The Role of the Stress Hormone Prolactin and Sex Differences in Early Psychosis

A Cumulative Dissertation

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by

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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, September 2017

Sarah Ittig

Abbreviations

APS	attenuated psychotic symptoms
ARMS	at-risk mental state
ARMS-NT	at-risk mental state without later transition to psychosis
ARMS-T	at-risk mental state with later transition to psychosis
BLIPS	brief limited intermittent psychotic symptoms
BPRS	Brief Psychiatric Rating Scale
BS	basic symptoms
BSIP	Basel Screening Instrument for Psychosis
CPT	Continuous Performance Test
DUI	duration of untreated illness
DUP	duration of untreated psychosis
EEG	electroencephalography
FCQ	Frankfurt Complaint Questionnaire
FEP	first episode psychosis
FePsy	Basel Projekt zur ***F***rüh***e***rkennung von ***Psy***chosen
GRD	genetic risk and deterioration syndrome
HC	healthy controls
CHR	clinical high-risk state
MRI	magnetic resonance imaging
PACE	Personal Assessment and Crisis Evaluation
PIF	prolactin inhibiting factor
PS	Paranoid Scale
SSP	Selfscreen-Prodrome
TAP	Test of Attentional Performance
UHR	ultra-high risk
UPS	unspecified prodromal symptoms
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children

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Abstract

In the last 20 years, a huge effort has been made to implement and apply the principles of early diagnosis and treatment, already well established in other branches of medicine, to the field of psychotic disorders. The goal of research on early detection was and still is to prospectively identify people at-risk of developing full-blown psychosis. However, until now it is still not possible to predict transition to psychosis with adequate accuracy. Therefore, the prospective ***F***rüh***e***rkennung von ***Psy***chosen (***Fepsy***) study aims at improving early detection of psychosis via a multilevel assessment containing a systematic assessment of psychopathological symptoms, a neuropsychological examination, blood sampling, electroencephalography (EEG) and magnetic resonance imaging (MRI). The present dissertation addresses the role of the hormone prolactin in emerging psychosis on one hand and on the other hand aims to elucidate whether there are any sex differences in emerging psychosis specifically regarding the hormone prolactin, cognitive functioning and the correlation of self- and observer-ratings of psychopathology. In the first publication, the role of the hormone prolactin in early psychosis is discussed whereas the topic of possible sex differences is covered by all of the publications included in this dissertation (1, 2 and 3).

The first study validates literature by providing further evidence for frequent hyperprolactinemia in emerging psychosis and that it can even be observed in antipsychotic-naïve patients (>30%). Hence, prolactin is not necessarily elevated as a side effect of antipsychotics but can also be a pre-existing condition probably in relation with the function of prolactin as stress hormone. Furthermore, all three publications which are included in this dissertation consider the aspect of sex differences, which may help to elucidate pathogenic mechanisms underlying psychosis that are specific to women or men. The first study demonstrated higher prolactin levels in women even after correction for the normal biological variation in prolactin levels between the sexes, which potentially provides an indication for a sex dependant stress reaction regarding the hormone prolactin. The results of our second study suggest that sex differences in cognitive functioning in patients are not different from those seen in healthy controls (HC). Specifically, the female advantage in verbal learning and memory, which has frequently been found in HC seems to be equally present in patients with an at-risk mental state (ARMS) for psychosis as well as in patients with a first episode psychosis (FEP). The third study shows that the associations of self- and observer-ratings of psychopathology were rather low and generally not different for men and women. Therefore, the results imply that self-rating scales cannot be a substitute for the more time-consuming observer-rating scales neither for men nor for women.

In summary, prolactin plays a possible role in emerging psychosis in relation with its function as stress hormone and stress reactivity seems to be enhanced in women. Overall, there were few sex differences which could have been shown in the second and third study.

Regarding sex differences in cognitive functioning (publication 2), they resemble those of the general population and were not different between HC and patients (ARMS, FEP).

1 General Introduction

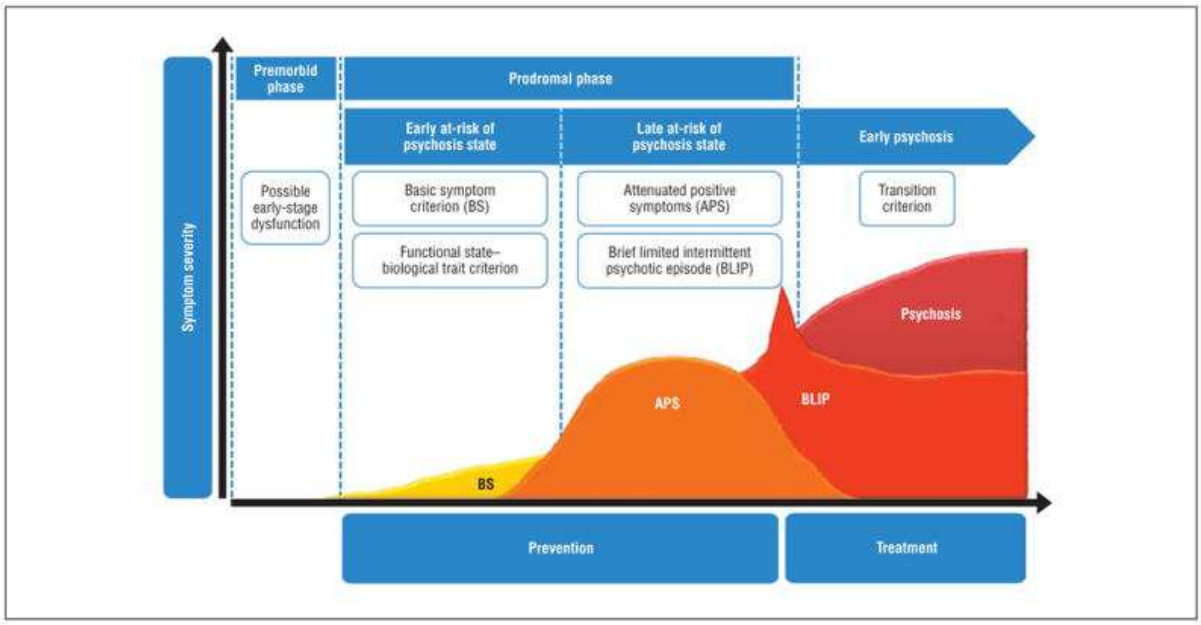
1.1 Early detection of psychosis

During the past two decades, clinicians and researchers had the goal to implement and apply the principles of early diagnosis and treatment which are established in other branches of medicine, such as in oncology or in cardiovascular diseases, to the field of psychotic disorders. Usually, psychosis is preceded by prodromal symptoms often occurring during a critical life period characterized by important steps in education and building up of social networks. Therefore, prodromal symptoms can have serious consequences for the patient already in these early stages of the disease. The concepts of DUP (duration of untreated psychosis) and DUI (duration of untreated illness) are used to illustrate the delay of diagnosis and treatment. DUP, with presentation of positive psychotic symptoms, lasts on average 1 to 3 years whereas DUI is a so-called “unspecific prodromal phase” lasting on average 2 to 5 years also capturing subthreshold psychotic symptoms (A. Riecher-Rössler et al., 2006). A longer DUP has been associated with a worse overall prognosis/global outcome, lower level of symptomatic and functional recovery, severity of negative symptoms (Murru & Carpiniello, 2016; Perkins, Gu, Boteva, & Lieberman, 2005), poorer social functioning (Perkins et al., 2005), stronger impairment of psychological and social development (A. Riecher-Rössler et al., 2006), poorer treatment response (Perkins et al., 2005) and higher overall treatment costs (Ricciardi, McAllister, & Dazzan, 2008). In this context, researchers supposed to achieve better outcomes for the patients by intervening (early pharmacological and psychological treatment) already in the potential prodromal phase (Amminger et al., 2010; McGorry et al., 2014; Phillips et al., 2007; Woods et al., 2007). Moreover, most patients do also present other symptoms which require clinical attention and treatment.

Therefore, the goal of the early detection movement is to prospectively identify people at-risk for developing full-blown psychosis. To capture this pre-psychotic phase, the construct of a clinical high-risk state (CHR) has evolved (Figure 1; Fusar-Poli et al., 2013). Basically, two complementary sets of criteria have been used to diagnose the CHR state, namely ultra-high risk (UHR) and basic symptoms (BS) criteria which are used in help-seeking individuals. UHR criteria describe four main sets of clinical criteria: Attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), genetic risk and deterioration syndrome (GRD) and unspecified prodromal symptoms (UPS). They were developed with the aim of detecting a risk for developing a first episode psychosis (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015).

The criteria adapted from BS are subjectively experienced disturbances of different domains, including perception, thought processing, language and attention. They were developed to detect the risk for psychosis even before functional impairment appeared and are mainly assessed with the Schizophrenia Proneness Instrument, adult version (SPI-A; Schultze-Lutter, Ruhrmann, Picker, & Klosterkotter, 2006).

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 (Fusar-Poli et al., 2013)



BS: Basic symptoms; APS: Attenuated psychotic symptoms; BLIP: Brief limited intermittent psychotic episode.

Several interviews have been developed to assess the UHR criteria. For a detailed description see Fusar-Poli et al. (2013) and Schultze-Lutter et al. (2015). Depending on the interview conducted, the criteria to identify UHR patients are slightly different and also the denomination of the so called “prodromal phase” depends on the instrument used. One of these interviews is the Basel Screening Instrument for Psychosis (BSIP; A. Riecher-Rössler et al., 2008), which has been developed in Basel in the framework of the early detection of psychosis project (***FePsy: F***rüh***e***rkennung von ***Psy***chosen). In agreement with the criteria applied in the BSIP we will use the term “at-risk mental state” (ARMS) in this dissertation for all patients with a risk of developing psychosis.

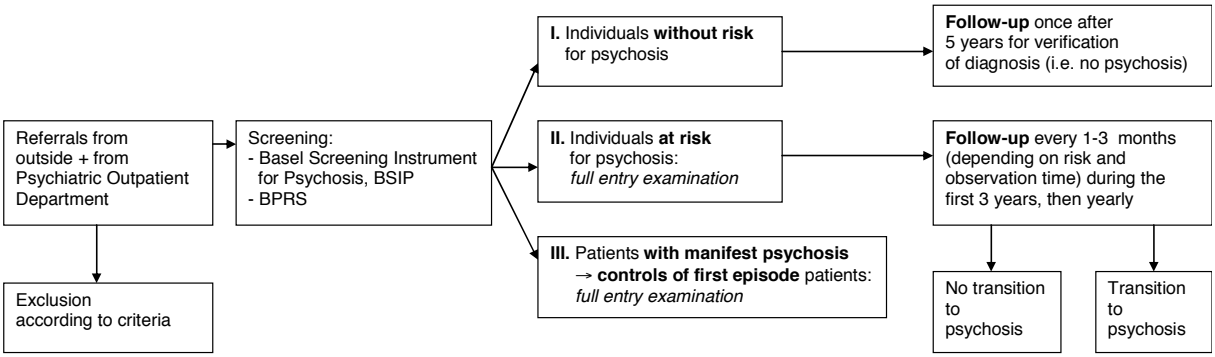
Independent of the psychometric instrument used less than 40% of patients identified as being in an ARMS, will actually transition to full-blown psychosis. The cumulative transition rates have been estimated as follows: 18% (12% - 25%) at 6 months of follow-up, 22% (17% - 28%) at 1 year, 29% (23% - 36%) at 2 years, 32% (24% - 35%) at 3 years, and 36% (30% - 43%) after 3 years (Fusar-Poli et al., 2013). Hence, most of the patients identified as being in an ARMS will never develop a full-blown psychosis and adequate accuracy in predicting

conversion to psychosis is not yet possible. Therefore, early pharmacological intervention (antipsychotic medication already in the ARMS) is difficult to legitimate as side effects are not uncommon. Hence, several research projects exist around the world with the goal to improve prediction of psychosis. One of the first is the ***FePsy***-study in Basel, which serves as basis for the present dissertation (all data presented were collected within the framework of the ***FePsy***-study) and is described in the following section.

1.2 Fepsy-study

The ***FePsy***-study is an open, prospective clinical study with a study design as depicted in Figure 2. All individuals are screened with the BSIP (A. Riecher-Rössler et al., 2008) which is largely based on the Personal Assessment and Crisis Evaluation (PACE) inclusion/exclusion criteria (Yung et al., 1998). The BSIP additionally allows inclusion of patients displaying a combination and minimal amount of certain unspecific risk factors/prodromes (different from other screening instruments). The patients are classified as being in an ARMS for psychosis, having a first episode of psychosis (FEP), or being not at risk for psychosis (usually other psychiatric disorders). In Table 1, BSIP criteria to fulfil an ARMS as well as BSIP criteria for transition to psychosis are described.

Figure 2: Design of the ***FePsy***-study (A. Riecher-Rössler et al., 2007).



BSIP: Basel Screening Instrument for Psychosis; BPRS: Brief Psychiatric Rating Scale.

All ARMS patients are 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; A. Riecher-Rössler, Pflueger, et al., 2009) in order to distinguish those who later transition to frank psychosis (ARMS-T) from those who do not (ARMS-NT) using the transition criteria of Yung et al. (1998). Exclusion criteria are as follows: age below 18 years, insufficient knowledge of German, IQ < 70, previous episode of schizophrenic psychosis, psychosis clearly due to organic reasons or substance abuse, or psychotic symptomatology within a clearly

diagnosed affective psychosis or borderline personality disorder. Subjects treated with antipsychotics for more than 3 weeks or who exceeded 2500mg cumulative chlorpromazine equivalent dose were excluded as well.

