light & Swerdlow, 2015; Yung, Phillips, Yuen, & McGorry, 2004). However, knowledge about the causes of schizophrenia still remains incomplete and further clarification is demanded.

The present thesis aims at adding evidence to the existing literature by examining different risk indicators for schizophrenia manifestation that are described in the following studies. The general introduction provides an overview of some well-established schizophrenia risk factors across different developmental stages, followed by a brief presentation of various existing approaches that are used for the early detection of psychosis. Subsequently, important potential neuropsychological and (neuro-)physiological illness markers that could support at-
risk diagnostics are described. The general introduction is concluded by the scope of the present thesis, covering a short outline of the three included studies and a presentation of the hypotheses regarding the risk markers and factors that were selected for the present investigations.

1.1. Risk factors for schizophrenia development

There are various genetic or environmental risk factors for psychosis that have been identified across the early life span from birth to adolescence (Mäki et al., 2005). The following section provides a brief overview of several important risk factors, with a focus on the risk factors that are part of the present thesis.

One major risk factor is familial occurrence of psychosis, which increases the illness risk in relatives, depending on their degree of relationship (Gottesman, 1991). For instance, a first-degree relative of a schizophrenic patient has a 10-fold elevated risk for developing the disorder (Lu et al., 2018). Heritability measured in twin studies was estimated at about 80% (Cannon et al., 1998; Sullivan, Kendler, & Neale, 2003). Hence, there are discussions about candidate genes that might play a role for schizophrenia manifestation. However, there is a lack of robust and replicable genetic findings and no specific candidate gene that would be directly linked to schizophrenia could be identified yet (Farrell et al., 2015). Johnson and colleagues (2017) found that the top 25 historical candidate genes were not more strongly associated with schizophrenia in comparison to other non-candidate genes. Yet, past genetic research paved the way for new promising approaches, like genome-wide association studies, that could identify
specific loci being related to schizophrenia and they could show that we are dealing with a highly polygenic disease (Kim, Zerwas, Trace, & Sullivan, 2011).

Additional schizophrenia risk factors have been found during pregnancy and childhood birth. For instance, obstetric complications (as hypoxia), infections, or maternal malnutrition and stress were stated to be associated with an increased risk (Dean & Murray, 2005). Yet, pre- and perinatal risk factors are not specific to schizophrenia and might lead to a variety of psychiatric disorders and they only achieve a modest effect size in studies (Mäki et al., 2005).

Furthermore, just after childbirth there are additional environmental factors that enhance the risk for psychosis. Early adverse childhood experiences, such as child abuse and neglect, are reported to foster later psychiatric disorders, including the development of schizophrenia (Mayo et al., 2017; Redman, Corcoran, Kimhy, & Malaspina, 2017). Childhood adversities are highly prevalent among vulnerable ultra-high risk individuals (Kraan et al., 2015). However, early maltreatment was not only found to be related to psychosis onset but also to low functioning levels and increased psychotic symptoms in vulnerable at-risk individuals (Heins et al., 2011; Yung et al., 2015). Walker and Diforio (1997) proposed that the link between stressful experiences and psychosis is mediated by a dysregulated stress axis response, which is supposed to even elevate the vulnerability for future stressors and hence schizophrenia proneness.

Finally, there is another environmental risk factor that becomes relevant in (early) adolescence: the use of cannabis. Cannabis is a commonly used substance among vulnerable individuals that is reported to increase the risk for schizophrenia (Kraan et al., 2016; Valmaggia et al., 2014). Studies hint at a
causal relationship between cannabis use and psychosis onset (Arseneault, Cannon, Witton, & Murray, 2004; Drewe, Drewe, & Riecher-Rössler, 2004). The individual’s risk rises with the early onset of cannabis consumption or with higher doses and frequent use (Arseneault et al., 2004; Moore et al., 2007). Since not every individual with early or excessive cannabis use converts to manifest psychosis, the interaction of cannabis with an individual genetic vulnerability is supposed (Henquet et al., 2008). In general, different genotypes could influence an individual’s psychosis vulnerability upon the exposure to certain environmental influences (Binder, 2018; Vinkers et al., 2013).

The suggested interplay between schizophrenia risk factors stresses the difficulty of estimating the isolated contribution of one risk factor to psychosis onset. Nevertheless, some of the mentioned risk markers are already used to improve the identification of at-risk individuals and to estimate their transition risk.

1.2. Early detection of vulnerable individuals

With the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS), Häfner and colleagues (1992) developed one of the first instruments to measure the length and quality of the prodromal phase in schizophrenia patients. However, the development of the latest interviews and instruments aimed at the early assessment of vulnerable individuals without manifest psychosis to facilitate early support and intervention.
In recent years, several approaches for the identification of at-risk individuals have been established and many different clinical departments and research programs use and evaluate standardized interviews to achieve comparability, validity, and reliability in at-risk diagnostics (Miller et al., 2003; Phillips, Yung, & McGorry, 2009; Riecher-Rössler et al., 2008; Yung et al., 2005). Those individuals that meet the defined at-risk criteria are referred to as “at-risk mental state”, “prodromal”, “ultra-high risk”, or “clinical high risk” (Fusar-Poli et al., 2013).

Some of the widely applied instruments include the previously described risk enhancing factors, yet most of these instruments are guided by the individual’s self-reported psychopathology and they are based on the so-called “ultra-high risk” (UHR) criteria (Phillips et al., 2009). The UHR criteria consist of the presence of either (1) attenuated (i.e., subthreshold) psychotic symptoms (like mild forms of hallucinations or delusions), or (2) the history of brief limited intermittent psychotic symptoms within the past 12 months (the occurrence of frank psychotic symptoms for less than one week with a spontaneous remission), or (3) a trait vulnerability (family history of psychosis or schizotypical personality disorder) in combination with a significant decrease of at least 30% in functioning scores (Global Assessment of Functioning, GAF) compared to the premorbid level (Phillips et al., 2009; Yung et al., 2008).

Common instruments that use these UHR criteria are the Comprehensive Assessment of At-Risk Mental States (CAARMS) by Yung and colleagues (2005), the Structured Interview for Prodromal Syndromes (SIPS) with the included Scale of Prodromal Symptoms (SOPS) by Miller and colleagues (2003), or the Ba-
General introduction

sel Screening Instrument for Psychosis (BSIP) that was developed by Riecher-Rössler and colleagues (2008). All of the mentioned instruments are (semi)-structured interviews that rely on patients’ self-reports and should be conducted by trained mental health specialists. While CAARMS and SIPS/SOPS comprise similar symptom and risk categories, the BSIP adds another 4th risk category to the existing UHR criteria by the fulfillment of a minimal amount and combination of specific (e.g. marked deterioration of psychosocial functioning, odd beliefs, or disturbances of speech) and unspecific (e.g. psychiatric history or drug abuse) risk factors or prodromal symptoms (Riecher-Rössler et al., 2007, 2008). The BSIP is also the instrument that was chosen for all at-risk assessments within the studies of the present thesis.

Another commonly used assessment method is the basic symptoms approach. Basic symptoms are early subjective disturbances of cognition or perception (like problems with thought or speech and language processing or visual/acoustic distortions) that are not as prominent as psychotic symptoms (Schultze-Lutter, 2009). They are said to precede the presence of UHR symptoms, hence they are supposed to be present in the very early prodromal phase. Basic symptoms can be assessed via the Bonn Scale for the Assessment of Basic Symptoms (BSABS, Gross, Huber, Klosterkötter, & Linz, 1987) or the Schizophrenia Proneness Instrument (adult version, SPI-A, Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). The SPI-A comprises two sets of symptom clusters, the COPER (cognitive-perceptive basic symptoms) and the COGDIS criteria (cognitive basic symptoms). Recent studies often combined the assessment of basic symptoms with an instrument that assesses UHR criteria.
(Schultze-Lutter, Klosterkötter, & Ruhrmann, 2014) to achieve better prediction of conversion to psychosis.

A meta-analysis by Fusar-Poli et al. (2015a) yielded very good prognostic accuracy across a range of the previously mentioned instruments. The overall sensitivity (after 38 months follow-up) was excellent (.96), while the analyses only yielded modest specificity to rule in future psychosis converters (.49). The BSIP interview itself also achieved excellent sensitivity (1.0) and low, but acceptable specificity (.35; Papmeyer et al., 2018). The relatively low specificity values show that a large group of at-risk individuals subsequently does not develop full-blown psychosis and happen to be “false positives”. Transition to psychosis is usually given if a certain threshold of psychotic symptom severity or/and symptom duration in the respective at-risk assessment is fulfilled. Transition rates depend on the length of follow-up periods since the first diagnosis of being “at-risk” but are comparable between the different psychometric interviews. In their meta-analysis, Fusar-Poli et al. (2012a) state transition rates of about 18% after 6 months, 22% after 12 months, 29% after two years, and 36% after three years.

The assignment to an “at-risk state” is the necessary prerequisite for the justification and implementation of early prevention programs or therapeutic interventions. Consequently, researchers strive to improve the specificity of current at-risk interviews, for example by adding objective measures like known physiological or psychological indices to the standard diagnostic procedures.
1.3. Potential illness markers in the prodromal phase

In order to identify individuals in the prodromal stage, we need a reliable index that is already present and measurable before actual illness onset. For that purpose, recent investigations focus on objective measures that are well-established indices in (chronic) schizophrenia patients, some of them being discussed as potential biomarkers of the disorder (Allen, Griss, Folley, Hawkins, & Godfrey, 2009; Miller & Rockstroh, 2013, 2016; Turetsky et al., 2007).

There are several abnormal neurocognitive, neurophysiological, or biological indices known from schizophrenia research, that could already be found in high-risk individuals compared to healthy controls. Neuropsychological deficits, like poor attention or processing speed (Bora et al., 2014), and different event-related potentials in EEG/MEG, such as deficient P50 sensory gating, mismatch negativity or deviating P300 amplitudes have already been reported in the prodromal illness phase (Bodatsch, Brockhaus-Dumke, Klosterkötter, & Ruhrmann, 2015). Moreover, structural anomalies in brain imaging (Nenadic et al., 2015), or altered biochemical indices, like abnormal prolactin or cortisol levels (Labad et al., 2015), are among those numerous findings.

In the following paragraphs, the potential risk markers that are part of the present thesis are presented and described in more detail: the event-related potential of the mismatch negativity, neuropsychological test performance across different domains, and cortisol concentration as marker of the neuroendocrine stress system.
One of the most robust measures to distinguish between chronic schizophrenia patients and healthy control subjects is the auditory ERP component of the mismatch negativity (MMN, Erickson, Ruffle, & Gold, 2016; Näätänen et al., 2012; Umbricht & Kriljes, 2005). The auditory MMN is usually elicited with an oddball paradigm by presenting a set of repeating standard tones, which are interrupted irregularly by rare deviant tones. The MMN is supposed to reflect the brain's change discrimination ability in the auditory cortex and the sensory echoic memory, hence MMN dysfunction is thought to represent an index of cognitive decline (Näätänen, 1995; Näätänen et al., 2012). The MMN is generated by subtracting the response to standard tones from the one to deviant stimuli and usually shows a fronto-central negativity that peaks in a post-stimulus range of 100-250 ms (Duncan et al., 2009). Abnormally reduced MMN was stated to be specific to schizophreniform disorders and could therefore be of diagnostic use (Umbricht et al., 2003). A significant reduction in auditory MMN was already reported in schizophrenia patients within their first episode or in early treatment phases (Haigh, Coffman, & Salisbury, 2017; Hay et al., 2015).

Recent studies even found reduced, but less pronounced, MMN in individuals at risk for developing a psychotic illness and that prior MMN deficits could predict conversion to psychosis (Atkinson et al., 2017; Bodatsch et al., 2011; Näätänen, Todd, & Schall, 2016; Perez et al., 2014). Nevertheless, research on first-episode patients also produced inconsistent findings. Several studies could not confirm differences in MMN amplitudes between individuals during their first schizophrenic episode and healthy controls (Magno et al., 2008; Mondragón-Maya et al., 2013; Umbricht, Bates, Lieberman, Kane, & Javitt, 2006).
Impaired cognitive functioning is another distinctive feature in schizophrenia patients, which is supposed to be a core characteristic of the illness (August, Kiwanuka, McMahon, & Gold, 2013; Dickinson, Ragland, Gold, & Gur, 2008; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005). Cognitive deficits in chronic schizophrenia patients (compared to healthy subjects) could be found across a wide range of different domains and are, to a similar extent, already present in first-episode and first-admission patients (Addington, Brooks, & Addington, 2003; Carolus et al., 2014; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Cognitive performance is closely related to long-term functioning and subsequently represents an important aspect in the diagnostic and treatment process (Green et al., 2004). Additionally, it was reported that cognitive dysfunction is already highly prevalent among individuals at risk for psychosis or in prodromal patients (Bora & Murray, 2014; Keefe et al., 2006; Lencz et al., 2006). Riecher-Rössler and colleagues (2009) stated that cognitive impairment (i.e., speed of information processing) in at-risk-mental-state individuals could even help predict transition to psychosis. Therefore, neuropsychological impairment, as a potential trait marker of schizophrenia, is considered as an important measure for identifying individuals at risk for psychosis (Bora & Murray, 2014).

Moreover, abnormal stress responses, mostly measured by cortisol concentration, are closely related to early life stress and adverse childhood experiences in schizophrenia (Baumeister, Lightman, & Pariante, 2014; Walker, Mittal, & Tessner, 2008). Blunted cortisol levels to stress and awakening, and elevated basal cortisol concentrations were repeatedly found in schizophrenia patients.
and similar results were recently also stated for individuals at risk for psychosis (Pruessner, Cullen, Aas, & Walker, 2017). The relationship between cortisol levels and symptom severity is still unclear, since research produced inconsistent findings (Karanikas, Antoniadis, & Garyfallos, 2014). However, higher baseline salivary cortisol was found in individuals who transitioned to psychosis compared to those who did not develop manifest psychosis (Walker et al., 2013). Therefore, altered stress axis functioning already seems to affect vulnerable individuals and cortisol concentration could be relevant for psychosis prediction and serve as risk marker.

However, the use of the mentioned illness markers as a standard diagnostic tool to improve at-risk assessments is still not common. Due to the high variety of potential risk markers and the lack of sufficient and replicable evidence it is not feasible to prioritize a single potential illness marker as additional diagnostic criterion and the field demands further research.

1.4. Scope of the present thesis

Based on the previous findings on schizophrenia risk factors and illness markers, the need for further investigations in the field of early detection of psychosis is undoubted. The present thesis strives to contribute to the current at-risk psychosis research by gaining further insights about the presence or absence of selected risk indicators in vulnerable individuals and diagnosed schizophrenia patients.
While studies on risk indicators usually use longitudinal assessments to monitor transition to psychosis and compare psychosis converters to non-converters, it is often difficult to implement long follow-up periods in clinical research. In order to investigate risk indices in different illness stages, the current approach is the compromise of using the comparison of four cross-sectional assessments of individuals characterized by different stages in the hypothetical course of schizophrenia psychopathology: (1) Individuals contacting health professionals because of irritating non-specific signs of functional impairment (at school or peer group) were referred for the assessment of “at-risk” status (via BSIP), (2) inpatients admitted for the first time for treatment with a diagnosis of schizophrenia spectrum disorder, (3) inpatients defined as chronic because of multiple inpatient treatments, were compared to healthy individuals screened for the absence of current and lifetime diagnosis of psychiatric illness.

The present thesis compared different potential risk indices in the same dataset between these samples in order to determine the stage at which an indication of “abnormality” (deviance from healthy controls) would become manifest. With this goal, assessments included symptom levels, cognitive functioning, mismatch negativity (cortical level), and hair cortisol concentration (biological marker). Moreover, potential risk factors were evaluated by family history of mental illness, childhood adversity history, and early cannabis use, regarding their prevalence in vulnerable individuals and their association with symptom severity. The current thesis comprises three different studies, targeting the following hypotheses and open questions.
**General introduction**

*Study (1)* focuses on abnormal event-related brain potentials (ERP) and cognitive test performance as potential risk markers of schizophrenia onset and as markers of illness progression (Hirt, Schubring, Schalinski, & Rockstroh, in press). Brain potentials, the auditory ERP component of the mismatch negativity (MMN), were measured via EEG, and neuropsychological performance was assessed using the MATRICS Consensus Cognitive Battery (MCCB, Nuechterlein & Green, 2006), which comprises seven different cognitive domains, ranging from attention to social cognition. The first study aims at elucidating to what extent these risk markers contribute to psychopathology or illness progression and if they represent core features of schizophrenia across different illness stages. It is expected that the two measures should distinguish vulnerable individuals as well as schizophrenia patients from the healthy control group. Furthermore, as markers of illness progression, both markers should further differentiate between at-risk and diagnosed schizophrenia subjects and predict symptom severity at a 6-month follow-up examination.

*Study (2)* comprises the investigation of adverse childhood experiences (ACE) as risk factor of schizophrenia and its impact on psychotic symptoms, while considering the role of cortisol as potential neuroendocrine marker and the interconnectedness between these measures (Hirt, Schalinski, & Rockstroh, 2019). ACE (including the subtypes abuse and neglect) were assessed via the Maltreatment and Abuse Chronology of Exposure (MACE, Teicher & Parigger, 2015) and neuroendocrine regulation was measured with hair cortisol concentration (HCC). The concrete associations between ACE, HCC, and symptom severity remain to be clarified, and especially knowledge about the amount of HCC in
prodromal individuals is rare. It is hypothesized that vulnerable individuals and schizophrenia patients exhibit more ACE than healthy controls and that high amounts of ACE are related to elevated symptom severity. Additionally, significant associations between ACE, altered HCC and symptom severity are expected.

*Study (3)* deals with the three established risk factors family history of schizophrenia, cannabis use, and ACE, their prevalence in at-risk psychosis individuals or schizophrenia patients, and their individual impact on psychosis manifestation. ACE were again screened by the MACE and early (prior to age 16) and current (in the past year) cannabis use, as well as family history of psychosis, were assessed via retrospective self-reports. The study goal is to find out which of the mentioned risk factors is the most suitable to identify at-risk individuals or schizophrenia patients and to gain knowledge about the relationships between these markers and symptom severity in the clinical population. Hypotheses are that vulnerable individuals and schizophrenia patients exhibit higher rates of cannabis use, psychosis family history, or ACE compared to healthy individuals. Risk factors are supposed to predict group affiliation and especially ACE and cannabis use should be related to symptom severity in the clinical population.

