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Universitäre Psychiatrische Kliniken Basel

A multi-perspective approach to early detection of psychosis

A Cumulative Dissertation

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by

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Inhalt

List of abbreviations

APS	Attenuated Psychotic Symptoms
ARMS	At-Risk Mental State
BDNF	Brain-Derived Neurotrophic Factor
BIP	Basel Interview for Psychosis
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BS	Basic Symptoms
BSIP	Basel Screening Instrument for Psychosis
BPRS	Brief Psychiatric Rating Scale
CM	Case-Manager
CPT	Continuous Performance Test
CS	Chronic Schizophrenia
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
HC	Healthy Control
FCQ	Frankfurt Complaint Questionnaire
FEP	First-Episode Psychosis
FePsy	Früherkennung für Psychosen (English: Early Detection Of Psychosis)
GRD	Genetic Risk and Deterioration syndrome
ICD-10	International Classification of Diseases 10th Revision
LPS	Leistungsprüfsystem, scale 3
MWT-A	Mehrfachwahl-Wortschatz Test Version A
NP	Neuopsychology
PS	Paranoid Scale
SANS	Scale for the Assessment of Negative Symptoms
SCID	Structured Clinical Interview for DSM-IV
TAP	Test of Attentional Performance
ToH	Tower of Hanoi
UPK	Universitäre Psychiatrische Kliniken (English: University of Basel Psychiatric Hospital)

Abstract English

Background: Early detection of psychosis has been a highly investigated field of research in the last 20 years. However, decreasing transition rates show the need for further markers to improve prediction of transition of those with a potential risk of developing psychosis.

Methods: In the present doctoral thesis I aimed at improving early detection of psychosis by using a multimodal approach. Therefore, neurocognition, (potential) biological markers namely serum and plasma BDNF (study 1) and, prolactin (study 2), and psychopathology (study 3) were investigated. At-risk mental state (ARMS), first-episode psychosis (FEP), and in one study also chronic schizophrenia (CS) patients were recruited. Furthermore, a special focus was on potential gender differences because knowledge about these differences can lead to improved early detection and treatment.

Results: Altered BDNF levels were found, with lowest in ARMS, intermediate in FEP, and highest in CS. Plasma BDNF correlated positively with executive functioning. Also, prolactin levels were found to be altered in antipsychotic naïve ARMS and FEP patients, with hyperprolactinemia being more frequent in women compared to men in both groups even after correction for the normal biological variation. Lastly, small gender differences were found in very first self-perceived symptoms with women reporting more frequently anxiety and (sub-threshold) hallucinations and men more often cognitive and negative symptoms.

Discussion: Taken together the altered levels in the investigated biological markers are promising and might contribute to the improvement of early detection of psychosis. The observed small gender differences in psychopathology match previous results. A multimodal approach combining the different known predictors of psychosis is promising but more research is needed before the above named biological markers can be included in such a model.

Danksagung

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Ein großer Dank gilt auch meiner Familie und meinen Freunden für die Unterstützung, die aufmunternden und ermutigenden Worte und den Ausgleich zur Arbeit. Zu guter Letzt möchte ich mich auch noch von Herzen bei meinem Mann bedanken, der mich nicht nur ausgehalten, sondern in vielerlei Hinsicht unterstützt hat, und auch in anstrengenden Momenten an meiner Seite war und ist.

In jede hohe Freude mischt sich eine Empfindung der Dankbarkeit.

(Marie Freifrau von Ebner-Eschenbach)

Declaration by candidate

Hiermit erkläre ich, dass die Dissertation von mir selbst ohne unerlaubte Beihilfe verfasst worden ist. Die zur Promotion eingereichten Zeitschriftenbeiträge wurden in Zusammenarbeit mit den jeweiligen Koautoren angefertigt. Es handelt sich dabei um Originalarbeiten, die weder von den Beteiligten noch von anderen Personen an anderer Stelle veröffentlicht wurden.

Basel, Mai 2018

Ulrike Heitz

Preface

The present dissertation encompasses the following three original publications which have all been accepted or published in peer-reviewed journals:

1. **Heitz, U.**, Papmeyer, M., Studerus, E., Egloff, L., Ittig, S., Andreou, C., …& Riecher-Rössler, A. (2018). Plasma and serum brain derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients. The World Journal of Biological Psychiatry (accepted)

2. Ittig, S., Studerus, E., **Heitz, U.**, Menghini-Müller, S., Beck, K., Egloff, L., ... & Riecher-Rössler, A. (2017). Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women. Schizophrenia research, 189, 111-116.

3. **Heitz, U.**, Studerus, E., Menghini-Müller, S., Papmeyer, M., Egloff, L., Ittig, S., ... & Riecher-Rössler, A. (2017). Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis. Early intervention in psychiatry.

Introduction

Over the last 20 years research has focused on the early detection of psychosis. The aim of these efforts is to detect people with a so called at-risk mental state (ARMS) for psychosis before they potentially develop the full-blown illness to decrease the time of untreated psychosis (DUP), and subsequently improve the treatment outcome, or ideally even to prevent the onset of psychosis (Fusar-Poli et al., 2012).

In the following I will give a brief overview of the following topics. First, I will elucidate the importance and current knowledge in the field of research of early detection of psychosis. Second, the results regarding psychopathology in ARMS as compared to first-episode psychosis (FEP) patients will be described. Third, the current knowledge of neuropsychological deficits in FEP and ARMS will be reviewed. Fourth, the present knowledge regarding potential biomarkers, especially peripheral brain-derived neurotrophic factor (BDNF) and prolactin will be reviewed. Fifth, the psychopathology of FEP and ARMS will be reviewed. Sixth, gender specific knowledge in FEP and ARMS will be summarized. And lastly, the hypothesis of the present doctoral thesis will be given.

Early detection of psychosis

Psychosis is still considered as one of the most severe mental illnesses. It has an important impact on the patients, their families but also regarding health care costs. Even though, the live time prevalence is only about 1 percent according to a recent review the costs are estimated to range from 0.02% to 1.65% of the gross domestic product with 80% of the included studies coming from high-income countries (Chong et al., 2014).

A fast onset of an adequate treatment of psychosis is considered to be of great importance for the later prognosis of the illness. It has been found that a delayed treatment can have severe negative consequences on several domains which will be briefly named in the following. The prognosis is poorer and the remission of the symptom is later and/ or incomplete. Furthermore, the compliance of the concerned individuals has been found to be poorer with a delayed treatment which in turn again impacts the prognosis. Also, the cognitive performances were found to deteriorate further with a delayed treatment onset. Moreover, the psychological and social development are stronger impaired and the quality of live was found to be lower in patients with a later treatment. Considering all these points it is understandable that the costs for the health care system are increased and that the burden for the patients and the families are heavier (Olesen et al., 2012).

As a result of these negative consequences of a delayed treatment of psychosis researches have focused on investigating the prodromal phase of this illness.

Definition of an at-risk mental state

It is now known, that in most cases the onset of a full-blown psychosis is preceded by a so called prodromal phase as shown in Figure 1. The following risk criteria are commonly used to detect ARMS patients (Fusar-Poli et al., 2012):

- Basic symptoms (BS): There exist different definitions of basic symptoms. Basic symptoms are subtle, subclinical disturbances in stress tolerance, drive, affect, thinking, speech, (body) perception, motor action, and central-vegetative functions that are self-experienced with full insight into their abnormal nature(Schultze-Lutter & Theodoridou, 2017).
- Genetic Risk and Deterioration syndrome (GRD): Since it is known that there is a high genetic component in the development of psychosis, many research groups also include patients with first degree relatives in their at-risk group. Most study groups combine this category with a drop in functioning or other symptoms are present and only include patients if both are present.
- Attenuated psychotic symptoms (APS): These describe sub-threshold psychotic symptoms which differ in terms of intensity from full-blown psychotic symptoms e.g. alterations in perception such as hearing noises but knowing that these are not real as compared to acoustic hallucinations of voices with the persuasion that these are real. These symptoms must be present at least several times per week persisting for more than one week.
- Brief Limited Intermittent Psychotic Symptoms (BLIPS): Defined as clearly psychotic symptoms with an intensity as seen in a full-blown psychotic episode but lasting no longer than 7 days and remitting spontaneously without antipsychotic medication.

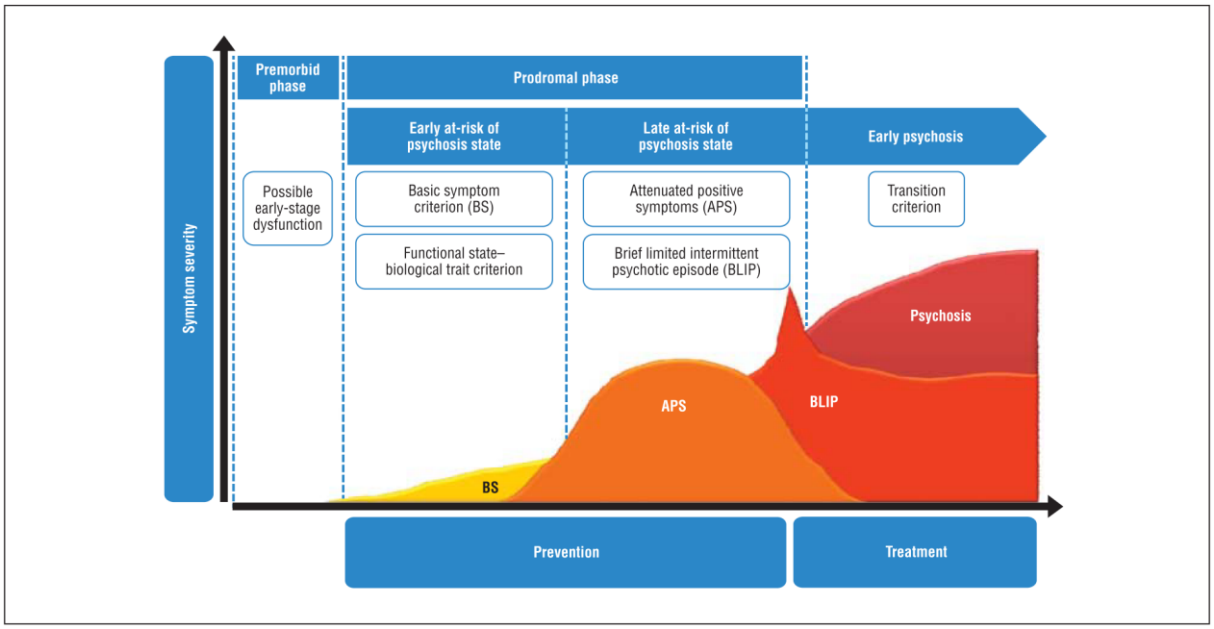

Figure 1: Model of psychosis onset from the clinical high-risk state. The higher the line on the y-axis, the higher the symptom severity (from Fusar-Poli et al., 2013)

Depending on the study protocol the above described prodromal states are used to assess if a patient is at-risk of developing psychosis. Accordingly, different instruments have been developed to assess the risk status. The most common are listed in Table 1.

Name	Author (Year)	Risk categories
BSABS (Bonn Scale for the Assessment of Basic Symptoms)	Gross et al. (1987)	BS
BSIP (Basel Screening Instrument for Psychosis)	Riecher-Rössler et al. (2008)	APS BLIPS GRD “Unspecific risk category”
CAARMS (Comprehensive Assessment of At-risk Mental States)	Yung et al. (2005)	APS BLIPS GRD
SPI-A (Schizophrenia Proneness Instrument, Adult version)	Miller et al. (1999)	BS
SIPS (Structured Interview for Prodromal Symptoms)	McGlashan et al. (2001)	APS BLIPS GRD

Table 1: Overview of commonly used interviews assessing a potential at-risk mental state.

Patients with a risk status are hence defined slightly differently depending on the instrument used and the research group. Accordingly, also the name given to patients with an elevated risk for developing psychosis vary depending on these factors. The following terms are the most commonly used ones:

- ARMS: At-risk mental state
- CHR: clinical-high risk
- UHR: ultra-high risk
- PRS: psychosis risk syndrome

In the present thesis the term ARMS will be used. Independent of the diagnostic criteria, a significant clinical distress can be observed in patients with an ARMS. Therefore, those who fulfil these criteria are referred to as being "patients" instead of individuals in this thesis to account for the clinical implications of the risk status.

It should be noted that recently the "attenuated psychosis syndrome" (APS) has been incorporated in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013) in Section III under "conditions for further study" showing the growing recognition and importance of subthreshold psychotic experiences and the (potential) prodromal phase of psychotic disorders.

Transition to psychosis

The transition to psychosis is commonly defined according to the criteria developed by Yung et al., (1998): At least one positive psychotic symptom occurring at least several times per week for more than one week. The following symptoms are therefore considered according to their definition in the Brief Psychiatric Rating Scale (BPRS): Hallucinations (≥ 4); Unusual thought content (≥ 5); Suspiciousness (≥ 5); Conceptual disorganisation (≥ 5).

At the beginning of this field of research transition rates were found to be as high as 50% within the first year of follow-up (Miller et al., 2002). However, in recent years transition rates have been found to decrease as summarized in a meta-analysis finding transition rates of 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years (Fusar-Poli et al., 2012). A recent study with a cohort of 202 ultra-high risk individuals who were followed up for 12 months found a transition rate of only 15.8% (Polari et al., 2018). Several potential reasons for this drop in transition rates have been suggested such as earlier and more accurate interventions for those at risk (Simon, Umbricht, Lang, & Borgwardt, 2014; Alison R. Yung et al., 2007). This increase of false positives however shows the need for further markers for those truly at risk to improve the prediction of transition.

In an attempt to improve the prediction of transition to psychosis the North American Prodrome Longitudinal Study (NAPLS) developed an Individualized Risk Calculator (Cannon et al., 2016) which was also validated by another group (Carrión et al., 2016) using a multimodal approach including different potential predictors of transition to psychosis. This approach also offers the benefit for the

concerned patients to have a more accurate estimation of their individual risk of transition which in turn might lead to more individualized treatment options such as pharmacological interventions for those with a high risk of transition.

The FePsy Study

The studies of the present doctoral thesis were part of the FePsy (Früherkennung für Psychosen; English: early detection of psychosis) project which is conducted at the Universitäre Psychiatrische Kliniken (UPK; English: University of Basel Psychiatric Hospital) Switzerland.

FePsy is an open, prospective clinical study aiming at facilitating and improving the early assessment of beginning psychoses respectively of the risk for psychosis and contributing to the knowledge about the potential prodromal stage of this disorder and improving the prediction of transition to psychosis.

Patients are thoroughly examined at study entry and ARMS patients are followed up for 5 years. Follow-ups take place monthly during the first year, every three months during year two and three, and annually in the last two years of the study. See Figure 2 for a flowchart of the procedure.

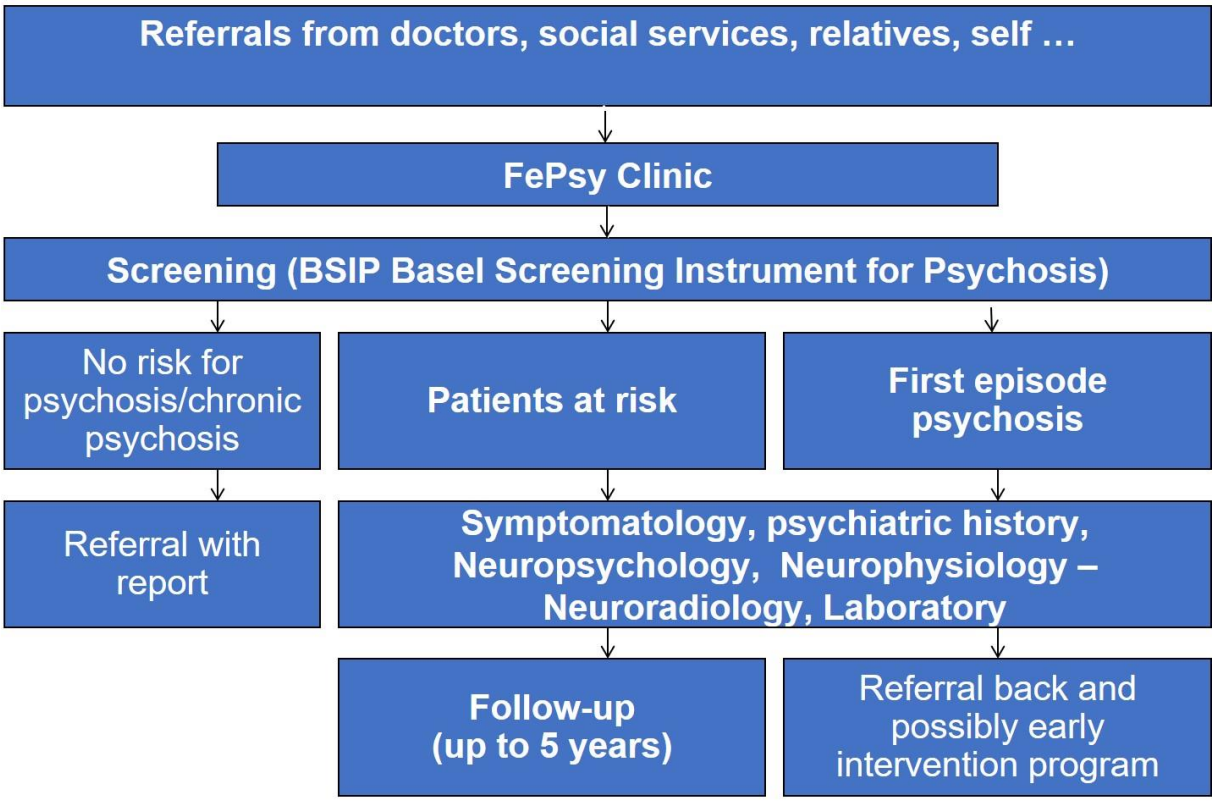

Figure 2: Design of the FEPSY Study.