Table 1: At-risk mental state and transition criteria in the BSIP

Clinical signs	
At-risk mental state (ARMS)	**I) State (Prepsychotic)*** - APS – "attenuated" psychotic symptoms: psychotic symptoms below decompensation limit (BPRS scales: hallucinations 2-3, unusual thought content 3-4, suspiciousness 3-4) at least several times per week, in total persisting for more than 1 week or - BLIPS – brief limited intermittent psychotic symptoms: psychotic symptoms above decompensation limit (BPRS scales: hallucinations ≥ 4, unusual thought content ≥ 5, suspiciousness ≥ 5, conceptual disorganisation ≥ 5), each time less than 1 week with spontaneous remission. **II) Trait + State (Genetic +)*** Genetic risk and further risk factors according to screening instrument (first or second degree relative with psychotic disorder and at least two further risk factors according to the screening instrument. **III) Mixed category (Unspecific)** Combination and minimal amount of certain unspecific risk factors according to screening instrument. **But transition criteria not yet fulfilled!** *corresponding to PACE criteria (Yung et al., 1998)
Transition criteria	- At least one of the following symptoms: • **Suspiciousness** (BPRS ≥ 5) Says others are talking about him/her maliciously, have negative intentions or may harm him/her (incidence more than once a week OR partly delusional conviction) • **Unusual thought content** (BPRS ≥ 5) Full delusion(s) with some preoccupation OR some areas of functioning disrupted (not only ideas of reference/persecution, unusual beliefs or bizarre ideas without fixed delusional conviction) • **Hallucinations** (BPRS ≥ 4) Occasional hallucinations OR visual illusions > 2/week or with functional impairment (not only hearing of own name, non-verbal acoustic or formless visual hallucinations/illusions) • **Conceptual disorganisation** (BPRS ≥ 5) Speech difficult to understand due to circumstantiality, tangentiality, neologisms, blockings or topic shifts (most of the time OR 3 to 5 instances of incoherent phrases) - Symptoms at least several times a week - Change in mental state lasting more than one week

BSIP: Basler Screening Instrument for Psychosis; BPRS: Brief Psychiatric Rating Scale.

All included patients (ARMS and FEP) undergo a full entry multidomain examination comprising potential risk factors for transition to psychosis including systematic assessment of psychopathological symptoms, neuropsychological examination, analyses of different blood parameters, resting state electroencephalography (EEG) and structural magnetic resonance imaging (MRI). All these examinations serve as well to exclude any organic reason leading to psychosis.

The dissertation at hand addresses the topic of the hormone prolactin in relation to psychosis on one hand and on the other hand aims to elucidate whether there are any sex differences

regarding this specific hormone (prolactin), regarding cognitive functioning and regarding correlation of self- and observer-ratings of psychopathology. The role of prolactin in early psychosis is discussed in the first publication and the topic of possible sex differences is covered by all of the publications (1, 2 and 3) included in this dissertation.

We used some additional exclusion criteria specifically for analysing prolactin values (first publication): All patients who had ever taken any antipsychotics or any prolactin-influencing medication (i.e. hormonal contraception) at the time of assessment were excluded. Likewise, all patients with a medical condition potentially influencing prolactin status, such as hypothyroidism or pituitary abnormalities were excluded.

For the second publication (Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects) a sample of HC from trade schools, hospital staff and through advertisements has been recruited. HC subjects with a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of psychiatric disorder were excluded (for more detailed information see methods section in respective publication).

2 Theoretical Background

2.1 The role of prolactin in emerging psychosis

Prolactin is a polypeptide hormone involved in a broad spectrum of functions, including reproduction and lactation (Fitzgerald & Dinan, 2008). It is predominantly synthesized and secreted by lactotroph cells of the anterior pituitary gland. Prolactin release is stimulated by sucking but also by psychosocial stress (Fitzgerald & Dinan, 2008; Lennartsson & Jonsdottir, 2011). There is compelling epidemiological evidence that psychosocial stress is implicated in the development of psychotic symptoms (van Winkel, Stefanis, & Myin-Germeys, 2008). A recent study found that the risk of developing psychosis increases with the number of life events experienced (Shevlin, Houston, Dorahy, & Adamson, 2008). Moreover, several studies have shown an association of environmental factors, which could be proxies for psychosocial stress, with psychosis (van Os, 2004; van Os, Hanssen, Bak, Bijl, & Vollebergh, 2003; van Os, Pedersen, & Mortensen, 2004). More specifically, both growing up in an urban environment and having a migration background, which is associated with discrimination, increase the risk for psychosis (Cantor-Graae & Selten, 2005). Moreover, immediate stress is assumed to play a role in triggering psychosis. Previous research has shown an association between cortisol levels and severity of positive and nonspecific symptoms (Aiello, Horowitz, Hepgul, Pariante, & Mondelli, 2012; Holtzman et al., 2013; Walker et al., 2013). Stress is also thought to influence the volume of the pituitary gland, which was indicated by magnetic resonance imaging (MRI) studies. ARMS as well as FEP patients showed enlarged pituitary

gland volumes independent of antipsychotic treatment (Büschlen et al., 2011; Pariante et al., 2005; Walter et al., 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. Thus, dopamine is the main prolactin inhibiting factor (PIF; Fitzgerald & Dinan, 2008). On the other hand, the dopaminergic neurotransmission plays an important role in the pathophysiology of schizophrenic psychoses (Howes et al., 2009). This inference was made from the link between the antipsychotic efficacy of neuroleptic drugs and their affinity for the dopaminergic D2 receptor (Bennett, 1998). Consequently, hyperprolactinemia is often described as a side effect of antipsychotics in patients with schizophrenic psychoses (Peuskens, Pani, Detraux, & De Hert, 2014). Nonetheless, recent reports have described hyperprolactinemia also in antipsychotic-naïve FEP and ARMS patients. In these patients, hyperprolactinemia could be due to psychosocial stress (A. Riecher-Rössler et al., 2013) as stress is implicated in the development of psychotic symptoms (van Winkel et al., 2008) and known to stimulate prolactin synthesis and release (Lennartsson & Jonsdottir, 2011). Riecher-Rössler (2013) formulated the following hypothesis: ”It might be speculated that stress induced hyperprolactinemia plays a role in triggering the outbreak of acute psychotic symptomatology because hyperprolactinemia induces the production of PIF, which is more or less identical with dopamine”. Several studies found either elevated prolactin levels (above the reference level) or increased prolactin levels compared to a control group in antipsychotic-naïve FEP and schizophrenia patients (Aston et al., 2010; Gonzalez-Blanco et al., 2016; Petrikis et al., 2016; A. Riecher-Rössler et al., 2013). Furthermore, even in ARMS patients a high proportion of hyperprolactinemia or increased prolactin levels compared to healthy controls (HC) have been reported (Aston et al., 2010; Labad et al., 2015). In addition, a study conducted in patients with pituitary microadenoma 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 (Cheng, Wen, Tang, Zhong, & Gan, 2013).

One main goal of this work (first publication) was to further explore the role of prolactin in emerging psychosis. Therefore 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) and II) higher prolactin levels in FEP as compared to ARMS patients. As prolactin is also a stress hormone and stress is thought to be associated with psychopathological symptoms (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013) we hypothesized to find III) a positive association of prolactin with psychopathological

symptoms as measured with the Brief Psychiatric Rating Scale Expanded Version (BPRS-E; Lukoff, Nuechterlein, & Ventura, 1986; Ventura et al., 1993). IV) According to the hypothesis of stress induced prolactin release leading to dopamine increase and thereby triggering the outbreak of psychosis (see above) we also hypothesized higher baseline prolactin levels being predictive of transition to psychosis in ARMS patients.

2.2 Sex differences in schizophrenia, first episode psychosis and at-risk mental state for psychosis patients

Sex has been shown to impact on brain anatomy and cognitive functioning through a complex interplay of biological and psychosocial factors. Given that differences between women and men with schizophrenia have been described regarding many aspects of the illness, including age of onset, symptomatology, treatment response, course and psychosocial outcome (Abel, Drake, & Goldstein, 2010; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012; A Riecher-Rössler, Pflueger, & Borgwardt, 2010), it seems obvious that this topic is of high importance. One of the most consistent findings is that women are older than men when first symptoms arise (Eranti, MacCabe, Bundy, & Murray, 2013; Häfner et al., 1994). Furthermore, women seem to have a more favourable outcome than men (Ochoa et al., 2012; A. Riecher-Rössler & Rössler, 1998). Therefore, the decision was made to have a closer look at possible sex differences in some of the parameters, which are assessed in the ***FePsy***-study. A better knowledge of specific sex differences may elucidate pathogenic mechanisms underlying schizophrenia that are specific or unequally distributed in women and men, potentially leading to improved treatment strategies.

2.2.1 Sex differences in normalized prolactin levels

As described above, elevated prolactin serum levels have been described in antipsychotic-naïve ARMS and FEP patients and are supposed to play a role in emerging psychosis. Prolactin reference levels are different for healthy men and women with higher normal levels in women. Nevertheless, independent of normal biological variation, sex differences in prolactin levels have been described in a metaanalysis of Gonzalez-Blanco showing more pronounced group differences in men (between patients and controls) than in women. Therefore, we wanted to analyse possible sex differences in prolactin levels in our sample and hypothesized to find more elevated prolactin levels in men than in women (Gonzalez-Blanco et al., 2016).

2.2.2 Sex differences in cognitive functioning

The impairment of cognitive functioning is recognized as a core feature of schizophrenia and is closely related to the outcome of the disease (Kahn & Keefe, 2013; Palmer, Dawes, & Heaton, 2009). It is not only present in patients with schizophrenic psychoses, but already

evident in individuals with an ARMS for psychosis (Hauser et al., 2017; Pflueger, Gschwandtner, Stieglitz, & Riecher-Rossler, 2007). In addition, it has been shown that ARMS individuals with later transition to psychosis perform worse on tests measuring verbal fluency and memory (Hauser et al., 2017) and speed of information processing (Brewer et al., 2005; A. Riecher-Rössler, Pflueger, et al., 2009) compared to those without transition. It has been consistently reported that prediction of psychosis can be improved by considering neurocognitive performance measures (Koutsouleris et al., 2012; A. Riecher-Rössler, Pflueger, et al., 2009; Studerus, Papmeyer, & Riecher-Rössler, 2014).

Sex differences in cognitive functioning in healthy individuals are well known. Generally, women tend to perform better than men in tasks measuring verbal abilities, whereas the opposite is true for visuo-spatial skills (Halari et al., 2005; Halpern, 2004; Miller & Halpern, 2014). In schizophrenia patients, there are similar differences in cognitive functioning between men and women. Many studies have shown a sex difference in schizophrenia patients in the domain of verbal learning and memory with better performance in women (Albus et al., 1997; Bozikas et al., 2010; Goldstein et al., 1998; Han et al., 2012; Hoff et al., 1998; Longenecker, Dickinson, Weinberger, Elvevag, & Dickinson, 2010; Vaskinn et al., 2011) which is line with findings in HC. However, results in other cognitive domains (executive functions, attention, working memory and IQ) have been largely inconsistent. This could be due to different patient groups used (chronic schizophrenia patients vs. first episode psychosis patients), medication, neuropsychological tasks for assessing the same cognitive domain and also varying statistical power. Only one study has been conducted in ARMS patients. In this study, men as compared to women showed a better performance in picture completion (WISC-III and WAIS-III; Walder, Mittal, Trotman, McMillan, & Walker, 2008). No study has yet analysed sex-related cognitive performance differences in ARMS and FEP patients together. In consideration of the fact that cognitive impairment is recognized as core feature of schizophrenia, it is conceivable that sex differences in cognitive functioning developing over different stages of the disease could give rise to new hypotheses indicating pathogenic mechanisms of the illness. Therefore, we wanted to study sex differences in cognitive functioning in ARMS, FEP and HC subjects and also whether sex differences vary between the investigated groups. Based on previous research, a better performance of women in the domain of verbal learning and memory was expected in all groups.

2.2.3 Influence of sex on the correlation between self- and observer-ratings of psychopathology

Self-rating scales are easily applicable and are not time-consuming. In contrast, observer-rating scales are more time consuming and need a well-trained professional (Hartmann, Fritzsche, & Lincoln, 2013) but considered objective measures of psychopathological symptoms in patients with psychotic disorder (Niv, Cohen, Mintz, Ventura, & Young, 2007).

Yet, it is not clear whether psychosis patients report their symptoms accurately which would be a requirement for coherent self- and observer-rating. It has long been assumed that self-ratings are not reliable in schizophrenia patients because they have many features like poor insight, denial, delusions and cognitive deficits that probably make a self-rating of their symptoms impossible or at least hamper it (Amador & David, 1998). However, previous empirical work (6 different studies) points towards a good agreement between self- and observer-rating of positive psychotic symptoms (Hamera, Schneider, Potocky, & Casebeer, 1996; Iancu, Poreh, Lehman, Shamir, & Kotler, 2005; Lincoln, Ziegler, Lullmann, Muller, & Rief, 2010; Liraud, Droulout, Parrot, & Verdoux, 2004; Preston & Harrison, 2003). Only three studies did not support this finding and reported poor correlations (Biancosino et al., 2007; Lasalvia, Ruggeri, & Santolini, 2002; Morlan & Tan, 1998).