The three introduced studies are presented separately in the style of self-contained manuscripts with the common repeating structure (introduction, methods, results, and discussion) in the following chapters 2-4.
Chapter 2

Study (1): Mismatch negativity and cognitive performance in the course of schizophrenia

Abstract

Background: Cognitive deficits and abnormal event-related brain potentials (ERP) have been proposed as risk markers for the development of schizophrenia. Evidence is inconclusive whether these markers indicate a risk for the development of psychosis or illness progression.

Methods: The present study aimed at further clarification by comparing symptom expression (Brief Psychiatric Rating Scale, BRPS), the ERP Mismatch Negativity (MMN), and neuropsychological performance on the MATRICS Consensus Cognitive Battery between healthy controls (HC, n = 38) and individuals at different stages of illness: individuals at risk for psychosis (ARP, n = 33), patients at first admission, thus, early stage (ES, n = 35), chronic schizophrenia patients (CS, n = 25). Moreover, symptom expression was reassessed for ARP and ES at a 6 months follow-up.

Results: MMN was smaller in individuals with manifest psychosis (ES, CS) than in HC, but did not differ between ARP and HC. In contrast, ARP showed similar cognitive deficits as ES and CS, all three groups differing from HC. Lower cognitive performance predicted higher symptom severity at index assessments and 6 months follow-up in ARP and ES, while MMN did not explain additional variance.

Conclusion: MMN seems to mark manifest psychosis, independent of early or chronic stage, while cognitive deficits mark early present psychopathology in individuals at risk for and with diagnosed psychosis rather than illness progression.
2.1. Introduction

Risk markers for schizophrenia

Chronic schizophrenia is associated with functional impairment, high unemployment rates, and low quality of life (Palmer et al., 2002; Penttilä et al., 2014; Ritsner, Lisker, & Arbitman, 2012). Evidence of diminished functional efficiency in cognitive and social domains many years before manifest symptoms and first hospitalization (Fusar-Poli et al., 2012b) emphasized the need to identify psychotic developments as early as possible in order to prevent or alleviate severe illness courses (e.g. Bechdolf et al., 2012; Fusar-Poli et al., 2015b; McGorry et al., 2002; Thompson et al., 2015). Structural abnormalities, such as grey matter loss (e.g. DeLisi et al., 2006; Dietsche, Kircher, & Falkenberg, 2017), and functional anomalies, e.g. smaller event-related brain potentials (P50 orMismatch Negativity, MMN), are already evident in prodromal states and were proposed as risk markers for psychotic development (Allen et al., 2009; Feldcamp & Wong, 2008; Miller & Rockstroh, 2013, 2016; Turetsky et al., 2007). Verification of such risk markers should help to identify individuals early in their course of illness and inform diagnostics and treatment strategies (Koike et al., 2013; Koutsouleris et al., 2012; Light & Swerdlow, 2015). Yet, diverse, controversial or unclear results (Luck, Mathalon, Donnell, Hämäläinen, & Spencer, 2011; Mäki et al., 2005), together with the complex interaction of trait and risk markers (Thomas et al., 2017), indicate that the substantiation of risk markers is still under way.
The present study examined the strength of MMN and cognitive dysfunction to distinguish stages in the course of schizophrenia spectrum disorder by comparing individuals characterized by different stages of illness within the same protocol. Previous studies evaluated target measures in distinct diagnostic samples (e.g. Baldeweg et al., 2004; Higuchi et al., 2013), related them to illness progression across extended follow-up periods (e.g. Koshiyama et al., 2017; Salisbury et al., 2007), or compared samples defined as chronic and first-episode (e.g. Salisbury et al., 2018; Umbricht et al., 2006), ultra-high risk (e.g. Solís-Vivanco et al., 2014), or combined all stages (Jahshan et al., 2012). The present study sought to expand this evidence by comparing both measures, MMN and cognitive test performance, across four distinct samples: Individuals with non-specific symptoms being considered at risk for developing psychosis, schizophrenia patients in an early illness stage, and chronic schizophrenia patients were compared to a sample of healthy participants.

**MMN as risk marker**

The electromagnetic MMN is elicited during passive listening to a series of auditory stimuli. It is defined as amplitude difference between frequent standard and rare deviant auditory stimuli, 100-250 ms after stimulus onset, and has been related to fundamental auditory information discrimination (Duncan et al., 2009; Näätänen, 1995; Näätänen et al., 2012). It accounts for substantial portions of variance in clinical, cognitive, and psychosocial functioning in schizophrenia (Light & Swerdlow, 2015). Smaller-than-normal MMN in chronic schizophrenia patients, first-episode and at-risk individuals, especially those who later devel-
oped psychoses, qualified the MMN as risk marker (Bodatsch et al., 2011, 2015; Erickson et al., 2016; Hay et al., 2015; Lepock et al., 2018; Näätänen, Todd, & Schall, 2016; Nagai et al., 2013a; Perez et al., 2014; Salisbury et al., 2002, 2018; Shaikh et al., 2012; Solís-Vivanco et al., 2014; Umbricht & Krljes, 2005). Furthermore, MMN was found to decrease with illness progression (Salisbury et al., 2007). Inconsistent results on MMN in at-risk individuals (Atkinson et al., 2017; Mondragón-Maya et al., 2013) and patients early in their course of illness (Haigh, Coffman, & Salisbury, 2017; Magno et al., 2008; Mondragón-Maya et al., 2013; Salisbury et al., 2017, 2018; Umbricht et al., 2006) may have resulted from different at-risk definition, sample heterogeneity and specific MMN types. For instance, duration MMN was found to distinguish early schizophrenia individuals from healthy controls more often than frequency MMN (Jahshan et al., 2012; Koshiyama et al., 2017, 2018; Nagai et al., 2013b, 2017).

Cognitive deficits as risk marker

Deficits in key cognitive domains like attention, working memory, visual/verbal learning and processing speed have been confirmed for chronic, first-episode, and first-admission schizophrenia patients (Addington et al., 2003; Carlu, 2014, 2015; Mesholam-Gately et al., 2009), and have been described as core characteristics or endophenotypes of schizophrenia (August et al., 2013; Dickinson et al., 2008; Fioravanti et al., 2005; Miller & Rockstroh 2013, 2016). Retrospective assessments have verified the emergence of non-specific symptoms, including cognitive decline up to 5 years before the manifestation of frank psychotic symptoms (Häfner et al., 1995). Poor cognitive test performance of in-
MMN and cognitive performance in the course of schizophrenia

dividuals at risk for psychosis (Bora & Murray, 2014; Keefe et al., 2006; Lencz et al., 2006) suggests that cognitive deficits reflect characteristic psychopathology, and therefore qualify as risk marker for psychosis (Seidman et al., 2016).

**MMN and cognitive deficits as predictors of psychotic symptoms**

Cross-sectional studies on the relationship between MMN, cognitive deficits, and symptom severity yielded diverse results. Relationships between MMN and positive or negative symptoms were reported for early-course or chronic patients (Javitt, Shelley, & Ritter, 2000; Salisbury et al., 2002; Todd et al., 2008), while most studies could not confirm associations with any clinical symptoms (Atkinson et al., 2017; Erickson et al., 2017; Jordanov et al., 2011; Perez et al., 2014). Associations of cognitive indices with (especially negative) symptoms were neither consistently reported (Addington et al., 2003; August et al., 2013; Nieuwennyten, Aleman, & de Haan, 2001; O'Leary et al., 2000 vs. Schaefer et al., 2013). The potential mediating role of cognitive deficits and negative symptoms between auditory processing and functional outcome, as shown by structural equation modeling (Thomas et al., 2017), may add to the complex pattern of evidence.

**The present study**

In light of this complex pattern of evidence, the present study targeted the meaning of MMN and cognitive dysfunction as risk and progression marker by comparing groups of individuals, who were characterized by different stages of schizophrenia within the same study. This comparison should elucidate to what
extent measures reflect core features of psychopathology and/or disease progression. MMN and cognitive performance were compared between individuals with non-specific or attenuated symptoms diagnosed as at risk for psychosis (ARP), individuals diagnosed with schizophrenia spectrum disorder during first or second inpatient treatment for schizophrenia, labeled early-stage schizophrenia (ES), and patients with multiple inpatient treatments, labeled chronic schizophrenia (CS). These groups were compared to a healthy control (HC) group. Moreover, the power of MMN and cognitive measures to predict the course of illness was examined in at-risk and early-stage individuals by regressing these measures to symptom severity 6 months later. Measures that distinguished different illness stages should be further examined as indices of illness progression. It was hypothesized that (1) as risk markers, MMN and cognitive test performance, distinguish the three groups, ARP, ES and CS, from HC. (2) As markers of illness progression, reduction in MMN amplitude and poor cognitive test performance is less pronounced in ARP than in ES and CS. (3) As markers of illness progression, MMN and cognitive measures predict further symptom development in ARP and ES. Regressing MMN and cognitive performance at index assessment to symptom severity at 6-months follow-up tested this hypothesis.

2.2. Methods

Participants

The study sample comprised altogether \( N = 101 \) participants, who were recruited from the population of eligible individuals assigned for at-risk diagnos-
tics to the outpatient clinic, or treated for diagnosed schizophrenia spectrum disorder on specialized units of the local Center for Psychiatry (Figure 1). Exclusion criteria were a comorbid diagnosis of mental retardation and a history of neurological condition or disorder, including epilepsy or head trauma with loss of consciousness. Table 1 summarizes demographic and clinical data of all participants who were assigned to the following three groups.

(1) \( n = 33 \) participants defined as at risk for psychosis (ARP); diagnoses were given by trained psychologists based on the Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al., 2008). BSIP defines at-risk status, when (a) attenuated psychotic (pre-psychotic) symptoms (i.e. severity of suspiciousness, hallucinations, unusual thought content and conceptual disorganization per Brief Psychiatric Rating Scale, BPRS) are present currently or within the last 14 days, but do not justify a diagnosis of manifest psychosis, and/or when (b) short episodes (< 1 week) of transient isolated psychotic symptoms were experienced in the past (brief limited intermittent psychotic symptoms, BLIPS), and/or when (c) genetic liability (per family history) occurs together with prodromal symptoms (according to DSM-III; peculiar behavior, magical thinking or unusual perceptual experiences and unspecific risk factors, like depression, anxiety or attention deficits), or when (d) only prodromal symptoms are reported (see also Table 2).

(2) \( n = 35 \) individuals with diagnoses of schizophrenia spectrum disorder being admitted to first or second treatment were assigned to the early schizophrenia (ES) group. Among these, \( n = 22 \) met ICD-10 criteria of paranoid-hallucinatory schizophrenia (ICD-code F20.0), \( n = 10 \) of acute psychotic episodes
(F23.0, F23.1, F23.2), n = 2 of schizoaffective disorder (F25.1, F25.2), and n = 1 of delusional disorder (F22.0).

(3) n = 25 patients with at least 5 inpatient admissions (M = 11.08, SD = 6.93) were defined as chronic schizophrenia patients (CS). Among these, n = 22 met criteria of ICD-codes F20.0, F20.1, F20.4, n = 3 of F25.0, F25.1. All diagnoses were given by experienced psychiatrists or psychologists based on ICD-10 criteria. At the time of recruitment and assessment, n = 11 (of 33) ARP, n = 33 (of 35) ES, and all CS patients were medicated with first- and/or second-generation neuroleptics (chlorpromazine equivalents in Table 1). Symptom severity and global functioning were determined by the respective psychologist or psychiatrist in charge, using the 24-item Brief Psychiatric Rating Scale (BPRS; Lukoff, Nuechterlein, & Ventura, 1986) and the Global Assessment of Functioning (GAF, DSM-IV Axis V; Table 1).

ARP, ES, and CS did not differ in gender distribution, years of school education and IQ (tested with a German test for premorbid intelligence, MWT-B; Lehrl, 2005), but CS were older than ES and ARP (Table 1). ARP and ES did not differ in age, symptom severity (BPRS), level of functioning (GAF) or medication (CPZ), whereas CS displayed higher symptom severity and achieved lower GAF scores than ES and ARP.

After contacting all ARP and ES 6 months after the first assessment, n = 21 ARP and n = 19 ES could be recruited for follow-up evaluation of symptom severity (BPRS and re-evaluation of BSIP criteria; Figure 1).

N = 38 healthy comparison participants (HC) were recruited among the university student pool and the local community to be demographically compa-
rable to the clinical samples. They were screened with the Mini International Neuropsychiatric Interview (Ackenheil, Stotz-Ingenlath, Dietz-Bauer, & Vossen, 1999) to exclude psychiatric and neurological disorder. Groups did not differ in gender balance and years of school education, but HC subjects had a higher IQ and were younger than the other three samples (Table 1).

**Fig. 1.** Flowchart of sample recruitment with follow-up after 6 months. HC, healthy controls. ARP, at-risk psychosis. ES, early-stage schizophrenia. CS, chronic schizophrenia. BSIP, Basel Screening Instrument for Psychosis. MMN, Mismatch Negativity. MCCB, MATRICS Consensus Cognitive Battery. Subsamples marked as grey were used for statistical analyses. Three individuals had to be excluded due to a neurological condition and 4 individuals, recruited as HC, had to be excluded due to suspected mental illnesses. Eight individuals without risk for psychosis were excluded after BSIP screening and 3 individuals with psychotic transition were assigned to the early schizophrenia sample.
Table 1. Sample characteristics.

<table>
<thead>
<tr>
<th></th>
<th>HC (n=38)</th>
<th>ARP (n=33)</th>
<th>ES (n=35)</th>
<th>CS (n=25)</th>
<th>HC vs. PAT</th>
<th>ARP vs. ES</th>
<th>ES vs. CS</th>
<th>ARP vs. CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (f/m)</td>
<td>14/24</td>
<td>8/25</td>
<td>12/23</td>
<td>5/20</td>
<td>$\chi^2(1)=1.28, p=.26$</td>
<td>$\chi^2(1)=.83, p=.36$</td>
<td>$\chi^2(1)=1.47, p=.23$</td>
<td>$\chi^2(1)=.15, p=.70$</td>
</tr>
<tr>
<td>Age, M±SD</td>
<td>23.97 ±</td>
<td>22.55 ±</td>
<td>24.14 ±</td>
<td>36.00 ±</td>
<td>$t(120.42)=-2.50,$</td>
<td>$t(66)=-1.47, p=.15$</td>
<td>$t(33.16)=-5.89,$</td>
<td>$t(31.29)=-6.79,$</td>
</tr>
<tr>
<td></td>
<td>4.40 ±</td>
<td>4.13 ±</td>
<td>4.77 ±</td>
<td>9.23</td>
<td>$p=.01$</td>
<td>$p&lt;.001$</td>
<td>$p&lt;.001$</td>
<td>$p&lt;.001$</td>
</tr>
<tr>
<td>Education, M±SD</td>
<td>11.68 ±</td>
<td>11.24 ±</td>
<td>11.46 ±</td>
<td>11.60 ±</td>
<td>$t(129)=.97, p=.34$</td>
<td>$t(66)=-.59, p=.56$</td>
<td>$t(58)=-.37, p=.71$</td>
<td>$t(56)=-.96, p=.35$</td>
</tr>
<tr>
<td></td>
<td>1.32 ±</td>
<td>1.46 ±</td>
<td>1.56 ±</td>
<td>1.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQ, M±SD</td>
<td>110.00 ±</td>
<td>100.88 ±</td>
<td>102.09 ±</td>
<td>106.24 ±</td>
<td>$t(129)=3.61, p&lt;.001$</td>
<td>$t(66)=-.53, p=.60$</td>
<td>$t(40.59)=-1.34,$</td>
<td>$t(41.33)=-1.71,$</td>
</tr>
<tr>
<td></td>
<td>9.50</td>
<td>9.49</td>
<td>9.45</td>
<td>13.35</td>
<td></td>
<td></td>
<td>$p=.16$</td>
<td>$p=.08$</td>
</tr>
<tr>
<td>BPRS Sum, M±SD</td>
<td>42.12 ±</td>
<td>44.29 ±</td>
<td>48.72 ±</td>
<td></td>
<td>$t(66)=-1.23, p=.22$</td>
<td>$t(58)=-2.02, p=.048$</td>
<td>$t(56)=-3.04, p=.004$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.03</td>
<td>7.47</td>
<td>9.49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ, M±SD</td>
<td>276.82 ±</td>
<td>367.54 ±</td>
<td>618.88 ±</td>
<td></td>
<td>$t(42)=-.97, p=.34$</td>
<td>$t(56)=-1.98, p=.05$</td>
<td>$t(34)=-2.08, p=.045$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>226.77</td>
<td>362.61</td>
<td>521.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAF, M±SD</td>
<td>48.36 ±</td>
<td>50.71 ±</td>
<td>42.00 ±</td>
<td></td>
<td>$t(65)=-1.17, p=.25$</td>
<td>$t(58)=3.68, p=.001$</td>
<td>$t(56)=2.60, p=.01$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.41</td>
<td>7.96</td>
<td>10.21</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Note. M±SD: means ± standard deviation for age, years of school education, IQ per German standard test, MWT-B; Lehrl, 2005, BPRS, Brief Psychiatric Rating Scale, CPZ, chlorpromazine equivalent (for medicated patients: n = 11 ARP, n = 33 ES and all CS) and GAF, Global Assessment of Functioning. HC, healthy control subjects. ARP, at-risk psychosis individuals. ES, early-stage schizophrenia patients. CS, chronic schizophrenia patients. PAT, patient samples (including ARP, ES and CS). Level of significance was set at $p \leq .05$. If homogeneity of variance was not given, adjusted t-statistics were reported.
Table 2. Risk categories and comorbid diagnoses of ARP sample.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Number of ARP individuals (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) APS</td>
<td>n = 22</td>
</tr>
<tr>
<td>b) BLIPS</td>
<td>n = 8</td>
</tr>
<tr>
<td>c) Genetic disposition &amp; prodromal signs</td>
<td>n = 5</td>
</tr>
<tr>
<td>d) prodromal signs</td>
<td>n = 7</td>
</tr>
<tr>
<td>Combination of categories a-c</td>
<td>n = 8</td>
</tr>
</tbody>
</table>

Comorbid diagnoses (ICD-10)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affective disorders (F30, F31, F32, F33)</td>
<td>n = 25</td>
</tr>
<tr>
<td>Psychoactive substance abuse (F10, F12, F19)</td>
<td>n = 7</td>
</tr>
<tr>
<td>Anxiety or stress-related disorders (F40, F41, F42, F43)</td>
<td>n = 7</td>
</tr>
<tr>
<td>No comorbid disorders</td>
<td>n = 3</td>
</tr>
<tr>
<td>1 comorbid disorder</td>
<td>n = 21</td>
</tr>
<tr>
<td>&gt; 1 comorbid diagnoses</td>
<td>n = 9</td>
</tr>
</tbody>
</table>

Note. ARP, at-risk psychosis. APS, attenuated psychotic symptoms. BLIPS, brief intermittent psychotic symptoms. ICD-10, international classification of diseases 10th revision.