The following clinical interviews are part of the FePsy study (in order of conduct): BSIP (Riecher-Rössler et al., 2008), Structured Clinical Interview for DSM (SCID; First, Gibbon, Spitzer, & Benjamin, 1997) and BIP (A. Riecher-Rössler et al., 2015). BPRS (Lukoff, Nuechterlein, & Ventura, 1986; Ventura

et al., 1993) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989) are used as observer-rating instruments. The participants are also asked to complete the following self-rating questionnaires: Frankfurt Complaint Questionnaire (FCQ) and paranoid scale (PS). In addition, a neuropsychological assessment is carried out testing multiple cognitive domains (see below). Finally, MRI, EEG and blood tests are also part of the initial assessment.

At the follow-up assessments only the clinical interviews are repeated with the BPRS being used for the monthly and three-monthly assessments and BIP, SANS and BPRS at the annual assessments.

In the FePsy study a case-manager (CM) approach is used. Each patient is taken care of by one CM throughout the entire screening and follow-up period, e.g. all different assessments such as EEG, MRI and clinical interviews are organized by the CM and the interviews are also carried out by the responsible CM. Case-managers are either psychologists or psychiatrists who get an extensive training prior to their first assessments. Moreover, all CM participate in monthly psychopathology trainings which include all used scales and interviews. The trainings are conducted by experienced clinical psychologist or the head psychiatrist.

Further details regarding the FePsy study procedure can be found in previous publications (Riecher-Rössler et al., 2007, 2009).

Neurocognition

Neurocognition in FEP

Neurocognitive deficits have been a core symptom of psychotic disorders since their first description by Kraepelin who initially called his observed syndrome “dementia praecox” as severe cognitive deficits seemed to be the core of the disorder. Nowadays it is known that neurocognitive deficits are only one of the main symptoms of psychotic disorders, but they are still considered as one of its core features.

Cognitive deficits can be observed already in patients with an ARMS, have repeatedly been found in FEP patients and continue to exist over the course of the disorder. However, recent meta-analysis did show that these deficits do not deteriorate over time but seem to be rather stable after illness onset.

Cognitive deficits have been observed in almost all cognitive domains including working memory, verbal memory, executive function, attention, speed of information processing and visuo-spatial abilities (Bora & Murray, 2014; Fusar-Poli, Deste, et al., 2012; Hauser et al., 2017).

Neurocognition in ARMS

Also, in ARMS patients, significant cognitive deficits have been found across cognitive domains. Hence cognitive performances have also been used to improve the prediction of a transition to psychosis (Studerus, 2016).

A recent meta-analysis by Hauser et al. (2017) revealed the following: Compared to HCs, people with CHR performed significantly worse in 7 of 9 domains (attention/vigilance Hedges g effect size [95% confidence limit] = -0.17 [-0.30, -0.04]; verbal learning, speed of processing g=0.42 [-0.64, -0.20]; social cognition g=-0.43 [-0.68, -0.18]). Compared to FEP subjects, people with CHR performed significantly better in 5 of 6 domains (speed of processing g=0.29 [0.03, 0.56]; attention/vigilance, verbal learning g=0.39 [0.17, 0.62]; working memory g=-0.40 [0.18, 0.64]). Those with a later transition to psychosis performed significantly worse in 6 of 8 domains (attention/vigilance g=-0.24 [-0.44, -0.03]; verbal learning g=-0.49 [-0.76, -0.22]; visual learning g=-0.54 [-0.80, -0.27]).
Other reviews and meta-analyses found similar results with cognitive deficits being already present in ARMS and being more pronounced in those with later transition as compared to those without transition (Bora & Murray, 2014).
Overall cognitive deficits seem to exist already in the prodromal phase of psychosis and might improve the prediction of transition in those individuals at risk.

Biological markers

Overview of biological markers

In an attempt to further improve the prediction rate of ARMS patients to full-blown psychosis numerous potential biomarkers have been investigated. In a recent review of investigated biomarkers (Anita Riecher-Rössler & Studerus, 2017) the authors found the following biological approaches in early detection of psychosis: MRI (structural and functional), EEG, ERP, cognition, visual saccades, binocular depth inversion, olfactory deficits, metabolic/ proteomic profiles, cortisol and genes.

Considering the number of potential biomarkers in the field of early detection of psychosis the focus will only be on prolactin and BDNF in the following.

Prolactin was chosen since hyperprolactinemia has been found in antipsychotic-naïve ARMS and FEP patients and as dopamine is the main prolactin inhibiting factor and is thought to be involved in the aetiology psychotic disorders. Moreover, hyperprolactinemia it is a known side effect of antipsychotics. Additionally, prolactin is also synthesized in response to stress. Based on all these findings the inclusion of this potential biomarker was made (Ittig et al., 2017).

BDNF was of special interest due to its role in cognitive processes (Carlino, De Vanna, & Tongiorgi, 2013) which are a core deficit in psychotic disorders and are also already present in the prodromal phase as described above.

Prolactin

Prolactin is a polypeptide hormone which is secreted by lactotroph cells of the anterior pituitary gland. It is involved in numerous biological functions, such as reproduction related processes including pregnancy and lactation, but also in growth and development. Prolactin secretion can be influenced by several factors namely gender, smoking, childbirth or psychopharmacological medication. Furthermore, it is also released in response to psychosocial stress (Fitzgerald & Dinan, 2008; Lennartsson & Jonsdottir, 2011).

Prolactin secretion is mainly regulated by dopamine which is considered to be the main prolactin inhibiting factor (PIF) (Fitzgerald & Dinan, 2008).

Hyperprolactinemia can lead to numerous adverse effects such as amenorrhea and galactorrhea, an acceleration of osteoporosis in women, and a lack of libido and erectile dysfunction in men, and may increase the risk of breast cancer in women (Rajkumar, 2014).

Prolactin in FEP

Two observations lead to an increasing interest in prolactin in FEP patients. First, antipsychotic medication act on the dopaminergic system, specifically the D2 receptor (Bennett, 1998) and it was found that dopamine neurotransmission is involved in the pathophysiology of psychosis (Howes et al., 2009). Furthermore, hyperprolactinemia was often observed as an adverse effect of antipsychotic treatments in schizophrenic patients (Peuskens, Pani, Detraux, & De Hert, 2014). Second, increasing evidence points towards the role of psychosocial stress in the development of psychotic symptoms (Aiello, Horowitz, Hepgul, Pariante, & Mondelli, 2012; van Winkel, Stefanis, & Myin-Germeys, 2008). As described above psychosocial stress is also known to influence the secretion of prolactin. It was therefore considered to be of interest to investigate the potential influence of prolactin on the development of psychotic disorders especially in interaction with psychosocial stress.

Studies investigating prolactin in participants suffering from psychotic disorders found correlations between the stress hormone prolactin and psychopathological symptoms (Rajkumar, 2014). Interestingly, it was also found that hyperprolactinemia does not only exist in psychotic patients receiving antipsychotics but also already in antipsychotic-naïve FEP patients. For example the European First Episode Schizophrenia Trial (EUFEST) found elevated prolactin levels in 40.5% of antipsychotic-naïve FEP patients (Riecher-Rössler et al., 2013).

These authors suggested the following explanation for these observations: as psychosocial stress is involved in the development of psychotic symptoms and is equally known to lead to prolactin synthesis and release it might hence possible that stress induces hyperprolactinemia and the release of dopamine is subsequently increased to down-regulate prolactin, leading to an increase of psychotic symptoms (Riecher-Rössler et al., 2013).

Prolactin in ARMS

Regarding prolactin levels in ARMS patients only few studies exist so far. Aston et al. (2010) found hyperprolactinemia in 23.8% of ARMS patients who were all antipsychotic-naïve. Labdad et al. (2015) also investigated a potential correlation of prolactin levels with a later transition to psychosis in ARMS patients and found that those with a later transition had higher prolactin levels than those without later transition. However, in a Cox Regression adjusted for sex, cannabis use and antidepressant treatment prolactin was not associated with the time to psychosis transition. Furthermore Perkins et al. (2015), used a machine learning algorithm to improve prediction of transition to psychosis. In their model prolactin was not selected as a potential predictor of transition in a sample of 72 ARMS patients.

BDNF

BDNF is the most common neurotrophin in the human brain. It is known to be involved in the synthesis, differentiation, maintenance, and survival of neurons, both in the central and in the peripheral nervous system (Kuipers & Bramham, 2006). It has repeatedly been shown to have an important role in cognitive processes especially learning and memory, as supported by animal (Bekinschtein et al., 2008; Yamada & Nabeshima, 2003) and human studies (Carlino et al., 2013).

In line with these findings BDNF is found to be highly expressed in cortical areas involved in these cognitive processes such as hippocampal and prefrontal areas (Bekinschtein et al., 2008; Conner, Lauterborn, Yan, Gall, & Varon, 1997).

BDNF can also be detected in the peripheral nervous system, where it can be assessed in blood serum and plasma. Although the exact source of the peripheral BDNF is not yet completely understood, it is known that BDNF can cross the blood-brain barrier, as shown in animal studies (Pan, Banks, Fasold, Bluth, & Kastin, 1998). Additionally, cortical and peripheral BDNF levels have been found to correlate positively in various animal studies (Karege, Schwald, & Cisse, 2002; Klein et al., 2011).

BDNF in FEP

Due to the well-known cognitive deficits in patients with psychotic disorders and the role of BDNF in cognitive impairments this patient group has become a focus of interest and cortical and peripheral BDNF levels were found to be altered in patients with schizophrenia. Post-mortem studies in these patients allowed to localise altered central BDNF levels in memory related areas such as the hippocampus (Durany et al., 2001; Weickert et al., 2003). A study investigating serum BDNF levels and those assessed in the cerebrospinal fluid also found a positive correlation of these two measures

(Pillai et al., 2010). Based on the so far described knowledge about the correlation of cortical and peripheral BDNF levels in general and in this patient group the peripheral measure of serum and plasma BDNF are commonly used in this field of research. Reviews and meta-analyses of peripheral BDNF levels in patients with schizophrenia point towards decreased levels in FEP patients which further decrease in chronic, and accordingly older, psychosis patients (Buckley, Pillai, & Howell, 2011; Fernandes et al., 2014; Green, Matheson, Shepherd, Weickert, & Carr, 2011; Martinotti et al., 2012; Toll & Mane, 2015).

The potential association of peripheral BDNF levels and cognitive performances in patients with schizophrenia has also been investigated in several studies. While most of these studies point towards a positive association of certain cognitive functions with peripheral BDNF levels (Asevedo et al., 2013; Carlino et al., 2011; Hori et al., 2017; Niitsu et al., 2011; Ruiz de Azua et al., 2013; Zhang, Chen da, et al., 2012; Zhang, Liang, et al., 2012) others found mixed results, i.e., positive or negative correlations of peripheral BDNF with cognition depending on the assessed cognitive domain (Niitsu et al., 2014; Xiao et al., 2017) or no association between these two parameters (Buckley, Pillai, Evans, Stirewalt, & Mahadik, 2007; Fisher, Mellon, Wolkowitz, & Vinogradov, 2016; Goto et al., 2009; Man et al., 2018; Theleritis et al., 2014; Vinogradov et al., 2009). The authors of a meta-analysis concluded that there is a small but significant positive association of peripheral BDNF with reasoning and problem-solving, and with overall cognitive capacity in patients with schizophrenia (Ahmed, Mantini, Fridberg, & Buckley, 2015).

BDNF in ARMS

Despite the strong interest in the prodromal phase of psychosis and the above described observed onset of cognitive deficits prior to transition to frank psychosis, no study investigated peripheral BDNF levels in an ARMS sample at the time of submission of our article investigating this aspect.

However, recently the first findings regarding peripheral BDNF levels in ARMS patients was published from the Longitudinal Youth at Risk Study (Yee, Lee, & Lee, 2018). According to the authors, ARMS patients had significantly higher baseline levels of serum BDNF compared with a healthy control group. However, baseline levels of serum BDNF did not predict the development of psychosis or remission from the ARMS status.

Gender specific aspects of psychosis

Gender differences in schizophrenic psychoses have been discussed since the beginning of research in this field. Already Kraepelin described an earlier onset in men with poorer premorbid development, more affective flattening and social anhedonia as compared to female patients (Lewine, 1988).

The aim of the research investigating potential gender differences in patients suffering from psychotic disorders is to better understand the aetiology of the disorder, and to further improve the treatment with potentially gender specific interventions.

In the field of early detection, the knowledge about potential gender differences might contribute to an improvement of the detection of individuals at-risk and to further improve the prediction of transition.

Gender specific aspects in FEP

An earlier age of onset in men is one of the most replicated findings regarding gender differences in schizophrenia (see Figure 1Figure 3), while women have a second peak of illness onset around menopause (Cascio, Cella, Preti, Meneghelli, & Cocchi, 2012; Eranti, MacCabe, Bundy, & Murray, 2013; Häfner et al., 1991, 1993, 1998). It has been suggested that the higher oestrogen levels in women prior to menopause have a protective effect leading to the later age of onset (Häfner et al., 1991, 1993; Anita Riecher-Rössler, 2017).

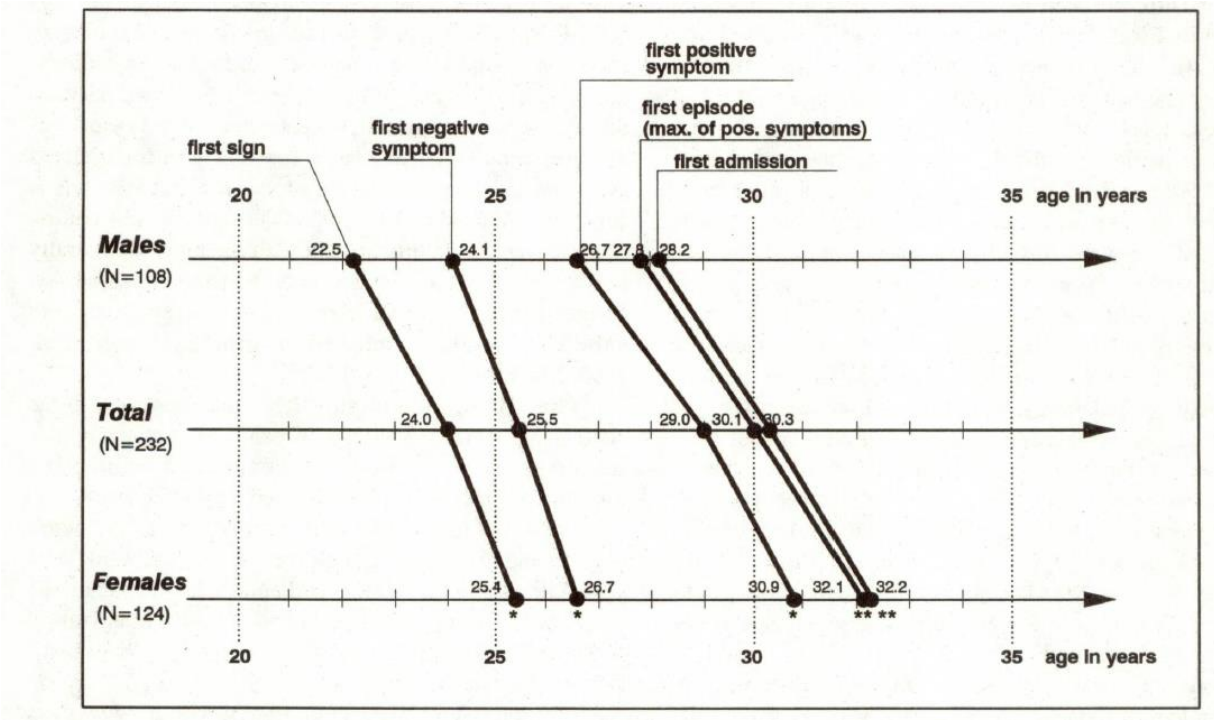

*Figure 3: Differences between men and women: *p≤0.05; p≤0.01. (First episode sample of broad definition schizophrenia, n=232.), from Häfner et al (1998).*

Additionally, recent reviews indicate a slightly increased incidence of schizophrenic psychoses in men compared to women (Aleman, Kahn, & Selten, 2003; McGrath, 2006; van der Werf et al., 2014). Moreover, men have been found to abuse substances more frequently and to have less illness insight, worse treatment adherence, and poorer functional and social outcome (Abel, Drake, & Goldstein, 2010; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Regarding symptomatology research

points toward more negative symptoms and lower levels of (social) functioning in men and more affective and positive psychotic symptoms in women (Cotton et al., 2009; Thorup et al., 2014; Waford et al., 2015). However, these findings are not consistent with some groups finding no or only small gender differences regarding symptomatology (Barajas, Ochoa, Obiols, & Lalucat-Jo, 2015; Bertani et al., 2012).