Concerning negative symptoms, correlations between self- and observer-ratings seem to be inconsistent (Bell, Fiszdon, Richardson, Lysaker, & Bryson, 2007; Bottlender et al., 2003; Hamera et al., 1996; Iancu et al., 2005; Liraud et al., 2004; Preston & Harrison, 2003).

The concordance between self- and observer-ratings regarding depressive symptomatology in psychosis patients was pretty good in most of the studies (Biancosino et al., 2007; Morlan & Tan, 1998; Rush et al., 2006).

The existing studies vary in some factors such as disease stage and distribution between the sexes, which potentially can influence the agreement between self- and observer-rating. In a previous study, FEP patients were found to have more impaired insight than ARMS patients (Lappin et al., 2007) and therefore it is reasonable to assume that ARMS patients would also show a higher agreement between self- and observer-rating than FEP patients.

As already mentioned above, sex differences in schizophrenia have been described in many aspects of the illness (Abel et al., 2010; Ochoa et al., 2012; A. Riecher-Rössler & Häfner, 2000) but it is not clear if sex also influences the agreement between self- and observer-rating. In mixed patient samples or patients with depression some studies point towards a higher agreement regarding affective symptoms in women (Jolly, Wiesner, Wherry, Jolly, & Dykman, 1994; Shain, Naylor, & Alessi, 1990). As opposed to the precedent studies, there are also studies conducted with samples of psychotic and non-psychotic major depression patients which do not support a better agreement regarding affective symptoms in women (Domken, Scott, & Kelly, 1994; Rush et al., 2006). Only one study specifically investigated the influence of sex on the agreement between self- and observer-rating of positive psychotic symptoms in schizophrenia patients and could not show a difference between men and women (Lincoln et al., 2010).

The goal of the third study was thus to compare self- and observer-ratings of affective, negative and positive symptoms in ARMS and FEP patients and to investigate whether the agreement was dependent on disease stage (ARMS, FEP) and sex (men, women). Based

on the above mentioned previous research we expected a higher association between self- and observer-rating in ARMS as compared to FEP patients and a stronger correlation in women as compared to men.

3 Empirical Studies

Ittig S., Studerus E., Heitz U., Menghini-Müller S., Beck K., Egloff L., Leanza L., Andreou C., Riecher-Rössler A., (2017), Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women. ***Schizophrenia Research.*** [Epub ahead of print]

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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.

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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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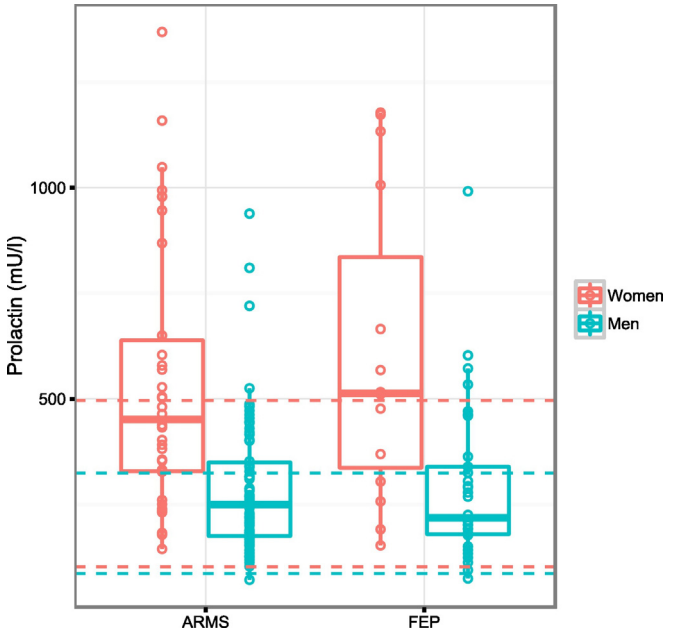

Fig. 1. Prolactin serum levels in ARMS and FEP patients subdivided by sex. The dotted horizontal lines represent the upper and lower reference levels for men and women. ARMS = at-risk mental state; FEP = first episode psychosis.

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; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ (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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Original article

Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects

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ABSTRACT

Background: Several sex differences in schizophrenia have been reported including differences in cognitive functioning. Studies with schizophrenia patients and healthy controls (HC) indicate that the sex advantage for women in verbal domains is also present in schizophrenia patients. However, findings have been inconsistent. No study focused on sex-related cognitive performance differences in at-risk mental state for psychosis (ARMS) individuals yet. Thus, the aim of the present study was to investigate sex differences in cognitive functioning in ARMS, first episode psychosis (FEP) and HC subjects. We expected a better verbal learning and memory performance of women in all groups.
Methods: The neuropsychological data analysed in this study were collected within the prospective *F*rüherkennung von *Psy*chosen (FePsy) study. In total, 118 ARMS, 88 FEP individuals and 86 HC completed a cognitive test battery covering the domains of executive functions, attention, working memory, verbal learning and memory, IQ and speed of processing.
Results: Women performed better in verbal learning and memory regardless of diagnostic group. By contrast, men as compared to women showed a shorter reaction time during the working memory task across all groups.
Conclusion: The results provide evidence that women generally perform better in verbal learning and memory, independent of diagnostic group (ARMS, FEP, HC). The finding of a shorter reaction time for men in the working memory task could indicate that men have a superior working memory performance since they responded faster during the target trials, while maintaining a comparable overall working memory performance level.

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1. Introduction

Sex differences in schizophrenia are described in almost all aspects of the illness, including age of onset, symptomatology, treatment response, time course and psychosocial outcome [1,50,59]. One of the most consistent findings is that women are older than men when first symptoms arise [16,24]. Furthermore, women – especially at younger ages – seem to have a more favourable outcome than men [50,55].

Closely related to the outcome of the disease is the impairment of cognitive functioning which is recognized as a core feature of schizophrenia [37,51] that is not only present in patients with schizophrenic psychoses, but already evident in individuals with an at-risk mental state (ARMS) for psychosis [9,20,53]. In addition, it has been shown that ARMS individuals with later transition to psychosis perform worse on tests measuring verbal fluency and memory [9,18] and speed of information processing [12,56] compared to those without transition. It has been consistently reported that prediction of psychosis can be improved by considering neurocognitive performance measures [40,56]. However, deficits in specific cognitive domains among ARMS and schizophrenia patients are at least in part explained by differences in IQ [31].

Sex differences in cognitive functioning are well known in healthy individuals. In general, women tend to perform better than men in tasks measuring verbal abilities, whereas the opposite is true for visuo-spatial skills [25,26,28,47]. Kimura suggested that tasks measuring verbal memory account for the most prominent sex differences [38].

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Differences in cognitive functioning between men and women have also been reported in schizophrenia patients. Many studies have shown that women with schizophrenia perform better than men with schizophrenia in the domain of verbal learning and memory [3,11,22,27,32,45,65,72], which is in line with findings in healthy controls (HC). In other cognitive domains, however, results have been largely inconsistent. In the domain of executive functions, two studies have demonstrated that women with schizophrenia perform better as compared to men with schizophrenia [22,61], two studies showed a worse performance of female patients as compared to male patients [5,32] and three studies did not find any performance differences [3,11,42]. In the domain of attention, two studies showed a better performance of women in relation to men with schizophrenia [22,72], one showed a worse performance of female patients [52] and five studies could not detect any sex differences [3,11,21,27,65]. With regard to working memory, one study found that women with schizophrenia perform worse, while three studies did not detect any performance differences. Interestingly, when comparing clinical with healthy control samples, Longenecker et al. reported an interaction effect in the working memory domain: Men with schizophrenia failed to exhibit the sex advantage during a working memory task which was evident in the healthy control sample [45]. In relation to IQ estimates, three studies out of four showed an equal performance for both sexes of schizophrenia patients [3,8,21]. For speed of processing, there is one study which showed a better performance for women [65] and one study, which depicted no sex difference in schizophrenia patients [11]. Only one study has been conducted with ARMS patients showing a better performance of men compared to women in picture completion (WISC-III and WAIS-III) [68]. These largely inconsistent findings could be due to using different patient groups (FEP, first episode schizophrenia, or chronic patients), medication, neuropsychological tasks for assessing the same cognitive domain and varying statistical power (mean sample size = 140; range: 31–360).

Furthermore, no study has yet analysed sex-related cognitive performance differences in ARMS individuals and first episode psychosis (FEP) patients together. Since cognitive impairment is recognized as a core feature of schizophrenia, sex differences in cognitive functioning developing over different stages of the disease could give rise to new hypotheses explaining pathogenic mechanisms of the illness. Thus, the aim of the present study was to investigate sex differences in cognitive functioning in ARMS, FEP and HC subjects and whether sex differences vary between the examined groups. Based on the above-cited studies, we expected a better performance of women in the domain of verbal learning and memory in all groups.

2. Methods

2.1. Setting and recruitment

The neuropsychological 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 [57,56]. Participants were recruited for the study via the FePsy Clinic at the Psychiatric University Outpatient Department of the Psychiatric University Clinics Basel, which was set up specifically to identify and treat individuals in the early stages of psychosis.

We recruited a sample of HC from trade schools, hospital staff and through advertisements. HC subjects with a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of psychiatric disorder were excluded.

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 [58]. This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria [70,71] 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 [58]. Individuals were classified as being in an ARMS for psychosis, having a FEP, or being not at-risk for psychosis (usually other psychiatric disorders). We included ARMS, FEP as well as a sample of HC in the present study.

2.3. Neuropsychological assessment

All neuropsychological assessments were conducted by psychologists and well-trained, supervised advanced psychology students. The test battery covered the following domains: general intelligence, executive functions, working memory, attention, verbal learning and memory [57,56].

General intelligence was estimated with the Mehrfachwahl-Wortschatz Test (MWT-A) [41] and the Leistungsprüfsystem, Scale 3 [34], which are well established German intelligence scales for assessing verbal and non-verbal (abstract reasoning) abilities.

Executive functions were assessed with the Tower of Hanoi (ToH) [19], Wisconsin Card Sorting Test (WCS) [14,30], and Go/No-Go subtest of the Test of Attentional Performance (TAP) [73].

Working memory was measured with the 2-back task of the TAP [73] and vigilance with the Continuous Performance Test (CPT-OX) [60].

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) [13].

For the Go/No-Go subtest and the 2-back task of the TAP as well as for the CPT-OX test that requires subjects to discriminate between two possible stimuli, we used the Signal Detection Theory (SDT) to measure performance in terms of "response bias" and "sensitivity". Response bias reflects the tendency to respond with yes and was quantified by the measure c, whereas sensitivity indicates the degree of overlap between the signal and the noise distributions and was quantified by the measure d'. Both measures were calculated according to the formulas provided by Wright [69] using the R package SDTALT [69]. The main advantage of using SDT measures is the separation of response bias and sensitivity [62].

A summary cognitive score was calculated by performing a principal component analysis on the test scores of the above-described tasks and extracting the factor scores of the first principal component. Thus, test scores were integrated in the summary score with different weights, depending on how much they loaded on the first principal component. The first principal component explained 22% of the total variance.

2.4. Psychopathological assessments

Positive psychotic symptoms (i.e., hallucinations, suspiciousness, unusual thought content and conceptual disorganisation) were assessed with the Brief Psychiatric Rating Scale (BPRS) [46,66] and negative symptoms with the Scale for the Assessment of Negative Symptoms (SANS) [4].

2.5. Statistical analyses

All data were analysed using the R environment for statistical computing [63]. Differences in sociodemographic and clinical

characteristics between men and women within each diagnostic group (ARMS, FEP, HC and total group) were tested with t and χ^2 tests.

The following procedure was applied to investigate the effects of sex (men, women) and diagnostic group (ARMS, FEP, HC) on cognitive functioning. All of the 25 dependant variables, reflecting cognitive functioning were screened for outliers. Values that were 3 standard deviations above or below the mean were treated as missing if they could be attributed to misunderstanding of instructions or truncated (i.e., replaced by the mean ± 3 standard deviations) if no obvious cause for their emergence could be found. The Box-Cox transformation [10] was applied to the outcome measures, which did not conform to assumptions of normality and/or homogeneity of variance. The Box-Cox procedure automatically selects exponential transformations that are optimal with regard to normalizing distributions and equalizing variances (Supplementary Table 1).

Since some of the outcome measures contained missing data (Supplementary Table 1), we next performed multiple imputation (MI) using the Multivariate Imputation by Chained Equations software [64]. MI is considered the method of choice of handling complex incomplete data problems because it yields unbiased parameter estimates and standard errors under a missing at random (MAR) or missing completely at random (MCAR) missing data mechanism and maximizes statistical power by using all available information [15]. Although the MAR or MCAR assumption is not directly testable [54], it was considered plausible in the present situation because the variables with the highest proportion of missing values, such as those of the CVLT, resulted from changes in the study design over the years and so the probability of being missing was unlikely to be directly dependent on the missing values themselves.

We generated 100 imputations of the missing values such that 100 completed datasets were obtained to protect against a potential power falloff from a too small number of imputations [23]. The analyses of interest were then conducted in each completed data set and parameter estimates were pooled according to Rubin's rules [44].

Analyses of covariance models (ANCOVA) were applied to evaluate the main effects of sex and group (ARMS, FEP, HC) as well as their interactions on cognitive functioning. We included sex and diagnostic group (ARMS, FEP, HC) as between subject factors and influence of age, years of education and use of antipsychotics as covariates. In case of significant interaction between sex and diagnostic group, sex differences were explored within each diagnostic group separately. The results are presented with and also without correction for multiple testing. Each table contains a column with the uncorrected and a column with the corrected P-values (Benjamini's and Hochberg's correction [7]).