Design and procedure

The study was reviewed and approved by the Institutional Review Board of the local university. Participants provided written informed consent prior to the assessments and received 20 Euros upon completion of the MMN task, and an additional 10 Euros after completion of the cognitive test battery.

Electrocortical data acquisition and analysis

The auditory oddball design was adapted from Jordanov and colleagues (2011). Across the pseudorandom sequence of 2200 stimuli, 1800 standard tones (500 Hz, 20 ms) varied with 200 stimuli that deviated from standards by dura-
tion (500 Hz, 60 ms) and 200 frequency deviant stimuli (550 Hz, 20 ms). A minimum of three and a maximum of six standards separated two deviants. Auditory stimuli were presented binaurally via earphones with an interstimulus interval of 270 ± 15 ms (providing short measurement sessions of about 10 minutes), and were presented at 50 dB above each subject’s individual hearing threshold (determined prior to the assessment). Participants were instructed to passively listen, and to keep their eyes open and fixated on a point (about 1 m distance in front of the subjects) throughout stimulation.

The EEG was recorded with a high-density EGI 256 channels system and a HydroCel Geodesic Sensor Net with a Net Amps 200 amplifier and the software NetStation 4.3 (Electrical Geodesics, Inc., Eugene, Oregon, USA). EEG was recorded continuously with a sampling rate of 1000 Hz and 0.1 Hz high-pass and 400 Hz low-pass hardware filters. Reference was the vertex electrode (Cz). Impedances for most sensors were kept below 30 kΩ (Cz < 10 kΩ) according to EGI guidelines and high input impedances of the system.

Data preprocessing and analyses used Matlab software (The MathWorks, Inc., Natick, Massachusetts) with the open source toolbox FieldTrip (Oostenveld et al., 2011). Continuous data were filtered with a 30-Hz low-pass, hamming-windowed sinc FIR filter (-6 dB, transition width 7.5 Hz, order 440) with a maximum passband deviation of 0.22% and a stopband attenuation of -53dB. Epochs of 600 ms including 200 ms pre-stimulus and 400 ms post-stimulus were selected for further analysis of all stimuli, standard tones, frequency and duration deviants. The selected time window was longer than the time window of interest (-100 ms to 250 ms, see below) to avoid a possible confound with edge artifacts.
Data were downsampled to 100 Hz for further analyses. Channels with impedances exceeding 100 kΩ were automatically rejected. In addition, trials and channels that showed artifacts and noise contamination were excluded upon visual inspection. Missing channels were interpolated by averaging their neighbors, using a distance of 3 cm. The smallest number of remaining trials across all participants was determined for standard tones and deviant conditions separately. Subsequently, the first 136 artifact-free responses to duration and frequency deviants and the first 1234 artifact-free responses to standards were selected for each participant. Stimulus-related responses were baseline corrected for a 100-ms pre-stimulus interval.

For statistical analyses, data were subject to a two-sided cluster-based, dependent-sample *t*-test with 1000 Monte Carlo randomizations (Maris & Oostenveld, 2007), which identifies sensor clusters of significant differences within an a priori time window. Across participants, channels that significantly distinguished standard and deviant tones during a time window of 100-250 ms after stimulus onset (selected for MMN analysis) were selected for group comparisons. A cluster (with $p \leq .05$) was defined as a set of adjacent sensors at less than 3 cm distance with 5.4 neighbors per channel on average, which showed significant differences between standards and deviants in *t*-values and magnitude. The resulting clusters included 97 channels for duration deviants and 98 channels for frequency deviants in a fronto-central area (Figure 2 shows averaged waveforms based on these channels).

MMN difference waveforms were determined separately for each participant by subtracting the response to standards from the response to frequency
and duration deviants. MMN peak latencies were established as the most negative deflection in the difference waveform 150-250 ms after stimulus onset. MMN amplitudes were then defined (following Näätänen et al., 2004) as the mean voltage at a 40-ms time window around these group-specific peak latencies. With the aim to control for outliers, winsorizing replaced values lower than 5% or higher than 95% across the range of all data by the min/max values at the respective threshold.

Signal-to-noise ratio (SNR) was computed according to Hu et al. (2010) as the MMN amplitude divided by the standard deviation of the baseline activity (100 ms pre-stimulus). A mean SNR of $M = 4.20 \pm 3.48$ ($SD$) was obtained for dMMN (ARP: $5.14 \pm 4.21$; ES: $3.40 \pm 2.88$; CS: $3.60 \pm 2.84$; HC: $4.53 \pm 3.56$) and of $M = 3.74 \pm 3.23$. for fMMN (ARP: $4.96 \pm 4.36$; ES: $2.70 \pm 2.11$; CS: $2.63 \pm 2.44$; HC: $4.38 \pm 2.94$). Groups differed in their SNRs for fMMN ($F(3,127) = 4.62$, $p = .004$), while dMMN SNR’s were similar across groups ($F(3,127) = 1.85$, $p = .14$). For all groups, the signal was at least more than twice as large as the respective noise.

---

2 This time window served to control for possible confound by N100 differences between conditions (Duncan et al., 2009)
MMN and cognitive performance in the course of schizophrenia

Fig. 2. (A) Mean event-related potentials (ERPs) of standard tones (green), frequency (red) and duration deviants (blue) per group. (B) Time course of ERP difference waveforms (dMMN, duration deviants, left and fMMN, frequency deviants, right). Mismatch Negativity (MMN) is represented by the post-stimulus negative deflection between 150 – 250 ms. HC, healthy controls (black). ARP, at-risk psychosis (green). ES, early-stage schizophrenia (blue). CS, chronic schizophrenia patients (red). M, mean. SE, standard error.

Cognitive performance assessment and analysis

Cognitive performance was assessed using the German version of the MA-TRICS Consensus Cognitive Battery (MCCB, Nuechterlein & Green, 2006), which has been designed for clinical trials in schizophrenia research (Green et al., 2004). The MCCB consists of seven cognitive domains, which distinguish schizophrenia patients from healthy individuals, including speed of processing,
attention, working memory, verbal learning, visual learning, reasoning/problem solving and social cognition.

Raw scores of the MCCB were converted into T-scores (normalized on a healthy USA representative community sample and corrected for age and gender) using the computer-based algorithm. An additional overall composite (OC) T-score integrates the domains to represent general performance.

**Statistical evaluation**

Differences of MMN and cognitive performance between groups were evaluated in separate repeated-measures ANOVAs, each including the between-subject factor Group (comparing ARP, ES, CS, and HC). MMN analyses included the within-subject factor Type (comparing duration-deviant dMMN, and frequency-deviant fMMN), and the analysis of cognitive test performance included the within-subject factor Domain (comparing the seven MCCB domains). The level of significance was set at \( p \leq .05 \). Normal distribution was examined with the Kolmogorov-Smirnov test. Since not all residuals of the computed models were normally distributed, data were bootstrapped to reduce bias. Significant main effects (of Group, Type or Domain, respectively) were verified by simple ANOVAs, and orthogonal planned contrasts tested specific group differences per hypotheses (1) and (2).

Changes in symptom severity (BPRS sum score) over time in ARP and ES as a function of MMN and cognitive performance at index assessment were examined (1) by a repeated measures ANOVA with the between-subject factor Group (comparing ARP and ES) and the within-subject factor Time (comparing
index assessment and 6-months follow-up), and (2) by multiple regression analysis regressing MMN and cognitive performance scores on BPRS symptom scores. Because of high collinearity between variables, only dMMN and the MCCB overall composite score (OC) were selected as predictors.

2.3. Results

MMN

Figure 2 illustrates group-averaged time courses of ERPs to standards, duration deviants, frequency deviants (A), and of the difference ERP waveforms dMMN and fMMN (B). A significant main effect of Group confirmed smaller dMMN and fMMN in CS and ES than in ARP and HC, \( p < .001 \) (see Table 3). Planned contrasts (Table 3) verified smaller MMN amplitudes in the three clinical samples (ARP, ES, and CS) than in HC for both dMMN and fMMN. The second contrast confirmed larger dMMN and fMMN in ARP than in ES and CS, while the third contrast confirmed similarly reduced MMN in ES and CS in contrast to ARP, who displayed similar MMN as HC.

Cognitive test performance

ARP, ES, and CS performed poorer than HC on all cognitive domains, except working memory (Group x Domain interaction, and main effects Group and Domain, \( p < .001 \); see Table 3 and Figure 3). Planned contrasts verified poorer test performance in ARP than in HC, and no differences between ARP, ES and CS on all domains, except visual learning (Table 3).
Table 3. ANOVA main effects and interactions and planned contrasts for dependent variables Mismatch Negativity (MMN) and performance on the MATRICS Consensus Cognitive Battery (MCCB).

<table>
<thead>
<tr>
<th></th>
<th>ANOVA</th>
<th>Planned contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1. HC vs. PAT</td>
</tr>
<tr>
<td>MMN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>$F(3,127)=8.91, p&lt;.001$</td>
<td>$t(127)=-2.39, p=.01, d=.49$</td>
</tr>
<tr>
<td>Type</td>
<td>$F(1,127)=1.93, p=.17$</td>
<td></td>
</tr>
<tr>
<td>Group x Type</td>
<td>$F(3,127)=.49, p=.69$</td>
<td></td>
</tr>
<tr>
<td>dMMN</td>
<td>$F(3,127)=6.28, p=.001$</td>
<td>$t(127)=2.39, p=.01, d=.49$</td>
</tr>
<tr>
<td>fMMN</td>
<td>$F(3,127)=6.93, p&lt;.001$</td>
<td>$t(127)=-1.75, p=.048, d=.34$</td>
</tr>
<tr>
<td>MCCB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>$F(3,126)=8.26, p&lt;.001$</td>
<td>$t(126)=5.70, p=.001, d=1.10$</td>
</tr>
<tr>
<td>Domain</td>
<td>$F(6.06,764.07)=31.52, p&lt;.001$</td>
<td>$t(126)=2.53, p=.02, d=.49$</td>
</tr>
<tr>
<td>Group x Domain</td>
<td>$F(18.19,764.07)=8.91, p=.004$</td>
<td>$t(126)=2.19, p=.09$</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>$F(3,126)=11.13, p&lt;.001$</td>
<td>$t(126)=2.70, p=.01, d=.52$</td>
</tr>
<tr>
<td>Attention</td>
<td>$F(3,126)=2.93, p=.04$</td>
<td>$t(126)=2.53, p=.02, d=.49$</td>
</tr>
<tr>
<td>Working memory</td>
<td>$F(3,126)=2.19, p=.09$</td>
<td>$t(126)=2.19, p=.09$</td>
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<tr>
<td>Verbal learning</td>
<td>$F(3,126)=2.83, p=.04$</td>
<td>$t(126)=2.70, p=.01, d=.52$</td>
</tr>
<tr>
<td>Visual learning</td>
<td>$F(3.83,85)=4.28, p=.004$</td>
<td>$t(79.46)=2.46, p=.02, d=.47$</td>
</tr>
<tr>
<td>Reasoning</td>
<td>$F(3,62.93)=5.66, p=.007$</td>
<td>$t(98.14)=4.02, p=.001, d=.77$</td>
</tr>
<tr>
<td>Social cognition</td>
<td>$F(3,126)=5.27, p=.002$</td>
<td>$t(126)=3.67, p=.001, d=.71$</td>
</tr>
<tr>
<td>Overall composite score</td>
<td>$F(3,126)=8.39, p&lt;.001$</td>
<td>$t(126)=4.67, p=.001, d=.90$</td>
</tr>
</tbody>
</table>

**Note.** ANOVA, Analysis of Variance. HC, healthy control subjects. PAT, patient samples (including ARP, ES, and CS). ARP, at-risk psychosis individuals. SZ, schizophrenia patients (including ES, and CS). ES, early-stage schizophrenia patients. CS, chronic schizophrenia patients. dMMN, Mismatch Negativity with duration deviants. fMMN, Mismatch Negativity with frequency deviants. Fw, Welch’s F. d, effect size Cohen’s d. Bootstrapped p-values were used for t-tests. If sphericity was violated, Huynh-Feldt correction was applied.
Fig. 3. Cognitive test performance in the MATRICS Consensus Cognitive Battery (MCCB) across all seven domains and the overall composite score. Means and standard errors of normed T-scores are displayed for healthy controls (HC), individuals at risk for psychosis (ARP), early-stage schizophrenia patients (ES) and chronic schizophrenia patients (CS).

Relationships between MMN, cognitive performance, and symptom severity

Symptom severity (BPRS sum score) did not change in ARP and ES from index assessment to 6 months follow-up (Time: \( F(1,38) = 2.07, p = .16 \)), and did not differ between groups (Group: \( F(1,38) = 1.11, p = .30 \); Group x Time: \( F(1,38) = 9.5, p = .34 \)). In contrast, GAF improved in both groups (Time: \( F(1,38) = 33.07, p < .001 \); Group: \( F(1,38) = .38, p = .54 \); Group x Time: \( F(1,38) = .13, p = .72 \)). Medication (per CPZ) did not differ between the \( n = 9 \) ARP and \( n = 16 \) ES, who received neuroleptics, and medication regimen did not change from index assessment to follow-up (Group: \( F(1,20) = .10, p = .76 \); Time: \( F < .001, p = .99 \); Group x Time: \( F(1,20) = .81, p = .38 \)).
Participants in the follow-up assessment did not differ from those individuals who dropped out, regarding age, education, IQ, CPZ values, symptom scores, global functioning, cognition or MMN amplitudes at index assessment. However, MMN at index assessment was smaller in those \( n = 12 \) ARP, who did not participate in the follow-up assessment, when compared to those \( (n = 21) \) who did: \( dMMN \ (t(31) = 2.20, p = .04) \) and \( fMMN \ (t(31) = 2.61, p = .01) \).

Multiple regression analysis indicated that (lower) overall cognitive performance (OC) varied with (higher) symptom severity (BPRS score) at first assessment and predicted symptom severity at follow-up (Table 4). Although \( dMMN \) did not vary with symptom severity, both measures together explained 15% of symptom variance at follow-up.

\textit{Table 4}. Regression analyses with MMN and cognitive performance regressed to BPRS symptom scores.

<table>
<thead>
<tr>
<th></th>
<th>( R^2 )</th>
<th>( F )-statistic</th>
<th>( \beta )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{BPRS sum 1st assessment} &amp; &amp; &amp; &amp;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( dMMN ) and OC</td>
<td>.12</td>
<td>( F(2,66)=4.62 )</td>
<td>.12</td>
<td>.01</td>
</tr>
<tr>
<td>( dMMN )</td>
<td></td>
<td></td>
<td>.17</td>
<td>.14</td>
</tr>
<tr>
<td>( OC )</td>
<td></td>
<td></td>
<td>-.31</td>
<td>.01</td>
</tr>
<tr>
<td>\textit{BPRS sum follow-up} &amp; &amp; &amp; &amp;</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>( dMMN ) and OC</td>
<td>.15</td>
<td>( F(2,38)=3.35 )</td>
<td>.15</td>
<td>.046</td>
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<tr>
<td>( dMMN )</td>
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<td></td>
<td>.13</td>
<td>.39</td>
</tr>
<tr>
<td>( OC )</td>
<td></td>
<td></td>
<td>-.35</td>
<td>.03</td>
</tr>
</tbody>
</table>

\textit{Note}. MMN, Mismatch Negativity. \( dMMN \), MMN to duration deviants. MCCB, MATRICS Consensus Cognitive Battery. BPRS, Brief Psychiatric Rating Scale. OC, overall composite score of cognitive performance.
2.4. Discussion

Many studies have shown reduced MMN and poor cognitive performance in schizophrenia patients at different stages of illness, advocating these measures as risk markers for symptom emergence and their progression. The present study examined this role for both MMN and cognitive functioning by comparing individuals at risk for psychosis and with manifest schizophrenia at early or chronic illness stage. Whereas MMN distinguished schizophrenia patients from at-risk individuals, who did not differ from healthy comparison participants, cognitive deficits were evident in all three clinical groups.

MMN and cognitive deficits as risk markers

Hypothesis (1) was partly confirmed, in that cognitive performance, but not MMN distinguished the three clinical groups (ARP, ES, and CS) from HC. In contrast to previous findings (e.g. Bodatsch et al., 2015), MMN was not reduced in the at-risk group, when compared to HC, while it was smaller in the two schizophrenia patient samples when compared to the other two groups. This result may in part be explained by the present ARP sample. An at-risk diagnosis is confirmed when individuals convert to psychosis within 12-24 months, which is expected for about one third of ARP individuals (Fusar-Poli et al., 2012a). Considering reports of marked grey matter loss in ultra-high risk or high-risk individuals, who later showed transition to psychosis (Dietsche et al., 2017), and considering the relationship between structural changes and ERP amplitude changes (Salisbury et al., 2007), it may be assumed that reduced MMN was evi-
dent only in the subsample of later converters. Yet, the present 6-months follow-up period was not long enough to witness potential transition, and then compare MMN between psychosis converters and non-converters.

Furthermore, even larger MMN amplitudes (relative to controls) have been reported in individuals converting to manifest psychosis, as a potential consequence of hyperexcitability (e.g. Atkinson et al., 2017; Rivolta et al., 2014) and an excitation-inhibition imbalance early in the course of schizophrenia (Krystal et al., 2017). The present at-risk individuals were characterized by a number of comorbid diagnoses with non-specific symptoms in addition to specific prodromal indices. Given that accentuated MMN amplitudes have also been reported in traumatized or depressive patients (Ge et al., 2011; He et al., 2010), it is possible that the inconspicuous MMN of the present ARP sample reflects an average of reduced (in converters), ‘normal’ or even elevated MMN, which limits firm conclusions on the role of MMN as risk marker.