Potential gender differences have also been investigated in biological markers of psychosis. For example the meta-regression of gender conducted by Nordholm (2013) suggests that differences in male/female ratio between patients and controls do have a major impact on pituitary gland volume, with a bigger pituitary volume in females. Also regarding hormonal functioning gender differences in patients with psychosis have been found (Canuso & Pandina, 2007; Anita Riecher-Rössler, 2017).

Gender specific aspects in ARMS

In order to get a better understanding of the origin of psychosis and to further improve early detection and prediction of transition potential gender differences have also been investigated in ARMS patients.

Poorer performances in men as compared to women in social and role functioning was found in ARMS patients, similar to the pattern observed in FEP patients (Barajas et al., 2015; Willhite et al., 2008).

Also, regarding symptomatology similar patterns were found in ARMS patients as compared to FEP patients, with men showing more severe negative and cognitive symptoms, while more positive sub-threshold psychotic symptoms and affective symptoms were found in female ARMS patients (Barajas et al., 2015; Corcoran et al., 2011; Holtzman, Shapiro, Trotman, & Walker, 2012; Willhite et al., 2008). However, other studies could not confirm these gender differences in symptomatology (Gonzalez-Rodriguez et al., 2014; Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005; Lemos-Giraldez et al., 2009; Rössler, Hengartner, Ajdacic-Gross, Haker, & Angst, 2012; Willhite et al., 2008; Ziermans, Schothorst, Sprong, & van Engeland, 2011).

Cocchi et al (2014) suggested that this discrepancy between findings in FEP and ARMS stems from the limitation that only a minority of ARMS patients develop full-blown psychosis which might explain why sex differences are less evident in ARMS samples.

The potential impact of gender specific knowledge on prediction of transition was investigated by Walder et al. (2013) who found that poorer baseline social functioning and baseline positive prodromal symptoms predicted significantly greater risk of conversion among males only.

Regarding potential gender differences in biological markers of ARMS patients no sound data are yet available as the research on these markers in this patient group is still ongoing.

Aim & Hypotheses

The aim of the present doctoral thesis was to contribute to the scientific knowledge about different characteristics of ARMS patients with the intention to advance the detection of individuals at risk and to improve the prediction of transition to psychosis in these individuals.

More specifically peripheral BDNF and prolactin levels were investigated to get a better understanding of the biological underpinnings of an emerging psychotic disorder, and in the case of BDNF their potential association with cognitive functioning in ARMS and FEP patients. Furthermore, potential gender differences in first self-perceived signs and symptoms were investigated to assess whether they might contribute to an improved early detection.

Hypotheses regarding peripheral BDNF levels

1. Both plasma and serum BDNF are highest in ARMS, intermediate in FEP, and lowest in CS
2. Higher BDNF levels are associated with better cognitive performance in all patient groups

Hypotheses regarding prolactin levels

1. Increased frequencies of hyperprolactinemia in ARMS and FEP patients
2. Higher prolactin levels in FEP as compared to ARMS patients
3. More elevated prolactin levels in men than in women after correction for normal gender variations
4. A positive association of prolactin with psychopathological symptoms
5. Higher baseline prolactin levels being predictive of transition to psychosis in ARMS patients

Hypothesis regarding potential gender differences in the symptomatology

1. Overall only small gender differences would be observable in the first self-perceived symptoms of ARMS and FEP patients

Discussion

Discussion of BDNF results

The observed pattern of higher peripheral BDNF levels in CS, intermediate in FEP and lowest in ARMS patients contradicts our hypothesis and previous research regarding the CS and FEP group (Green et al., 2011; Martinotti et al., 2012).

Regarding BDNF levels in ARMS only one recently published study exists so far. In this publication ARMS were found to have higher serum BDNF levels when compared to a healthy control group (Yee et al., 2018). Unfortunately, in our study we did not assess an HC group.

Furthermore, BDNF levels vary substantially between studies so that a direct comparison of the observed levels is also not suitable (Green et al., 2011). There are numerous potentially influencing factors regarding peripheral BDNF levels such as age (Xiu et al., 2009), gender (Begliuomini et al., 2007), medication (Rizos et al., 2010), nicotine (Bhang, Choi, & Ahn, 2010), stress (Brunelli et al., 2012), body weight (Pillai et al., 2012), season and sunlight (Molendijk et al., 2012). The so far existing studies vary regarding those influencing factors taken into account. It might hence be possible that those methodological differences lead to the observed differences in BDNF levels. Simply creating a mean of the so far measured BDNF levels does hence not seem to be appropriate considering the amount of potentially influencing factors and the considerable differences in BDNF levels. Taken together, no firm conclusion about BDNF levels in ARMS patients can be drawn yet. It seems however, that in both studies an unexpected pattern was observed, which deserves further investigation.

Due to the small sample size we were unable to differentiate further between those ARMS with and without later transition to psychosis. A prediction regarding the risk of transition based on BDNF levels is hence not possible based on our data. However, in the one existing study also investigating serum BDNF levels in an ARMS sample, the authors found no predictive value of baseline serum BDNF levels. Similarly, BDNF levels also did not predict remission from the ARMS status (Yee et al., 2018).

Based on these surprising results it is not yet possible to draw any firm conclusions regarding peripheral BDNF levels in patients with schizophrenia over the course of the illness, and especially in the (potential) prodromal phase. Nevertheless, the surprisingly low BDNF levels in ARMS patients might point towards pathological processes preceding the transition to psychosis. Regarding our data it might also be speculated that BDNF levels normalize during the course of the illness and possibly due to the (pharmacological) treatment of the patients, while cognitive deficits persist, which has been shown in previous meta-analyses of longitudinal studies (Bora & Murray, 2014; Irani, Kalkstein, Moberg, & Moberg, 2011).

Plasma BDNF levels were significantly and positively associated with Tower of Hanoi (ToH) performance, as a measure of executive function, and at a trend-level with global cognitive performance, which is in line with our hypothesis. Also most previous studies investigating the potential association between cognition and peripheral BDNF points towards a positive correlation of these two parameters, as supported by a recent meta-analysis (Ahmed et al., 2015) which found higher BDNF levels to be associated with better performances in the domain of reasoning/problem solving and overall performances. The author argue however that the overall association might be driven by the positive association of reasoning/problem solving with BDNF. The same might be true for our fining, i.e. that the positive association of plasma BDNF with ToH performances lead to the trend-wise association of BDNF and global cognitive performances.

To improve our knowledge about peripheral BDNF levels in (emerging) psychosis the following considerations should be taken into account in future study designs. Bigger sample sizes are needed, as well as the inclusion of a healthy as well as a clinical control group, as altered BDNF levels have also been found in other patient groups (Cattaneo, Cattane, Begni, Pariante, & Riva, 2016). The inclusion of healthy controls should also be considered due to the considerable variation of BDNF levels between studies, which impedes a direct comparison of BDNF levels (Green et al., 2011). In order to get a deeper understanding of BDNF level changes in the course of psychotic illnesses longitudinal designs should be favoured over our cross-sectional study design.

Discussion of Prolactin results

Our results of an increased percentage of hyperprolactinemia in ARMS and FEP patients matched not only our hypothesis but also previous studies (Aston et al., 2010; Riecher-Rössler et al., 2013). In addition, we could replicate these findings in antipsychotic-naïve patients, with rigorous exclusion criteria and blood collection under controlled conditions.

Prolactin levels did not differ between ARMS and FEP patients, which is accordance with Montalvo et al. (2014) who also compared these two groups. As there are so far only few studies comparing BDNF levels in those two patient samples, it might only be speculated what the mechanism behind these observations is. One potential explanation might be that ARMS and FEP patients have equal levels of stress leading to similar amounts of prolactin. However, studies investigating cortisol, a stress hormone, reported higher levels in FEP as compared to ARMS patients contradicting this speculation (Aiello et al., 2012; Holtzman et al., 2012; Walker et al., 2013). Hence, more research is needed before any firm conclusion can be drawn about the factors leading to increased prolactin levels in ARMS and FEP patients.

Prolactin was also not found to be predictive of later transition based on our data, which is in line with one previous study (Perkins et al., 2015) and with the findings from Labad et al. (2015) when the

latter one included gender in their analysis. Taken together the few existing studies do not suggest a predictive value of prolactin in the prediction of transition to psychosis in ARMS patients.

The following sex difference emerged in the sample of our study: prolactin was more increased in women as compared to men, even after correction for the normal biological variation. This finding contradicts the results of a meta-analysis by Gonzalez-Blanco et al. (2016). However, in this meta-analysis only studies with healthy control groups were included leading to the exclusion of one previous study by Riecher-Rössler et al. (2013) also reporting hyperprolactinemia to be more frequent in antipsychotic-naïve FEP women compared to men.

As hyperprolactinemia can have severe clinical consequences such as an acceleration of osteoporosis in women and a lack of libido and erectile dysfunction in men (Rajkumar, 2014; Rubio-Abadal et al., 2016) it is of clinical importance to assess a potential alteration of prolactin levels especially in patients with psychotic disorders even prior to antipsychotic treatment. As these symptoms are often attributed to antipsychotic medication leading potentially to non-compliance regarding pharmacological treatment which in turn can have negative consequences regarding the prognosis of the illness. For all these reasons prolactin levels should be measured prior to any pharmacological treatment to offer the best available care.

It should be noted that it is so far still unknown if prolactin levels are specific for emerging psychosis or reflect general pathological mechanisms of emerging illness. Therefore, future studies should ideally include clinical as well as healthy control groups. Furthermore, stress is known to influence prolactin levels and in the present study stress levels were not assessed. This should also be considered for future study designs.

Discussion of Psychopathology results

The observed pattern of few gender differences with women reporting more anxiety and positive psychotic symptoms and men reporting (trend-wise) more frequently negative and cognitive symptoms as being among their first self-perceived signs and symptoms at illness onset are partly in line with the one previous study investigating first self-perceived symptoms in FEP patients who also reported more worrying in women and more trouble with thinking and concentration in men (Häfner et al., 1995). Moreover, other previous reports investigating current symptomatology in ARMS (Barajas et al., 2015; Pruessner et al., 2017; Rietschel et al., 2015; Waford et al., 2015) and FEP (Moukas, Gourzis, Beratis, & Beratis, 2010; Thorup et al., 2007) patients also point towards more negative symptoms in men and more (sub-threshold) positive symptoms in women. It should however be noted, that other studies did not find any gender differences regarding symptomatology in ARMS and FEP patients (Bertani et al., 2012; Gonzalez-Rodriguez et al., 2014; Kotlicka-Antczak et al., 2016).

Taken together the existing literature, it might be speculated that small gender differences exist regarding symptomatology with men showing more negativeand women more anxiety or affective and (sub-threshold) positive symptoms. It is however likely that the effect size of this gender difference is rather small which might explain the heterogeneity in findings due to a lack of statistical power. Furthermore, Fusar-Poli et al. (2012) pointed out that gender differences might be more pronounced in FEP patients compared to ARMS patients due to the unspecific nature of this latter group.

It should also be noted that Walder et al. (2013) suggested that the prediction of transition to psychosis could be improved by considering gender as it might moderate the influence of other important predictors, such as social functioning and positive psychotic symptoms.

Limiting our findings, it should be noted that despite our attempt to capture the first self-perceived symptoms as soon as possible there were on average almost five years between the appearance of the first symptoms and our assessment. This might have led to some recall bias. Furthermore, illness insight might be impaired in patients suffering from psychotic disorders, especially during the acute phase (Gerretsen, Plitman, Rajji, & Graff-Guerrero, 2014) while this is less likely to be altered in the premorbid phase. Also men and women may differ in their symptom perception, awareness, and their willingness to report specific symptoms (Berger, Addis, Reilly, Syzdek, & Green, 2012). It is hence not possible to eliminate the possibility that the observed gender differences are at least in part due to reporting and recall biases.

General discussion and further directions

In an attempt to synthesize the results of the studies included in the present dissertation the following conclusions can be drawn. Peripheral BDNF levels were surprisingly low in ARMS patients which might point towards an important pathological process prior to the onset of full-blown psychosis. The positive correlation of plasma BDNF levels with executive functions might provide a link to the well-established cognitive deficits of psychotic disorders which are already present in ARMS patients (U. Heitz et al., 2018). Also, prolactin levels have been found to be altered already in antipsychotic-naïve ARMS and FEP patients. And hyperprolactinemia was more frequently found in ARMS and FEP women as compared to men even after correction for the normal biological variation. This might be due to a sex specific stress reaction regarding prolactin (Ittig et al., 2017). Regarding psychopathology only small gender differences were found with women reporting more often anxiety and (sub-threshold) hallucinations and men more often cognitive and negative symptoms as being among their first self-perceived symptoms (Ulrike Heitz et al., 2017).

The surprisingly low BDNF levels in ARMS compared to FEP and CS patients might be a valuable further marker to detect individuals with an elevated risk to develop psychosis, especially when

combined with other biological and clinical markers such as prolactin, psychopathology or neuropsychology with the aim of improving the accuracy of early detection.

It should however be noted that especially regarding the above discussed biological markers, i.e. prolactin and particularly BDNF, only little is known so far in ARMS samples for example regarding the mechanisms leading to these altered levels. So clearly more research with sound methodology and representative samples are needed before any firm conclusions can be drawn. We hope that the present studies contribute to this ongoing process.

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Appendix

1. Publication 1: Plasma and serum brain derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients

2. Publication 2: Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women

3. Publication 3: Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first episode psychosis

4. Curriculum vitae

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ORIGINAL INVESTIGATION

Plasma and serum brain-derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients

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ABSTRACT

Objectives: Brain-derived neurotrophic factor (BDNF) is involved in numerous cognitive processes. Since cognitive deficits are a core feature of psychotic disorders, the investigation of BDNF levels in psychosis and their correlation with cognition has received increased attention. However, there are no studies investigating BDNF levels in individuals with an at-risk mental state (ARMS) for psychosis. Hence, the aims of the present study were: (1) assessing peripheral BDNF levels across different (potential) stages of psychosis; (2) investigating their association with cognition.

Methods: Plasma and serum BDNF levels and neuropsychological performance were assessed in 16 ARMS, six first-episode psychosis (FEP), and 11 chronic schizophrenia (CS) patients. Neuropsychological assessment covered intelligence, verbal memory, working memory, attention and executive functioning.

Results: Both plasma and serum BDNF levels were highest in CS, intermediate in FEP and lowest in ARMS. Multiple regression analysis revealed a significant positive association of plasma BDNF levels with planning ability across all groups.

Conclusions: The lower peripheral BDNF levels in ARMS compared to FEP and CS might point towards an important drop of this neurotrophin prior to the onset of frank psychosis. The associations of peripheral BDNF with planning-abilities match previous findings.

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1. Introduction

The presence of cognitive deficits is a consistent finding in patients with psychotic disorders. These apply to most cognitive domains including working memory, verbal memory, executive function, attention, speed of information processing and visuo-spatial abilities (Fusar-Poli et al. 2012; Bora and Murray 2014; Hauser et al. 2017), and are considered to be a core feature of these disorders (Szoke et al. 2008).

Long-term (Agnew-Blais et al. 2015) and cross-sectional studies (Bora et al. 2014) have shown that cognitive impairments are present long before the onset of overt psychotic symptoms (Riecher-Rössler et al. 2009; Mollon and Reichenberg 2017). However, they do not appear to progress after the transition to full-blown psychosis or during the further course of the illness (Szoke et al. 2008; Bozikas and Andreou 2011; Irani et al. 2011; Bora and Murray 2014; Bora et al. 2017). Moreover, among subjects identified as having an at-risk mental state (ARMS) for psychosis, those with a later transition exhibit more pronounced neurocognitive deficits than those who will not go on to develop a psychotic disorder (Studerus et al. 2016; Riecher-Rössler and Studerus 2017). However, despite their obvious significance for psychosis prediction as well as their importance for functional outcome, the neurobiological underpinnings behind the observed impairments remain largely unknown (Ruiz de Azua et al. 2013).