3. Results

3.1. Sample description

Hundred and thirty-six ARMS individuals and 104 FEP patients were recruited for the FePsy study from March 1st, 2000 to November 1st, 2013. We also recruited a sample of 97 HC participants. We excluded 18 ARMS, 16 FEP and 11 HC because their cognitive performance measures were not assessed.

Thus, we performed the analysis on the remaining sample consisting of 118 ARMS, 88 FEP and 86 HC subjects. The excluded individuals did not differ from the included ones with regard to sex, age, years of education, BPRS total score, BPRS psychosis/thought disturbance [62] and SANS total score. Sociodemographic as well as clinical characteristics of the included individuals are presented in Table 1. There were no sex differences in ARMS, FEP, HC and in the total group with regard to age, years of education, use of antipsychotics, BPRS total score and SANS total score except for more pronounced psychosis/thought disturbance of women in the total group (ARMS + FEP) and an older age of women in the HC group.

3.2. Effects of sex and diagnostic group on cognitive functioning

Sex differences between men and women in the total group as well as within each diagnostic group separately for each cognitive performance measure are displayed in Fig. 1. Means and S.D. per group are presented in Table 2. In the ANCOVA model used, diagnostic group (ARMS, FEP, HC) and sex served as between subject factors with age, years of education and use of antipsychotics being selected as covariates. There was one significant interaction effect in verbal IQ ($P = 0.028$; Table 3), which was due to a non-significantly worse performance of women in the ARMS ($d = -0.286$) (Supplementary Table 2) and FEP group ($d = -0.168$) (Supplementary Table 3) and a non-significantly better performance in the HC group ($d = 0.177$) (Supplementary Table 4). However, this interaction was no longer significant after correction for multiple testing.

Effects of diagnostic group are presented in Table 3 and have already been described previously [53]. We will not describe this aspect any further because it is not the focal point of the present study.

In the total group (ARMS + FEP + HC), women remembered more words in the CVLT trials 1–5 ($P = 0.046$, $d = 0.258$; Table 3, Supplementary Table 5) and showed less retroactive interference (i.e., influence of newly learned words on the recall of previously learned words, $P = 0.048$, $d = 0.270$; Table 3, Supplementary Table 5). By contrast, in the total group men demonstrated a shorter working memory reaction time ($P = 0.046$, $d = -0.236$; Table 3, Supplementary Table 5). However, all these significant sex differences did not withstand correction for multiple testing.

Considering each group separately there were no sex differences in ARMS and FEP (Supplementary Tables 2 and 3). In the group of HC, there was only one significant sex difference. Specifically, men demonstrated less response bias in the Go/No-Go task ($P = 0.011$, $d = -0.352$; Supplementary Table 4), but only if uncorrected for multiple testing.

Sex-related cognitive performance differences were also separately investigated in ARMS patients with and without later transition to psychosis (ARMS-T vs. ARMS-NT). The results of the ANCOVAs are reported in Supplementary Table 6 and Fig. 1, means and S.D. are provided in Supplementary Table 7, and stratified analyses are reported in Supplementary Tables 8 and 9.

4. Discussion

To the best of our knowledge, this is the first study investigating sex-related neurocognitive performance differences in a sample of HC, ARMS and FEP patients. In line with our hypothesis, we found that women perform better in the domain of verbal learning and memory independent of diagnostic group. Furthermore, men as compared to women showed a shorter reaction time in the working memory task. Additionally, we found a sex × group interaction effect on verbal IQ, which was due to a non-significantly worse performance of women in the ARMS and FEP group and a non-significantly better performance in the HC group. All these results, however, did not withstand correction for multiple testing. Given that sex-related cognitive performance differences have been found to be rather small [35], we decided to discuss findings that were only significant at an uncorrected level to account for potential false negative results.

Table 1
Sample description.

	Total group				ARMS			FEP			HC		
	Men ($n=174$)	Women ($n=118$)	*P*-value	*N*	Men ($n=73$)	Women ($n=45$)	*P*-value	Men ($n=56$)	Women ($n=32$)	*P*-value	Men ($n=45$)	Women ($n=41$)	*P*-value
Age	26.2 (6.67)	27.7 (8.92)	0.133	292	25.6 (6.36)	27.2 (9.67)	0.326	29.2 (7.35)	30.3 (10.4)	0.579	23.6 (4.77)	26.2 (6.22)	0.038*
Years of education	11.7 (2.99)	12.1 (3.04)	0.316	292	11.8 (3.04)	11.8 (3.00)	0.997	11.3 (3.08)	11.4 (3.12)	0.826	12.3 (2.74)	13.0 (2.87)	0.244
Antipsychotics currently[a]			0.989	290			0.150			0.770			1.000
No	148 (85.5%)	101 (86.3%)			70 (95.9%)	39 (88.6%)		33 (60.0%)	21 (65.6%)		45 (100%)	41 (100%)	
Yes	25 (14.5%)	16 (13.7%)			3 (4.11%)	5 (11.4%)		22 (40.0%)	11 (34.4%)		0 (0.00%)	0 (0.00%)	
Chlorpromazine equivalent dose (mg)	221 (179)	204 (141)	0.735	40	217 (76.4)	245 (155)	0.742	222 (190)	185 (138)	0.538	–	–	
Antipsychotics compound			0.123	290			0.198			0.124			1.000
None	148 (85.5%)	101 (86.3%)			70 (95.9%)	39 (88.6%)		33 (60.0%)	21 (65.6%)		45 (100%)	41 (100%)	
Aripiprazole	0 (0.00%)	2 (1.71%)			0 (0.00%)	0 (0.00%)		0 (0.00%)	2 (6.25%)		0 (0.00%)	0 (0.00%)	
Risperidone	6 (3.47%)	8 (6.84%)			1 (1.37%)	3 (6.82%)		5 (9.09%)	5 (15.6%)		0 (0.00%)	0 (0.00%)	
Quetiapine	6 (3.47%)	2 (1.71%)			0 (0.00%)	0 (0.00%)		6 (10.9%)	2 (6.25%)		0 (0.00%)	0 (0.00%)	
Olanzapine	13 (7.51%)	4 (3.42%)			2 (2.74%)	2 (4.55%)		11 (20.0%)	2 (6.25%)		0 (0.00%)	0 (0.00%)	
Antidepressants currently			0.692	290			0.854			0.694			1.000
No	139 (80.3%)	97 (82.9%)			49 (67.1%)	28 (63.6%)		45 (81.8%)	28 (87.5%)		45 (100%)	41 (100%)	
Yes	34 (19.7%)	20 (17.1%)			24 (32.9%)	16 (36.4%)		10 (18.2%)	4 (12.5%)		0 (0.00%)	0 (0.00%)	
Tranquilizer currently			0.525	290			0.242			0.835			1.000
No	148 (85.5%)	96 (82.1%)			61 (83.6%)	32 (72.7%)		42 (76.4%)	23 (71.9%)		45 (100%)	41 (100%)	
Yes	25 (14.5%)	21 (17.9%)			12 (16.4%)	12 (27.3%)		13 (23.6%)	9 (28.1%)		0 (0.00%)	0 (0.00%)	
BPRS total score	43.2 (11.7)	45.7 (12.7)	0.191	175	38.7 (9.57)	41.0 (10.7)	0.265	50.0 (11.4)	52.2 (12.6)	0.449	–	–	
BPRS psychosis/thought disturbance	7.85 (3.64)	9.10 (4.21)	0.045*	178	5.92 (2.29)	6.93 (3.02)	0.072	10.8 (3.33)	12.3 (3.67)	0.093	–	–	
SANS total score	24.8 (16.3)	21.2 (15.7)	0.166	155	25.3 (17.6)	18.9 (16.3)	0.084	24.2 (14.8)	24.2 (14.7)	0.992	–	–	

ARMS: at-risk mental state; FEP: first episode psychosis; HC: healthy controls; BPRS: Brief Psychiatric Rating Scale; SANS: Scale for the Assessment of Negative Symptoms. Regarding psychopathological measures (BPRS and SANS), the total group consists of ARMS + FEP (without the HC's); mean and standard deviation of chlorpromazine equivalent doses are shown for those patients on antipsychotics (not for the overall group); continuous variables are described by means and standard deviation in brackets.

[a] Three ARMS patients out of 110 (two men and one woman) and three FEP patients out of 55 not taking antipsychotics (two men and one woman) were antipsychotic free and not naive.

* $P < 0.05$.

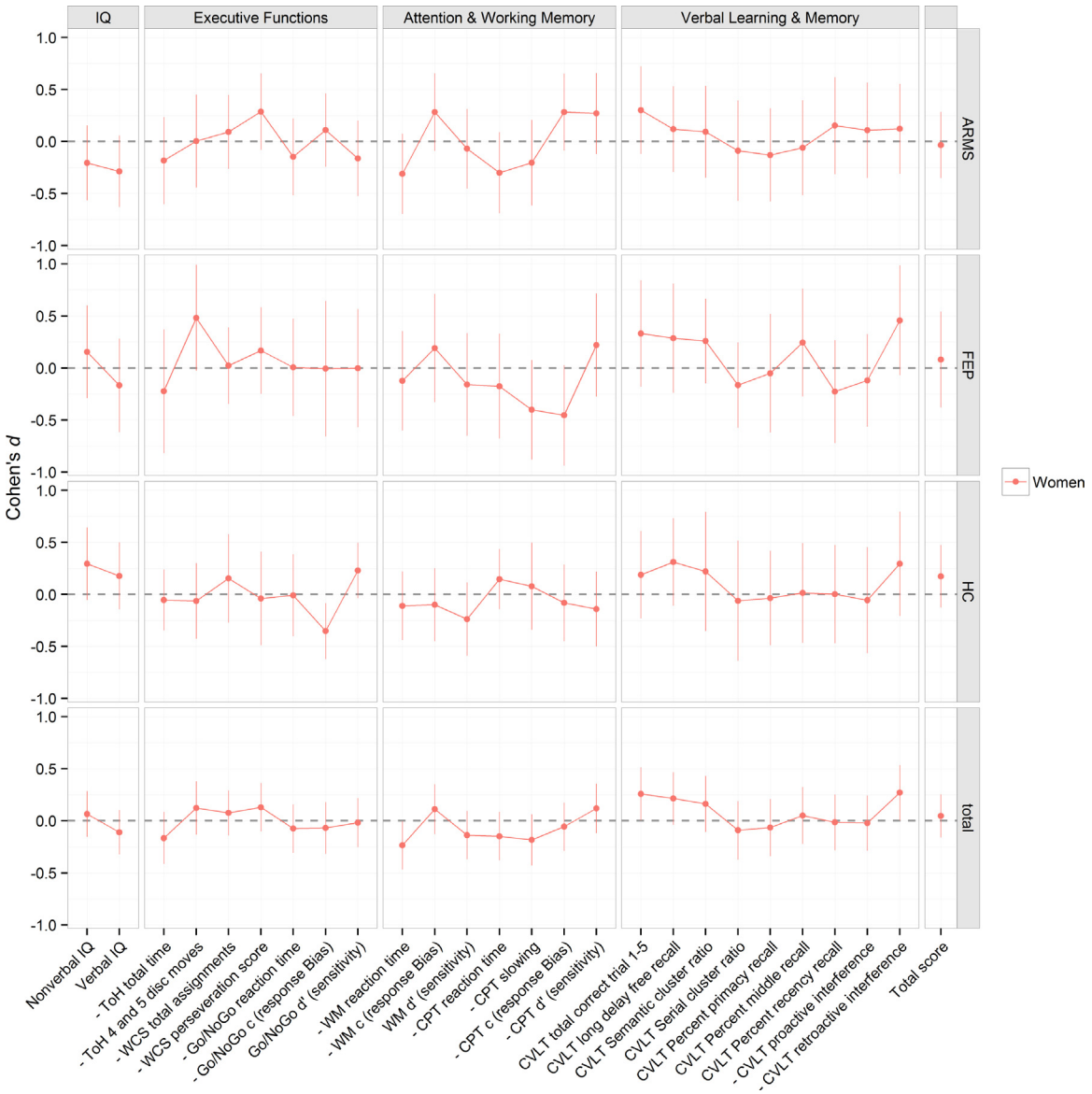

Fig. 1. Cognitive performance of women compared to men in at-risk mental state (ARMS) for psychosis individuals, first episode psychosis (FEP) patients, healthy controls (HC) and in the total group. The dotted horizontal line at zero represents the performance of men. Differences are expressed in units of Cohen's *d* and are significant if the 95% confidence interval (vertical line) does not overlap with zero. Variables with a minus sign were reversed so that positive scores always represent good performance. Differences are adjusted for the influence of age, years of education and use of antipsychotics. In the total group, we additionally corrected for diagnostic group. ARMS: at-risk mental state; FEP: first episode psychosis; HC: healthy controls; total: ARMS + FEP + HC; ToH: Tower of Hanoi; WCS: Wisconsin Card Sorting Test; CPT: Continuous Performance Task; CVLT: California Verbal Learning Task.