Cognitive performance distinguished the three clinical groups, at-risk individuals and schizophrenia patients, from HC. Being among the top measures distinguishing schizophrenia patients from healthy population (Heinrichs, 2005), cognitive deficits are thought to represent core symptoms of schizophrenia. Present results are in line with previous reports of cognitive deficits in chronic, early, and prodromal states and in ultra-high-risk individuals (e.g. August et al., 2013; Bora & Murray, 2014; Carolus et al., 2014; Carolus, Popova, & Rockstroh, 2015; Seidman et al., 2016). As cognitive performance did not differ between the clinical groups, it may be concluded that cognitive dysfunction reflects basic, early present psychopathology, thereby qualifying as risk marker.
Poor cognitive performance in present ARP may indicate the non-specific nature of cognitive deficits, which have been found in prodromal states of psychosis as well as in other psychiatric disorders (including those comorbid disorders noticed in the present ARP sample). Thus, cognitive deficits might be described as marker of illness vulnerability rather than as specific risk marker of psychotic development.

**MMN and cognitive deficits as markers of illness stage**

As proposed by hypothesis (2), MMN amplitude and cognitive test performance were expected to scale with severity and progression of illness, with MMN amplitudes being smaller and cognitive deficits larger in CS than in ES and in ARP individuals. Disconfirming this hypothesis, MMN did not differ between early and chronic schizophrenia patients, which matches some previous reports (e.g. Hay et al., 2015; Solís-Vivanco et al., 2014). Also divergent from previous evidence (e.g. Koshiyama et al., 2017, 2018; Nagai et al., 2013b, 2017), dMMN was not superior to fMMN in distinguishing early and chronic schizophrenia and in identifying early pathology.

It is conceivable that the present distinction of illness progression by number of inpatient treatments did not sufficiently reflect stages of illness or illness progression. Indeed, neither psychotic symptom severity nor medication regimen differed between ES and CS at first assessment. This suggests that the present samples might not sufficiently distinguish stages of illness for hypothesis testing.
Moreover, cross-sectional comparison of subsamples characterized by number of inpatient treatment may produce weaker, more variable results than longitudinal assessment of illness course. Additional understanding was therefore expected from re-assessing ARP’s and ES’s symptom severity 6 months after the index assessment and hospital discharge.

**Prediction of illness progression**

Hypothesis (3), proposing that MMN and cognitive measures in ARP and ES predict illness progression, was partly supported. Although cognitive performance and MMN at index assessment predicted symptom severity at follow-up, explained variance was weak (15%), and significant contribution was constraint to cognitive performance. Several factors may have influenced this result. Symptom severity did not substantially increase from index assessment to follow-up and significant associations between cognition and symptoms were already evident for index assessments. Thus, all participants showed improvement with inpatient treatment, and remained stable throughout the follow-up period. A 6-month follow-up may have been too short to evaluate illness progression. Moreover, follow-up samples may have been selective, as MMN was smaller in those ARP and ES not participating in the follow-up than in participants who were available for both assessments. Hence, follow-up participants may have been better than those, who dropped out, thereby weakening statistical prediction (a similar difference between patients available or unavailable for follow-up has been reported for cognitive performance at index assessment by Carolus et al., 2015).
Limitations

Further limitations have to be noted: (1) Though established prodromal indices were the main diagnostic criteria, at-risk individuals presented various non-specific symptoms and impairments that were severe enough to qualify for comorbid diagnoses. This dominance of non-specific symptoms and the heterogeneity of the ARP sample limit any conclusion on the validity of present markers as “schizophrenia risk marker”. Since the majority of previous studies (e.g. Koshiyama et al., 2017; Nagai et al., 2013b) included individuals labeled as “ultra-high risk” the present lack of MMN reduction in ARP individuals may also stem from distinct sample definitions.

(2) Given that only a fraction of individuals diagnosed as at risk will develop manifest schizophrenia within 12 months, large samples of at-risk individuals and longitudinal designs with sufficient follow-up periods are important for the evaluation of risk markers. For an expected effect size of .99 distinguishing MMN waveforms between schizophrenia patients and healthy subjects (Umbricht & Krljes, 2005), a sample size of at least 18 subjects per group is required (based on G*power estimates for sufficient power of .80 (two-tailed t-test with $\alpha = .05$; G*power 3.1; Faul et al., 2007). This requirement was met by the present sample sizes of $n = 38$ healthy controls, $n = 35$ early stage, and $n = 25$ chronic stage patients. Still, aiming for MMN difference between at-risk individuals and healthy controls with a moderate effect size of .40 (Erickson et al., 2016) had required a sample size of 100 individuals per group for a minimum power of .80. Not meeting this requirement for the present ARP sample size and for the fol-
low-up assessments limits firm conclusions from the present results. Based on BSIP, 14% transition rate is expected during a 6-month follow-up (Riecher-Rössler et al., 2009; in general 36% transitions are to be expected within three years, Fusar-Poli et al., 2012a). Hence, only two of the 21 ARP who participated in the follow-up assessment had converted to psychosis (according to BSIP transition criteria) and subsequent statistical comparisons were not feasible. Yet, the low retention rate of about 60% implies a high chance of missing out possible converters. This would explain why at-risk individuals who dropped out at follow-up showed significantly reduced MMN amplitudes in comparison to reassessed individuals.

(3) An impact of antipsychotic medication on cognitive deficits and MMN is unclear (Horton et al., 2011 vs. Bora & Murray, 2014; Umbricht & Krljes, 2005). In particular, the use of antipsychotics in at-risk or prodromal individuals has been questioned (Corcoran et al., 2005; Ruhrmann et al., 2005) and is not recommended (Riecher-Rössler et al., 2006). Yet, 30% of the present ARP sample received antipsychotics. Though the percentage of antipsychotic naïve individuals was significantly higher in ARP than in ES, whereas cognitive deficits did not differ, an influence of antipsychotic medication on present results cannot be ruled out.

(4) Overall MMN in the present study was small, which may have affected, but not eliminated, group differences. The present study implemented the auditory oddball task established for MMN analysis by Jordanov et al. (2011), which includes interstimulus intervals of $270 \pm 15$ ms and stimulus-onset asynchrony (SOA) of $290 \pm 15$ ms or $330 \pm 15$ ms for duration deviants respectively.
The small SOA aimed at increasing the number of trials without extending the task duration beyond the limit acceptable by psychiatric patients. Yet, short SOAs around 300 ms have been reported to reduce MMN amplitudes (Baldeweg et al., 2004; Näätänen et al., 2004) and Baldeweg et al. (2004) emphasize that schizophrenia patients may not display the expected negative MMN deflection at frontal electrodes but even positive deflections (at Fz- and Cz-electrodes) in the MMN time window while using relatively short SOA. This is in line with 17.6% participants exhibiting positive dMMN, and 14.5% positive fMMN in the present study. Another potential explanation of small MMN amplitudes in designs with short SOA may be an overlap with later potentials, such as P300 during the baseline period. However, averaging the signal across a minimum of 3 to 6 standard tones prior to every deviant should reduce contamination of the elicited activity by preceding deviants (see also Baldeweg & Hirsch, 2015). Yet, we cannot completely exclude a potential confounding by the preceding P300 activity on the present MMN waveforms.

**Conclusion**

Cognitive deficits and MMN have been discussed as risk markers for schizophrenia. Present results suggest both measures as indices of psychopathology, while cognitive deficits rather reflect non-specific general psychopathology and MMN seems to be specifically impaired in schizophrenia patients. Present measures do not mark illness progression as indexed by different stages of schizophrenia and symptomatology examined here. Cognitive deficits have been confirmed as risk marker, as they already predict the emergence of psycho-
sis from performance in childhood (Jones & Done, 1997). Yet, the present study
could not confirm the validity of MMN as risk marker by predicting the transi-
tion to psychosis, hence, further longitudinal studies will be required.
Chapter 3

Study (2): Decoding the impact of adverse childhood experiences on the progression of schizophrenia

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Decoding the impact of ACE on the progression of schizophrenia

Abstract

Adverse childhood experiences are frequently present in patients with mental disorders, including those with schizophrenia. Whereas an impact of childhood adversities on psychopathology and potential neuroendocrine/biological mediators has been reported for posttraumatic stress disorder, depression, and anxiety disorders, the relationships in schizophrenia remain to be clarified. The present study compared amount and types of adverse childhood experiences (screened by interview) between individuals at risk for psychosis ($n = 29$), early schizophrenia patients with 1-2 admissions ($n = 34$), chronic schizophrenia patients with multiple admissions ($n = 24$), and healthy comparison participants ($n = 38$). It was expected that at-risk individuals and early-stage as well as chronic patients report more childhood adversities than controls, and that adversity load predicts psychotic symptom severity and altered neuroendocrine regulation based on hair cortisol concentration. Results confirmed more childhood adversities in clinical groups than in controls, and relationships between total childhood adversities and increased positive symptom severity. Hair cortisol concentration did not differ between groups, but early abuse experiences predicted lower hair cortisol concentration, and the latter predicted severity of specific psychotic symptoms in the clinical sample. In conclusion, individuals at risk and with manifest schizophrenia experienced substantial childhood maltreatment, as reported for other diagnoses. The present findings suggest childhood adversities as sensitizing (environmental) factor in vulnerable individuals. Lower hair cortisol concentration may indicate lasting effects of past stress experiences on stress axis function in schizophrenia, which might modulate unfolding psychopathology.
3.1. Introduction

Numerous studies confirmed the impact of adverse childhood experiences (ACE) on mental health and the development of psychiatric disorders (Carr et al., 2013; Jaffee, 2017; Kerker et al., 2015; Pirkola et al., 2005; Tailieu et al., 2016), and established relationships between ACE and symptom severity or unfavorable illness courses (Nanni, Uher, & Danese, 2012; Schalinski, Fischer, & Rockstroh, 2015; Teicher & Samson, 2013). Whereas the majority of reports targeted depression and anxiety disorders (including posttraumatic stress disorder), recent studies also confirmed high prevalence of ACE in schizophrenia patients (e.g. Bonoldi et al., 2013; Pietrek et al., 2013; Read et al., 2014; Schalinski et al., 2017). Further findings suggest relationships between ACE and elevated general psychopathology, positive symptoms, or cognitive deficits (see Duhig et al., 2015; Longden, Sampson, & Read, 2016; Schalinski et al., 2015a, 2018; van Nierop et al., 2015). Moreover, ACE were found to predict lower functioning in individuals at risk for psychosis and/or individuals expressing attenuated psychotic symptoms (Addington et al., 2013; Boyda & McFeeters, 2015; Kraan et al., 2015; Yung et al., 2015). Additionally, more ACE varied with increased psychotic symptoms in a general population sample (Janssen et al., 2004) or genetically high-risk individuals (Heins et al., 2011; see also reviews and meta-analysis by Mayo et al., 2017; Redman et al., 2017; Varese et al., 2012). In sum, these findings suggest an impact of ACE on psychotic development in (genetically) vulnerable individuals.

In addition to the overall amount of ACE, specific types of ACE (such as emotional, physical, or sexual abuse or neglect) have been studied to decode the
meaning of childhood experiences in psychotic symptom generation. Yet, results are diverse and inconclusive (Bailey et al., 2018). Several studies reported a particular impact of childhood abuse on the severity of positive symptoms, like hallucinations or delusions, but not negative symptoms in schizophrenia patients and vulnerable individuals (Braehler et al., 2013; Heins et al., 2011; Rajkumar, 2015; Read et al., 2003; Schenkel et al., 2005; Thompson et al., 2009). Other studies found an impact of both childhood abuse and neglect on positive symptoms (Abajobir et al., 2017; Schalinski et al., 2017; Üçok & Bıkmaz, 2007), on both positive and negative symptoms (Longden et al., 2016), and again others verified a specific relationship between physical neglect and negative symptoms (Vogel et al., 2011). Different relationships between childhood experiences and symptom severity in adult patients may in part result from factors potentially moderating ACE effects during the time between experience and symptom assessment, for instance, recent life events, personality traits (Pos et al., 2016) or cognitive functioning (Berthelot et al., 2015; see also review Jaffee, 2017).

ACE exert their effects on psychological function and dysfunction through their impact on the development of brain and neuroendocrine systems that are relevant for learning, memory and coping with stress (Andersen & Teicher, 2008; Pruessner et al., 2017; Walker, Mittal, & Tessner, 2008). Moreover, ACE-related long-term alteration of the stress response system is discussed as factor moderating the risk for psychiatric disorders (Read et al., 2014; Rietschel et al., 2016; White et al., 2017). Animal and human research indicate lasting effects of chronic stress and trauma on the hypothalamus-pituitary-adrenal (HPA) axis (Baumeister, Lightman, & Pariante, 2014; Curley & Champagne, 2016; McCrory,
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de Brito, & Viding, 2010; White et al., 2017), indexed by blunted (salivary) awakening cortisol, elevated basal cortisol concentrations, attenuated stress evoked cortisol responses, and elevated hair cortisol concentration (HCC; Andrade et al., 2016; Brenner et al., 2009; Girshkin et al., 2014; Mondelli et al., 2010). Such indices of altered HPA axis function have been reported in chronic schizophrenia patients, first-episode schizophrenia patients, and individuals at risk for psychosis (e.g. Belvederi Murri et al., 2012; Mondelli et al., 2010; Pruessner et al., 2013, 2017; Walker et al., 2008), whereas evidence on their association with psychotic symptoms is inconsistent (Karanikas et al., 2015). For hair cortisol concentration as index of long-term accumulated cortisol levels, relationships of high ACE and elevated hair cortisol levels were reported in women with stress-related disorders (Schalinski et al., 2015b) and postpartum in mothers with the minor allele of the FKBP5 genotype (Koenig et al., 2018). Other studies reported lower hair cortisol concentration upon exposure to ACE in children/adolescents (White et al., 2017), in students (Kalmakis et al., 2015) or depressed patients (Hinkelmann et al., 2013). Recently, Steudte-Schmiedgen et al. (2016) suggested an initial increase of hair cortisol concentration upon traumatic experiences and a subsequent long-term attenuation. Regarding the meaning of hair cortisol concentration in clinical disorders, results differ depending on diagnoses and the relationship with symptoms. For instance, augmented hair cortisol concentration in first-episode patients (relative to healthy controls) was reported together with a relationship between general symptoms and hair segment changes over time (Andrade et al., 2016). In contrast, Streit et al. (2016) found elevated hair cortisol levels only in bipolar but not in schizophrenia patients,
although hair cortisol concentration was related to manic symptoms in both groups\(^3\). Moreover, the relationship between ACE, hair cortisol concentration, and psychopathology remains to be clarified. It might be assumed that a higher ACE load affects HPA axis regulation, and that it is reflected by altered hair cortisol concentration.

The present study aimed at clarifying the impact of amount and type of ACE on presence and severity of psychotic symptoms and hair cortisol concentration by comparing individuals with subclinical and manifest schizophrenia symptoms. Three samples characterized by the severity of psychotic psychopathology were recruited: individuals defined as “at risk”\(^4\) (AR) on the basis of prodromal psychotic symptoms, patients admitted for 1st or 2nd treatment for schizophrenia spectrum disorder (ICD-10 diagnoses F2) characterized as “early stage” (ES), and chronic schizophrenia patients (CS) with at least 5 inpatient admissions. These clinical groups were compared to a sample of healthy comparison participants (HC) recruited from the community. We investigated the prevalence of ACE and relationships between ACE and hair cortisol concentrations as an index of long-term stress effects on HPA axis regulation (Russell et al., 2012; Stalder et al., 2017). In the clinical samples, we additionally examined the relationship between ACE, hair cortisol concentration and symptom severity. Investigations were based on the following hypotheses:

(1) The amount of ACE is higher in at-risk individuals and patients with manifest schizophrenia than in HC. As previous research did not indicate clear

\(^3\) These studies did not evaluate ACE.

\(^4\) The meaning of ‘at risk for psychosis’ varies with criteria/definition of risk, such as genetic risk (with ultra-high risk, UHR, defining individuals with affected first-degree relatives) or presence of subclinical, attenuated symptoms. The latter definition informed the present at-risk sample.
differences in ACE between at-risk individuals, first-episode, and chronic patients, and was inconclusive regarding the type of experience, no specific hypotheses for group and/or type differences were formulated.

(2) The amount of ACE varies with symptom severity (measured by Brief Psychiatric Rating Scale, BPRS sum score). In view of inconclusive evidence on the relationship between types of ACE and positive and negative symptoms, no specific hypotheses were formulated.

(3) ACE modulates hair cortisol concentration in psychotic patients and this varies with psychotic symptom severity. In view of diverse findings on reduced, normal or increased hair cortisol concentration in patients compared to controls, no hypothesis on the direction of association between the three measures ACE, hair cortisol concentration, and symptom severity was phrased.

3.2. Methods

Participants

In total, \( N = 101 \) participants were recruited at the outpatient clinic and wards specialized for the treatment of psychoses of the local Center for Psychiatry. Eligible persons (see Figure 1 for an overview of recruitment and sample sizes per stage of assessments and Table 1 for demographic and clinical characteristics of participants) were assigned to three groups, (1) \( n = 29 \) individuals diagnosed as at risk for psychosis (AR) by trained psychologists applying the Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al., 2008). Risk status was fulfilled if (a) attenuated psychotic symptoms (i.e. hallucinations,
suspiciousness, unusual thought content and conceptual disorganization as items of the BPRS) were present at the current moment or within the last 2 weeks, and/or (b) past episodes (< 1 week) of transient distinct psychotic symptoms (brief limited intermittent psychotic symptoms, BLIPS) were reported, and/or (c) genetic disposition combined with prodromal symptoms according to DSM-III-R (e.g. magical thinking, unusual perceptual experiences, peculiar behavior; DSM-III criteria were chosen because prodromal symptoms were no longer included in DSM-IV) and unspecific risk factors (like depression, attention deficits, anxiety), or (d) only prodromal symptoms were present (see Table 1b for risk categories and comorbid psychopathology).

(2) $n = 34$ inpatients with diagnoses of schizophrenia spectrum disorders during their first or second admission were defined as early schizophrenia patients (ES). They were diagnosed by experienced psychiatrists/psychologists meeting diagnoses of paranoid-hallucinatory schizophrenia (ICD-10 code: F20.0, $n = 22$), acute psychotic episodes (F23.1, F23.2, $n = 10$), or delusional disorder (F22.0, $n = 1$). Comorbid diagnoses in ES patients were harmful cannabis use ($n = 10$; F12.1), harmful use of multiple drugs ($n = 2$; F19.1), cannabis dependence syndrome ($n = 1$; F12.2), harmful alcohol use ($n = 1$; F10.1), mixed personality disorder ($n = 1$; F61.0), post-traumatic stress disorder ($n = 1$; F43.1), and disturbance of activity and attention ($n = 1$; F90.0).