Over the last years, the role of brain-derived neurotrophic factor (BDNF) in cognitive impairments in patients with psychosis has become a focus of interest. BDNF is the most common neurotrophin in the human brain and is involved in the synthesis, differentiation,

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maintenance and survival of neurons, both in the central and in the peripheral nervous system (Kuipers and Bramham 2006). Its role in learning and memory has previously been supported by animal (Yamada and Nabeshima 2003; Bekinschtein et al. 2008) as well as human studies (for a review see Carlino et al. 2013). In line with these observations, BDNF is highly expressed in hippocampal and prefrontal cortical areas, which are crucial for these cognitive processes (Conner et al. 1997; Bekinschtein et al. 2008).

BDNF is also found in the peripheral nervous system and can be assessed in blood serum and plasma. Although the exact source of the peripheral BDNF is not yet completely understood, animal studies have shown that BDNF can cross the blood–brain barrier (Pan et al. 1998). Furthermore, several animal studies have reported positive correlations between serum BDNF and BDNF in both the prefrontal cortex and hippocampus (Karege et al. 2002; Sartorius et al. 2009; Elfving et al. 2010), suggesting that there might be a link between peripheral and central BDNF. Moreover, Klein et al. (2011) reported that blood BDNF concentration reflects brain-tissue BDNF level even across species.

Also, altered BDNF levels were found in patients suffering from psychotic disorders. Post-mortem studies in patients with schizophrenia point towards decreased cortical BDNF levels, especially in memory-related brain areas such as the hippocampus (Durany et al. 2001; Weickert et al. 2003).

Peripheral BDNF levels have also been investigated in patients with psychosis. In drug-naïve first-episode psychosis (FEP) patients, serum BDNF levels have also been reported to positively correlate with BDNF levels measured in the cerebrospinal fluid (Pillai et al. 2010). Based on these findings, BDNF blood levels are widely used in research as correlates of cortical BDNF. However, so far there is no consensus whether plasma or serum BDNF levels are more suitable correlates of cortical BDNF levels. While some authors have suggested to use serum as it might provide a more reliable measurement (Tsuchimine et al. 2014), others have argued in favour of plasma as it might better reflect processes in the central nervous system (Fernandes et al. 2014).

In patients with psychotic disorders, recent reviews and meta-analyses point towards reduced peripheral BDNF levels, with peripheral levels being already decreased in FEP patients and further declining in chronic and accordingly older patients (Buckley et al. 2011; Green et al. 2011; Martinotti et al. 2012; Fernandes et al. 2014; Toll and Mane 2015).

Until now, several studies have investigated the association between cognitive impairments and BDNF in patients with psychosis. The findings of these studies (summarized in Supplementary Table 1S) are inconsistent regarding the link of peripheral BDNF levels to cognition. The majority of these studies point towards a positive association of certain cognitive functions with peripheral BDNF levels (Carlino et al. 2011; Niitsu et al. 2011; Zhang, Chen et al. 2012; Zhang, Liang, et al. 2012; Asevedo et al. 2013; Ruiz de Azua et al. 2013; Hori et al. 2016; Sun et al. 2016; Hori et al. 2017; Zhang et al. 2018). However, other studies found mixed results, i.e. positive and negative associations depending on the cognitive domain (Niitsu et al. 2014; Xiao et al. 2017). Lastly, other research groups did not find any association between these two parameters (Buckley et al. 2007; Goto et al. 2009; Vinogradov et al. 2009; Theleritis et al. 2014; Fisher et al. 2016; Man et al. 2018). A recent meta-analysis concluded that there is a small but significant positive association of peripheral BDNF with reasoning and problem solving, and with overall cognitive capacity in patients with schizophrenia (Ahmed et al. 2015).

Despite the strong interest in the prodromal phase of psychosis and the above described observed onset of cognitive deficits prior to transition to frank psychosis, no study has investigated peripheral BDNF levels in an ARMS sample yet. Therefore, we aimed (1) to investigate plasma and serum BDNF levels across different (potential) stages of psychosis, including for the first-time ARMS as well as FEP and chronic schizophrenia (CS) patients, and (2) to examine the association of BDNF with neurocognitive performance in these patient groups.

Based on the above described literature, the following hypotheses were formulated: (1) both plasma and serum BDNF are highest in ARMS, intermediate in FEP and lowest in CS; (2) higher BDNF levels are associated with better cognitive performance in all patient groups.

2. Methods

2.1. Recruitment and setting

FEP and ARMS patients were recruited via the Früherkennung von Psychosen project (FePsy; English: early detection of psychosis) within the University of Basel Psychiatric Hospital (UPK), Switzerland. ARMS and FEP criteria were assessed using the Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al. 2008), which is based on the PACE criteria (Yung et al. 1998) and includes parts of the Brief Psychiatric Rating Scale (BPRS, expanded version by Lukoff et al. 1986; Ventura et al. 1993). A detailed

description of the FePsy study design can be found elsewhere (Riecher-Rössler et al. 2007; Riecher-Rössler et al. 2009). Individuals were classified as being in an ARMS if they met one of the following inclusion criteria: (1) attenuated or brief limited psychotic symptoms according to the criteria by Yung et al. (1998); (2) familial aggregation of psychotic disorders in combination with at least two further risk factors according to screening instrument in line with the criteria by Yung et al. (1998); (3) a minimal amount and combination of certain risk factors according to screening instrument by Riecher-Rössler et al. (2007). FEP patients had to fulfil the transition criteria of Yung et al. (1998), namely one of the following symptoms: suspiciousness (BPRS $\geq$5), unusual thought content (BPRS $\geq$5), hallucinations (BPRS $\geq$4), or conceptual disorganisation (BPRS $\geq$5), with the symptom occurring at least several times a week and being present for more than 1 week. Exclusion criteria were age $<$18 years, insufficient knowledge of German, IQ $<$70, previous psychotic episode, antipsychotic medication exceeding a cumulative chlorpromazine equivalent (CPE) dose of 2500 mg (according to Gardner et al. (2010) and Leucht et al. (2014)), psychosis clearly due to organic brain diseases or substance use, or psychotic symptomatology within a clearly diagnosed affective psychosis or borderline personality disorder.

CS patients were recruited in the forensic department of the UPK and had a diagnosis of schizophrenia, paranoid type according to ICD-10 criteria (International Statistical Classification of Diseases and Related Health Problems; World Health Organization 1994). There were no restrictions regarding comorbidities or medication in this group.

Only male participants were included in the present study, as BDNF levels can vary between the sexes and fluctuate along the menstrual cycle (Begliuomini et al. 2007). Additionally, nicotine use was measured in cigarettes per day, as nicotine has previously been found to be associated with higher BDNF levels in clinical and non-clinical populations (Bhang et al. 2010; Zhang et al. 2010). All participants gave their written informed consent. The study was approved by the committee of North-West and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz (EKNZ)) and was carried out in accordance with the declaration of Helsinki.

2.2. BDNF measures

Peripheral BDNF is mainly stored in blood platelets, while a small part circulates freely. Therefore, we assessed total soluble BDNF in serum, which includes BDNF released from platelets through clotting, in addition to plasma BDNF levels. For the assessment of BDNF levels, a blood sample was drawn between 07:00 and 09:00 h after overnight fasting according to a standardised protocol, using serum vacutainer tubes (Becton Dickinson) or citrate vacutainer tubes (Becton Dickinson). For serum sampling, the tube was inverted gently five to six times and allowed to stand for 60 min at room temperature. Subsequently, it was centrifuged at 1300 $\times$ *g* for 10 min. Regarding plasma BDNF, poor-platelet plasma was carefully prepared from blood centrifuged at 2000 $\times$ *g* for 10 min. All samples were stored in aliquots at $-80\,^{\circ}C$ before assaying BDNF content. Serum and plasma BDNF levels were assessed with an enzyme-linked immunosorbent assay (ELISA) kit (Promega BDNF Emax, Madison, WI, USA). Serum samples were appropriately diluted (between 1:100 and 1:150), while plasma samples were used undiluted, and detection of BDNF was carried out in an antibody sandwich format as described in the manufacturer's protocol. The absorbance was measured within 30 min in a microplate reader set at 450 nm and a correction wavelength set to 690 nm, to determine BDNF concentrations according to the standard curve. All assays were carried out in duplicate and means were calculated.

2.3. Neuropsychological assessment

The following measures were used to cover the cognitive domains of interest:

- Verbal and non-verbal intelligence: Mehrfachwahl-Wortschatz Test (MWT-A; Lehrl 1977) and Leistungsprüfsystem, scale 3 (LPS-3; Horn 1983), respectively.
- Verbal learning and memory: California Verbal Learning Test (CVLT; Delis et al. 1987).
- Working memory: two-back test of the Test of Attentional Performance (TAP; Zimmermann and Fimm 2002).
- Executive functioning: computerised version of the Tower of Hanoi (ToH; Gedika and Schöttke 2001) and Go/No-Go task of the TAP (Zimmermann and Fimm 2002).
- Sustained attention: computerised version of the Continuous Performance Test (CPT-OX; Rosvold et al. 1956).

2.4. Statistical analyses

BDNF values were tested for normality and plasma levels were log-transformed to achieve a normal distribution.

In all subsequently described analyses, the log-transformed plasma values were used. BDNF levels were compared between the patient groups (i.e. ARMS, FEP and CS) using a one-way ANOVA, with Bonferroni-corrected post hoc pairwise comparisons. Due to the small sample size, bootstrapping was performed to provide more robust estimates. Subsequently, an ANCOVA was carried out including age, CPE and cigarettes per day as possible confounding factors. In case of no antipsychotic or nicotine use, a value of 0 was used to include these participants in the analysis.

A global neuropsychology score comprising all tested domains was created. Furthermore, composite scores for each test of the neuropsychological battery were created. Variables for which high values indicated worse performance (e.g. reaction times) were inverted prior to the *z*-transformation, so that high values always indicated good performance. The test specific composite scores were the averages of the *z*-transformed performance scores of each test. The global cognitive performance score was the average over all *z*-transformed performance scores. This procedure was used to reduce the number of tests and hence to reduce the risk of false-positive results due to multiple testing. A description of this procedure can also be found in a previous publication of our research group (Rapp et al. 2013). An overview of the test variables used to create the composite scores can be found in the appendix (Supplementary Table 2S).

The composite scores were compared between patient groups using a one-way ANOVA, with Bonferroni-corrected post hoc comparisons. Again, bootstrapping was performed due to the small sample size. A second group comparison was carried out using an ANCOVA including age and CPE as possible confounding factors.

A Bonferroni-corrected multiple linear regression analysis was performed to assess the associations of group, age, years of education, CPE, and the two BDNF measures with each neuropsychological composite score.

Statistical significance was set at $\alpha \leq 0.05$. All analyses were carried out using IBM SPSS Statistics Version 24 running on Windows 7 Enterprise.

3. Results

3.1. Sample characteristics

A total of 33 participants were included in this study: 16 ARMS, six FEP and 11 CS patients. The CS sample was significantly older than the two other groups and received higher antipsychotic dosages (see Table 1). Nicotine use, measured in cigarettes per day, differed significantly between groups, being highest in CS, intermediate in FEP and lowest in ARMS individuals. There were no significant group differences regarding years of education.

3.2. BDNF

A significant main effect of group was found for both plasma and serum BDNF levels (Table 2 and Figure 1). Post hoc pairwise comparisons revealed that serum BDNF was significantly lower in ARMS as compared to both other groups (FEP $p = .033$; CS $p < .001$), while plasma BDNF differed at a significant level only

Table 1. Sample characteristics.

Variable	ARMS ($n = 16$)	FEP ($n = 6$)	CS ($n = 11$)	Significance
Age (years)	24.56 (±5.27)	29.40 (±6.27)	38.38 (±6.63)	>0.001
Years of education	12.69 (±2.80)	11.25 (±1.37)	10.91 (±1.26)	0.211[a]
Current use of antipsychotics (yes/no)	1/15	4/2	11/0	
CPE	20 (±0)	85.00 (±88.49)	1216.78 (±987.92)	0.049[b]
Current use of nicotine (yes/no)[c]	11/5	4/2	11/0	
Cigarettes per day[c]	11.82 (±11.68)	15.00 (±16.58)	31.88 (±14.62)	0.044[a]

Note. Mean (± standard deviation).
[a]Kruskal-Wallis test, otherwise one-way ANOVA.
[b]Independent sample *t*-test.
[c]Mean calculated based on those participant with current use only; antipsychotic dosage in chlorpromazine equivalents (CPE); at-risk mental state (ARMS), first-episode psychosis (FEP), chronic schizophrenia (CS); not applicable (n.a.).

Table 2. BDNF level comparison between ARMS, FEP and CS patients.

BDNF (ng ml^{-1})	ARMS ($n = 16$)	FEP ($n = 6$)	CS ($n = 11$)	Significance (ANOVA)	Significance (ANCOVA)[c]
Serum	19.11 (±4.67)	24.48 (±2.40)	28.08 (±3.99)	$F(2, 30) = 15.688$; $p < .001$	$F(2, 5) = 5.322$; $p = .015$
Plasma	0.30 (±0.29)[a]	0.54 (±0.54)[a]	1.31 (±1.06)[a]	$F(2, 30) = 9.835$; $p = .001$[b]	$F(2, 5) = 2.761$; $p = .090$[b]

Mean (± standard deviation).
[a]Non-log transformed values reported.
[b]Analysis carried out using the plasma log value.
[c]Significance after inclusion of age, nicotine use and chlorpromazine equivalent (CPE) as covariates; brain-derived neurotrophic factor (BDNF), at-risk mental state (ARMS), first-episode psychosis (FEP), chronic schizophrenia (CS).

between the ARMS and CS group ($p < .001$), again with lower values in the ARMS group. Plasma BDNF levels differed at a trend level between CS and FEP patients ($p = .089$), being lower in FEP.

After controlling for age, CPE and cigarettes per day use, serum BDNF values still differed significantly between the groups, while the main effect for plasma levels was only significant at a trend level (see Table 2). None of the included covariates had a significant effect on BDNF parameters.

3.3. Neuropsychology

The unadjusted group comparison of the neuropsychological composite scores revealed significant differences for the following tests: TAP Go/No-Go and the CVLT (see Table 3).

Post hoc pairwise comparisons indicated that the differences in Go/No-Go performance were due to poorer performance of the FEP group as compared to the other groups (ARMS $p = .004$; CS $p = .003$). The CS

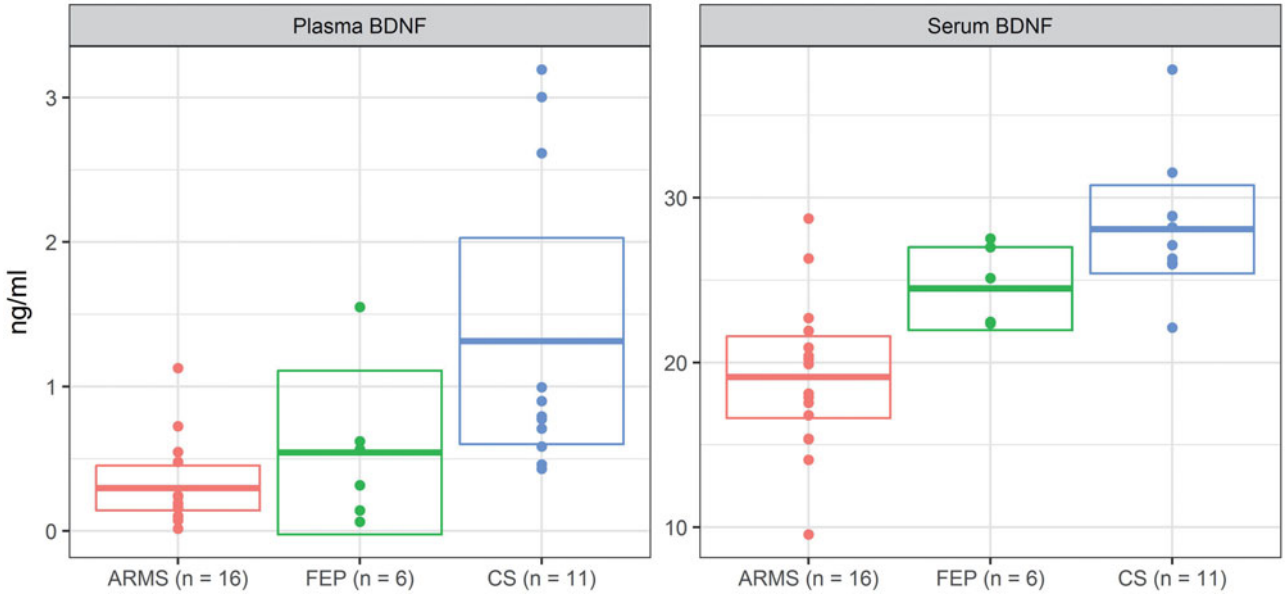

Figure 1. Plasma and serum BDNF levels in ARMS, FEP and CS. BDNF: brain-derived neurotrophic factor; ARMS: at-risk mental state for psychosis; FEP: first-episode psychosis; CS: chronic schizophrenia. Plasma and serum BDNF values are presented as non-log transformed values (ng/ml) with mean and 95% confidence intervals of the mean.