Our finding that women perform better in the domain of verbal learning and memory across all diagnostic groups is consistent with a large body of evidence [11,25,36,45,67]. Since we did not find an interaction between diagnostic group and verbal learning and memory, our results suggest that the sex advantage of women in verbal learning and memory is equally present in ARMS as in FEP and HC individuals [49]. As previous studies did not compare ARMS with HC and FEP individuals, this has not been demonstrated previously. Unexpectedly, we found that men had a shorter reaction time in the 2-back task than women independent of diagnostic group. This could indicate that men have a superior working memory performance since they responded faster during the target trials, while maintaining a comparable overall performance level. This result cannot be better explained by a generally enhanced processing speed as no sex differences in reaction time during CPT and Go/No-Go were detected. Our finding of a significant sex × group interaction in verbal IQ is difficult to explain as it is not substantiated by the literature. One potential explanation for a worse performance of women in the ARMS and FEP group could be that women in our sample have more severe positive symptoms than men as indicated by the BPRS psychosis/thought disturbance dimension score. However, an association between positive symptoms and verbal IQ has not been established in the literature and only appears to exist for negative and disorganised symptom dimensions [2,6].

Some earlier studies [21,48], which did not detect any sex differences in cognitive functioning were conducted in chronic schizophrenia patients who were seriously impaired and therefore represented a different patient population. It is conceivable that sex differences at a very low level of functioning do not exist or that they could not be detected because of floor effects. In the present study, we included mainly antipsychotic naïve ARMS and FEP

Table 2
Means and standard deviations of neuropsychological test data in ARMS, FEP, and HC.

	Total group			ARMS			FEP			HC		
	[ALL] (n = 292)	Men (n = 174)	Women (n = 118)	[ALL] (n = 118)	Men (n = 73)	Women (n = 45)	[ALL] (n = 88)	Men (n = 56)	Women (n = 32)	[ALL] (n = 86)	Men (n = 45)	Women (n = 41)
Non-verbal IQ	28.0 (5.67)	27.8 (5.63)	28.3 (5.74)	28.0 (5.38)	28.5 (5.64)	27.1 (4.82)	25.4 (5.97)	25.2 (5.54)	25.8 (6.73)	30.8 (4.37)	29.9 (4.43)	31.6 (4.18)
Verbal IQ	29.0 (4.13)	29.1 (4.19)	29.0 (4.08)	28.9 (4.01)	29.4 (3.80)	28.1 (4.25)	27.9 (4.81)	28.0 (5.07)	27.6 (4.44)	30.4 (3.10)	29.8 (3.45)	31.1 (2.58)
ToH total time	563 (385)	548 (355)	588 (433)	532 (329)	517 (305)	564 (377)	739 (513)	704 (474)	807 (583)	443 (236)	426 (175)	464 (293)
ToH 4 and 5 disc moves	83.3 (35.5)	85.5 (36.5)	79.8 (33.8)	82.3 (36.1)	83.2 (38.2)	80.6 (31.8)	95.1 (36.5)	101 (39.1)	83.1 (27.9)	74.0 (31.0)	71.5 (21.7)	76.8 (39.2)
WCS total assignments	82.0 (10.6)	82.6 (10.6)	81.0 (10.5)	82.5 (10.5)	82.9 (10.8)	81.6 (9.99)	85.9 (9.89)	85.9 (10.1)	85.9 (9.77)	77.5 (9.74)	78.2 (9.55)	76.7 (10.0)
WCS preservation score	21.3 (17.4)	22.5 (17.7)	19.5 (16.8)	21.4 (17.1)	23.2 (17.8)	18.2 (15.4)	26.6 (18.0)	27.6 (18.1)	24.9 (17.9)	16.1 (15.7)	15.6 (15.1)	16.6 (16.6)
Go/No-Go reaction time	544 (96.3)	543 (91.3)	545 (103)	557 (107)	550 (95.5)	569 (122)	563 (88.0)	566 (87.7)	558 (89.8)	507 (78.4)	506 (78.1)	508 (79.6)
Go/No-Go c (response bias)	0.05 (0.22)	0.04 (0.24)	0.05 (0.19)	0.04 (0.19)	0.04 (0.17)	0.04 (0.22)	0.09 (0.32)	0.10 (0.36)	0.07 (0.24)	0.02 (0.11)	−0.01 (0.13)	0.04 (0.08)
Go/No-Go d' (sensitivity)	3.94 (0.63)	3.94 (0.60)	3.94 (0.67)	3.97 (0.59)	4.04 (0.42)	3.87 (0.79)	3.72 (0.84)	3.69 (0.88)	3.78 (0.79)	4.11 (0.28)	4.07 (0.30)	4.15 (0.26)
WM reaction time	651 (215)	637 (217)	671 (211)	691 (233)	659 (240)	743 (212)	688 (220)	683 (220)	698 (222)	559 (149)	547 (138)	571 (161)
WM c (response bias)	0.48 (0.33)	0.50 (0.36)	0.46 (0.30)	0.56 (0.31)	0.58 (0.32)	0.52 (0.30)	0.45 (0.41)	0.46 (0.44)	0.42 (0.34)	0.42 (0.25)	0.40 (0.25)	0.43 (0.25)
WM d' (sensitivity)	3.02 (0.90)	3.05 (0.90)	2.97 (0.91)	2.96 (0.88)	3.00 (0.88)	2.91 (0.88)	2.72 (1.00)	2.76 (1.00)	2.64 (1.01)	3.38 (0.71)	3.46 (0.62)	3.28 (0.79)
CPT reaction time	439 (124)	433 (121)	449 (129)	454 (134)	432 (117)	490 (153)	470 (133)	463 (137)	482 (127)	392 (82.1)	399 (95.5)	384 (64.4)
CPT slowing	1.04 (0.13)	1.04 (0.13)	1.05 (0.13)	1.04 (0.11)	1.03 (0.11)	1.05 (0.12)	1.07 (0.16)	1.05 (0.17)	1.09 (0.15)	1.02 (0.10)	1.03 (0.11)	1.02 (0.10)
CPT c (response bias)	0.12 (0.20)	0.11 (0.17)	0.13 (0.24)	0.09 (0.19)	0.10 (0.16)	0.06 (0.22)	0.18 (0.23)	0.15 (0.18)	0.24 (0.30)	0.10 (0.17)	0.08 (0.16)	0.12 (0.17)
CPT d' (sensitivity)	4.99 (0.54)	4.99 (0.54)	4.97 (0.54)	4.96 (0.53)	5.01 (0.48)	4.89 (0.60)	4.85 (0.64)	4.88 (0.67)	4.80 (0.59)	5.14 (0.41)	5.10 (0.44)	5.18 (0.36)
CVLT total correct trial 1–5	59.1 (9.90)	57.9 (10.0)	60.9 (9.52)	59.4 (9.76)	58.6 (9.70)	60.9 (9.84)	55.8 (10.5)	54.8 (10.5)	57.4 (10.5)	63.6 (7.03)	62.0 (8.21)	65.4 (4.99)
CVLT long delay free recall	13.4 (2.53)	13.1 (2.69)	13.8 (2.24)	13.9 (1.95)	13.8 (1.99)	13.9 (1.90)	12.3 (3.10)	11.9 (3.35)	12.8 (2.69)	14.2 (1.84)	13.6 (2.11)	14.8 (1.30)
CVLT semantic cluster ratio	1.79 (0.90)	1.73 (0.86)	1.90 (0.95)	1.78 (0.94)	1.79 (0.92)	1.78 (0.99)	1.64 (0.74)	1.57 (0.72)	1.76 (0.78)	2.06 (1.01)	1.87 (0.96)	2.27 (1.04)
CVLT serial cluster ratio	0.12 (0.11)	0.13 (0.12)	0.12 (0.10)	0.13 (0.12)	0.13 (0.13)	0.13 (0.11)	0.11 (0.08)	0.11 (0.08)	0.10 (0.07)	0.12 (0.15)	0.13 (0.16)	0.11 (0.14)
CVLT percent primacy recall	27.6 (3.86)	27.7 (3.81)	27.6 (3.97)	27.4 (3.81)	27.4 (3.30)	27.5 (4.65)	28.4 (4.60)	28.5 (4.90)	28.3 (4.17)	26.8 (2.16)	26.9 (2.21)	26.7 (2.16)
CVLT percent middle recall	46.8 (4.17)	46.8 (4.56)	47.0 (3.51)	47.1 (4.22)	47.2 (4.37)	46.9 (3.99)	46.0 (4.71)	45.7 (5.38)	46.6 (3.41)	47.6 (2.84)	47.7 (2.83)	47.5 (2.91)
CVLT percent recency recall	25.5 (3.47)	25.6 (3.57)	25.4 (3.34)	25.5 (3.72)	25.4 (3.88)	25.6 (3.47)	25.5 (3.74)	25.8 (3.75)	25.1 (3.74)	25.6 (2.42)	25.4 (2.30)	25.8 (2.59)
CVLT proactive interference	0.97 (2.39)	0.95 (2.43)	0.99 (2.34)	0.87 (2.58)	0.95 (2.67)	0.72 (2.45)	1.44 (2.09)	1.36 (1.97)	1.57 (2.30)	0.40 (2.34)	0.21 (2.50)	0.62 (2.18)
CVLT retroactive interference	0.98 (1.67)	1.17 (1.69)	0.68 (1.60)	0.99 (1.58)	1.03 (1.56)	0.91 (1.65)	1.10 (1.89)	1.36 (1.93)	0.68 (1.76)	0.76 (1.46)	1.12 (1.57)	0.33 (1.24)
Total score	0.00 (1.00)	−0.06 (0.98)	0.08 (1.02)	−0.01 (0.85)	0.04 (0.82)	−0.10 (0.90)	−0.65 (1.05)	−0.71 (1.03)	−0.54 (1.10)	0.68 (0.62)	0.60 (0.59)	0.77 (0.64)

ARMS: at-risk mental state; FEP: first episode psychosis; HC: healthy controls; ToH: Tower of Hanoi; WCS: Wisconsin Card Sorting Test; WM: working memory; CPT: Continuous Performance Task; CVLT: California Verbal Learning Task.

Table 3
P-values of ANCOVAs with ARMS, FEP and HC.

	Uncorrected			Corrected		
	Group	Sex	Group × sex	Group	Sex	Group × sex
IQ						
Non-verbal IQ	<0.001***	0.516	0.797	0.002**	0.777	0.945
Verbal IQ	0.014	0.308	0.028*	0.033*	0.665	0.739
Executive functions						
ToH total time	0.006**	0.192	0.650	0.016*	0.665	0.945
ToH 4 and 5 disc moves	0.015*	0.344	0.916	0.034*	0.665	0.945
WCS total assignments	0.002**	0.496	0.921	0.011*	0.777	0.945
WCS preservation score	0.059	0.272	0.558	0.101	0.665	0.945
Go/No-Go reaction time	0.003**	0.530	0.634	0.013	0.777	0.945
Go/No-Go *c* (response bias)	0.238	0.580	0.505	0.310	0.777	0.945
Go/No-Go *d′* (sensitivity)	0.170	0.877	0.763	0.237	0.908	0.945
Attention and working memory						
WM reaction time	<0.001***	0.046*	0.639	<0.001***	0.413	0.945
WM *c* (response bias)	0.005**	0.358	0.103	0.015*	0.665	0.945
WM *d′* (sensitivity)	0.001**	0.239	0.290	0.008**	0.665	0.945
CPT reaction time	0.004**	0.212	0.821	0.013*	0.665	0.945
CPT slowing	0.173	0.141	0.913	0.237	0.665	0.945
CPT *c* (response bias)	0.061	0.627	0.334	0.101	0.777	0.945
CPT *d′* (sensitivity)	0.019*	0.326	0.410	0.038*	0.665	0.945
Verbal learning and memory						
CVLT total correct trial 1–5	0.012*	0.046*	0.938	0.031*	0.413	0.945
CVLT long delay free recall	0.062	0.098	0.859	0.101	0.634	0.945
CVLT semantic cluster ratio	0.267	0.241	0.624	0.316	0.665	0.945
CVLT serial cluster ratio	0.324	0.522	0.279	0.367	0.777	0.945
CVLT percent primacy recall	0.746	0.636	0.660	0.775	0.777	0.945
CVLT percent middle recall	0.256	0.716	0.767	0.316	0.810	0.945
CVLT percent recency recall	0.579	0.908	0.945	0.627	0.908	0.945
CVLT proactive interference	0.101	0.870	0.890	0.155	0.908	0.945
CVLT retroactive interference	0.920	0.048*	0.362	0.920	0.413	0.945
Composite						
Total score	<0.001***	0.658	0.886	<0.001***	0.777	0.945

ARMS: at-risk mental state; FEP: first episode psychosis; HC: healthy controls; ToH: Tower of Hanoi; WCS: Wisconsin Card Sorting Test; WM: working memory; CPT: Continuous Performance Task; CVLT: California Verbal Learning Task.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

individuals and therefore it should be noticed that our sample is not comparable to chronic schizophrenia patients. There are four studies, which included a FEP or first episode schizophrenia sample in their analysis of sex dependant cognitive performance differences. Ayesa-Arriola et al. [5] included 160 FEP and 159 HC in their study. Women outperformed men (FEP + HC) in a task of verbal memory (Rey auditory verbal learning test: trials 1–5) whereas men outperformed women on measures of reaction time (CPT reaction time), visual memory (Corsi blocks backward, Rey figure recall) and executive functions (Tower of London: total move score). Hoff et al. [32] could show a better performance for women in verbal learning and memory (CVLT) and a better performance of men in executive functioning measured by the WCST. Albus et al. [3] found a difference between the sexes (first episode schizophrenia patients and HC) in verbal learning and memory (CVLT) showing a better performance of women. The study of Zhang et al. [72] depicted no sex differences in neuropsychological task performance in first episode schizophrenia patients but they did not measure verbal learning and memory. To sum up: 3 out of 4 studies described better performance of women in verbal learning and memory and 2 out of 4 studies described an advantage of men in executive functioning. The better functioning in verbal learning and memory is in line with our findings whereas the finding of better performance of men in executive functioning was not supported by our data.