(3) $n = 24$ inpatients with a minimum of 5 admissions for schizophrenia spectrum disorders ($M = 11.08$, $SD = 6.93$) were defined as chronic schizophrenia (CS) patients. Patients met ICD diagnoses of F20.0, F20.1 or F20.4 ($n = 21$) or F25.0 or F25.1 ($n = 3$). Comorbid diagnoses in CS patients were harmful alcohol
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use \((n = 4; F10.1)\), harmful use of multiple drugs \((n = 2; F19.1)\), and harmful cannabis use \((n = 1; F12.1)\).

All participants had been admitted to the hospital for acute symptoms but were in a post-acute, stable state at the time of assessment. For early-stage and chronic patients, the time between admission and assessment varied between 2 and 4 weeks. At-risk individuals were assessed within the 1st or 2nd week after admission, as they were most often released within 1-2 weeks. At the time of the assessments, \(n = 10\) (of 29) AR, \(n = 32\) (of 34) ES and all 24 CS patients were medicated with first- or second-generation antipsychotics (see Table 1 for chlorpromazine equivalents). Inpatients were invited to participate in the hospital’s standard rehabilitation program, which includes 2-3/week individual psychotherapy sessions, group cognitive and social skill trainings, work therapy, and physical exercise. Except for individual psychotherapy, attendance was optional with most inpatients attending 1-3 treatment offers. Alcohol consumption is not allowed during inpatient treatment, while smoking is usually intense in medicated schizophrenia patients, as in our samples (see Table 1).

The three clinical groups (AR, ES, CS) did not differ in gender, years of school education nor IQ scores (measured by a German test for premorbid intelligence; Lehrl, 2005), and antipsychotic medication (only comparing medicated individuals). Chronic patients were older, had higher BPRS negative symptom scores and obtained lower functioning levels (GAF) than early-stage patients and at-risk individuals, who did not differ in age, positive BPRS symptom scores, and global functioning (see Table 1).
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\( N = 38 \) healthy controls (HC) were recruited among university students and the local community to be demographically comparable to the at-risk and schizophrenia patient samples. HC were screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) for exclusion of any current or past psychiatric disorder. Patient samples and HC did not differ in gender distribution and years of school education, but HC attained higher IQ scores and were younger than the total clinical sample (see Table 1).

![Flowchart of sample composition](image)

**Fig. 1.** Flowchart of sample composition. HC = healthy controls, AR = at-risk individuals, ES = early-stage schizophrenia patients, CS = chronic schizophrenia patients, BSIP = Basel Screening Instrument for Psychosis, MACE = Maltreatment and Abuse Chronology of Exposure. Samples included in statistical analyses are displayed in grey. \( n = 6 \) individuals dropped out prior to the assessments since they did not provide consent to the interview. \( n = 36 \) individuals dropped out before hair cortisol analyses due to either insufficient hair length \((n = 15)\), lack of consent \((n = 5)\), uncompleted hair sample analyses \((n = 9)\) or exclusion of outliers \((n = 7)\).
<table>
<thead>
<tr>
<th>Table 1. Characteristics of the clinical samples and the healthy control group: demographic data, clinical variables, adverse childhood experiences, hair sample variables, and symptom severity.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Gender (f/m)</td>
</tr>
<tr>
<td>Age, M(SD)</td>
</tr>
<tr>
<td>Education, M(SD)</td>
</tr>
<tr>
<td>IQ, M(SD)</td>
</tr>
<tr>
<td>Cig./day, M(SD)</td>
</tr>
<tr>
<td>GAF, M(SD)</td>
</tr>
<tr>
<td>CPZ, M(SD)</td>
</tr>
<tr>
<td>ACE variables</td>
</tr>
<tr>
<td>MACE total, M(SD)</td>
</tr>
<tr>
<td>Abuse, M(SD)</td>
</tr>
<tr>
<td>Neglect, M(SD)</td>
</tr>
</tbody>
</table>
Continuation of Table 1.

<table>
<thead>
<tr>
<th>Hair sample variables</th>
<th>6.12</th>
<th>6.68</th>
<th>6.63</th>
<th>6.06</th>
<th>$F(3,82)=.18$, $p=.91$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC in pg/mg, $M(SD)$</td>
<td>6.12</td>
<td>6.68</td>
<td>6.63</td>
<td>6.06</td>
<td>$F(3,94)=2.06$, $p=.11$</td>
</tr>
<tr>
<td>Hair washes/week, $M(SD)$</td>
<td>5.40</td>
<td>4.98</td>
<td>4.42</td>
<td>3.91</td>
<td>$\chi^2(3)=2.42$, $p=.49$</td>
</tr>
<tr>
<td>Semi-permanent hair coloration, %</td>
<td>22.6</td>
<td>10.5</td>
<td>26.1</td>
<td>30.8</td>
<td>$\chi^2(3)=2.42$, $p=.49$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>42.10</th>
<th>44.21</th>
<th>48.58</th>
<th>$F(2,83)=3.58$, $p=.03$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS Sum, $M(SD)$</td>
<td>42.10</td>
<td>44.21</td>
<td>48.58</td>
<td>$F(2,83)=3.58$, $p=.03$</td>
</tr>
<tr>
<td>BPRS PS, $M(SD)$</td>
<td>8.71</td>
<td>8.76</td>
<td>9.58</td>
<td>$F(2,83)=.66$, $p=.52$</td>
</tr>
<tr>
<td>BPRS NS, $M(SD)$</td>
<td>7.46</td>
<td>7.59</td>
<td>10.50</td>
<td>$F(2,83)=7.64$, $p=.01$</td>
</tr>
</tbody>
</table>

| Note. $M(SD)$ = mean (standard deviation). Age in years, Education = years of school education, IQ = score according to the German standard test, MWT-B; Lehrl, 2005, Cig./day = number of cigarettes per day, GAF = Global Assessment of Functioning, CPZ = chlorpromazine equivalent (for $n = 10$ AR, $n = 32$ ES and all CS), ACE = adverse childhood experiences, MACE = Maltreatment and Abuse Chronology of Exposure, HCC = hair cortisol concentration, BPRS = Brief Psychiatric Rating Scale (PS, positive symptoms and NS, negative symptoms), HC = healthy control subjects, AR = at-risk individuals, ES = early-stage schizophrenia patients, CS = chronic schizophrenia patients. Level of significance was set at $p \leq .05$. If homogeneity of variance was not given, Welch-tests were reported. Statistics for hair cortisol were computed with the natural log-transformed data and the covariate hair washing frequency. Non-significant group differences were not followed-up by specific comparisons between samples. Games-Howell post hoc tests were applied. 95% bootstrapped confidence intervals are reported for post hoc tests in square brackets. |
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Table 1b. Risk categories defining at-risk individuals and their comorbid diagnoses.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Number of AR individuals, n = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) APS</td>
<td>n = 20</td>
</tr>
<tr>
<td>b) BLIPS</td>
<td>n = 7</td>
</tr>
<tr>
<td>c) Genetic disposition &amp; prodromal signs</td>
<td>n = 2</td>
</tr>
<tr>
<td>d) only prodromal signs</td>
<td>n = 6</td>
</tr>
<tr>
<td>Combination of categories a-c</td>
<td>n = 5</td>
</tr>
</tbody>
</table>

Comorbid diagnoses (ICD-10)

- Affective disorders (F30, F31, F32, F33) n = 22
- Psychoactive substance abuse (F10, F12, F19) n = 6
- Anxiety or stress-related disorders (F40, F41, F42, F43) n = 6
- No comorbid disorders n = 2
- > 1 comorbid diagnoses n = 7

Note. AR = at-risk individuals, APS = attenuated psychotic symptoms, BLIPS = brief intermittent psychotic symptoms, ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Measures and Design

The study was approved by the Institutional Review Board of the local university. Participants provided written informed consent prior to the assessment, which included the interview on childhood adversities and hair sampling. Participants received 15 Euros upon completion of the assessment, which lasted about 1-2 hours.

Adverse childhood experiences were assessed using the German version (Isele et al., 2014) of the Maltreatment and Abuse Chronology of Exposure (MACE) scale (Teicher & Parigger, 2015). The MACE consists of 75 items that
retrospectively screen 10 different types of childhood maltreatment, of which 2 are subsumed under the category ‘neglect’ (emotional and physical neglect) and 8 refer to experiences of ‘abuse’ (parental physical abuse, parental verbal abuse, parental non-verbal emotional abuse, sexual abuse, peer emotional violence, peer physical violence, witnessed violence towards parents and witnessed violence towards siblings). Severity of each experience is evaluated between 0 to 10, with the sum of all items (interpolated to account for the number of items per type) representing the severity per subscale. The sum of all subscales and their severity scores add up to the total ACE score. Severity scores were determined separately for abuse and neglect types as the sum of 8 abuse and 2 neglect subscales. The abuse, neglect and the total score were divided by the included respective subscales, resulting in the applied abuse, neglect, and MACE total scores ranging from 0 to 10. ACE age and duration can be determined by noting the age of experience (0-18 years) for each item/attested experience (in the present analysis this measure was used only for probing the importance of early experiences).

Symptom severity was rated for each at-risk individual and each schizophrenia patient by the responsible psychologist or psychiatrist using the Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986). Presence and severity of each of 24 symptoms is rated on 7-point scales and ratings were summed up separately for positive and negative symptoms (following Ventura et al., 2000), and for all symptoms as measure of general severity.

Hair cortisol concentration (HCC) was determined from hair strands (of at least 3 cm length) that were cut from two different posterior vertex locations in close proximity to the participant’s scalp. Hair samples were stored at room tem-
perature protected from daylight in separate pieces of aluminium foil. In the laboratory, hair strands were cut into samples of 3 cm length for further analyses. Assuming a hair growth of about 1 cm per month (see also Wennig, 2000, and Stalder et al., 2017 for factors that determine and modify HCC measures) accumulated cortisol levels for the past 3 months were analyzed. See Figure 1 for the number of analyzed hair samples per group and respective drop-out rates due to insufficient hair length, individual rejection or missing data. 4-10 mg hair extracts were washed with 2.5 ml isopropanol and glucocorticoids were retrieved with 1800 ml methanol at 45°C for 18 hours. In the resuspended extracts, cortisol concentration was measured by a commercial immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany). For a detailed protocol of cleaning, processing and analyses of the hair samples see Kirschbaum et al. (2009). A natural log-transformation served to reduce positive skewness of HCC (pg/mg). In addition, \( n = 7 \) participants with a difference of more than 2 standard deviations from the mean were excluded as outliers prior to further statistical analyses.

**Statistical hypothesis testing**

Statistical tests were accomplished using the software IBM SPSS Statistics 25.0. The level of significance was set at \( p \leq .05 \). Normal distribution was examined with the Kolmogorov-Smirnov test. As normal distribution of residuals was not verified for all models, bootstrapping was applied to reduce bias.

As further assumptions for parametric testing were fulfilled, differences in ACE between groups per hypothesis (1) were examined by repeated measures
analyses of variance with the between-subject factor Group (comparing AR, ES, CS, and HC) and the within-subject factor Type (abuse and neglect). In separate univariate analyses of variance, (1) total number of experiences, and (2) the accumulated number of abuse and neglect experiences were compared between groups. A significant main effect of Group was verified in post-hoc tests (Games-Howell) for specific group differences.

Addressing hypothesis (2), Pearson’s correlations tested relationships between ACE and symptom severity (separately for BPRS sum score, positive and negative symptoms score). Symptom severity correlated with age, since CS patients achieved both the highest age and the highest symptom scores ($r = .30, p = .006$). Addressing hypothesis (3), HCC was compared between groups by means of an analysis of covariance (ANCOVA), including hair washing frequency as covariate (see Dettenborn, Tietze, Kirschbaum, & Stalder, 2012; Stalder et al., 2017; after verifying that HCC did not vary with age, $r = -.07, p = .50$, and gender distribution, $r = -.15, p = .18$). The relationship between ACE, HCC, and symptom scores was examined regressing overall load and subtypes on HCC, and HCC on BPRS symptom scores across at-risk individuals and schizophrenia patient groups.
3.3. Results

ACE distribution

Figure 2 illustrates that at-risk individuals and schizophrenia patients (ES and CS) reported more total ACE than HC. The group differences were evident for both abuse and neglect (see Table 1 for mean values). A main effect Group ($F(3,121) = 8.41, p < .001$) confirmed higher total ACE in the three clinical groups compared to HC. The main effect Type ($F(1,121) = 14.07, p < .001$) verified more abuse than neglect across all groups (for simple effects, see group statistics in Table 1). A significant Group x Type interaction ($F(3,121) = 4.49, p = .01$) resulted from similar neglect experiences in ES and HC, in contrast to more neglect experiences in at-risk individuals and CS than in HC (see Table 1).

As groups differed in age and, hence, during the time elapsed between childhood experiences and retrospective ACE assessment, participants may have experienced further stressful events (e.g. Matz, Pietrek, & Rockstroh, 2010 for psychosis, and Stalder et al., 2017 for HCC), a potential impact of age was evaluated by Pearson’s correlations. While there was no significant relationship between total ACE and age ($r = .13, p = .16$), more ACE varied with lower IQ as a trend ($r = -.16, p = .07$). Moreover, an analysis of covariance with age and IQ as covariates showed similar results as reported above for total ACE ($F(3,119) = 6.06, p = .001$), abuse ($F(3,119) = 6.22, p = .001$), and neglect ($F(3,119) = 5.48, p = .001$)\(^5\).

\(^5\) It should be noted that conclusions from such covariates are limited (Miller & Chapman, 2001).
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**Fig. 2.** Adverse childhood experiences displayed as overall experience load (MACE total), abuse and neglect separately for the four groups per means ± standard deviations. MACE = Maltreatment and Abuse Chronology of Exposure. MACE scores were adjusted for the number of included subtypes. HC = healthy controls, ARP = at-risk individuals, ES = early-stage schizophrenia patients, CS = chronic schizophrenia patients. All comparisons between the clinical samples and the HC group were significant, except for the neglect score of the ES group. There were no significant differences among the clinical samples themselves.

**Relationship between ACE and symptom severity**

Pearson’s correlations (Table 2) confirmed that more total ACE, more abuse, and more neglect experiences were associated with higher symptom severity (BPRS sum). Evaluating positive and negative symptoms separately supported significant relationships between (more) abuse and (more) neglect experiences and (more) positive symptoms, whereas no relationships were confirmed for negative symptoms. The relationship between total ACE and positive symp-
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toms was prominent in AR ($r = .40, p = .01$) and CS ($r = .44, p = .03$), but not in ES ($r = .12, p = .51$). Yet, correlation coefficients did not differ significantly between groups.

Table 2. Pearson’s correlations between ACE and symptom severity across all clinical samples.

<table>
<thead>
<tr>
<th>ACE Measure</th>
<th>BPRS sum</th>
<th>BPRS PS</th>
<th>BPRS NS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE total</strong></td>
<td>$r = .44$, $p = .001$, CI [.17 .64]</td>
<td>$r = .36$, $p = .007$, CI [.13 .61]</td>
<td>$r = -.08$, $p = .56$, CI [-.33 .18]</td>
</tr>
<tr>
<td><strong>Abuse</strong></td>
<td>$r = .44$, $p = .001$, CI [.18 .65]</td>
<td>$r = .34$, $p = .01$, CI [.11 .57]</td>
<td>$r = -.12$, $p = .40$, CI [-.37 .16]</td>
</tr>
<tr>
<td><strong>Neglect</strong></td>
<td>$r = .29$, $p = .03$, CI [.02 .55]</td>
<td>$r = .32$, $p = .02$, CI [.07 .56]</td>
<td>$r = .05$, $p = .73$, CI [.17 .29]</td>
</tr>
</tbody>
</table>

*Note. ACE = adverse childhood experiences, BPRS = Brief Psychiatric Rating Scale, PS = positive symptoms, NS = negative symptoms. Clinical samples include at-risk individuals, early-stage, and chronic schizophrenia patients. Level of significance was set at $p \leq .05$. 95% bootstrapped confidence intervals are reported.*

Relationships between hair cortisol concentration, ACE and symptom severity

The ANCOVA did not verify HCC differences between groups after controlling for hair washing frequency ($F(2,81) = .40, p = .76$; see Table 1 for the estimated marginal means and standard errors of the original HCC values (pg/mg) per group). HCC neither varied with total experience load, nor with abuse or neglect (see Table 3), nor with BPRS sum, positive or negative symptom scores. An exploratory analysis of abuse and neglect experiences prior to the age of 11,
showed that both types together predicted HCC with 21% explained variance (see Table 3), although only early abuse, but not neglect, varied significantly with lower HCC. Moreover, exploratory analyses of relationships between HCC and distinct symptoms, in particular those considered relevant for at-risk diagnosis, showed that higher scores of suspiciousness and conceptual disorganization predicted lower HCC ($p \leq .007$ after Bonferroni correction for multiple comparisons).
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Table 3. Regression analyses with 1) ACE regressed on HCC, and 2) HCC regressed on symptoms.

<table>
<thead>
<tr>
<th>1) ACE (\rightarrow) HCC</th>
<th>(R^2)</th>
<th>(F)-statistic</th>
<th>(\beta)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE total</td>
<td>.10</td>
<td>(F(2,54)=2.96)</td>
<td>-.20</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Multiple regression ACE types (\rightarrow) HCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse and neglect</td>
<td>.11</td>
<td>(F(3,54)=2.00)</td>
<td>.13</td>
<td></td>
</tr>
<tr>
<td>Abuse</td>
<td></td>
<td></td>
<td>-.22</td>
<td>.30</td>
</tr>
<tr>
<td>Neglect</td>
<td></td>
<td></td>
<td>.02</td>
<td>.92</td>
</tr>
<tr>
<td><strong>Multiple regression early ACE types (\rightarrow) HCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early abuse and neglect</td>
<td>.21</td>
<td>(F(3,54)=4.64)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Early abuse</td>
<td></td>
<td></td>
<td>-.31</td>
<td>.02</td>
</tr>
<tr>
<td>Early neglect</td>
<td></td>
<td></td>
<td>-.16</td>
<td>.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2) HCC (\rightarrow) symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple regressions on BPRS (sub-)scales</strong></td>
</tr>
<tr>
<td>BPRS sum</td>
</tr>
<tr>
<td>BPRS PS</td>
</tr>
<tr>
<td>BPRS NS</td>
</tr>
</tbody>
</table>

*Psychotic subscales in BSIP:*

| Hallucinations                 | .002   | \(F(2,54)=.06\)  | -.05    | .75   |
| Suspiciousness                 | .15    | \(F(2,54)=4.64\) | -.38    | .003  |
| Unusual thought content        | .09    | \(F(2,54)=2.50\) | -.31    | .01   |
| Conceptual disorganisation     | .13    | \(F(2,54)=3.97\) | -.35    | .005  |

*Note.* ACE = adverse childhood experiences, HCC = hair cortisol concentration, MACE = Maltreatment and Abuse Chronology of Exposure, BPRS = Brief Psychiatric Rating Scale, PS = positive symptoms, NS = negative symptoms, BSIP = Basel Screening Instrument for Psychosis. Bootstrapped \(p\)-values are reported and tests including hair cortisol were controlled for hair washing frequency. After a Bonferroni correction for 7 multiple comparisons, level of significance was set at \(p \leq .007\) for the regression between HCC and symptom severity. The upper half (1) of the table displays a simple regression of the ACE total score on hair cortisol and two multiple regressions of abuse/neglect and early abuse/early neglect on hair cortisol concentration. The lower half (2) shows several simple regressions of hair cortisol concentration regressed on BPRS symptom scores and subscales.
3.4. Discussion

Evidence for the impact of childhood maltreatment on mental health in individuals suffering from psychological disorder and in potentially vulnerable individuals has been accumulated in recent years. Yet, insufficient or inconclusive evidence in schizophrenia asks for further clarification of the role of adverse childhood experiences in the emergence of psychopathology in (genetically) vulnerable individuals. The present study aimed at clarifying this impact by addressing overall amount and specific types of ACE (abuse and neglect) and symptom severity in individuals at different stages of a psychotic illness (at risk, early and chronic stage), and by examining altered stress-axis function, indexed by HCC, as potential moderator of ACE on emerging psychopathology.