Table 3. Neuropsychological composite score comparison between ARMS, FEP and CS.

Variable	ARMS ($n = 13$)	FEP ($n = 5$)	CS ($n = 9$)	Significance (ANOVA)	**Significance (ANCOVA)[a]**
IQ	0.12 (±0.78)	−0.37 (±0.61)	−0.25 (±0.87)	$F(2, 24) = 1.027$; $p = .373$	$F(4, 25) = 1.041$; $p = .409$
ToH	−0.04 (±0.56)	−0.66 (±1.11)	0.25 (±0.85)	$F(2, 24) = 2.176$; $p = .135$	$F(4, 25) = 1.226$; $p = .330$
TAP Go/No-Go	0.18 (±0.55)	−0.93 (±0.95)	0.29 (±0.33)	$F(2, 24) = 8.171$; $p = .002$*	$F(4, 25) = 3.529$; $p = .024$*
TAP WM	0.02 (±0.77)	0.07 (±0.82)	−0.05 (±0.43)	$F(2, 24) = 0.019$; $p = .981$	$F(4, 25) = 0.134$; $p = .968$
CPT	0.12 (±0.47)	0.17 (±0.39)	−0.23 (±0.84)	$F(2, 24) = 1.027$; $p = .373$	$F(4, 25) = 0.807$; $p = .535$
CVLT	0.42 (±0.63)	0.36 (±0.94)	−0.71 (±0.84)	$F(2, 24) = 6.402$; $p = .006$*	$F(4, 25) = 2.744$; $p = .056$
Global	0.13 (±0.3)	−0.24 (±0.43)	−0.08 (±0.38)	$F(2, 24) = 1.881$; $p = .174$	$F(4, 25) = 0.952$; $p = .454$

Mean (± standard deviation).
*Significant at $p < .05$.
[a]Including age and chlorpromazine equivalent as covariate; at-risk mental state (ARMS), first-episode psychosis (FEP) and chronic schizophrenia (CS).

Table 4. Multiple regression.

Predictor	Global	IQ	ToH	TAP Go/No-Go	TAP WM	CPT	CVLT
Group	−0.241 (192)	−0.137 (0.375)	−0.028 (0.392)	0.039 (0.340)	0.422 (0.362)	−0.875 (0.302)°	−0.505 (0.375)
Age	−0.289 (0.015)	0.303 (0.030)	−0.328 (0.029)	0.153 (0.027)	−0.434 (0.029)	0.055 (0.024)	−0.343 (0.030)
Years of education	0.073 (0.038)	0.219 (0.074)	−0.153 (0.072)	0.408 (0.066)°	−0.063 (0.071)	−0.124 (0.059)	0.060 (0.072)
CPE	−0.116 (0.000)	−0.095 (0.000)	0.023 (0.000)	0.241 (0.000)	−0.381 (0.000)	0.100 (0.000)	−0.116 (0.000)
Serum BDNF	−0.230 (0.022)	−0.148 (0.043)	−0.435 (0.042)	−0.312 (0.040)	−0.376 (0.041)	0.252 (0.036)	0.404 (0.044)
Plasma BDNF	0.560 (0.150)°	−0.042 (0.205)	0.804 (0.201)*	o.132 (0.183)	0.298 (0.198)	0.406 (0.163)	0.026 (0.202)

Standardized coefficient (standard error).
*Significant at $p < .05$; °trend at $p < .1$.

group performed worse in the CVLT than the other groups (ARMS $p = .007$; FEP $p = .058$).

After including age as covariate, only the main effect for the TAP Go/No-Go remained significant ($p = .003$).

3.4. Multiple regression

The results of the multiple regressions can be found in Table 4. There was a significant positive association between plasma BDNF and ToH performance ($p = .015$) and trend-wise significant positive association between plasma BDNF and global cognitive performance ($p = .071$).

4. Discussion

In this cross-sectional study we found that plasma and serum BDNF levels differed between ARMS, FEP and CS patients, with the highest levels being evident in CS and the lowest in ARMS patients. Moreover, higher plasma BDNF levels were significantly associated with better ToH performance and at a trend-level with a better global cognitive performance score.

The observed pattern regarding peripheral BDNF levels contradicts the existing literature (Green et al. 2011; Martinotti et al. 2012) as well as our hypothesis of higher BDNF levels in ARMS and a decrease over the course of illness. In the present study, serum BDNF levels were significantly lower in ARMS patients compared to both other groups, but did not differ between FEP and CS patients. Plasma levels were only significantly lower in ARMS compared to CS patients. Unfortunately, we were not able to differentiate further between those ARMS patients who transitioned to psychosis and those who did not; therefore, it is not possible to interpret the observed pattern regarding transition to psychosis and hence the presence of a true prodromal state. Based on the present findings it might be speculated that the low peripheral BDNF levels in ARMS patients are associated with the clinical observation of a drop in functioning prior to the onset of frank psychosis, including poorer cognitive performance which occurs already in the pre-psychotic phase (Riecher-Rössler et al. 2009; Bora and Murray 2014). This might imply that the low BDNF levels in ARMS point towards pathological processes preceding the actual transition to psychosis. It might be possible that, during the course of the illness and possibly due to the (pharmacological) treatment of psychotic disorders, BDNF levels normalise while cognitive deficits persist, as the latter have been suggested by meta-analyses of longitudinal studies (Irani et al. 2011; Bora and Murray 2014). However, as this is the first study to investigate peripheral BDNF levels in ARMS individuals, more research is needed before any firm conclusions can be drawn.

The factors leading to altered BDNF levels in patients with psychotic disorders are still under debate. A review by Martinotti et al. (2012) revealed higher peripheral BDNF levels in patients suffering from paranoid psychosis compared to other psychotic subtypes. As the CS sample in the present study consisted only of patients with such a diagnosis, the higher plasma and serum BDNF levels in the CS group might partly be related to this factor. The restriction to the paranoid type in our study was made to reduce the variability in this patient group and to avoid a potential symptomatic overlap between depressive symptoms and negative symptoms, the latter being more present in other types of schizophrenia, since peripheral BDNF levels are also altered in patients with depression (Molendijk et al. 2014).

Contrary to previous studies (Zhang et al. 2010; Green et al. 2011) that reported an influence of age and nicotine on BDNF levels, these factors were not found to influence BDNF in the present study. Regarding medication, the observed lack of effect on BDNF levels in our study is in line with the meta-analysis of Green et al. (2011). However, in the more recent meta-analysis of Fernandes et al. (2014), the authors found an increase of BDNF in plasma but not in serum after antipsychotic medication, independent of the patient's response to the treatment. In our study, the inclusion of CPE reduced the significance to a trend level in plasma but not in serum. It might be speculated that plasma levels react more sensitively to antipsychotic treatment, but clearly more research is needed before any firm conclusions can be drawn. It should, however, be mentioned that it is still possible that these factors do influence BDNF levels, and that the present sample was too small to detect this association. We can, therefore, not completely rule out the possibility that the unexpectedly higher BDNF levels in the CS group compared to ARMS and FEP patients was influenced by the higher medication dosage and longer medication intake with a larger cumulative medication dose in the chronic patients.

Plasma BDNF levels were significantly and positively associated with ToH performance and at a trend-level with global cognitive performance, which is in line with our hypothesis and with most previous reports investigating the association of peripheral BDNF levels with neurocognitive performances. A recent meta-analysis (Ahmed et al. 2015) also indicated a positive association of peripheral BDNF levels with neurocognition

in patients with schizophrenia. In the meta-analysis, higher BDNF levels were associated with better performance in reasoning/problem solving and with overall performance across all neurocognitive measures. However, the authors suggested that the association with combined neurocognitive measures was driven by the positive association of BDNF levels with reasoning/problem solving. A similar pattern could also underlie the present results.

Due to its exploratory character, the present study suffers from certain limitations. First, the small sample size limits statistical power, which might have impeded the detection of group differences, and prevented further subgroup analyses. Second, no healthy control or clinical control groups were included. Therefore, the specificity of the results for psychosis cannot be clarified, especially as altered BDNF levels have also been found in other psychiatric disorders such as depression, bipolar disorder and anorexia (for a review see Cattaneo et al. 2016). Furthermore, BDNF levels in healthy control groups vary considerably across studies due to methodological differences (Green et al. 2011), so that the present BDNF levels cannot be compared to previous reports. Third, many factors that are known to affect BDNF levels, such as antidepressant medication (Polyakova et al. 2015), sleep deprivation (Guzman-Marin et al. 2006), stress (Giese et al. 2013), body weight (Pillai et al. 2012), drug consumption (D'Souza et al. 2009) or physical exercise (Dinoff et al. 2017) were not assessed in the present study. However, we tried to account for the most important confounding factors, namely age, years of education, nicotine use and antipsychotics. Fourth, the cross-sectional design limits the interpretability of the findings. Longitudinal studies are warranted to investigate the time course of BDNF levels across different stages of psychosis.

Strengths of the present study should also be mentioned, especially the inclusion of innovative elements that led to new insights. First, this is the first study to investigate BDNF levels in an ARMS sample. The pattern of results indicates that it is vital to further study peripheral BDNF levels in this patient population, to promote understanding of the biological underpinnings of clinical and cognitive processes preceding the onset of frank psychosis. A second strength of this study is the simultaneous analysis of plasma and serum BDNF, considering that there is no consensus so far as to which of the two parameters is a more suitable peripheral biomarker. Our results indicate that the free circulating plasma BDNF may be more closely associated with cognitive performance and should therefore be considered in future investigations.

In summary, the present study observed lower serum and plasma BDNF levels in ARMS patients compared to FEP and CS. This finding, although unexpected at first glance, might point towards an important pathological process prior to the onset of full-blown psychosis. The observed positive correlation between plasma BDNF and executive functions might provide a link to the well-established cognitive deficits of psychotic disorders, which are already present in the ARMS.

Regarding the potential implications of our study for the field of early detection, the surprisingly low peripheral BDNF levels in ARMS patients might be a valuable further marker to detect individuals at-risk for psychosis which might, in combination with other markers, improve the accuracy of early detection.

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Statement of interest

All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

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Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women

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ABSTRACT

Background: Hyperprolactinemia is a known side effect of antipsychotics. In recent reports it has also been shown in antipsychotic-naïve at-risk mental state (ARMS) and first-episode psychosis (FEP) patients. Prolactin is not only involved in reproduction and lactation, but is also synthesized in response to stress. As stress is thought to play an important role in the onset and relapse of schizophrenia, the aim of this study was to further elucidate the influence of prolactin in emerging psychosis.
Methods: The data analysed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen (***FePsy***) study. Blood sample collection took place under standardized conditions between 8 and 10 am after an overnight fast and 30 minutes of rest. All patients were antipsychotic-naïve and did not take any prolactin influencing medication.
Results: Our sample consisted of 116 antipsychotic-naïve ARMS and 49 FEP patients. Hyperprolactinemia was shown in 32% of ARMS and 35% of FEP patients. After correction for the normal biological variation between the sexes, we still found higher average prolactin levels in female than in male patients ($\beta = 0.42$; $t = 2.47$; $p = 0.01$) but no difference in prolactin levels between ARMS and FEP patients ($\beta = -0.05$; $t = -0.30$; $p = 0.76$). The survival analysis revealed no significant predictive value for prolactin levels to predict transition to psychosis.
Conclusion: Our findings support a possible role of prolactin in emerging psychosis and it could be speculated that stress, which can induce hyperprolactinemia, has a stronger effect on women than on men in emerging psychosis.

1. Introduction

Prolactin is a polypeptide hormone that is predominantly synthesized and secreted by lactotroph cells of the anterior pituitary gland. While its main function is to elicit lactation in mammals (Fitzgerald and Dinan, 2008), it is also involved in a broad spectrum of functions beyond reproduction and lactation. Most importantly, it is also released in response to psychosocial stress (Fitzgerald and Dinan, 2008; Lennartsson and Jonsdottir, 2011). There is compelling epidemiological evidence that psychosocial stress is implicated in the development of psychotic symptoms (Aiello et al., 2012; van Winkel et al., 2008). Previous research has shown an association between cortisol levels and severity of positive and nonspecific symptoms (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013), as well as correlations between the stress hormone prolactin and psychopathological symptoms (Rajkumar, 2014).

The main regulatory mechanism acting on prolactin is the inhibition of prolactin synthesis by dopamine. Dopamine itself is synthesized in neurons of the hypothalamus and then secreted through portal blood into the anterior pituitary where it exerts its inhibitory actions on prolactin-producing cells through D2 receptors. Dopamine is thus the main prolactin inhibiting factor (PIF) (Fitzgerald and Dinan, 2008). On the other hand, dopaminergic neurotransmission plays an important role in the pathophysiology of schizophrenic psychoses (Howes et al., 2009) which was inferred from the link between the antipsychotic efficacy of neuroleptic drugs and their affinity for the dopaminergic D2 receptor (Bennett, 1998). Hence, hyperprolactinemia is often described as a side effect of antipsychotics in patients with schizophrenic psychoses (Peuskens et al., 2014). However, there have also been recent reports on hyperprolactinemia in antipsychotic-naïve FEP and ARMS patients. Hyperprolactinemia in these patients could probably be explained by psychosocial stress (Riecher-Rössler et al., 2013), as it is implicated in the development of psychotic symptoms (van Winkel et al., 2008) and

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known to stimulate prolactin synthesis and release (Lennartsson and Jonsdottir, 2011). Riecher-Rössler et al. (2013) suggested that stress induces hyperprolactinemia and the resulting increase of dopamine in psychosis might be, at least in part, a regulatory mechanism to down regulate prolactin. The European First Episode Schizophrenia Trial (EUFEST) (Riecher-Rössler et al., 2013) found elevated prolactin levels in 40.5% of antipsychotic-naïve FEP patients. In a further study by Aston et al. (2010) hyperprolactinemia was found in 33.3% of antipsychotic-naïve FEP patients and even in 23.8% of ARMS patients. A recent meta-analysis (Gonzalez-Blanco et al., 2016) reported higher prolactin levels in antipsychotic-naïve male and female patients with schizophrenia compared to control groups of the same gender, although the effect was much more pronounced in men than in women. A recent study also found higher prolactin serum levels in drug naïve newly diagnosed patients with schizophrenia and other psychotic disorders compared to HC (Petrikis et al., 2016). Furthermore, Labad et al. (2015) showed that ARMS patients who later made a transition to psychosis (ARMS-T) had higher prolactin levels than those who did not (ARMS-NT). Moreover, one study conducted in patients with pituitary microadenoma (Cheng et al., 2013) showed significantly higher prolactin serum levels in antipsychotic-naïve patients with a pituitary microadenoma *with* psychosis than in patients with a pituitary microadenoma *without* psychosis. All these findings provide further evidence for an association of elevated prolactin levels and psychosis.

To further elucidate the role of prolactin in emerging psychosis we formulated the following hypotheses based on previous findings. We expected I) increased frequencies of hyperprolactinemia in ARMS and FEP patients (Aston et al., 2010), II) higher prolactin levels in FEP as compared to ARMS patients, and III) more elevated prolactin levels in men than in women (Gonzalez-Blanco et al., 2016). Moreover, as prolactin is also a stress hormone and stress is thought to have an influence on psychopathology (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013) we hypothesized to find IV) a positive association of prolactin with psychopathological symptoms and V) higher baseline prolactin levels being predictive of transition to psychosis in ARMS patients.

2. Methods

2.1. Setting and recruitment

The data analysed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen **(*FePsy*)** study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009). Participants were recruited for the study via the ***FePsy*** Clinic at the Psychiatric University Outpatient Department of the Psychiatric University Hospital Basel, which was set up specifically to identify and treat individuals in the early stages of emerging psychosis.

The study was approved by the ethics committee of the University of Basel and all participants provided written informed consent.

2.2. Screening procedure

Screening was performed with the Basel Screening Instrument for Psychosis (Riecher-Rössler et al., 2008). This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung et al., 2007; Yung et al., 1998) and has been shown to have a good interrater reliability ($\kappa = 0.67$) for the assessment of the main outcome category "at risk for psychosis" and a high predictive validity (Riecher-Rössler et al., 2008). Individuals were classified as being in an ARMS for psychosis, having a FEP, or being not at risk for psychosis (usually other psychiatric disorders).