The following limitations should be taken into account: Our neuropsychological tasks were originally selected to assess the risk of psychosis and not specifically to detect sex differences. Therefore, our test battery did not include some of the most sensitive tasks to detect sex differences such as visuo-spatial or mental rotation tasks. Furthermore, meta-analyses suggest that sex-related cognitive performance differences are rather small [35]. Hence, our modest sample size could have precluded the detection of some sex effects. Another important aspect to consider is the conceptual difference of gender and sex. While gender refers to masculinity/femininity rooted in sociocultural descriptions (measured by a questionnaire), sex is a biologically reduced and dichotomous term. Results of Lewine et al. [43] indicate stronger gender than sex effects. Accordingly, in this paper we used the term sex because we did not evaluate gender. Finally, it should be noted that neuropsychological performance in women has been shown to fluctuate with their monthly cycle [17,29,33,39], which we did not control in this study. High levels of ovarian hormones in the midluteal phase may facilitate certain skills that show a female advantage, while being detrimental to skills that normally show a male advantage [39]. Thus, it is possible that some effects would have been more pronounced if we had measured women at a specific point during their monthly cycle.

Taken together, our results suggest that sex differences in cognitive functioning in ARMS and FEP patients are not different from those seen in HC. Specifically, the female advantage in verbal learning and memory, which has frequently been found in HC seems equally present in ARMS and FEP patients. Future studies should also consider menstrual status in women as well as making a distinction between gender and sex to identify potential differences in cognitive functioning.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2014.11.006.

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Publication 3: Correlations between self-rating and observer-rating of psychopathology in at-risk mental state and first episode psychosis patients: Influence of disease stage and gender.

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Original Article

Correlations between self-rating and observer-rating of psychopathology in at-risk mental state and first-episode psychosis patients: influence of disease stage and gender

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Abstract

Aim: Research findings on the correlations between self-rating and observer-rating of schizophrenic psychopathology are inconsistent and have rarely considered first-episode psychosis (FEP) and at-risk mental state (ARMS) for psychosis patients. This study investigates these correlations in ARMS and FEP patients and how they are moderated by disease stage and gender.

Methods: In the Basel *F*rüh*e*rkennung von *Psy*chosen (*FePsy*) study, positive and negative psychotic and affective symptoms were rated in 126 ARMS and 94 FEP patients using two observer- and three self-rating scales. The agreement between self-rating and observer-rating and the moderating influence of disease stage and gender was quantified using Pearson correlation and multiple regression models.

Results: Correlations between self- and observer-rated subscales covering the same symptom dimension were low and mostly non-significant except for one correlation of positive and one of negative symptoms. There was no moderating influence of disease stage and gender on the correlations between self-rating and observer-rating except for one higher association in positive symptoms in FEP compared to ARMS and in women compared to men. However, these significant interaction effects did not withstand correction for multiple testing.

Conclusions: This study suggests that the agreement between self-rating and observer-rating in FEP and ARMS patients is rather low, similar across symptom dimensions, and only partially dependent on disease stage and gender. However, low correlations between self-rating and observer-rating do not necessarily indicate that these patients have difficulties reporting their symptoms. They could also have occurred because the scales did not exactly cover the same symptom dimensions.

Key words: gender, observer-rating, psychosis, self-rating.

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INTRODUCTION

The coherence between self-rating and observer-rating in the assessment of psychopathology of schizophrenic psychoses is an emerging topic in current research.[1–4] Observer-rating scales are widely used[1,4,5] and considered objective measures of the severity of psychopathological symptoms in patients with a psychotic disorder,[6] but they need a well-trained professional and are time-consuming.[1,3] Self-rating scales, on the other hand, are more easily applicable. However, it is unclear whether self- and observer-rating scales measure similar constructs and whether psychosis patients are able to report their symptoms with sufficient accuracy.[7]

As schizophrenia patients have many features (e.g. poor insight, denial, delusions, cognitive

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deficits) that could hinder an accurate self-rating of their symptoms, it has long been assumed that self-ratings – especially of positive psychotic symptoms – are unreliable in these patients.[8,9] However, our literature research revealed that at least six studies found a good agreement between self-rating and observer-rating of positive psychotic symptoms in psychosis patients[3,4,9–12] and only three studies found poor correlations.[13–15]

With respect to negative symptoms, the concordance between self- and observer-rating scales seems to be rather inconsistent. Some studies found negative symptoms more difficult to be accurately reported than positive symptoms,[3,9,10] whereas other studies suggested that even patients with a schizophrenic, schizoaffective or acute psychotic disorder are able to accurately report them.[11,12] A further study by Bottlender *et al.*[16] found equivocal results as it showed good agreement in the SANS (Scale for the Assessment of Negative Symptoms) total score but not in the subscales Apathy, Alogia and Attention.

Studies assessing the concordance between self-rating and observer-rating of depressive symptomatology in psychosis patients mostly showed good agreements.[13,15,17] A recent study identified 49.2% of the patients to have equal self-rating and observer-rating in depressive symptoms.[1] However, Lasalvia *et al.*[14] found significant correlations between affective symptoms only in non-psychosis but not in psychosis patients.

One explanation for these inconsistent results is that in many studies self- and observer-rating scales did not tap exactly the same symptom dimension. Additionally, existing studies vary in several factors that can potentially moderate the relationship between self-rating and observer-rating, such as disease state, diagnostic group, degree of insight and gender distribution. However, only few studies have investigated the influence of these moderating factors. Below, we will summarize the literature regarding the influence of disease stage and gender, as our study will focus specifically on these factors.

To our knowledge, no study has investigated whether the agreement between self-rating and observer-rating differs between patients with a first-episode psychosis (FEP) and those who have an at-risk mental state (ARMS) for psychosis. Existing studies have only focused on one of these disease stages. FEP patients were found to have a good association in positive but not in negative symptoms,[10] whereas ARMS patients were shown to have more psychosis risk symptoms in self-reports than in clinical interviews.[18] However, as lack of insight can lead to a decreased agreement between self-rating and observer-rating[4] and as FEP patients were found to have more impaired insight than ARMS patients,[19] it is reasonable to assume that a direct comparison between ARMS and FEP patients would show a higher agreement in ARMS patients.

Although gender differences in schizophrenia have been described in almost all aspects, including age of onset, incidence, symptomatology, treatment response and outcome,[20–22] little is known about whether gender influences the agreement between self-rating and observer-rating. Some studies showed a higher agreement of affective symptoms in women compared to men in mixed patient samples or patients with depression.[23,24] However, other studies do not support these findings in samples with psychotic and non-psychotic major depression.[17,25] To our knowledge, only one study investigated the influence of gender on the agreement between self-rating and observer-rating of positive psychotic symptoms in schizophrenia patients.[4] This study found no influence of gender.

To improve on previous studies, this study aimed to compare self-rating and observer-rating of affective, negative and positive symptoms in both ARMS and FEP patients. Furthermore, we aimed to investigate whether the agreement was dependent on disease stage and gender. We hypothesized that the association between self-rating and observer-rating is higher in ARMS than in FEP patients and higher in women than in men.

METHODS

Setting and recruitment

All data were collected as part of the Basel ***F***rüh***er***kennung von ***Psy***chosen (***FePsy***) project, a prospective multilevel study, which aims to improve the early detection of psychosis.[26,27] The study was approved by the ethics committee of the University of Basel, and all participants provided written informed consent. Patients were recruited from 1 March 2000 to 31 January 2013 via the ***FePsy*** Clinic, which was specifically set up to identify, assess and treat individuals in the early stages of psychosis.

Screening procedure

Screening of ARMS and FEP patients was performed with the Basel Screening Instrument for Psychosis (BSIP), which has been shown to have a good interrater reliability (K = 0.67) and a high predictive validity.[28] Individuals were classified by the BSIP as being in an ARMS for psychosis, having a FEP, or

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being not at risk for psychosis using criteria corresponding to those of Yung *et al*.[29]

Assessment of psychopathology

The Brief Psychiatric Rating Scale Expanded Version (BPRS-E)[30] and the SANS[31] were used as observer-ratings and the Frankfurt Complaint Questionnaire (FCQ),[32] the Selfscreen-Prodrome (SSP)[33] and the Paranoid Scale (PS)[34] were used as self-ratings of psychopathological symptoms.

The BPRS-E is a widely used rating scale for assessing general psychopathology and consists of 24 items, which can be grouped to the four subscales Depression/Anxiety, Psychosis, Negative Symptoms and Activation.[35] All BPRS-E items are rated on a 7-point severity scale.

The SANS is a 24-item scale for assessing negative symptoms. The items of the SANS are rated on a 5-point ordinal scale and are grouped to five subscales: Affective Flattening, Alogia, Apathy/Avolition, Anhedonia/Asociality and Attention.

The FCQ contains 98 dichotomous items and is used to assess so-called 'basic symptoms', which are abnormal subjective experiences that can occur in a prodromal state of psychosis and that seem to have a predictive validity for the onset of psychosis.[36] These symptoms have been called 'basic' to indicate their proximity to hypothesized basic neural dysfunctions of schizophrenia.[37] The FCQ contains four factors: Depression, Disturbances of automated responses, Perceptual disturbances and Overinclusion.[32]

The PS consists of a subset of items of the Paranoid Depression Scale that contains paranoid and depressive symptoms. The PS comprises 14 items which can be grouped into the three subscales Paranoid Tendencies, Test Motivation and Denial of Illness.

The SSP is a screening instrument to identify patients with a risk for psychosis. It consists of 32 dichotomous items regarding prodromal and prepsychotic symptomatology.

All observer measures were conducted by well-trained psychologists or psychiatrists.

Statistical analysis

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 19, and the R environment for statistical computing.[38] Differences in sociodemographic and clinical characteristics between ARMS and FEP patients were tested with t and χ^2 tests.

First we used Pearson correlations to compare the already existing and published subscales of the five self- and observer-rating instruments. However, because these rating scales frequently differ in their item content, we also constructed new subscales from self-rating items that were as similar as possible to the original scales in the BPRS and SANS. Specifically, by applying hierarchical item cluster analysis[39] and based on theoretical knowledge about the dimensional structure of psychopathology, we grouped the items of each self-rating scale to the subscales Affective Symptoms, Positive Symptoms and Negative Symptoms in such a way that they were most similar to BPRS Depression/Anxiety, BPRS Psychosis and SANS total score, respectively. For assessing negative symptoms, we used the SANS total score instead of the BPRS subscale for negative symptoms because it covers this symptom dimension more completely and reliably. With the PS items, only the new subscale ('Positive Symptoms') was formed. The items of each newly formed subscale are shown in Supplementary Table S1. To evaluate the internal consistency and homogeneity of the new subscales, Cronbach's α[40] and Revelle's β[39] were calculated. In case of dichotomous and polytomous items, these measures were based on tetrachoric and polychoric correlations, respectively.

To evaluate the correlations between all self- and observer-rated scales we generated a Multitrait-multimethod matrix. This approach evaluates the construct validity of measures of different concepts assessed by different methods.[41] It shows how the correlations between different measures vary as a function of different item content and method.

Although all psychopathological assessments were obtained at baseline, they were not always obtained at the same visit. Hence, in accordance with previous studies,[10,16] we correlated only those measures of each patient that were obtained within a period of 7 days.

To examine whether gender and disease stage moderate the correlations between self-rating and observer-rating, multiple regression models with the observer-rating scale as dependent variable, the self-rating scale as the first independent variable and disease stage or gender as the second independent variables, and the interactions between these variables were performed. To facilitate interpretation, continuous variables were z-transformed.

To correct for multiple testing, *P*-values were adjusted using the Benjamini–Hochberg method.[42]

RESULTS

Sample description

Sociodemographic sample characteristics are presented in Table 1. ARMS did only differ from

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TABLE 1. Sociodemographic sample characteristics

	Total	ARMS (n = 126)	FEP (n = 94)	P-value
Gender				0.649
Female	81	48	33	
Male	139	78	61	
Age mean (SD)	27.4	25.7 (7.5)	29.8 (8.6)	<0.001***
Years of education mean (SD)	11.4 (3.0)	11.7 (3.1)	11.1 (3.0)	0.109

*P < 0.05; **P < 0.01; ***P < 0.001.t-tests for independent samples were used for continuous variables, χ^2 tests for categorical variables. ARMS, at-risk mental state; FEP, first-episode psychosis.