Results confirmed the previously reported high amount of childhood maltreatment in schizophrenia patients, and also in individuals with attenuated psychotic symptoms showing signs of being at risk for a conversion into psychosis (e.g. Mayo et al., 2017). It is tempting to conclude that childhood adversities foster the emergence of manifest psychosis in vulnerable individuals. However, an impact of childhood maltreatment on psychotic development can be inferred only from individuals who convert to psychosis within 12 – 24 months, and only about one-third of individuals diagnosed as at risk are expected to meet these criteria of conversion (Fusar-Poli et al., 2012a). It has to be assumed that the present at-risk sample included individuals who converted to manifest psychosis, individuals who developed another severe psychiatric disorder within the year after the assessment, and individuals who showed transient psychotic symptoms but did
not receive a diagnosis of psychosis on the long run. Clear results with sufficient statistical power would have required longitudinal assessments over 1-2 years in sufficiently large samples. The lack of both, a larger sample of at-risk individuals and sufficient follow-up, clearly limit the strength of the present results.

The presence of comorbid disorders in at-risk individuals might support their risk or prodromal state. Yet, psychotic symptoms have been found in adversity-exposed members of the general population (Janssen et al., 2004). Moreover, similar relationships between childhood maltreatment and non-specific symptoms (including psychotic symptoms) in patients with diagnoses other than schizophrenia (e.g. Matheson et al., 2013; Misiak et al., 2017; Pietrek et al., 2013; Read et al., 2014; Weber et al., 2008) suggest that ACE do not foster specific disorders but moderate the emergence of mental illnesses in generally vulnerable individuals.

The present study showed more abuse and neglect experiences across all samples, without marked dominance of one or the other type (as in Üçok & Bıkmaı, 2007). This underscores that not only severe traumata impact development and/or severity of psychiatric disorders. When compared between samples, at-risk individuals and chronic patients reported more neglect experiences than patients at early stage of illness. Present results may suggest that it is the overall experience load or the accumulation of abuse and neglect experiences that influence the emergence of psychopathology. Similar prominence of abuse and neglect experiences has previously been found, particularly in studies which used similar screening instruments as the present study (Prokopez et al., 2018; Simpson et al., 2018). Thus, a potential influence of the assessment method on
present results cannot be ruled out, which limits firm conclusions about the role of distinct types of adversity in schizophrenia.

Severity of childhood maltreatment predicted symptom severity independent of stage of illness. Given that positive symptom severity did not differ significantly between the three clinical groups (see Table 1), the similar relationships, too, support the assumption that ACE may sensitize for the development of psychopathology in vulnerable individuals (van Nierop et al., 2015). An impact of early experiences on the course of illness can only be verified by longitudinal assessment. The present relationships across samples at different stages of illness suggest a sensitizing effect of childhood adversities rather than an impact on a severe course of disorder. A relationship between severe childhood maltreatment and positive symptoms, as demonstrated in the present assessment, has been repeatedly reported (e.g. Daalman et al., 2012; Hacioglu Yildirim et al., 2014; Sar et al., 2010; Schalinski et al., 2015a/b, 2017; Thompson et al., 2009; Üçok & Bıkmaı, 2007). Yet, reports on the relationship between childhood maltreatment and symptom characteristics are inconsistent, and may vary with the assessment instrument and the sample (acute or chronic states are characterized by different symptom accentuation), and by the time gap between childhood experience and assessment of symptoms that may have blurred the relationship between positive/negative symptoms and specific experiences. Thus, the potential relationship between childhood adversities and symptom severity needs further clarification.

Previous results of elevated HCC (stable over 3 months) in drug-naive first-episode patients (Andrade et al., 2016) were not supported by present in-
conspicuous HCC in at-risk individuals and schizophrenia patients. Streit and colleagues (2016) reported higher HCC in bipolar but also confirmed unaltered HCC in schizophrenia patients (compared to controls) and no HCC changes over 6 months despite a decrease of perceived stress. Thus, HCC may serve as a relatively stable cortisol index.

Still, the exploratory inspection indicated that intense early abuse experiences were associated with lower HCC in at-risk individuals and schizophrenia patients. Evidence on the relationship between childhood maltreatment, HCC and psychotic psychopathology is mixed and still rare (Steudte-Schmiedgen et al., 2016; Andrade et al., 2016 vs. Streit et al., 2016). This might be due to various basic and stress-related variables that modify HCC (see Abell et al., 2016; Stalder et al., 2017). For instance, higher-than-normal HCC was often found in individuals who experienced childhood maltreatment but also more recent life events experiences or chronic stress (Stalder et al., 2017). The latter was not screened in the present sample. As previous studies indicated a sensitizing effect of childhood maltreatment on later life events (Matz et al., 2010), one might speculate that prodromal/attenuated symptoms and hospital admissions meet criteria of chronic stress. Indeed, Streit and colleagues (2016) found higher HCC in psychotic patients upon admission than in remitted outpatients. However, Koenig et al. (2008) reported that the association between childhood maltreatment and HCC in women postpartum differed depending on the respective FKBP5 genotype. The present study did not consider genetic factors and therefore we cannot draw conclusions about potential gene-environment interactions that might have influenced HCC.
Recent trauma has been found to vary with lower HCC in students and depressive patients (Hinkelmann et al., 2013; Kalmakis et al., 2015) and White and colleagues (2017) verified a relationship between more childhood maltreatment and reduced HCC in children and adolescents at age 9-16 years, and a gradual reduction of HCC with increasing age. Moreover, lower-than-normal HCC has been reported for patients with anxiety disorders including PTSD (Stalder et al., 2017; Steudte-Schmiedgen et al., 2016). Thus, present results show that ACE might be a factor modulating HCC in at-risk individuals and patients with manifest psychosis.

There is agreement, that chronic stress early in life, particularly maltreatment experience during sensitive periods of neuroendocrine development, alters long-term HPA axis function (Fries et al., 2005; Kuhlmann et al., 2017; Trickett et al., 2010). Long-term modification upon chronic stress is considered maladaptive (Stalder et al., 2017), as it may sensitize HPA reactivity to ongoing or anew stress experiences later in life, particularly in individuals vulnerable for mental disorder including schizophrenia (Lardinois et al., 2011; Myin-Germeys, Delespaul, & van Os, 2005; Pruessner et al., 2017). With caution in view of insufficient control of basic determinants of HCC the present negative relationships between early maltreatment and lower HCC and between lower HCC and psychotic symptoms (such as suspiciousness and conceptual disorganization) support HPA dysregulation following early stress. If substantiated in further studies, this link should strengthen the hypothesized functional impact of severe (early) maltreatment - potentially by way of altered HPA axis regulation - on the development of psychopathology in (genetically) vulnerable individuals.
Limitations

Further limitations have to be noted: (1) The present cross-sectional study design does not allow conclusions about the development and course of disorder. Similar amounts of ACE and similar psychotic symptoms across samples, characterized by different stages of illness, need to be complemented by longitudinal assessment for causal conclusions. (2) The reliability of retrospective self-reports of childhood maltreatment in adulthood has been questioned, as the retrieval of past events may be blurred with elapsing time (e.g. Conus et al., 2010). It has also been assumed that self-reports of psychotic patients are modulated by acute, positive symptoms. Yet, reliability of retrospective self-reports has been verified in psychotic patients (Fisher et al., 2011). Moreover, good psychometric properties of the highly structured MACE have been confirmed (Isele et al., 2014; Teicher & Parigger, 2015). While potential memory distortion of retrospective self-reports can never be completely ruled out, a major impact on the present results is not assumed. (3) Whereas amount and type of childhood maltreatment did not correlate with age in the present data set, age might influence reported ACE and their relationship with symptom severity, as age is related to the time between adverse experience and unfolding of manifest psychosis. Such an influence should have become evident in a different amount of reported ACE between groups, which differed in age. Yet, neither self-reported total ACE dose nor its relationship with symptom severity clearly differed between groups. (4) In the present study, age differed between groups, but did not vary with HCC. Inconsistent results may have resulted from basic factors that differed between studies, such as age or hair treatment. Whereas the influence of hair-washing fre-
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...quency was controlled for, we could not control for every basic factor that might modulate HCC, which clearly limits the interpretation of present results.

Conclusion

The present results confirm reports of more adverse childhood experiences in at-risk individuals as well as early-stage and chronic schizophrenia inpatients compared to healthy controls. Moreover, positive correlations between adverse childhood experiences and positive symptom severity support the hypothesis that maltreatment during childhood moderates later psychotic symptom manifestation. The significant relationship between higher reports of early abuse and lower hair cortisol concentration, as well as lower hair cortisol concentration and more severe psychotic symptoms hints at a possible long-term attenuation of the HPA axis function resulting from early experiences. Hence, low cortisol levels leading to increased stress sensitivity might play an important role for the emergence of psychotic symptoms. Consequently, the assignment to at-risk state could benefit from examining an individual’s history of (early) experiences in combination with assessing hair cortisol concentration, also adding to a better understanding of psychosis development.
Chapter 4

*Study (3):* Family history, cannabis use, and adverse childhood experiences as risk factors of schizophrenia
Abstract

Background: Family history of schizophrenia, cannabis use, and adverse childhood experiences (ACE) are known risk factors for the onset of psychosis. They were found to increase the conversion risk to frank psychosis and influence symptom severity, yet their individual contribution to psychosis proneness is still unknown and awaits further clarification.

Methods: We investigated the three mentioned risk factors across three different stages of schizophrenia illness course: in \( n = 29 \) at-risk psychosis individuals (ARP, screened per Basel Screening Instrument for Psychosis), \( n = 34 \) early-course schizophrenia patients (ES) and \( n = 24 \) chronic schizophrenia patients (CS). The clinical samples were compared to \( n = 38 \) healthy controls (HC) concerning their early (prior to age 16), current (during the past year) cannabis use, ACE screened per retrospective interview, and reported history of familial psychiatric illnesses.

Results: Family history of schizophrenia was only present in the schizophrenia samples, while ACE were highly prevalent in all clinical groups, including ARP, compared to HC. Current cannabis use was especially common among the young ES sample, while early cannabis use did not differ across groups. Early cannabis use and ACE significantly predicted symptom severity in the clinical samples.

Conclusion: Findings show that family liability is related to manifest schizophrenia, while ACE represent unspecific pathology, and early environmental factors (ACE and adolescent cannabis use) influence later symptomatology. Yet, further research is needed to specify the gene-environment interactions leading to psychosis onset.
4.1. Introduction

Research suggests varying indices that increase the risk of developing manifest schizophrenia, like sub-threshold psychotic symptoms, neurocognitive performance or abnormal brain measures (Cannon et al., 2016; Mäki et al., 2005; Smieszkova et al., 2010). Among these, studies repeatedly also state the importance of family history of schizophrenia, cannabis use, and adverse childhood experiences (ACE) for the emergence of psychotic disorders (e.g., Lu et al., 2018; Misiak et al., 2017; Semple, McIntosh, & Lawrie, 2005). These potential risk factors would represent either genetic (family history) or environmental (cannabis and ACE) factors, which are supposed to contribute to psychosis vulnerability in a complex interaction (van Os, Rutten, & Poulton, 2008). Due to the high amount of potential risk factors for psychosis development, there is an increasing interest in finding the most suitable factors to distinguish vulnerable individuals from unaffected subjects at an early illness stage (Cannon et al., 2016). Yet, the extent of contribution of known risk factors to psychosis manifestation and illness progression (and functioning) remains to be specified and should benefit from investigating the relative influence of several risk factors in the same population sample. Hence, the present study aimed at investigating the three mentioned risk factors and their contribution to illness emergence and manifestation (symptom severity) across three stages of psychosis development: in vulnerable at-risk individuals, schizophrenia patients during their first or second inpatient admission, and chronic schizophrenia patients.
Firstly, family history of schizophrenia was reported to be associated with an increased individual's risk of developing frank psychosis (Chou et al., 2017). The lifetime risk of schizophrenia was found to be elevated with the degree of genetic relatedness to family members with schizophrenia: First-degree relatives are associated with an increased schizophrenia risk of 13% for a child of a schizophrenic parent or 9% for a sibling. Second-degree relatives contribute to a risk of 5% in grandchildren or 4% in nieces/nephews, compared to a lifetime risk of about 0.5% in the general population (see Gottesman, 1991; Saha et al., 2005). Lu et al. (2018) recently also stated that a family history with at least one first-degree relative with schizophrenia was related to a ten fold increased psychosis risk. However, not only the family history of schizophrenia is associated with higher prevalence of the disorder: psychiatric disorders in general (in first-degree relatives) are reported to increase the risk of schizophrenia (Agerbo et al., 2015; Mortensen, Pedersen, & Pedersen, 2010). These findings stress the hypothesis of a genetic liability for the emergence of psychotic disorders.

As another potential risk factor in schizophrenia, cannabis is widely used among schizophrenia patients with up to five times higher prevalence rates compared to healthy individuals (Thomasius et al., 2009), and is also very common among at-risk individuals (Valmaggia et al., 2014). Cannabis use is often reported to precede psychosis onset (Arseneault et al., 2004). Moreover, cannabis abuse or dependence was found to predict psychosis transition in at-risk individuals (Drewe, Drewe, & Riecher-Rössler, 2004; Kraan et al., 2016), hence a causal relationship is suggested. Cannabis use disorders are especially common among young (first-episode), male schizophrenia patients and prevalence rates of can-
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Cannabis use decrease with schizophrenia chronicity (Koskinen et al., 2010). Mostly, a dose-dependent relationship between cannabis use and psychosis risk is suggested. However, even the single use of cannabis was found to increase psychosis proneness (Moore et al., 2007). Especially early cannabis use (prior to age 15/16) shows stronger associations with later development of psychotic symptoms than cannabis use by age 18 (Arseneault et al., 2002; Stefanis et al., 2004), indicating a phase of vulnerability in early adolescence. Moreover, (continued) cannabis use can lead to elevated positive symptoms and low levels of functioning (Clausen et al., 2014; Grech et al., 2005; Seddon et al., 2016; Schoeler et al., 2016). Yet, there are inconsistent results about the (either harmful or beneficial) effects of cannabis on functional outcome or cognition (Auther et al., 2012; Núñez et al., 2016 vs. Mallet et al., 2017).

Lastly, the impact of ACE on the manifestation of psychiatric disorders is also undoubted (Carr et al., 2013; Kerker et al., 2015; Tailieu et al., 2016). Individuals with mental illnesses who report high amounts of ACE more likely show unfavorable chronic illness courses with treatment resistance, severe psychopathology, and low cognitive abilities in comparison to individuals with less ACE (Nanni et al., 2012; Schalinski et al., 2015a, 2017, 2018). In particular, ACE were found to play an important role in psychosis onset: they are highly prevalent among schizophrenia patients (Bonoldi et al., 2013; Pietrek et al., 2013) and increase the risk of developing psychosis (recent reviews and meta-analysis: Mayo et al., 2017; Redman et al., 2017; Varese et al., 2012). Importantly, the occurrence of ACE fosters unfortunate outcomes with low functioning levels in schizophrenia patients but also in at-risk individuals with attenuated psychotic symp-
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toms (Addington et al., 2013; Boyda & McFeeters, 2015; Kraan et al., 2015; Yung et al., 2015).

The present study investigates the presence of these mentioned risk factors across psychosis illness course with the following hypotheses derived from the current literature:

(1a) There are more individuals with a family history of schizophrenia in first-degree relatives among the clinical samples (schizophrenia and at-risk individuals), especially the schizophrenic patients, compared to the healthy control group (HC). There are also more individuals with a family history of any psychiatric disorder in the clinical population compared to HC. (1b) Cannabis use (both current use and early use) is higher in the clinical samples (ES, CS, and at-risk individuals) than in healthy control subjects and is more often used by young ES patients and at-risk individuals than CS patients. (1c) ACE are more prevalent among individuals in the clinical samples (ES, CS, and ARP) compared to HC.

(2) Group affiliation (clinical sample vs. HC or schizophrenia vs. at-risk state) can be predicted by these risk factors. If a risk marker only differentiates between clinical samples and HC, it is supposed to reflect unspecific (or attenuated psychotic) psychopathology but if it differentiates risk state from schizophrenia patients it is supposed to represent an illness-specific factor. (3) In the clinical samples, high reports of cannabis use (early and current) and ACE are associated with increased symptom severity.
4.2. Methods

Participants

For a complete overview of participants and sample composition see the methods section in the previous Chapter 3. At the local Center for Psychiatry, we recruited $n = 29$ at-risk psychosis individuals (ARP) screened by trained psychologists via Basel Screening Instrument (BSIP, Riecher-Rössler et al., 2008), $n = 34$ early schizophrenia (ES) patients during their first or second inpatient admission with schizophrenia spectrum disorder, and $n = 24$ chronic schizophrenia (CS) patients with at least 5 inpatient admissions. Furthermore, $n = 38$ healthy individuals, screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) matched by age (for ARP and ES samples) and gender, were recruited as healthy controls (HC). See Table 1 in Chapter 3 for sample characteristics. The clinical samples (ARP, ES, and CS) did not differ in gender, school education in years, and IQ. However, CS were older than the other samples, achieved higher symptom scores, and lower levels of functioning than ARP and ES. In comparison to HC, clinical samples obtained lower IQ scores and were older than HC.