For this study we included all ARMS and FEP patients that were recruited for the ***FePsy*** study from March 1, 2000 to February 29, 2016 who had undergone prolactin measurement. We excluded all patients who had ever taken antipsychotics or any prolactin-influencing medication at the time of assessment (i.e. hormonal contraception). Likewise, we excluded all patients with a medical condition potentially influencing prolactin status, such as hypothyroidism or pituitary abnormalities or in whom blood sampling and psychopathological assessment were >60 days apart.

All ARMS patients were followed-up at regular intervals for up to 5 years (in the first year monthly, second and third year 3-monthly and the last two years every year) (Riecher-Rössler et al., 2009) in order to distinguish those who later transitioned to frank psychosis (ARMS-T) from those who did not (ARMS-NT) using the transition criteria of Yung et al. (1998).

2.3. Prolactin measurement

The patients were asked to avoid stress, sports, physical activity, stimulation of breast and smoking during the last 12 h before blood sampling. Blood sample collection took place between 8 and 10 am after overnight fast and 30 min of rest (7.5 ml whole blood without any additions).

The **E**lectro**C**hemi**L**uminescence **I**mmuno**A**ssay "ECLIA" (Ref. Number 03203093 190, Roche Diagnostics GmbH D-68305 Mannheim) was used to measure prolactin levels. The method has been standardized against the 3rd IRP WHO Reference Standard 84/500 and hyperprolactinemia in this reference is defined as a value above the 97.5th percentile, that is >324 mU/l in men and >496 mU/l in women.

2.4. Psychopathological assessment

The Brief Psychiatric Rating Scale Expanded Version (BPRS-E) (Lukoff et al., 1986; Ventura et al., 1993) was used to assess positive psychotic symptoms, symptoms of depression/anxiety, negative symptoms as well as symptoms of activation as defined by Velligan et al. (2005).

2.5. Statistical analyses

All data were analysed using the R environment for statistical computing (R Core Team, 2015). Differences in sociodemographic and clinical characteristics between ARMS and FEP patients were tested with *t* and χ^2 tests. Prolactin was analysed both on a continuous and binary scale (above reference range of corresponding sex vs. within normal range) using linear and logistic regression models, respectively. In both models, prolactin served as dependent variable and group (ARMS vs. FEP) and sex (men, women) as independent variables. The models also included an interaction term between group and sex. When analysed on a continuous scale, prolactin values were first log-transformed (to accommodate positive skew) and then normalized for men and women separately based on the log transformed reference ranges for healthy men and women. The means and SDs of the log transformed normative samples for men and women were calculated by taking the means of log transformed upper and lower bounds of the reference ranges and by dividing the differences between log transformed upper and lower bounds of the reference ranges by 3.92, respectively. Thus, the normal sex difference in prolactin seen in healthy individuals was partialled out from our continuous prolactin measure before inclusion to the models.

To analyse the relationship between prolactin, group (ARMS, FEP) and psychopathology, linear regression models were performed with the four BPRS composite scores (see psychopathological assessment) serving as dependent variables. All continuous variables were centered and all analyses were performed with and without covariates (age and current use of antidepressants). Furthermore, *p*-values were adjusted for multiple testing using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

Finally, to test whether prolactin is predictive of later transition to psychosis (event) in the ARMS group and whether its association with

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Table 1
Socio-demographic and clinical sample characteristics.

	Total group $N = 165$	ARMS $N = 116$	FEP $N = 49$	p-Value
Gender				1.000
Women	49 (29.7%)	34 (29.3%)	15 (30.6%)	
Men	116 (70.3%)	82 (70.7%)	34 (69.4%)	
Age	26.1 (6.90)	25.1 (6.16)	28.4 (7.99)	0.011*
Years of education	11.6 (2.97)	11.5 (2.90)	11.7 (3.14)	0.774
Antidepressants ever	48 (29.1%)	42 (36.2%)	6 (12.2%)	0.004**
Antidepressants currently	41 (24.8%)	35 (30.2%)	6 (12.2%)	0.025*
Anxiolytics ever	31 (18.8%)	25 (21.6%)	6 (12.2%)	0.238
Anxiolytics currently	26 (15.8%)	20 (17.2%)	6 (12.2%)	0.568
BPRS Depression/Anxiety	9.38 (3.77)	8.81 (3.46)	10.8 (4.17)	0.007**
BPRS Psychosis/Thought Disturbance	7.56 (3.77)	6.05 (2.30)	11.3 (4.11)	<0.001***
BPRS Activation	5.79 (2.33)	5.39 (1.84)	6.75 (3.04)	0.008**
BPRS Negative Symptoms	5.33 (2.73)	4.95 (2.44)	6.26 (3.18)	0.017*
BPRS Total Score	42.0 (12.3)	37.8 (9.30)	52.4 (12.5)	<0.001***

ARMS = at-risk mental state; FEP = first episode psychosis; BPRS = brief psychiatric rating scale; *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$; continuous variables are described by means and standard deviation in parentheses.

later transition is different for men and women, survival analysis using a Cox proportional hazard model was performed. For this purpose, all ARMS patients regardless of their follow-up duration were included in the analyses since survival analyses take into account censored observations (no event during observation time). The Cox regression model included time to transition as dependent variable and prolactin (log-transformed and normalized) and sex and their interaction as predictors. Age and current use of antidepressants served as covariates in our model.

3. Results

3.1. Sample description

181 ARMS and 132 FEP patients were recruited for the ***FePsy*** study from March 1, 2000 to February 29, 2016. Because of missing prolactin measurements we excluded 46 ARMS and 53 FEP patients. Further, we excluded 19 ARMS and 30 FEP patients either because of lifetime antipsychotic medication, current hormonal contraception, any other current prolactin influencing medication or because blood sampling and psychopathological assessment were >60 days apart. Thus, we performed the analyses on the remaining sample consisting of 116 ARMS and 49 FEP patients. The excluded individuals did not differ from those included with regard to sex, age, years of education and BPRS total score. The mean difference between the assessment of the BPRS and blood sample collection was 8.18 days (S.D. = 9.52). Sociodemographic as well as clinical characteristics of the included individuals are presented in Table 1.

3.2. Hyperprolactinemia in ARMS and FEP patients

Hyperprolactinemia, i.e. blood levels higher than the normal range, was present in 32% of ARMS (28% of men and 41% of women) and 35% of FEP patients (26% of men, 53% of women) (Table 2).

3.3. Effect of sex and patient group on prolactin levels

When prolactin was analysed on a continuous scale, there was a significant main effect of sex ($\beta = 0.35$; $t = 2.47$; $p = 0.01$) but no significant main effect of group (ARMS vs. FEP) ($\beta = -0.04$; $t = -0.30$; $p = 0.76$) and no significant interaction between sex and group ($\beta = -0.07$; $t = -0.48$; $p = 0.63$). The main effect of sex was due to significantly higher average prolactin levels in female than in male patients even after correction for the normal sex difference in prolactin levels of healthy individuals.

Prolactin values in ARMS and FEP patients subdivided in men and women are displayed in Fig. 1. For the means, S.D., median and range of the normalized prolactin values per patient group (ARMS/FEP) and sex (men/women) see Table 2.

When prolactin was analysed on a binary scale (Hyperprolactinemia vs. normal prolactin values), there was again a significant main effect of sex ($\beta = 0.44$; $z = 2.25$; $p = 0.02$), no significant main effect of group ($\beta = -0.10$; $z = -0.53$; $p = 0.60$) and no significant interaction between sex and group ($\beta = -0.14$; $z = -0.74$; $p = 0.46$), indicating that hyperprolactinemia was more frequent in female than in male patients independent of diagnostic group.

When repeating the analyses with covariates age and antidepressants the results did not change.

3.4. Effects of prolactin and patient group on psychopathology

For each BPRS subscale (Total, Psychosis/Thought Disturbance, Depression/Anxiety, Negative Symptoms, Activation) there was a significant main effect of patient group, which was due to more severe psychopathology in FEP compared to ARMS patients (see Table 3).

However, there were no significant main effects of prolactin on these BPRS subscales and no significant interactions between prolactin and diagnostic group (ARMS/FEP) after correction for multiple testing (see Table 3, also for uncorrected values). When repeating the analyses

Table 2
Hyperprolactinemia and normalized prolactin values in antipsychotic-naive ARMS and FEP patients.

	ARMS			FEP		
	Men ($n = 82$)	Women ($n = 34$)	Total ($n = 116$)	Men ($n = 34$)	Women ($n = 15$)	Total ($n = 49$)
Proportion of patients with hyperprolactinemia, n (%)	23 (28)	14 (41)	37 (32)	9 (26)	8 (53)	17 (35)
Prolactin normalized						
Mean ± S.D.	1.201 ± 1.481	1.766 ± 1.451	1.366 ± 1.489	1.150 ± 1.695	1.989 ± 1.601	1.407 ± 1.696
Median	1.188	1.723	1.355	0.787	2.043	1.507
Range	−2.526–5.103	−1.104–4.476	−2.526–5.103	−2.398–5.265	−0.962–4.104	−2.398–5.265

ARMS = at-risk mental state; FEP = first episode psychosis.
S.D., standard deviation.

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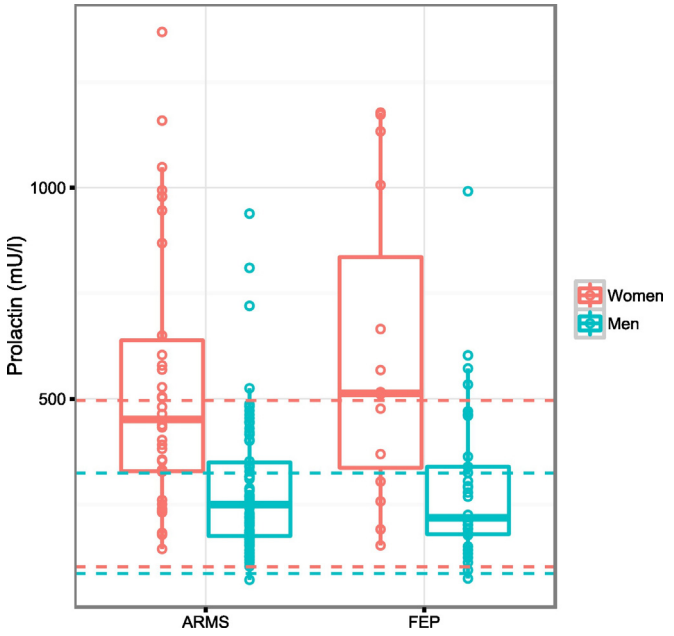

Fig. 1. Prolactin serum levels in ARMS and FEP patients subdivided by sex. The dotted horizontal lines represent the upper and lower reference levels for men and women. ARMS = at-risk mental state; FEP = first episode psychosis.

with the covariates age and antidepressants the results did not change substantially (see Table 3).

3.5. Prolactin as predictor of transition to psychosis

To investigate if prolactin values can predict later transition to psychosis and if the predictive value is different for men and women, we conducted a survival analysis within the ARMS group ($n = 116$, number of events 23, follow-up duration ARMS-NT: mean = 2.99 years, SD = 0.19, follow-up duration ARMS-T: mean = 1.24, S.D. = 0.32). The analyses revealed no significant predictive value of prolactin levels and no interaction effect with the variable sex (see Table 4).

4. Discussion

In this study, the role of prolactin was investigated in 116 antipsychotic-naïve ARMS and 49 antipsychotic-naïve FEP patients. In line with our hypothesis, we could replicate the finding of an increased percentage of patients suffering from hyperprolactinemia in antipsychotic-naïve ARMS and FEP patients even when blood was taken under controlled conditions and rigorous exclusion criteria were applied. Furthermore, we found that prolactin was more increased in women than in men after correction for the normal biological variation between the sexes. Contrary to our hypotheses, we could not show a difference in prolactin levels between ARMS and FEP patients; prolactin was not significantly associated with any BPRS subscale and none of these associations were moderated by patient group (ARMS, FEP). Moreover, prolactin was not a significant predictor of transition to psychosis.

While only 2.5% of people in the normal population are expected to fulfil criteria for hyperprolactinemia according to our reference standard, we found in our sample of antipsychotic-naïve ARMS and FEP patients that 32% of ARMS and 35% of FEP suffered from hyperprolactinemia. Similarly high proportions have been reported in previous studies (Aston et al., 2010; Riecher-Rössler et al., 2013). Hyperprolactinemia requires clinical attention because it can have severe consequences, including amenorrhea, galactorrhea, an acceleration of osteoporosis in women and a lack of libido and erectile dysfunction in men (Rajkumar, 2014; Rubio-Abadal et al., 2016). These consequences

Table 3
Influence of prolactin and diagnostic group (ARMS, FEP) on psychopathological symptoms.

	Model 1 BPRS Psychosis/Thought Disturbance *without covariates*	Model 2 BPRS Depression/Anxiety	Model 3 BPRS Negative Symptoms	Model 4 BPRS Activation	Model 5 BPRS total	Model 6 BPRS Psychosis/Thought Disturbance *with covariates*	Model 7 BPRS Depression/Anxiety	Model 8 BPRS Negative Symptoms	Model 9 BPRS Activation	Model 10 BPRS total
Prolactin normalized	−0.20	−0.17	−0.06	−0.12	−0.52	−0.16	−0.20	−0.08	−0.09	−0.45
	(0.13)	(0.17)	(0.12)	(0.10)	(0.48)	(0.13)	(0.17)	(0.12)	(0.10)	(0.48)
Group (FEP/ARMS)	5.23***[***]	2.00**[**]	1.35**[**]	1.39**[***]	14.77***[***]	4.84***[***]	2.23**[**]	1.49**[**]	1.10**[**]	13.90***[***]
	(0.52)	(0.66)	(0.48)	(0.40)	(1.85)	(0.53)	(0.68)	(0.50)	(0.41)	(1.91)
Prolactin normalized: Group (FEP/ARMS)	−0.31	−0.36	0.15	−0.40	−1.03	−0.36	−0.34	0.17	−0.44[*]	−1.15
	(0.27)	(0.34)	(0.25)	(0.21)	(0.95)	(0.26)	(0.34)	(0.25)	(0.20)	(0.95)
Covariate Age						0.07	0.01	−0.02	0.08*[**]	0.24
						(0.03)	(0.04)	(0.03)	(0.03)	(0.12)
Covariate Antidepressants currently						−1.03	1.55[*]	0.39	−0.27	−0.57
						(0.56)	(0.71)	(0.52)	(0.43)	(2.00)
R^2	0.41	0.07	0.06	0.10	0.31	0.44	0.10	0.06	0.15	0.32
Adj. R^2	0.40	0.05	0.04	0.08	0.29	0.42	0.07	0.03	0.12	0.30
Num. obs.	152	151	151	151	151	152	151	151	151	151
RMSE	2.92	3.69	2.68	2.24	10.34	2.88	3.67	2.69	2.20	10.28

Linear regression coefficients and standard deviation in brackets; $^{*}p \le 0.05$; $^{**}p \le 0.01$; $^{***}p \le 0.001$ (after correction for multiple testing). Stars in [] represent uncorrected p-values. BPRS = brief psychiatric rating scale; Group = ARMS or FEP (at risk-mental state patient group or first-episode of psychosis patient group).

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Table 4
Prolactin as potential predictor of transition to psychosis - Cox proportional hazard model.

	Hazard ratio	95% CI	*p*
Prolactin normalized	1.151	0.737–1.798	0.536
Prolactin normalized * sex	1.095	0.690–1.739	0.699
Sex	1.078	0.679–1.710	0.749
Age	1.037	0.980–1.098	0.204
Antidepressants currently	1.281	0.794–2.065	0.31

CI = confidence interval.

are often attributed to antipsychotics and can be a reason for non-compliant behaviour. Thus, it is of utmost importance to measure prolactin levels before treatment to reveal a possible pre-existing hyperprolactinemia.

Contrary to the meta-analysis of Gonzalez-Blanco et al. (2016) we found higher normalized prolactin levels and more frequent hyperprolactinemia in women than in men. Gonzalez-Blanco did only include studies with a healthy control group and therefore disregarded an important study in the field. Riecher-Rössler and the EUFEST study group (2013) found hyperprolactinemia to be present in 50% of antipsychotic-naïve female FEP patients but only in 36.5% of antipsychotic-naïve male FEP patients. Our finding of higher prolactin levels in women is also supported by a study of Lennartsson and Jonsdottir (2011) who demonstrated that women showed stronger prolactin responses to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), albeit only at a trend-level.