TABLE 2. Clinical sample characteristics

	Total	ARMS (n = 126)	FEP (n = 94)	P-value	N ARMS/FEP
BPRS Depression/Anxiety	9.86 (3.85)	9.23 (3.5)	10.66 (4.08)	0.008**	113/89
BPRS Psychosis/Thought Disturbance	8.61 (3.768)	6.44 (2.2)	11.38 (3.56)	<0.001***	114/89
BPRS Negative Symptoms	6.08 (2.87)	6.16 (2.93)	5.99 (2.79)	0.676	113/89
BPRS Activation	6.21 (2.65)	5.45 (1.89)	7.18 (3.14)	0.000***	113/89
BPRS Total score	45.64 (12.47)	40.4 (9.35)	52.29 (12.8)	<0.000***	113/89
SANS Affective Flattening	5.75 (6.42)	5.81 (6.40	5.67 (6.47)	0.878	112/85
SANS Alogia	3.39 (3.98)	3.27 (3.89)	3.55 (4.13)	0.624	113/84
SANS Avolition-Apathy	5.81 (3.28)	5.55 (2.98)	6.16 (3.62	0.206	114/85
SANS Asociality-Anhedonia	7.7 (5.23)	7.7 (5.18)	7.77 (5.32)	0.923	110/84
SANS Inattention	1.87 (2.01)	1.59 (1.59)	2.22 (2.42)	0.049*	100/78
SANS Total score	24.37 (16.76)	23.77 (16.28)	25.18 (17.44)	0.560	114/85
FCQ Disturbances of automated responses	6.74 (5.68)	5.51 (4.64)	8.38 (6.51)	0.005**	77/58
FCQ Perceptual disturbances	4.97 (5.22)	3.41 (3.03)	7.07 (6.65)	<0.001***	78/58
FCQ Depression	9.10 (6.52)	7.59 (5.82)	11.12 (6.90)	0.002**	78/58
FCQ Overinclusion	7.13 (4.65)	6.21 (4.00)	8.36 (5.17)	0.01*	77/58
FCQ Total score	28.32 (19.97)	23.14 (15.39)	35.19 (23.19)	0.001**	77/58
SSP Total	15.61 (9.89)	15.33 (6.71)	16.05 (7.23)	0.611	63/39
PS Paranoid Tendencies	7.58 (7.50)	4.79 (4.60)	11.21 (8.91)	<0.001***	73/56
Adapted subscales					
FCQ Affective Symptoms	3.41 (2.44)	2.94 (2.28)	4.05 (2.54)	0.008**	78/58
FCQ Positive Symptoms	6.88 (5.67)	5.29 (3.79)	9.02 (6.98)	<0.001**	78/58
FCQ Negative Symptoms	9.44 (8.00)	7.46 (6.28)	12.10 (9.27)	0.001**	78/58
SSP Affective Symptoms	3.98 (1.88)	4.08 (1.86)	3.82 (1.93)	0.503	65/93
SSP Positive Symptoms	2.44 (2.02)	2.12 (1.88)	2.97 (2.15)	0.037*	65/93
SSP Negative Symptoms	4.38 (2.47)	4.60 (1.86)	3.82 (1.93)	0.023*	65/93
PS Positive Symptoms	7.16 (7.32)	4.35 (4.42)	10.79 (8.65)	<0.001***	75/58

*P < 0.05; **P < 0.01; ***P < 0.001.
Scale scores are presented as means with standard deviations in parentheses. t-tests for independent samples were used for continuous variables, χ^2 tests for categorical variables.
ARMS, at-risk mental state; BPRS, Brief Psychiatric Rating Scale; FCQ, Frankfurt Complaint Questionnaire; FEP, first-episode psychosis; PS, Paranoid Scale; SANS, Scale for the Assessment of Negative Symptoms; SSP, Selfscreen-Prodrome.

FEP patients regarding age ($t(185) = -3.69$, $P < .001$).

Clinical characteristics of our sample are shown in Table 2. FEP patients had higher scores in all scales assessing positive and basic symptoms. However, they did not differ in negative symptoms scales except for a higher score of FEP patients in the newly constructed self-rating SSP Negative Symptom scale. With regard to affective symptoms, FEP scored higher in the BPRS Depression/Anxiety and self-rating FCQ Affective Symptoms scales, but not in the self-rating SSP Affective Symptoms scale.

Associations between self-rating and observer-rating

Correlations of the original subscales between self-rating and observer-rating are illustrated in Figure 1. The highest correlations between subscales with similar item content were between

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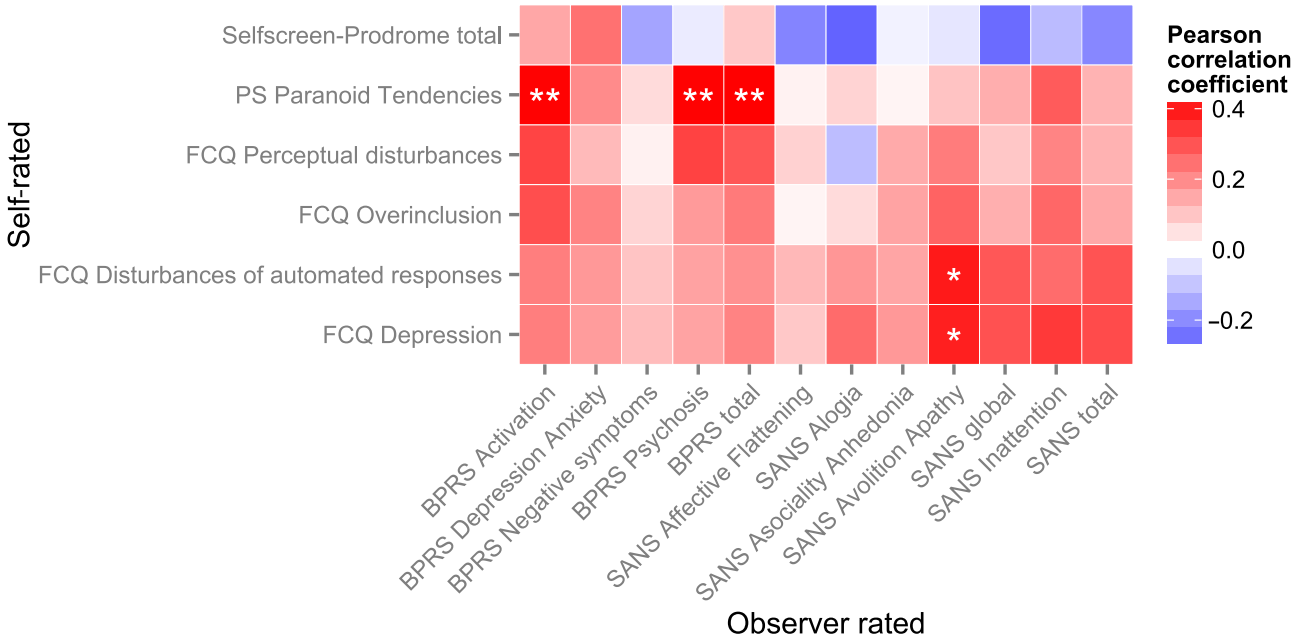
FIGURE 1. Correlations of original self- and observer-rating subscales. *P < 0.05, **P < 0.01, ***P < 0.01, adjusted for multiple testing by the Benjamini–Hochberg method. BPRS, Brief Psychiatric Rating Scale; FCQ, Frankfurt Complaint Questionnaire; PS, Paranoid Scale; SANS, Scale for the Assessment of Negative Symptoms; SSP, Selfscreen-Prodrome.



FCQ Perceptual disturbances and BPRS Psychosis (r(63) = .342, P adjusted = .056) as well as between PS Paranoid Tendencies and BPRS Psychosis (r(70) = .455, P adjusted = .002).

Correlations between the self-rating and observer-rating, internal consistencies, homogeneities and sample sizes of the newly constructed subscales are illustrated in Table 3. The newly constructed subscales showed a good internal consistency (α = .86–.96) and homogeneity (β = .7–.85). However, internal consistencies of the BPRS Psychosis and Depression/Anxiety subscales were α < .8 and α < .7, respectively. Heterotrait–monomethod correlations were higher than monotrait–heteromethod correlations suggesting that there was more common variance due to the method than the content. There were only two significant correlations between self- and observer-rating scales covering the same symptom dimension. Specifically, the FCQ Negative Symptoms subscale correlated significantly with the SANS scale (r(66) = .317, P adjusted = .021) and the PS Positive Symptoms correlated significantly with the BPRS Positive Symptoms subscale (r(70) = .454, P adjusted < .001).

Influence of disease stage and gender on the association between self-rating and observer-rating

As shown in Figure 2, there were no Group × Self-rating scale interactions in affective and negative symptomatology. However, in positive symptoms, there was one significant Disease stage × Self-rating scale interaction with the FCQ Positive Symptom scale, R^2 = .534, F(1,63) = 7.38, P = .009, η^2 = .108, which was due to a higher correlation between self-rating and observer-rating in FEP than in ARMS patients. However, when corrected for multiple testing, this interaction effect was only significant at a trend level (P adjusted = .060).

In the analyses including gender, there was only one statistically significant Gender × Self-rating scale interaction, namely, with the SSP Positive Symptoms subscale, R^2 = .168, F(1,53) = 6.009, P = .018, η^2 = .105, suggesting that women showed a higher correlation of this subscale with the BPRS Positive Symptom scale than men (Fig. 3). However, this significant interaction effect did not withstand correction for multiple testing (P adjusted = .124).

DISCUSSION

The aim of this study was to investigate the correlations of self-rating and observer-rating in ARMS and FEP patients and the influence of disease stage and gender on these correlations. Using the original subscales, we found relatively high correlations in positive symptom dimensions but not in the other symptom dimensions. When the scales were adapted to have better matching item contents, we found two significant correlations between

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TABLE 3. Multitrait-multimethod (MTMM) matrix of the adapted subscales

		Subscales	Observer-rating			Self-rating						
			BPRS		SANS	FCQ			SSP			PS
			A	P	N	A	P	N	A	P	N	P
Observer-rating	BPRS	A	$\alpha = 0.72$ $\beta = 0.51$	203	166	65	65	65	55	55	55	72
		P	0.277**	$\alpha = 0.63$ $\beta = 0.51$	166	65	65	65	55	55	55	72
	SANS	N	0.144	0.073	$\alpha = 0.95$ $\beta = 0.77$	68	68	68	53	53	53	76
Self-rating	FCQ	A	0.210	0.071	0.344*	$\alpha = 0.87$ $\beta = 0.78$	136	136	57	57	57	92
		P	0.222	0.227	0.249*	0.659**	$\alpha = 0.9$ $\beta = 0.79$	136	57	57	57	92
		N	0.201	0.271	0.317*	0.754**	0.711**	$\alpha = 0.96$ $\beta = 0.85$	57	57	57	92
	SSP	A	0.192	−0.146	−0.035	0.496**	0.253	0.280	$\alpha = 0.89$ $\beta = 0.7$	104	104	56
		P	0.130	0.201	−0.180	0.268	0.247	0.226	0.443**	$\alpha = 0.86$ $\beta = 0.7$	104	56
		N	0.236	−0.129	0.138	0.521**	0.442**	0.486**	0.679**	0.393**	$\alpha = 0.88$ $\beta = 0.75$	56
	PS	P	0.246	0.454**	0.185	0.512**	0.577**	0.494**	0.227	0.577**	0.077	$\alpha = 0.92$ $\beta = 0.8$

*$P < 0.05$; **$P < 0.01$; adjusted for multiple testing by Benjamini–Hochberg method.α, Cronbach's α; β, Revelle's β; A, affective symptoms; BPRS, Brief Psychiatric Rating Scale; FCQ, Frankfurt Complaint Questionnaire; N, negative symptoms; P, positive symptoms; PS, Paranoid Scale; SANS, Scale for the Assessment of Negative Symptoms; SSP, Selfscreen-Prodrome. Above diagonal denotes sample size; below diagonal denotes correlation between symptom dimensions; grey denotes matching subscales (validity).

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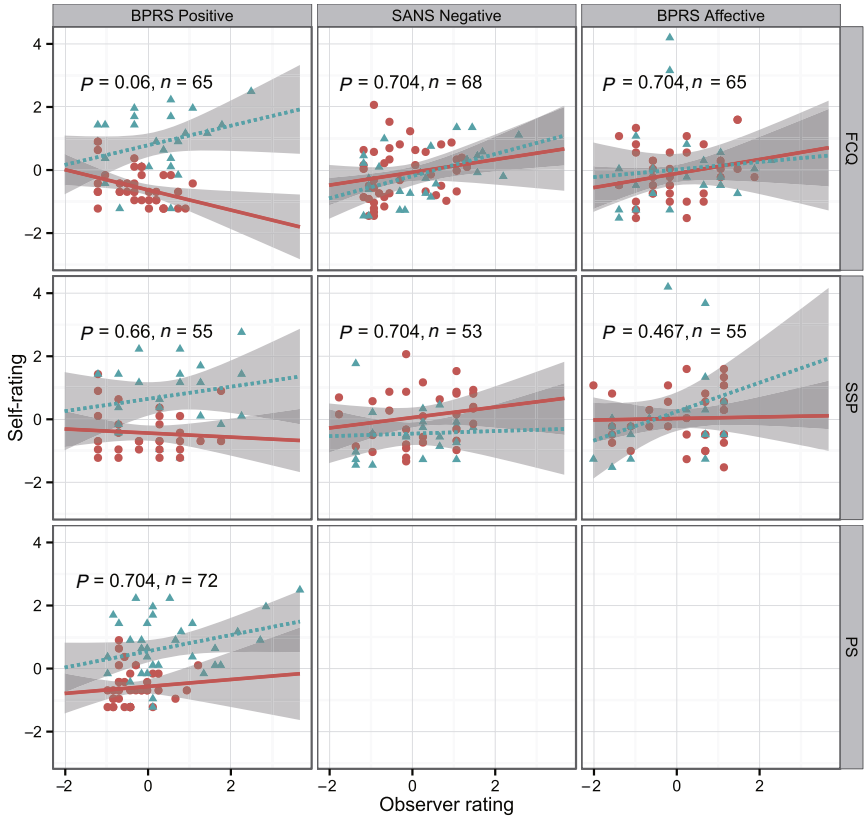
FIGURE 2. Diagnostic Group × Self-rating scale interactions. *P*-values were adjusted for multiple testing by the Benjamini–Hochberg method. ARMS, at-risk mental state; BPRS, Brief Psychiatric Rating Scale; FCQ, Frankfurt Complaint Questionnaire; FEP, first-episode psychosis; PS, Paranoid Scale; SANS, Scale for the Assessment of Negative Symptoms; SSP, Selfscreen-Prodrome; Grey shaded area denotes confidence interval. —●—, ARMS; ---▲---, FEP.



self-rating and observer-rating covering the same symptom dimension, namely, one with positive and one with negative symptoms. Furthermore, disease stage and gender each moderated one pair of self/observer-ratings, but only if *P*-values were uncorrected for multiple testing.