Procedure and Measures

The present study was approved by the Institutional Review Board of the University of Konstanz and prior to all assessments participants provided written informed consent. For the assessment of ACE, cannabis use, and family history (1-2 hours) patients received 15 Euros.
We assessed ACE via the Maltreatment and Abuse Chronology of Exposure (MACE, Teicher & Parigger, 2015; applied German version by Isele et al., 2014). This retrospective interview contains 75 items and comprises 10 different forms of childhood maltreatment (parental physical abuse, parental verbal abuse, parental non-verbal emotional abuse, sexual abuse, peer emotional violence, peer physical violence, witnessed violence towards parents, witnessed violence towards siblings, emotional, and physical neglect). Severity scores were computed for each form of ACE separately with interpolated scores according to the number of included items. Subscales were added up to an overall MACE sum score, ranging from 0 to 100.

*Family history* of psychiatric illnesses in first-degree relatives and schizophrenia in first- and second-degree relatives were assessed and documented as part of the MACE interview.

*Cannabis use* during childhood and adolescence was assessed for each year 0-18 separately (“yes” or “no” for any use of cannabis in the respective year). *Early cannabis use* was defined as any use prior to age 16. *Current cannabis use* was additionally assessed for the past 12 months (also “yes” or “no”; doses were not assessed).

*Symptom severity* was assessed by the respective psychologists or psychiatrists in charge, applying the 24-item Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986).
Statistical analyses

Statistical tests were run with IBM SPSS Statistics 25.0 and level of significance was set at $p \leq .05$. Normal distribution was assessed by Kolmogorov-Smirnov tests and to reduce bias, data were subsequently bootstrapped. We conducted $\chi^2$-tests for group differences concerning psychiatric family history and cannabis use and an analysis of variance (ANOVA) for ACE group differences. Post-hoc tests were conducted for statistical significant analyses. Logistic regression was conducted with the three risk factors as predictors of group affiliation (clinical sample vs. healthy sample and schizophrenia patients vs. at-risk individuals). At last, a multiple regression was conducted with the predictors “early cannabis use”, “current cannabis use”, and “ACE” for the dependent variable symptom severity.

4.3. Results

In a first $\chi^2$-test, family history of psychiatric disorders in first-degree relatives was not significantly associated with group, $\chi^2(3) = 1.44, p = .70$. Yet, relative to the other groups, HC showed the lowest percentage of first-degree family members with psychiatric disorders. However, family history of schizophrenia in first-degree ($\chi^2(3) = 10.44, p = .015$) and first- and second-degree relatives ($\chi^2(3) = 14.09, p = .003$) was significantly associated with group. CS patients were showing the highest rates of affected family members. Due to the missing or low number of cases in HC and ARP standardized residuals could not be fully interpreted for this test and further regression analyses did not include family history as predicting variable (see Fig. 1 and Table 1).
The $\chi^2$-test revealed a significant association between group and current cannabis use ($\geq 1$ consumption of cannabis during the past year), $\chi^2(3) = 10.87, p = .012$. Standardized residuals indicated that more ES patients than expected reported current cannabis use. However, there were no significant associations between group and early cannabis use prior to age 16 ($\chi^2(3) = 2.72, p = .44$), although we can observe a trend with the highest rate of early cannabis use among ES patients and the lowest among HC (see Fig. 2 and Table 2).

The ANOVA revealed significant ACE sum differences across all groups, $F(3,121) = 8.04, p < .001$. Games-Howell post-hoc tests showed that HC reported significantly less ACE than all clinical groups (ARP, ES, and CS). There were no further differences between the clinical groups across different illness stages (see Fig. 3, Table 3).

Logistic regression was performed with ACE sum and current cannabis use as predicting variables of group affiliation for clinical cases vs. HC (family history and early cannabis use were not included as predictors due to missing cases of psychotic relatives in HC and non-significant group differences concerning early cannabis use and family history of any psychiatric illness). ACE sum as continuous variable was a significant predictor of group affiliation ($b = .083, SE = .02, p < .001, OR = 1.09$). Current cannabis use, however, was marginally not significant ($b = .99, SE = .52, p = .06, OR = 2.68$).

In another logistic regression ACE sum, current cannabis use, and familial psychosis (in first- and second-degree relatives) served as predictors of group affiliation for ARP vs. schizophrenia patients. Whereas ACE sum ($b = -.014, SE = .02, p = .36, OR = .99$) and current cannabis use ($b = .267, SE = .52, p = .61, OR = .99$) were not significant, familial psychosis was a significant predictor ($b = .82, SE = .29, p < .001, OR = 2.27$).
Family history, cannabis use, and ACE as risk factors of schizophrenia

= 1.31) did not serve as significant predictors, family history of psychosis could significantly differentiate between ARP and schizophrenia cases (β = 1.62, SE = .82, p = .048, OR = 5.04).

The multiple regression analysis revealed a significant prediction of symptom severity (BPRS sum) by early cannabis use (β = .26, p = .02) and ACE sum (β = .28, p = .01) with an explained variance of 17% (with early and current cannabis use and ACE as predictors; $R^2 = .17$, $F(3,82) = 5.56$, $p = .002$), independent of group affiliation.

![Figure 1](image)

**Fig. 1.** Proportion of individuals with a positive family history across samples. HC = healthy controls. ARP = at-risk psychosis individuals. ES = early-stage schizophrenia patients. CS = chronic schizophrenia patients. (A) refers to relatives with any psychiatric disorder, (B) and (C) only display the proportion of psychotic relatives.
Family history, cannabis use, and ACE as risk factors of schizophrenia

Table 1. Chi²-test of associations between groups and family liability.

<table>
<thead>
<tr>
<th>Group</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>∑ N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Psych. disorders, first-degree relatives</td>
<td>Psychosis, first-degree relatives</td>
<td>Psychosis, first- &amp; second-degree relatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>23.7</td>
<td>-.8</td>
<td>10</td>
<td>34.5</td>
<td>.4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>76.3</td>
<td>.5</td>
<td>38</td>
<td>65.5</td>
<td>-.3</td>
<td>22</td>
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<tr>
<td></td>
<td>0</td>
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<td>-1.6</td>
<td>0</td>
<td>0</td>
<td>.4</td>
<td>4</td>
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<tr>
<td></td>
<td>38</td>
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<td>0</td>
<td>100</td>
<td>100</td>
<td>-2.2</td>
<td>29</td>
</tr>
<tr>
<td>ARP</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>34.5</td>
<td>.4</td>
<td>19</td>
<td>65.5</td>
<td>-.3</td>
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<td>-.3</td>
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</tr>
<tr>
<td></td>
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<td>0</td>
<td>-1.6</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ES</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>35.3</td>
<td>.5</td>
<td>22</td>
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<td>64.7</td>
<td>.3</td>
<td>30</td>
<td>11.8</td>
<td>1.2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11.8</td>
<td>1.2</td>
<td>20</td>
<td>16.7</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td>CS</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
<td>%</td>
<td>std. res.</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>29.2</td>
<td>-.1</td>
<td>17</td>
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<td>70.8</td>
<td>.1</td>
<td>20</td>
<td>16.7</td>
<td>2.0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11.8</td>
<td>1.2</td>
<td>20</td>
<td>16.7</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>16.7</td>
<td>2.0</td>
<td>7</td>
<td>29.2</td>
<td>-.1</td>
<td>16</td>
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<tr>
<td></td>
<td>16</td>
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<td>70.8</td>
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<td>8</td>
<td>11.8</td>
<td>1.2</td>
<td>20</td>
<td>16.7</td>
<td>2.0</td>
<td>7</td>
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<td></td>
<td>117</td>
<td>83.3</td>
<td>-.5</td>
<td>16</td>
<td>83.3</td>
<td>.5</td>
<td>24</td>
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<tr>
<td></td>
<td>16</td>
<td>29.2</td>
<td>.1</td>
<td>17</td>
<td>70.8</td>
<td>.1</td>
<td>24</td>
</tr>
</tbody>
</table>

Note. ARP = at-risk individuals, ES = early-course schizophrenia patients, CS = chronic schizophrenia patients, HC = healthy controls, std. res. = standardized residuals, psych. disorders = psychiatric disorders.
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Fig. 2. Proportion of cannabis users across samples. HC = healthy controls. ARP = at-risk psychosis individuals. ES = early-stage schizophrenia patients. CS = chronic schizophrenia patients. (A) displays ≥ 1 cannabis use during the last 12 months, (B) shows first cannabis use during adolescence (< 16 years).

Table 2. Chi²-test of associations between groups and cannabis use.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cannabis use, past year</th>
<th>Cannabis use, ≤ age 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>HC</td>
<td>n</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>std. res.</td>
<td>-.1</td>
</tr>
<tr>
<td>ARP</td>
<td>n</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>std. res.</td>
<td>.0</td>
</tr>
<tr>
<td>ES</td>
<td>n</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>47.1</td>
</tr>
<tr>
<td></td>
<td>std. res.</td>
<td>2.2</td>
</tr>
<tr>
<td>CS</td>
<td>n</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>std. res.</td>
<td>-.1</td>
</tr>
<tr>
<td>Σ</td>
<td>N</td>
<td>34</td>
</tr>
</tbody>
</table>

Note. ARP = at-risk individuals, ES = early-course schizophrenia patients, CS = chronic schizophrenia patients, HC = healthy controls, std. res. = standardized residuals.
Fig. 3. Adjusted sum scores of adverse childhood experiences across samples. MACE = Maltreatment and Abuse Chronology of Exposure. ARP = at-risk psychosis individuals. ES = early-stage schizophrenia patients. CS = chronic schizophrenia patients.

Table 3. Games-Howell post-hoc tests with specific ACE group differences.

<table>
<thead>
<tr>
<th>Group comparisons</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-hoc tests</strong></td>
<td></td>
</tr>
<tr>
<td>HC vs. ARP</td>
<td>$p=0.001$, CI [-2.14, .64]</td>
</tr>
<tr>
<td>HC vs. ES</td>
<td>$p=0.003$, CI [-2.01, .42]</td>
</tr>
<tr>
<td>HC vs. CS</td>
<td>$p=0.001$, CI [-2.23, .60]</td>
</tr>
<tr>
<td>ARP vs. ES</td>
<td>$p=0.89$, CI [-0.71, 1.19]</td>
</tr>
<tr>
<td>ARP vs. CS</td>
<td>$p=1.0$, CI [-1.03, .98]</td>
</tr>
<tr>
<td>ES vs. CS</td>
<td>$p=0.92$, CI [-1.21, .76]</td>
</tr>
</tbody>
</table>

Note. ACE, adverse childhood experiences. HC, healthy control subjects. ARP, at-risk psychosis individuals. ES, early schizophrenia patients. CS, chronic schizophrenia patients. Games-Howell post-hoc tests were applied. Level of significance was set at $p \leq 0.05$. 95% bootstrapped confidence intervals are reported.
4.4. Discussion

The present study investigated three different risk factors of schizophrenia and their impact on illness course and psychopathology. Results showed that schizophrenia patients had more first- or second-degree family members sharing the same schizophrenia diagnosis than at-risk individuals or healthy controls. Furthermore, this variable reliably distinguished between diagnosed patients and ARP individuals. The higher prevalence of schizophrenic relatives among psychotic patients is in line with many previous studies (e.g., Chou et al., 2017; Lu et al., 2018) and confirms our hypothesis. Yet, the significantly larger prevalence of family history in schizophrenia patients does not only reflect heritability per se: the impact of family history on the manifestation of schizophrenia might be influenced by the individual’s genetic liability (Agerbo et al., 2015) and schizophrenia family history not only elevates schizophrenia risk but is associated with a general vulnerability for psychiatric disorders (Chou et al., 2017). Moreover, it is important to mention that family history of schizophrenia by itself does not increase the risk for conversion to psychosis in at-risk individuals (Cannon et al., 2016). However, family history should not be neglected as a risk factor, because it was also related to low functional outcomes in schizophrenia patients (Käkelä et al., 2014).

In contrast to the literature (e.g. Laursen et al., 2005; Mortensen et al., 2010) and hypothesis 1a, the rates of first-degree relatives with any psychiatric illness were not significantly higher in the clinical population than in the HC sample. However, there was the trend of a lower rate in HC subjects and the
highest rates were screened in the clinical samples. The lack of statistical significance could stem from the rather small sample sizes and the inclusion of every minor or major psychiatric disorder, while Mortensen and colleagues (2010) included a huge population and only considered mental disorders that led to psychiatric treatment.

For the second investigated risk factor cannabis use, results yielded significant differences between groups for current cannabis use with the highest consumption in ES patients. This is in line with reports that cannabis use and cannabis use disorder are more frequent among younger (first-episode) patients (Clausen et al., 2014; Koskinen et al., 2010, current use < 30 years: 38.5%). However, current cannabis use within the last 12 months could not reliably distinguish healthy and clinical samples. This could be explained by the low cannabis use rates in chronic patients, which is also supported by previous literature that states decreasing cannabis use with disease chronicity and among older individuals (Koskinen et al., 2010, > 30 years: 16.0%). The rather high cannabis use by the present healthy control group is supported by the recent 12-month prevalence of cannabis use reported by Piontek et al. (2016) with 20.6% among young adults (18-24 years).

Early cannabis use prior to age 16 did not significantly differ between groups, yet it was associated with elevated BPRS symptom scores. Stefanis et al. (2004) also reported that cannabis use below age 16 years was more strongly associated with elevated positive and negative symptoms than after that age (independent of frequency). This is in line with the findings that cannabis use in adolescence (prior to age 15 during a vulnerable developmental phase) increases the
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risk for conversion to psychosis and earlier age of cannabis use is related to an elevated risk (Arseneault et al., 2004; Valmaggia et al., 2014).

Lastly, as hypothesized, ACE were more often reported by the clinical samples (ARP, ES, and CS) than the HC sample and the amount of ACE was significantly related to increased symptom levels. This finding supports an ACE contribution to psychopathology emergence in vulnerably individuals and is in line with previous research that also reported higher rates of ACE in at-risk individuals (Mayo et al., 2017). Especially, high reports of ACE among the very heterogeneous group of ARP individuals stresses that ACE are not specific to psychosis but are common among vulnerable individuals, fostering a broad range of psychiatric disorders (Misiak et al., 2017; Pietrek et al., 2013). Yet, the positive correlation of ACE with overall BPRS symptom score in the clinical samples supports the hypothesis that ACE contribute to more severe psychopathology in general (e.g., van Nierop et al., 2015).

In view of the present findings, it remains difficult to unravel the distinct contributions of the mentioned risk factors on psychosis manifestation. Among families with first-degree schizophrenia relatives, there is also a higher probability of experiencing stressful family environments (Walder et al., 2014) and both family liability and environmental factors (like childhood maltreatment) were reported to contribute to the influence of cannabis use on psychosis development (Henquet et al., 2008). Furthermore, genetic variation is supposed to play a role for the combined impact of cannabis use and childhood maltreatment on psychosis (Vinkers et al., 2013) or the effect of adverse life events on general psychiatric vulnerability (Binder, 2018). It was also found that the risk for cannabis use and
the risk for schizophrenia share a certain genetic etiology (Power et al., 2014). These findings support a complex interplay of genetic liability and environmental factors that might underlie the psychosis risk state.

Limitations

Given a lifetime prevalence of about 4.0 per 1000 individuals (Saha et al., 2005), there are few cases of schizophrenia in our population in general and most of the patients do not have family members with the same diagnosis (according to Lu et al., 2018 only app. 10-14% first-degree relatives). Due to our relatively small sample sizes, we could not find sufficient cases with a positive family history to achieve sufficient statistical power.

Moreover, the assessment of cannabis use was based on self-reports, which might have underestimated the current prevalence rates. Especially, current cannabis use might have been underrated in schizophrenia patients due to restrictions of drug use during inpatient treatment. Furthermore, we did not collect data on dose or frequency of cannabis use. The importance of these variables have been shown in previous studies, stressing that continued cannabis use was associated with increased symptom severity (Schoeler et al., 2016) and frequent cannabis abuse and dependence was related to psychosis conversion in a dose-response relationship (Kraan et al., 2016; Valmaggia et al., 2014).

The current reports of ACE are also limited to subjective retrospective assessments and the reliability of this screening method is being discussed for patients with severe mental disorders (e.g. Conus et al., 2010). Although Fisher et
al. (2011) state high reliability and comparability of retrospective self-reports for psychotic patients, potential inaccuracy of ACE self-reports cannot be ruled out.

Another limitation of the present study is that there is high heterogeneity among individuals at risk for psychosis. Approximately two thirds of individuals diagnosed as at risk will not convert to psychosis (achieving remission, remaining in an at-risk state or developing other major disorders), so that conclusions on the impact of present risk factors for psychotic development can only be drawn for those individuals, who met criteria of manifest schizophrenia after 12-24 months (Mayo et al., 2017). Hence, longitudinal assessments would be required to measure transition rates and evaluate the present risk indices.

Conclusion

The present study confirmed higher prevalence rates of positive family history among schizophrenia patients, and found that early cannabis use and childhood adversities significantly predicted symptom severity in clinical samples with attenuated or full-blown psychotic symptoms (at-risk, early, and chronic schizophrenia). These findings support contributions of both genetic liability and early environmental factors to psychosis manifestation and clinical symptoms. However, present results have to be interpreted with caution, as we cannot draw any conclusion about the impact of a single risk factor to psychosis proneness. The underlying intricate gene-environment interplay remains to be clarified.
Chapter 5

General discussion

The present thesis examined a selection of different risk markers and risk factors of schizophrenia that are discussed as indicators for the prodromal illness phase and/or as predictors of psychosis onset. Investigations on risk indices across different stages of schizophrenia were divided into three studies that constituted the main part of this thesis. The findings of the three enclosed studies are summarized in the following section. Finally, subsequent implications for clinical practice, possible future prospects, and general limitations are discussed in the concluding part of this dissertation.

In chapter 2, the first study entitled “Mismatch negativity and cognitive performance in the course of schizophrenia” (Hirt et al., in press) revealed non-conspicuous mismatch negativity in at-risk psychosis individuals but confirmed significantly reduced amplitudes in early and chronic schizophrenia patients, compared to healthy controls. Cognitive deficits, however, were already prevalent among at-risk individuals. While mismatch negativity was not associated with symptom severity in the clinical samples, poorer cognitive performance was related to symptom severity at index assessments and at 6-month follow-up. Hence, cognitive deficits are suggested as marker of early non-specific psychopathology, already present in vulnerable individuals, whereas abnormal event-
related potentials, indexed by mismatch negativity, mark manifest psychosis independent of illness stage.