Our finding of a non-significant difference in prolactin levels between ARMS and FEP patients is in agreement with the only other study that compared prolactin levels between ARMS and FEP patients (Montalvo et al., 2014). This could indicate that stress levels are not higher in FEP than in ARMS patients. On the other hand, studies investigating the stress hormone cortisol have reported higher levels in FEP than in ARMS patients (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013). In a similar vein, our finding of non-significant associations between prolactin and BPRS subscales is difficult to reconcile with previous research which has shown an association between the stress hormone cortisol and the severity of positive and nonspecific symptoms (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013). However, it is consistent with our finding of no difference in prolactin levels between ARMS and FEP patients and with a study of Shrivastava and Tamhane (2000) who did not find an association of prolactin with BPRS (although their study had a small sample size: men; $N = 19$, women; $N = 8$). Further studies are needed to clarify the association between prolactin and psychopathological symptoms.

Although we could not confirm that prolactin is predictive of transition to psychosis, this result is consistent with Perkins et al. (2015) who measured expression of plasma analytes reflecting inflammation, oxidative stress, hormones and metabolism in a sample of 72 ARMS patients and found that prolactin was not selected as a predictor of transition to psychosis by a machine learning algorithm. However, contradictory results were found by Labad et al. (2015). Therefore, on the basis of the above described studies no definite conclusion can be drawn.

A limitation of our study is that blood sampling did not take place on the same day as the psychopathological assessment, and probably not at time of peak symptom severity. Thus, prolactin levels may have not entirely reflected stress levels at the time of psychopathological symptom assessment. Future studies should also assess individual perceived stress levels using, for example, the perceived stress scale (Cohen et al., 1983), ideally at the time of psychopathological assessment and at the time of blood sampling. The question whether elevated prolactin levels are specific for emerging psychosis or rather generally associated with emerging illness (e.g. depression etc.) still remains. Hence, recruitment of control groups (e.g. depressive controls but also healthy controls) would help to further clarify the role of prolactin in emerging psychosis.

Taken together, our results provide further evidence for frequent hyperprolactinemia in emerging psychosis and that this can be observed in antipsychotic-naïve patients (ARMS, FEP). Moreover, women in our patient sample (ARMS, FEP) had higher prolactin levels even after correction for the normal biological variation, which potentially provides an indication for a sex dependent stress reaction regarding the hormone prolactin.

Conflict of interest

All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

Contributions

SI was responsible for the literature review, the conduct of statistical analyses, the interpretation of the same and the drafting of the manuscript. ES assisted with the design of the analyses, the conduct and interpretation of the same. UH, SMM, KB, LE and LL were responsible for the data collection. ES, UH, SMM, KB, LE, LL, CA and ARR critically revised the manuscript. ARR conceived and designed the study and leads the project. All authors read and approved the final manuscript.

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WILEY

ORIGINAL ARTICLE

Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis

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Aim: Gender differences in the current symptomatology of patients with psychotic disorders have previously been described in the literature. However, it has not yet been investigated whether gender differences exist in the very first self-perceived signs or symptoms of illness onset. The aim of this study was to investigate this aspect in at-risk mental state (ARMS) and first-episode psychosis (FEP) patients.

Methods: ARMS and FEP were recruited via the early detection of psychosis (FePsy) clinic Basel, Switzerland. The Basel Interview for Psychosis (BIP) was used to retrospectively assess the first 3 self-perceived signs and symptoms at illness onset. Differences between gender and patient groups on single item and symptom cluster levels were analysed using logistic regression models.

Results: One-hundred-thirty six ARMS (91 men, 45 women) and 89 FEP patients (63 men, 26 women) could be recruited for this study. On a single item level, women more frequently reported "unusual anxiety, fears" and men (at a trend level) "social withdrawal" as being among their 3 first self-perceived symptoms, independent of diagnostic group. On the symptom cluster level, women more frequently reported "increased worrying/anxiety" and (sub-threshold) "hallucinations", independent of diagnostic group. Problems with "thinking, concentration" were reported more frequently by men in the ARMS group only.

Conclusion: Our results suggest that only few and relatively small gender differences exist in the first self-perceived signs and symptoms. While men initially mainly notice negative/cognitive symptoms, women first notice (sub-threshold) positive and affective symptoms.

KEYWORDS

BIP, gender, prodromal, psychopathology, psychotic disorder

1 | INTRODUCTION

Gender differences in schizophrenic psychoses have long been reported and debated. Among the most replicated findings are differences in age of onset, which is earlier in men, while women have a second peak of illness onset around menopause (Eranti, MacCabe, Bundy, & Murray, 2013; Häfner, Maurer, Löffler, & Riecher-Rössler, 1993; Häfner, Riecher-Rössler, Fätkenheuer et al., 1991; Häfner, Riecher-Rössler, Maurer et al., 1991)—a pattern suggested to be due to the protective effects of high oestrogen levels in women before menopause (Häfner, Riecher-Rössler, Maurer et al., 1991; Häfner, Riecher-Rössler et al., 1993; Riecher-Rössler, 2017). Additionally, recent reviews indicate a slightly increased incidence of schizophrenic psychoses in men compared to women (van der Werf et al., 2014). Moreover, men have been found to abuse substances more frequently and to have less illness insight, worse treatment adherence and poorer functional and social outcome (Abel, Drake, & Goldstein, 2010; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Gender differences have also been reported with respect to symptomatology, although results in this area are inconsistent: While some studies

point towards more negative and cognitive symptoms in men and more affective and positive psychotic symptoms in women (for an overview see for example Waford et al., 2015), other studies either could not confirm any gender differences (Barajas, Banos, & Ochoa, 2007; Bertani et al., 2012; Häfner, Riecher-Rössler, Fätkenheuer et al., 1991) or found only few differences regarding illness behaviour (Häfner, Riecher-Rössler, Fätkenheuer et al., 1991; Häfner, Riecher-Rössler, Maurer et al., 1991).

In patients with an at-risk mental state (ARMS) for developing a psychotic disorder, few studies have looked into potential gender differences in current symptomatology. A recent review by Barajas, Ochoa, Obiols, and Lalucat-Jo (2015) concluded that gender differences are at the most modest, the most replicated finding being more negative symptoms in men. However, this conclusion was based on just 4 original studies investigating gender differences regarding psychopathology published up to that point (Cocchi et al., 2014; Corcoran et al., 2011; Lemos-Giraldez et al., 2009; Willhite et al., 2008). Since then, further studies have been published. A study by our own group (Gonzalez-Rodriguez et al., 2014) in ARMS and first-episode psychosis (FEP) patients revealed more positive psychotic symptoms in women (n = 43; total sample n = 117) and more negative symptoms in men, which, however, did not withstand correction for multiple testing. Similar small gender differences were reported in three further ARMS studies-more negative symptoms in men (men n = 159, total sample n = 239; Rietschel et al., 2015), more unusual experiences in women (women n = 148, total sample n = 356; Waford et al., 2015) and more depressive symptoms in women (women n = 53, total sample n = 129; Pruessner et al., 2017). However, these studies did not correct for multiple testing. On the other hand, a recent study by Kotlicka-Antczak et al. (2016) in a Polish ARMS sample did not find any gender differences in symptoms (total sample n = 99, men n = 45). The inconsistent findings of previous studies might furthermore be due to methodological differences between the studies, as pointed out in a previous paper (Gonzalez-Rodriguez et al., 2014). Thus, study samples are sometimes quite selective and not representing *all* men and women with emerging illness of a defined catchment area. As some studies only had small sample sizes, their statistical power might have been too low to detect gender differences, which probably are of only small or moderate effect size. Furthermore, the instruments used to assess the risk status and the symptomatology, correction for multiple testing and adjustment for confounders varied between the studies, making it difficult to directly compare the findings.

To extend the existing literature regarding gender differences in symptoms of ARMS and FEP individuals, it might be interesting to investigate what symptoms the patients in question notice themselves at the onset of the change in their psychological well-being. These individually experienced changes will subsequently be referred to as "first self-perceived symptoms." Although several studies have investigated current clinical symptoms in ARMS and FEP patients, only few have retrospectively assessed the very first self-perceived symptoms at illness onset (i.e., when the first decline in functioning or well-being was noted by the patient), which has been estimated to occur on average 4-5 years before first contact with psychiatry (Riecher-Rössler et al., 2006). Among the first was the ABC study (Häfner, Maurer et al., 1993; Häfner, Riecher-Rössler et al., 1993), which found that female FEP patients most frequently reported restlessness, depression and worrying as their initial symptoms, while men most frequently reported trouble with thinking and concentration and anxiety when interviewed retrospectively with the instrument for the retrospective assessment of the onset of schizophrenia (IRAOS). Iyer et al. (2008) retrospectively also assessed first self-perceived symptoms in FEP patients (using the Circumstances of Onset and Relapse Schedule) and found symptoms of depression and anxiety to be the most frequent signs. However, the authors did not report gender-specific early symptoms. An earlier publication of our own group (Aston et al., 2012) compared first self-perceived symptoms independent of gender in ARMS, FEP and depressive disorder patients and found "loss of energy" and "difficulties concentrating" to be the most frequent first self-perceived symptoms in the ARMS group, while FEP patients reported "depression" and "irritability" as first self-perceived symptoms. Furthermore, there was a considerable overlap of the first self-perceived symptoms between the three groups.

To the best of our knowledge, no study has yet investigated gender differences in first self-perceived symptoms in both ARMS and FEP patients. Such investigations could improve not only our understanding of the aetiopathology of psychotic disorders but also their early detection and treatment (Riecher-Rössler & Häfner, 2000; Seeman, 2013), which has become a major goal in psychiatry during the last 2 decades (Riecher-Rössler & McGorry, 2016).

Thus, the aim of the present study was to contribute to this field of research by investigating whether there are gender differences in the very first self-perceived symptoms in male and female ARMS and FEP patients. Based on the above-described literature, we hypothesized that overall only small gender differences would be observable in the first self-perceived symptoms of ARMS and FEP patients.

2 | METHODS

2.1 | Recruitment and screening procedure

ARMS and FEP patients were recruited for this study from March 2000 to March 2016 via the FePsy (Früherkennung für Psychosen; English: early detection of psychosis) clinic of the University of Basel Psychiatric Hospital, Switzerland. A detailed description of the FePsy study procedure can be found elsewhere (Haller et al., 2009; Riecher-Rössler et al., 2007). ARMS patients were identified using the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008), which is based on the PACE criteria (Yung et al., 1998) with one additional inclusion category. Inclusion as ARMS patient required one or more of the following: (1) "attenuated" psychotic symptoms, (2) brief limited intermittent psychotic symptoms (BLIPS), (3) a first degree relative with a psychotic disorder plus at least two risk factors or (4) combination of unspecific risk factors according to the BSIP (Riecher-Rössler et al., 2008). For inclusion, FEP patients had to fulfil the transition criteria for psychosis according to Yung et al. (1998), which were also assessed with the BSIP.

The following exclusion criteria were applied: age below 18 years, insufficient knowledge of German, IQ < 70, previous episode of schizophrenic psychosis (treated with antipsychotics above a

chlorpromazine equivalent of 2500 mg), psychosis clearly due to organic reasons or substance abuse, or psychotic symptomatology within a clearly diagnosed affective psychosis or borderline personality disorder (Riecher-Rössler et al., 2007).

All patients gave written informed consent. The Ethics Committee northwest/central Switzerland (EKNZ) approved the present study.

2.2 | Assessment of first signs and symptoms and duration of illness

The first signs and symptoms at illness onset as well as the duration of illness (DUI) were assessed with the Basel Interview for Psychosis (BIP; Riecher-Rössler et al., 2015). The BIP is a semi-structured interview specifically developed to assess risk factors and indicators of emerging psychosis as well as the temporal development of psychiatric symptoms over the whole lifespan in ARMS and FEP patients. A more detailed description of the BIP including its psychometric properties was described in a previous publication of our group (Riecher-Rössler et al., 2015). The BIP contains the following 6 sections: (1) social and physical development and family, (2) signs and symptoms, (3) vulnerability, (4) help-seeking behaviour, (5) illness insight and (6) evaluation of the interview. In the item 2.2.2 of section 2, patients are asked to openly name the first three symptoms they noticed when they first experienced a drop in well-being or functioning. Only patients who could spontaneously recall at least one first self-perceived change were included in the present study.

Each of the reported symptoms was subsequently categorized by the rater to 1 of 62 pre-defined single symptoms and one of the following 14 symptom clusters: (1) Worries, agitation, anxiety; (2) Physical complaints; (3) Thinking, concentration; (4) Compulsions; (5) Mood, emotions; (6) Sensitivity, suspiciousness; (7) Social isolation, behavioural changes; (8) Supernatural, inexplicable experiences; (9) Derealisation, depersonalization; (10) Hallucinations; (11) Delusions; (12) Thought insertion, broadcasting and withdrawal; (13) Feeling controlled by outside forces and (14) Problems with social adjustment.

It should be noted that the clusters concerning hallucinations and delusions capture sub-threshold as well as full-blown psychotic symptoms.

DUI was determined with the BIP by assessing the date of the first self-perceived sign or symptom and the date of first contact with our early detection service, and by subsequently calculating the time difference in months.

In addition, the Brief Psychiatric Rating Scale, Expanded version (BPRS-E; Lukoff, KH, & Ventura, 1986; Ventura, Nuechterlein, Liberman, Green, & Shaner, 1993) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989) were used to obtain observer-based ratings of current symptomatology.

In the FePsy study, each patient is taken care of by a case-manager (CM) who is either a psychologist or psychiatrist. All assessments are organized by the responsible CM and all clinical interviews are carried out by the CM. The following clinical interviews are part of the FePsy study (in order of conduct): BSIP, structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-V) (SCID) and BIP. To assure a proper conduct of the interview, all CMs get an extensive training prior to their first assessment. Furthermore, all CMs take part in monthly psychopathology trainings including regularly the BIP. All trainings (pre-assessment trainings and monthly psychopathology trainings) are led by an experienced clinical psychologist or the head psychiatrist.

2.3 | Statistical analyses

The socio-demographic variables (i.e., age and years of education) as well as clinical characteristics (i.e., DUI, BPRS positive symptoms according to the factor analysis of Velligan et al., 2005, SANS total score) were compared between women and men in the ARMS, FEP and total groups using *t*-tests, except for the comparison of duration of untreated illness, where analyses were conducted using non-parametric Mann-Whitney U test, due to its non-normal properties.

The most frequently reported first self-perceived symptoms were listed on a single-item level. Logistic regression was used to compare the most commonly reported single items in the total sample, with presence of symptom (1 = yes/0 = no) as dependent variable and gender and group as independent variables.

Due to their great number, the single items were subsequently summarized on a cluster level in order to achieve more power in the analysis and to facilitate the interpretation of the results. Differences regarding the self-perceived symptoms on a cluster level were also analysed in the total group using logistic regression, with presence of symptom cluster (1 = presence of at least 1 symptom of the cluster/0 = otherwise) as dependent variable and gender and group as independent variables. In case of a significant interaction between gender and group, gender differences were analysed separately for ARMS and FEP patients. Complete case analysis was used to deal with missing values.

All data were analysed using the R environment for statistical computing (R Core Team, 2016). The level of significance was set at .05.

3 | RESULTS

3.1 | Socio-demographic and clinical characteristics

During the recruitment period, 181 ARMS and 132 FEP patients were recruited for the FePsy study. Of these, 136 ARMS (91 men, 45 women) and 89 FEP patients (63 men, 26 women) had completed the BIP items regarding first self-perceived symptoms and thus were included into this study. Excluded patients were not statistically different from included patients with regard to socio-demographic characteristics. Socio-demographic and clinical characteristics of the final sample are presented in Table 1. FEP patients were significantly older than ARMS patients. However, age did not differ between men and women, and there were no gender differences in years of education and DUI.

In the total sample, men scored significantly higher on the SANS total score than women. However, when ARMS and FEP patients were analysed separately, this difference was not significant.

TABLE 1 Socio-demographic and clinical characteristics

	All				ARMS				FEP			
	Women	Men			Women	Men			Women	Men		
	N = 71	*N* = 154	*P* value	*N*	*N* = 45	*N* = 91	*P* value	*N*	*N* = 26	*N* = 63	*P* value	*N*
Age	28.3 (9.59)	26.3 (6.41)	0.102	225	26.5 (9.20)	25.3 (6.06)	0.400	136	31.4 (9.62)	27.7 (6.65)	0.081	89
Years of education	11.9 (3.10)	11.3 (2.76)	0.189	225	11.5 (2.83)	11.3 (2.60)	0.624	136	12.5 (3.48)	11.4 (3.00)	0.153	89
Duration of untreated illness [months][a]	36.0 (76.1)	33.4 (61.7)	0.986	211	38.0 (72.0)	34.0 (60.0)	0.506	128	12.0 (55.3)	29.0 (68.0)	0.402	83
SANS total score	19.3 (15.7)	25.5 (17.0)	0.010*	218	18.6 (15.5)	24.4 (17.3)	0.056	133	20.6 (16.2)	27.2 (16.7)	0.105	85
BPRS positive symptoms	10.3 (4.34)	8.98 (4.44)	0.036*	218	7.84 (2.44)	6.42 (2.21)	0.002*	132	14.4 (3.58)	12.8 (4.20)	0.065	86

Values are given in means; standard deviation in parentheses.