Chapter 3 included the second study “Decoding the impact of adverse childhood experiences on the progression of schizophrenia” (Hirt et al., 2019). Results yielded more reported childhood adversities in the clinical population, including at-risk individuals, compared to the healthy control sample. Yet, hair cortisol concentration did not differ between the samples. A higher amount of childhood adversities was associated with higher symptom severity in the clinical samples and early abuse predicted lower hair cortisol concentration, while the latter was related to elevated psychotic symptoms in at-risk individuals and schizophrenia patients. Consequently, early childhood maltreatment seems to have a sensitizing effect on later psychopathology and psychosis manifestation. The relationship between early abuse, attenuated hair cortisol levels and psychotic symptoms suggests a long-term impact of adverse experiences on stress axis functioning and subsequent psychosis proneness.

In chapter 4, the third study with the title “Family history, cannabis use, and adverse childhood experiences as risk factors of schizophrenia” showed that current cannabis use was especially common among young early schizophrenia patients and family liability was only present in patients with manifest psychosis. As reported in the previous study, childhood adversities were common across all clinical samples, and already highly prevalent in at-risk individuals. Reported early cannabis use prior to age 16 did not differ between the samples. Yet, early cannabis use and more childhood adversities were significantly associated with increased symptom severity in the clinical population, across illness stages. The
current results suggest that adverse childhood experiences, early cannabis use, and family liability could qualify as risk markers of psychosis, yet their specific impact on psychopathology and illness manifestation still remains unclear.

5.1. Implications of the present thesis and future prospects

The main aim of the present dissertation was the examination of potential risk indicators for schizophrenia manifestation and their qualification as indices to improve the detection of at-risk individuals prior to psychosis onset. The three included studies focused on different risk markers and factors and some of them might be promising indicators to improve at-risk assessments. Ultimately, the questions that arise are, (1) what can we learn and derive from the findings of the present studies, and (2) what are current and potential future endeavors?

Suitability and applicability of the present risk indicators

The present investigations yielded both positive and negative results on the presence of different risk indices in individuals at risk for psychosis. Two of the assessed risk indices of the present dissertation could be detected in the investigated at-risk psychosis subjects (i.e., cognitive deficits and adverse childhood experiences), while others were only abnormal among early/chronic schizophrenia patients (i.e., mismatch negativity, family liability, and current cannabis use) compared to healthy controls.

Since cognitive deficits and high amounts of childhood adversities were already present in at-risk individuals with unspecific symptoms, these indices
seem to represent general psychopathology and vulnerability, not necessarily leading to future psychosis onset. Though, they hint at a higher risk for developing manifest psychiatric illnesses, including higher chances of frank psychosis, and could provide additional information to characterize high-risk individuals. Both cognitive dysfunction and childhood adversities were found to foster unfavorable low functioning outcomes (Green et al., 2004; Yung et al., 2015) and therefore the assessment of these variables could inform targeted treatments to ameliorate the deleterious long-term effects (via cognitive trainings or trauma focused therapy).

In contrast, the event-related potential mismatch negativity, family history of schizophrenia, and current cannabis consumption (in early psychosis) seemed to be more specific for manifest schizophrenia. They could serve as more specific illness markers to identify individuals with higher risks for psychosis transition. Although MMN seems to be a promising risk marker for psychosis onset, it is difficult to be interpreted on an individual level. The measured MMN amplitudes showed high variability and statistical significance was based on group means. Consequently, assessing an individual’s ERP might not add much information by itself (Luck et al., 2011). However, such measures could help to create subgroups with different vulnerabilities for psychosis onset.

Further current measures like early cannabis use or hair cortisol concentration could not differentiate between healthy subjects and the clinical samples. Yet, these measures were related to psychotic symptoms/BPRS symptom severity, showing that they might have an impact on illness expression and severity. Knowledge about such indices might add to a better understanding of illness
course and symptom manifestation and they show that psychotic symptoms could be associated with long-term influencing factors. No measures of illness progression/chronicity were found in the present thesis, which is a sign against further significant deterioration with age or longer duration of illness.

When it comes to choosing the right measures for standard at-risk assessments, costs and benefits have to be in a reasonable relation. The question arises as to what extent additional information is gained with further assessments. It is not applicable or endurable to undergo several hours of assessments and questioning in order to assess a variety of risk measures. Additionally, we have the aspiration to identify each individual as accurately as possible and to avoid “false positives” as well as “false negatives”. In this regard, approaches to achieve standardized processes and several additional caveats on the way have to be considered as a prerequisite for the introduction of early interventions.

Towards diagnostic improvements and standards for clinical practice

Investigations showed that the common instruments achieve very high sensitivity, i.e., they are good at ruling out psychosis in individuals not at risk. Yet, there is still a lack of specificity and research is aiming at finding the best risk measures to provide high prognostic accuracy. In this respect, it has been reported that a combination of several predictors yields the best prognostic results (Cannon et al., 2016; Yung et al., 2004). Yung and colleagues (2004) found that several highly predictive variables (like poor functioning, reduced attention, family history of psychosis, or depressive symptoms) improved psychosis prediction at 12 months, achieving a specificity of 92.6%, yet with a moderate sensitivi-
ty of 60%. Cannon et al. (2016) developed a “risk calculator” based on several predictive measures (i.e., decline in social functioning, high levels of unusual thought content and suspiciousness, low verbal learning, memory performance, and speed of processing, and younger age) and also stressed the trade-off between higher specificity and lower sensitivity.

Schmidt and colleagues (2017) suggested a three-stage method of individual risk stratification. They investigated different predictive models and sequential testing in at-risk diagnostics and to avoid a loss of sensitivity, they suggested the use of a common psychometric instrument to identify at-risk individuals in a first step. Only positively screened individuals would undergo a second step of additional tests with objective electrophysiological measures and a third step of testing blood markers. This multicomponent sequential approach serves to increase prognostic reliability and aims at avoiding unnecessary further diagnostic procedures or treatments for people who are very unlikely to develop manifest psychosis. If an individual obtained three positive results in the sequential testing suggested by the research group, probability of transition is estimated at about 98%.

Another important aim is to find a standard psychometric instrument for the identification of vulnerable individuals. It is important to notice that existing risk projects use different approaches or combinations of instruments for at-risk identification. There is a high similarity and diagnostic agreement between the commonly applied psychometric interviews (Fusar-Poli et al., 2016a), yet small deviations could lead to reduced comparability across studies. Since there is already high heterogeneity among examined at-risk individuals, it is important to
achieve standardized diagnostic processes to improve the explanation of sample variability. Standards in diagnostic procedures, requirements, or recruitment strategies could inform larger multi-center studies to test further predictors of psychosis transition and provide a solid base for intervention studies.

The recent introduction of the “attenuated psychosis syndrome” in section three of the DSM-5 as condition for further study should alleviate early detection of schizophrenia. The attenuated psychosis syndrome is supposed to be a transient diagnosis, which is expected to change over time into either a remitted state, manifest psychosis or other psychiatric disorders. The syndrome requires attenuated psychotic symptoms (like mild hallucinations or delusions) with intact reality testing and significant distress caused by these symptoms (Fusar-Poli, Yung, McGorry, & van Os, 2014; Wakefield, 2016). The consideration of a “psychotic risk syndrome”, however, was rejected as diagnosis in DSM-5 since being “at-risk” is rather unspecific and does not represent a tangible psychiatric disorder. Nevertheless, there is still a high chance of creating “false positives” by diagnosing the attenuated psychotic syndrome, since attenuated psychotic symptoms are also very common in the general population (Wakefield, 2016).

Still, there is a need for additional standards in prodromal research and for the assignment of at-risk states and recently, the European Psychiatric Association (EPA) formulated a guideline for the specification of at-risk identification (Schultze-Lutter et al., 2015). The guideline recommends, for instance, the application of psychometric instruments by trained and experienced specialists, the inclusion of the basic symptoms approach, and the sole application in already distressed and help-seeking individuals. Such guidelines and diagnostic classifi-
cations provide the opportunity to develop new research projects upon standardized at-risk assignment.

**The establishment of early interventions**

While it is still difficult to grasp the prodromal phase of schizophrenia, current research is already focusing on the investigation of prevention and intervention strategies for at-risk individuals. These early interventions target the reduction or delay of psychosis transition but should also ameliorate present psychopathology and distress. Thereby they are supposed to shorten the duration of untreated psychosis and prevent severe illness courses. Research shows promising results and suggests that early specific treatment is able to delay or prevent the onset of psychosis (Stafford, Jackson, & Mayo-Wilson, 2013). A meta-analysis across different treatment methods yielded a reduction of psychosis transition in ultra-high risk individuals by about 52-54% after a one-year follow-up and a reduced transition by about one third after more than two years (van der Gaag et al., 2013). Due to the variable at-risk state, a staging model of interventions is suggested to provide general low-threshold treatments in early phases of non-specific psychopathology to reduce subjective distress, and pharmacological treatments (i.e., low dose antipsychotics) for individuals in later phases with more concrete attenuated psychotic symptoms (Fusar-Poli et al., 2014). Low-threshold interventions, for instance, would include cognitive-behavioral therapy (Hutton & Taylor, 2014), cognitive remediation therapy, psychoeducation, or integrated psychological treatments (Bechdolf et al., 2012; Fusar-Poli et al., 2015b). Very early prevention programs are suggested for high-risk families.
with parents who suffer from psychosis, which include offers like prenatal care, parenting skills support, or early cognitive remediation in children (Liu, Keshavan, Tronick, & Seidman, 2015).

The EPA also set up a list of recommendations for early interventions in high-risk individuals, which states that cognitive-behavioral therapy is the first-choice intervention and should only be complemented by second-generation anti-psychotic medication if psychological treatments were not effective. Moreover, early therapies should already focus on comorbid psychiatric disorders (like anxiety or depression) and the application of proven treatment methods (Schmidt et al., 2015).

However, prevention of schizophrenia is limited and long-term studies show that often psychosis onset can only be delayed or symptoms can be weakened. Nevertheless, early intervention is mostly indicated due to the high levels of experienced distress, cognitive impairments, or loss of social functioning in high-risk individuals. Hence, the efficiency of different treatment methods urgently awaits further proof.

5.2. General limitations and considerations

There are several caveats that should be addressed in this dissertation that clearly limit the interpretation of the present results. The three studies in chapter 2-4 already mention and discuss some important limitations concerning the respective study design. The following section presents three general limita-
tions and considerations in more detail, which are especially relevant for investigations with at-risk samples.

**High sample heterogeneity**

Outcomes in at-risk individuals are very diverse and the majority (about two thirds) of those labeled as “being at risk for psychosis” will eventually develop other psychiatric disorders, experience persistent attenuated psychotic symptoms, or achieve remission (Addington et al., 2011; Lin et al., 2015). It means that only a fraction of identified at-risk individuals will eventually transition to psychosis and fulfill a schizophrenia spectrum disorder later in life. Therefore, the at-risk state rather represents a general risk for future psychopathology of any kind than a specific pre-psychotic phase.

Moreover, comorbid diagnoses are very common in prodromal patients: about 80% suffer from at least one additional psychiatric disorder. Most of these at-risk individuals meet the full criteria of depression or anxiety disorders (Addington et al., 2017). The presence of comorbid diagnoses in vulnerable individuals seems comprehensible, since comorbidity levels are also high among schizophrenia patients (Buckley, Miller, Lehrer, & Castle, 2009). Yet, these psychiatric diagnoses are often not sufficient to explain the individual’s reported distress and symptoms and the additional assignment to an at-risk state seems justified in these cases (Woods et al., 2009).

Another problem that creates heterogeneity is that the risk for psychosis is not equally high across vulnerable individuals. Depending on the severity of attenuated psychotic symptoms or the number of fulfilled risk factors, at-risk
samples usually include subjects with a range of lower to higher risk states (Fusar-Poli et al., 2016b). Even in samples with correct risk assignments, individuals are not exactly comparable regarding their duration of the prodromal phase (i.e., their remaining time until psychosis onset). Furthermore, the recruitment of vulnerable individuals in the general population with high numbers of self-referrals and faster referrals by professionals can lead to a dilution of pre-test risk and to increased heterogeneity among positively screened individuals (Fusar-Poli et al., 2016c; Wiltink et al., 2015).

The problem of sample size and longitudinal assessments

A very important limitation in the present at-risk sample, which applies for most studies with at-risk individuals, is the insufficient sample size. The evaluation of risk indicators would require very large sample sizes and long-term follow-ups, since only a small percentage of vulnerable individuals are true prodromal patients. One main reason for the lack of at-risk individuals is the low availability of potential candidates in the population. Given the low incidence rate of schizophrenia (median incidence rate 15.2 per 100,000; McGrath et al., 2004), the chances of detecting individuals in their prodromal phase during a limited time of study recruitment are not very high. The availability of potential candidates also might have been limited in the present study, since the local Center for Psychiatry Reichenau (ZfP) is situated in a less densely populated area (nearest city Konstanz with app. 85,000 inhabitants). Furthermore, the local program for early detection of psychosis (FePSY, ZfP Reichenau) was recently established in 2014 and awareness of the program among professionals in the
health care system still had to grow. In order to gain larger samples that provide efficient statistical power for the analysis of risk indicators, the conduction of more multi-center studies is required in the future.

The small sample sizes also add up to the problem of missing longitudinal assessments. Mostly, longitudinal assessments in at-risk research are not long enough to detect transition, considering a possible length of five years with prodromal symptoms. The present study design focused on a cross-sectional approach with a short 6-month follow-up period and therefore conclusions about psychosis conversion were not feasible. Long-term follow-ups are time-consuming and costly and low retention rates at follow-up assessments again decrease the number of participants in already small samples. The retention rate of the present study was 60% after 6 months, which leads to a high chance of missing out potential transitions. Good retention rates are essential for a continuous monitoring of transition rates in vulnerable individuals and could be achieved by programs that include patients in long-term health care projects that already offer social support, psychoeducation, psychotherapy, and guidance for relatives.

**Additional ethical considerations**

There is an ongoing ethical debate about the early labeling of individuals as risk candidates for future psychosis. Critics claim that the prognostic accuracy is not high enough, as psychometric instruments create approximately more than 50% false-positive cases (Cassetta & Goghiari, 2015). The falsely assigned risk state can lead to unnecessary fear or stress in form of early stigmatization. Like in a self-fulfilling prophecy, early stigma itself was shown to increase the
transition risk to psychosis (Rüsch et al., 2015). Moreover, there is the danger of unjustified medication with antipsychotics or other psychotropic drugs, which can cause harmful side effects. Current evidence is not sufficient to clearly recommend early interventions and there are no guidelines about type or length of pharmacological treatments in vulnerable individuals (Schmidt et al., 2015). Otherwise, early interventions can enable the patients and their families to receive psychoeducation on the current symptoms and to be prepared for a future illness onset, to seek help in the health system and therefore prevent early loss of social functioning (e.g. avoid school or work drop-out). Moreover, non-converters also suffer from serious, long-lasting psychopathology and/or reduced functioning levels and do not represent “healthy” individuals (Haroun, Dunn, Haroun, & Cadenhead, 2006; van der Gaag et al., 2013). Although evidence concerning early interventions in prodromal individuals is still scarce, there are also promising results on the cost-effectiveness of early treatment (Ising et al., 2015). Consequently, the consideration of ethical implications of at-risk assessments is very important and should shape the way of clearly communicating the result and consequences of being “at risk”. Yet, it seems also necessary to offer support and early intervention options to these highly distressed help-seeking individuals.
5.3. Final conclusion

The present dissertation investigated the presence of various risk indicators at different stages of psychosis. Results confirmed the presence of some risk indicators in prodromal subjects (as childhood adversities and cognitive dysfunction) but also showed that conclusions about the qualification of these measures as true “risk markers” are limited. It is difficult to grasp a mental disorder with a complex etiology and high heterogeneity by only focusing on single risk indicators. Therefore, the combination of clinical, environmental, and genetic/physiological risk indicators in a staging model, on the basis of proven screening instruments, seems favorable. Since most risk indicators are not specific for schizophrenia but predict various psychiatric illnesses, it is not recommendable to use a “one for all” approach, but a risk stratification approach to take into account potential different subtypes of at-risk individuals. In order to develop guidelines concerning the selection and application of specific risk measures, future longitudinal studies with sufficient follow-up periods and consistent monitoring, as well as large multi-center studies are urgently needed. Eventually, the identification of robust risk indicators will provide the basis for the future development and evaluation of necessary early interventions in vulnerable individuals.
Conducted studies and own contributions

The present dissertation includes three different studies, which were kindly supported and co-authored by several colleagues. Therefore, the author’s own research contributions are mentioned below.

Study (1)
“Mismatch negativity and cognitive performance in the course of schizophrenia”

Authors: Vanessa Hirt, David Schubring, Inga Schalinski, and Brigitte Rockstroh

My contributions: I supervised and organized the recruitment of study participants and collected the data with support by my colleagues. I processed the EEG data in collaboration with David Schubring and conducted the statistical analyses. I prepared the first draft of the manuscript, including tables and figures, with later adjustments by the co-authors and myself.
Study (2)

“Decoding the impact of adverse childhood experiences on the progression of schizophrenia”

Article published in *Mental Health and Prevention*.

Authors: Vanessa Hirt, Inga Schalinski, and Brigitte Rockstroh

**My contributions:** I supervised the recruitment of study participants and contributed to data collection, mainly in collaboration with Inga Schalinski. I conducted the statistical analyses and drafted the manuscript, tables, and figures with the support of my co-authors.

Study (3)

“Family history, cannabis use, and adverse childhood experiences as risk factors of schizophrenia”

**My contributions:** I contributed to data collection and conducted the statistical analyses. I prepared the manuscript, tables, and figures.
References


References


References


References


References


References

demiological, clinical, neuropsychological and biological findings. *Neuroscience and Biobehavioral Reviews*, 75, 393–406.


References


References


References


References


Vogel, M., Meier, J., Grönke, S., Waage, M., Schneider, W., Freyberger, H. J., & Klauer, T. (2011). Differential effects of childhood abuse and neglect: Mediation by posttraumatic dis-
tress in neurotic disorder and negative symptoms in schizophrenia? *Psychiatry Research*, 189, 121–127.