ARMS = at-risk mental state; FEP = first-episode psychosis.

[a] Values are given in median; interquartile range in parentheses.

*Significant at $P < .05$.

Women had significantly higher scores in the BPRS Positive Symptoms Scale than men, in the total sample as well as in the ARMS subgroup.

3.2 | Most common first self-perceived symptoms: Single-item level

The five most frequently reported first self-perceived signs and symptoms in male and female ARMS and FEP patients are listed in Table 2.

Logistic regression models for each of the five most commonly reported symptoms revealed a significant main effect of gender in the absence of a significant group x gender interaction for the symptom "Unusual anxiety, fears" ($P = .016$; OR = 0.361 [0.154; 0.830]), indicating that women reported this symptom more frequently than men, regardless of diagnostic group.

Two more effects were significant on a trend level: First, there was an interaction effect of group x gender for the item "Unusual difficulties concentrating" ($P = .062$; OR = 0.219 [0.043; 1.069]), which was due to a non-significantly higher frequency of this symptom in male ARMS compared to female ARMS patients ($P = .356$) and a trend-wise significantly higher frequency of this symptom in female FEP compared to male FEP patients ($P = .098$).

Second, there was a trend-wise main effect of gender for the item "Withdrawal, avoiding contacts" ($P = .056$; OR = 2.510 [1.051; 7.373]), indicating that this item tended to be more frequently reported by men than women, regardless of diagnostic group.

3.3 | Most common first self-perceived symptoms: Symptom cluster level

Frequencies of the 14 first self-perceived symptom clusters of the BIP in male and female ARMS and FEP patients are shown in Figure 1.

In the logistic regression models, we found significant main effects of gender in the absence of significant group x gender interactions for the symptom clusters "Worries, agitation, anxiety" ($P = .006$; OR = 0.395 [0.201; 0.769]) and "Hallucinations" ($P = .047$; OR = 0.294 [0.082; 0.974]), indicating that women reported these symptom clusters more frequently than men independent of diagnostic groups. However, as mentioned earlier, the cluster "Hallucinations" includes full-blown as well as sub-threshold symptoms.

Furthermore, there was a significant group × gender interaction for the symptom cluster "Thinking, concentration" ($P = .012$; OR = 0.152 [0.034; 0.652]), which was due to a significantly higher frequency of this symptom cluster in male ARMS compared to female ARMS patients ($P = .014$) and a non-significantly lower frequency in male FEP compared to female FEP patients ($P = .232$).

We also found a significant main effect of diagnostic group for the symptom cluster "Delusions" ($P = .039$; OR = 3.764 [1.190; 18.320]) in the absence of a significant group x gender interaction, indicating that FEP patients reported this symptom cluster more frequently than ARMS patients, independent of gender.

Additionally, there was a trend-wise main effect of diagnostic group for the symptom cluster "Mood, emotions" ($P = .059$; OR = 0.542 [0.281; 1.007]), which was due to a higher frequency of this symptom cluster in ARMS than in FEP patients.

4 | DISCUSSION

In this study, investigating for the first time gender differences in both AMRS and FEP patients in the first self-perceived signs and symptoms at illness onset, only few gender differences were found with women reporting more frequently anxiety and positive psychotic symptoms (single item "Unusual anxiety, fears"; symptom clusters "Worries, agitation, anxiety" and (sub-threshold) "Hallucinations") and men reporting (trend-wise) more frequently negative and cognitive symptoms (single items "Withdrawal, avoiding contacts" and in the ARMS group "Unusual difficulties concentrating"; symptom cluster "Thinking, concentration" only in the ARMS group).

When comparing ARMS and FEP independent of gender, the symptom cluster "Delusions" was more frequently reported by FEP than by ARMS patients while the symptom clusters "Mood, emotion" was more frequently reported by ARMS than FEP patients.

These findings are consistent, at least in part, with the only previous study that has investigated gender differences in first self-

TABLE 2 Most frequently reported first self-perceived signs and symptoms

Rank	Symptom	Frequency	Percentage
ARMS women (*N* = 45)			
1	Depressed, not able to feel joy	13	28.9
2	Unusual anxiety, fears	12	26.7
3	Loss of energy, slow, weak	8	17.8
4	Unusual difficulties concentrating	6	13.3
5	Sleeping problems for more than 1 week	5	11.1
5	Unusually sensitive, thin-skinned	5	11.1
5	Withdrawal, avoiding contacts	5	11.1
ARMS men (*N* = 91)			
1	Depressed, not able to feel joy	23	25.3
2	Unusual difficulties concentrating	18	19.8
3	Withdrawal, avoiding contacts	17	18.7
4	Loss of energy, slow, weak	14	15.4
5	Unusual anxiety, fears	13	14.3
FEP women (*N* = 26)			
1	Unusual difficulties concentrating	6	23.1
2	Depressed, not able to feel joy	5	19.2
2	Unusual anxiety, fears	5	19.2
4	Heard voices when nobody was there	4	15.4
5	More nervous, restlessness	3	11.5
5	More sorrows, not able to stop worrying	3	11.5
5	People tried to harm, poison, chase or kill me	3	11.5
5	Sleeping problems for more than 1 week	3	11.5
5	Unusually frequent headaches, other physical complaints	3	11.5
5	Unusually sensitive, thin-skinned	3	11.5
FEP men (*N* = 63)			
1	Depressed, not able to feel joy	15	23.8
2	Withdrawal, avoiding contacts	14	22.2
3	Irritable, annoyed, unusually quarrelsome	8	12.7
4	Loss of energy, retarded, weak	7	11.1
4	Unusually suspicious	7	11.1

ARMS = at-risk mental state; FEP = first-episode psychosis.

perceived symptoms in FEP patients (Häfner et al., 1995). This study also found higher rates of worrying among the very first self-perceived symptoms in women and found men to report more trouble with thinking and concentration as their first self-perceived symptom, which we could only find in our male ARMS patients.

The above-reported gender differences in first self-perceived symptoms was also reflected in our measures of current symptomatology (i.e., SANS and BPRS), in which men scored higher in negative symptoms and women in (sub-threshold) positive symptoms. Furthermore, these results are in line with some previous studies that have investigated gender differences in current symptomatology separately in ARMS (Barajas et al., 2015; Pruessner et al., 2017; Rietschel et al., 2015; Waford et al., 2015) and FEP patients (Moukas, Gourzis, Beratis, & Beratis, 2010; Thorup et al., 2007). These studies also pointed towards more negative symptoms in men and more (sub-threshold) positive symptoms in women in ARMS and FEP patients. However, as already discussed earlier, other studies could not confirm these findings and did not reveal significant gender differences in the psychopathology of ARMS and FEP patients (e.g., Bertani et al., 2012, Gonzalez-Rodriguez et al., 2014, Kotlicka-Antczak et al., 2016). In an attempt to synthesize the above findings, it might be speculated that small gender differences in symptoms of the emerging disease exist, with more negative and cognitive symptoms in men and more anxiety or affective/ (sub-threshold) positive symptoms in women. However, the size of this effect is probably small, such that differences in the statistical power of the studies led to heterogeneous results. It should be noted that it is possible that more pronounced gender differences might emerge in FEP patients as compared to the ARMS patients due to the more unspecific nature of this latter subsample (Fusar-Poli et al. 2012).

Still, as shown for example by Walder et al. (2013), gender could improve the prediction of psychosis by moderating the influence of other important predictors, such as social functioning and positive psychotic symptoms.

There are also several limitations of our study. First, the BIP items that we used to measure first self-perceived signs and symptoms did not allow differentiating between sub-threshold and full-blown psychotic symptoms. Hence, no final conclusion can be drawn on whether the reported gender difference in the symptom cluster "Hallucinations" was due to sub-threshold or full-blown symptoms. However, given that psychoses usually do not start abruptly (i.e., with full-blown symptoms), it is likely that the hallucinations that were reported as first symptoms were mostly of sub-threshold severity.

Second, despite the attempt to capture first self-perceived symptoms already in the prodromal phase, it needs to be noted that on average there were almost five years between the appearance of first symptoms and the time point of the interview, which may have led to a recall bias. However, as no gender difference was found in our sample regarding DUI, it is not likely that this has influenced the observed gender difference. Last, the smaller number of FEP patients in the present study might have led to a lack of power to detect possible gender differences in this group compared to the larger ARMS sample.

In interpreting these patterns, it should also be kept in mind that awareness of the symptoms and insight into the illness might be impaired in patients suffering from psychosis. According to a recent review by Gerretsen et al. (2014) insight into schizophrenia is especially impaired in first-episode patients, while it is still mostly intact in the premorbid phase. Furthermore, men and women may differ in their symptom awareness, their illness insight and their willingness and ability to report specific symptoms (Berger, Addis, Reilly, Syzdek, & Green, 2012; Riecher-Rössler, 2010). Thus, it is possible that the few observed differences are at least partly due to reporting bias.

In conclusion, this study revealed small gender differences in ARMS and FEP patients, with women reporting trend-wise less frequently negative and cognitive symptoms and significantly more often anxiety and (sub-threshold) positive symptoms than men. In clinical practice, it might be important to also think of an emerging psychotic disorder when women present with anxiety symptoms,

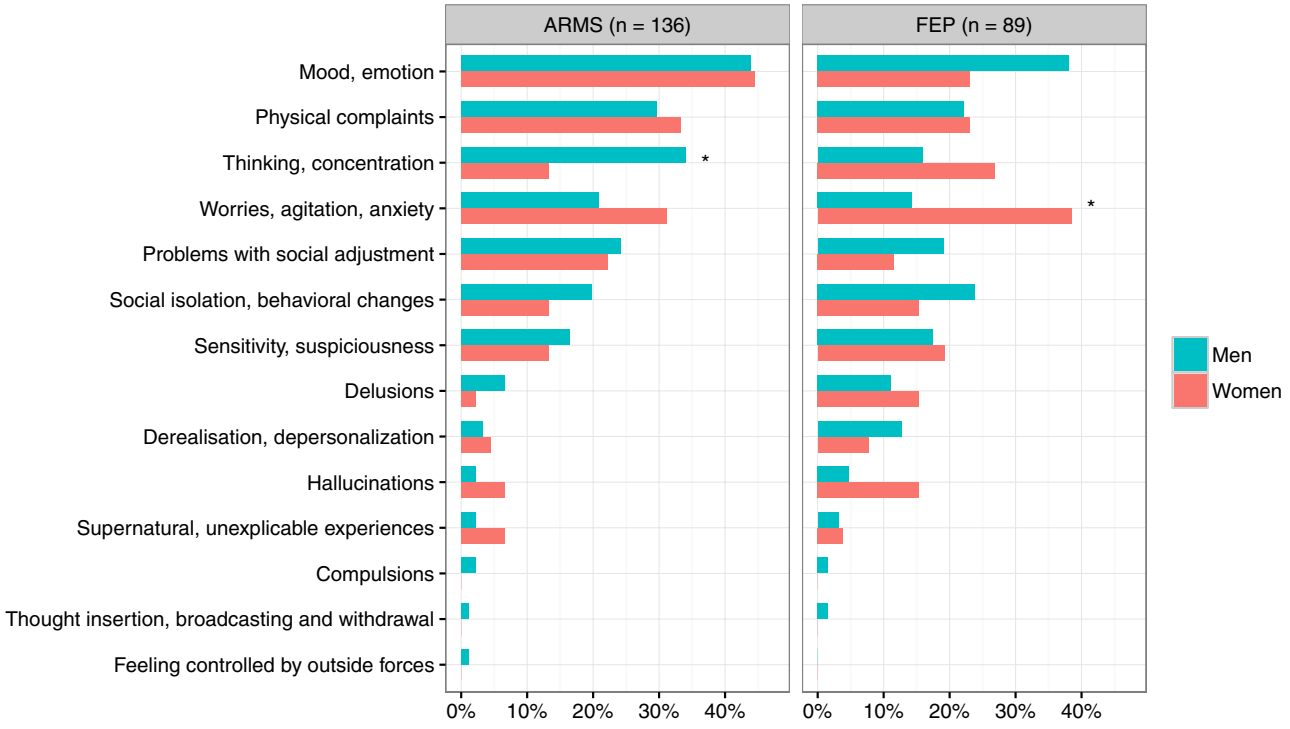

FIGURE 1 Frequencies and gender differences of the 14 first self-perceived symptom clusters of the Basel Interview for Psychosis (BIP) in both diagnostic groups; ARMS = at-risk mental state; FEP = first-episode psychosis; *significant at $P < .05$

because on one hand, these symptoms seem to mark more often the beginning of a psychotic disorder in women than in men, and on the other hand, because they might be more easily misattributed to a depressive disorder in women due to the higher prevalence of depression in women. In men, on the other hand, social withdrawal should be taken more seriously as a potential first sign of emerging psychosis.

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Akademische Ausbildung

Seit 2015	Ausbildung zur psychologischen Psychotherapeutin am Freiburger Ausbildungsinstitut für Verhaltenstherapie an der Universität Freiburg (FAVT), Freiburg, Deutschland
Seit 2014	Doktorandin an der Fakultät für Psychologie, Universität Basel, Schweiz; Betreuung durch Prof. Dr. rer. nat. Stieglitz und Prof. Dr. med. Riecher-Rössler, Basel, Schweiz
2011-2013	Maastricht University, Research Master in Cognitive and Clinical Neurosciences, Track Neuropsychology, Maastricht, Niederlande
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2008-2011	Université de Strasbourg, Bachelor in Psychologie, Straßburg, Frankreich
1999-2008	Fichtegymnasium, deutsch-französisches Abitur, Karlsruhe, Deutschland

Praktische Erfahrungen

2015-2016	Durchführung Psychopathologie Training des Zentrums für Gender Research und Früherkennung
2014-2016	Betreuung von Masterstudenten (Psychologie und Medizin)
2013	Klinisches Praktikum und Masterarbeit in der Abteilung für klinische Neuropsychologie des Universitätskrankenhauses Hamburg-Eppendorf bei Prof. Dr. phil. Moritz; Titel der Masterarbeit: *The effects of a single metacognitive training session on cognitive biases in patients with schizophrenia. An explorative study;* 4 Monate
2012-2013	Forschungspraktikum und Masterarbeit in der Abteilung für Psychosomatik und Psychotherapeutische Medizin bei Prof. Dr. med. Bohus am Zentral Institut für Seelische Gesundheit, Mannheim; Titel der Masterarbeit: *How does ostracism influence pain perception, heart rate and interactions in boderline personality disorder? Preliminary data*; 5 Monate
2012	Studentische Hilfskraft bei Prof. Dr. van Heugten; Literatursuche: *Kognitive Screening Instrumente für Schlaganfall Patienten*; 10 Monate
2011	Praktikum in der neuropsychologischen Forschungsabteilung des Zentral Instituts für seelische Gesundheit in Mannheim bei Prof. Dr. rer. soc. Flor (Forschungsgebiet: PTSD); 6 Wochen
2010	Praktikum in der neuropsychologischen Abteilung der Rehabilitationsklinik Schloss Bad Buchau bei Dr. rer. nat. Kringler; 4 Wochen

Sonstige Kenntnisse

Sprache:	Deutsch (Muttersprache) Englisch & Französisch (verhandlungssicher) Spanisch (Grundkenntnisse)
Computer:	MS Office, SPSS, Endnote

Klinische Interviews: SKID I& II, BSIP, CAARMS, SIPS, SPI-A

Publikationen

Heitz, U., Papmeyer, M., Studerus, E., Vogel, T., Römer, K., Ittig, S.,Borgwardt, S., Graf, M., Eckert, A., Riecher-Rössle A. (2018). *Plasma and serum brain derived neurotrophic factor levels and their association with neurocognition in at-risk mental state, first episode and chronic schizophrenia patients* The World Journal of Biological Psychiatry*, 1-10.*

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Egloff, L., Lenz, C., Studerus, E., **Heitz, U.**, Harrisberger, F., Smieskova, R., Schmidt, A., Leanza, L., Andreou, C., Borgwardt, S., Riecher-Rössler, A. *No associations between medial temporal lobe volumes and verbal learning/memory in emerging psychosis* (submitted)

Leanza, L., Egloff, L., Studerus, E., Andreou, C., **Heitz, U.**, Ittig, S., Beck, K., Uttinger, M., Riecher-Rössler, A. (2018) *The relationship between negative symptoms and cognitive functioning in patients at clinical high risk for psychosis* Psychiatry Research

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