The construction of new subscales with more homogeneous and better matching item content improved the interpretability of the results and led to higher self/observer agreements, particularly in the domain of negative symptoms. However, overall the correlations were still relatively small. Although all seven pairs of subscales covering the same symptom dimension correlated positively, only two were statistically significant, indicating that the agreements between self-rating and observer-rating were rather low. Furthermore, no clear pattern emerged with regard to strength of association and symptom dimension. As we found statistically significant correlations with both positive and negative symptoms, our results do not confirm earlier findings of Hamera *et al.*[9] and Preston and Harrison,[10] according to whom negative symptoms are more difficult to be accurately reported than positive symptoms, but support earlier findings of Bell *et al.*[12] and Liraud *et al.*[11] The lack of association between scales measuring affective symptoms stands in contrast to previous studies which reported good agreements in this dimension.[1,15]

With regard to the moderating influence of the disease stage, we could not confirm that the association between self-rating and observer-rating is higher in ARMS than in FEP patients. However, when *P*-values were not corrected for multiple testing, there was one significant interaction which was in the opposite direction of what we had expected. Specifically, FEP showed higher correlations than ARMS patients between the BPRS and FCQ Positive Symptom scales. One possible explanation is that lower occurrence of positive psychotic symptoms in the ARMS group led to a distribution of positive symptoms with a lower spread and higher positive skew than in the FEP group which in turn might have led to a stronger attenuation of the correlation.

With regard to the moderating influence of gender, we found that women showed a higher association between BPRS and SSP Positive Symptoms

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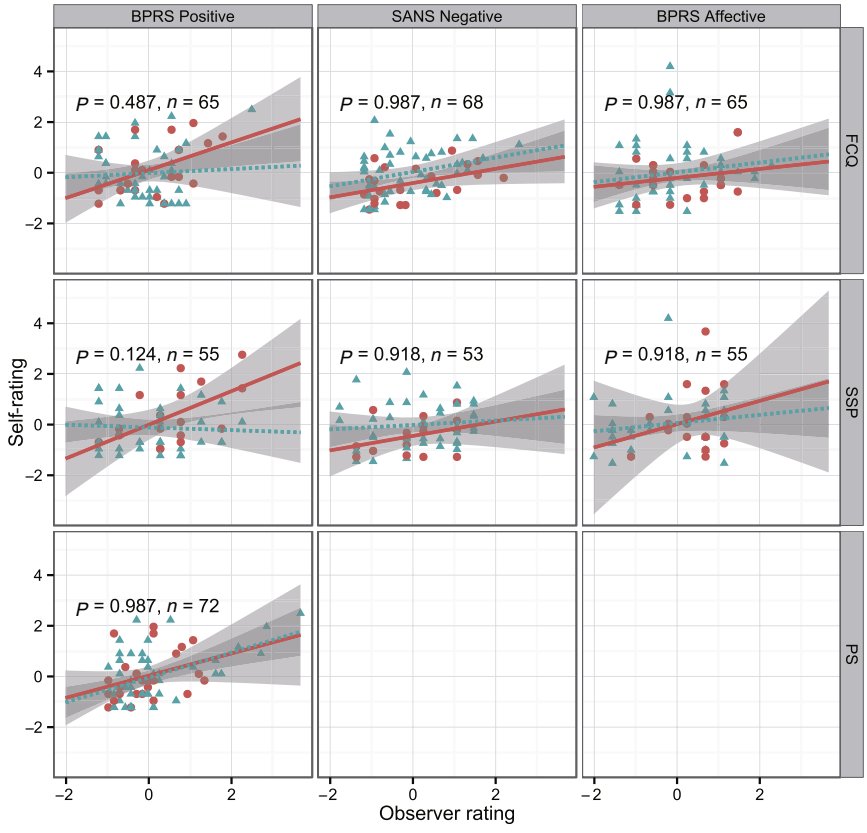
FIGURE 3. Gender × Self-rating scale interactions. *P*-values were adjusted for multiple testing by the Benjamini–Hochberg method. ARMS = at-risk mental state; BPRS, Brief Psychiatric Rating Scale; FCQ, Frankfurt Complaint Questionnaire; FEP, first-episode psychosis; PS, Paranoid Scale; SANS, Scale for the Assessment of Negative Symptoms; SSP, Selfscreen-Prodrome. Grey shaded area denotes confidence interval. —●—, women; ---▲---, men.



than men, suggesting that women are more accurate in reporting their positive psychotic symptoms. This finding stands in contrast to the study of Lincoln *et al.*[4] which did not find an influence of gender on the rating of positive psychotic symptoms. However, the gender effect we found should be interpreted with caution because there was no influence of gender in the two other comparisons regarding positive symptoms (i.e. BPRS vs. FCQ Positive Symptoms and BPRS vs. PS Positive Symptoms) and the effect was only significant when *P*-values were not corrected for multiple testing. Furthermore, our results did not support earlier studies demonstrating that women report their affective symptoms more accurately than men.[23,24] However, these studies are difficult to compare with our study because they were based on mixed patient samples.

Our study has some limitations. Firstly, even though we had improved the comparability of the scales by forming new subscales, we were quite limited in the item content and thus it is possible that our subscales still insufficiently covered the same symptom dimensions. Other studies solved this problem using newly constructed self-rating questionnaires,[9] modified observer-ratings to self-questionnaires[16] or concentrated their analysis on a special symptom dimension.[4] Secondly, although we had obtained self-rating and observer-rating from 220 patients in total, a relatively large proportion of these had to be excluded because the time difference between self-rating and observer-rating was too large. Thirdly, we assumed according to the literature[6] that observer-ratings are closer to 'the truth' and therefore represent the gold standard. However, in order to verify this we would have to link both types of assessment to an external criterion. Future studies should directly assess the value of both types of assessment. For example, it is likely that observer-ratings are better for an accurate diagnosis whereas self-ratings provide additional information that can help increase treatment compliance.[7]

Taken together, we found that the associations between self-rating and observer-rating were rather low. Contrary to our expectations, they were neither

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higher in ARMS than in FEP patients, nor higher in women than in men when corrected for multiple testing. The results of our study therefore imply that self-rating scales cannot be a substitute for the more time-consuming observer-rating scales and vice versa.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Items used for the adapted subscales.

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4 Discussion

The aim of this dissertation was on one hand to replicate findings of elevated prolactin levels in antipsychotic-naïve ARMS and FEP patients and to further investigate its relation to psychopathological symptoms and transition to psychosis. On the other hand we wanted to elucidate whether there are any sex differences in emerging psychosis specifically regarding the hormone prolactin, cognitive functioning and the correlation of self- and observer-ratings of psychopathology. In the following sections the results of the three publications are discussed.

4.1 The role of prolactin in emerging psychosis

In publication 1, the role of prolactin was investigated in 116 antipsychotic-naïve ARMS and 49 antipsychotic-naïve FEP patients. A high percentage of antipsychotic-naïve ARMS and FEP patients in our sample were suffering from hyperprolactinemia. We could not show a difference in prolactin levels between ARMS and FEP patients. Furthermore, prolactin was not significantly associated with any BPRS subscale and prolactin was not a significant predictor of transition to psychosis.

According to our reference standard only 2.5% of people in the normal population are expected to fulfil criteria for hyperprolactinemia. In contrast, in our ***Fepsy***-study sample 32% of ARMS and 35% of FEP patients presented with hyperprolactinemia. Similarly high proportions have been reported in previous studies (Aston et al., 2010; A. Riecher-Rössler et al., 2013). Because hyperprolactinemia can have severe consequences including amenorrhea, galactorrhoea, a lack of estrogen with acceleration of osteoporosis, urogenital symptoms and skin aging etc. in women and a lack of libido, erectile dysfunction, dry skin, and osteoporosis etc. in men (Rajkumar, 2014; A. Riecher-Rössler, Schmid, Bleuer, & Birkhäuser, 2009) it requires clinical attention. The negative consequences of hyperprolactinemia are often attributed to antipsychotics and can be a reason for non-compliant behaviour. Thus, it is important to measure prolactin levels before treatment to reveal a possible pre-existing hyperprolactinemia.

Prolactin levels in ARMS and FEP patients did not significantly differ. This finding is in accordance with the only other study that compared prolactin levels between ARMS and FEP patients (Montalvo et al., 2014) and 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). Similarly, we could not find associations between prolactin levels and BPRS subscales, whilst associations between the stress hormone cortisol and the severity of positive and nonspecific symptoms have been shown in the literature (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013). However, the non-significant associations

between prolactin levels and BPRS subscales are 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 also did not find an association of prolactin levels with BPRS subscales.

Even though, prolactin was not predictive of transition to psychosis, this finding is consistent with a study of Perkins et al. (2015) where the expression of plasma analytes reflecting inflammation, oxidative stress, hormones and metabolism was measured 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. Contradictory results were found by Labad et al. (2015). Hence, no definite conclusion can be drawn.

4.2 Sex differences in prolactin levels, cognitive functioning and its influence on correlations between self- and observer-rating of psychopathology

In this section I aim at summarizing and discussing all sex specific findings from publication 1, 2 and 3. Regarding the first publication entitled “Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women” (116 ARMS and 49 FEP have been included) we found that prolactin was more increased in women than in men after correction for the normal biological variation between the sexes (ARMS + FEP). This is not in line with our hypothesis which was formulated on the basis of the meta-analysis of Gonzalez-Blanco et al. (2016) who found more pronounced differences between patients and controls in men than in women. Additionally, hyperprolactinemia was more frequent in women than in men (ARMS + FEP). One possible explanation for the discrepancies of the results could be that in the metaanalysis of Gonzalez-Blanco (2016) only studies with a healthy control sample have been included. Therefore, they disregarded an important study in the field, namely, the study of Riecher-Rössler and the EUFEST study group (2013), which found hyperprolactinemia to be present in 50% of antipsychotic-naïve female FEP patients but only in 36.5% of antipsychotic naïve male FEP patients. There is additional support for our finding of higher prolactin levels in women by a study of Lennartsson and Jonsdottir (2011) who demonstrated that women showed stronger prolactin responses to the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993), albeit only at a trend-level.

The second publication “Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects” is the first study investigating sex-related neurocognitive performance differences in a sample of HC, ARMS and FEP patients. In total, 118 ARMS, 88 FEP and 86 HC completed a cognitive test battery covering the domains of executive functions, attention, working memory, verbal learning and memory, IQ and speed of processing (see also publication 2 for more details). Due to the fact that sex-

related cognitive performance differences have been found to be rather small (Hyde, 1981), we decided to discuss findings that were significant at an uncorrected level to account for potential false negative results.

Our main finding that women perform better in the domain of verbal learning and memory across all diagnostic groups (HC, ARMS, FEP) is in line with our hypothesis and consistent with a large body of evidence (Bozikas et al., 2010; Halari et al., 2005; Jimenez, Mancini-Marie, Lakis, Rinaldi, & Mendrek, 2010; Longenecker et al., 2010; Walder et al., 2006). The results suggest that the sex advantage of women in verbal learning and memory is equally present in ARMS as in FEP and HC individuals, as we did not find an interaction effect between diagnostic group (HC, ARMS, FEP) and sex (men, women) (Nieuwenhuis, Forstmann, & Wagenmakers, 2011). Additionally, we found that men had a shorter reaction time in the 2-back task than women independent of diagnostic group. Probably, this could indicate that men have a superior working memory performance since they responded faster during the target trials, while maintaining a comparable performance level. As no sex differences in reaction time during Continuous Performance Test (CPT-OX; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) and Go/No-Go (subtest of the Test of Attentional Performance [TAP]; Zimmermann & Fimm, 1993) were detected, the result above cannot be better explained by a generally enhanced processing speed. Additionally, we found a significant sex × group interaction effect in verbal IQ (better performance of women in HC and worse performance in ARMS and FEP) which is difficult to explain as it is not substantiated by the literature. A potential explanation for a worse performance of women in the ARMS and FEP group could be that women in our sample do present more severe positive symptoms than men as indicated by the BPRS psychosis/thought disturbance dimension score described by Velligan et al. (2005). We have included fewer women than men in the ***Fepsy***-study because we reached probably only the really severe ill female patients which could be the reason for more positive psychotic symptoms in women.

In the third publication, correlations between self-rating and observer-rating of psychopathology in ARMS and FEP patients and the influence of disease stage and sex on these correlations have been investigated in a sample of 126 ARMS and 94 FEP patients. The BPRS (Lukoff et al., 1986) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989) were used as observer-ratings and the Frankfurt Complaint Questionnaire (FCQ; Süllwold, 1986), the Selfscreen-Prodrome (SSP; Kammermann, Stieglitz, & Riecher-Rossler, 2009) and the Paranoid Scale (PS; Zerssen & Koeller, 1976) were used as self-ratings of psychopathological symptoms (see also publication 3 for more details). As the second important point of my thesis is sex differences in emerging psychosis, I will mainly discuss the aspect of the moderating factor sex in relation to the agreement between self- and observer-ratings and just shortly describe the other findings (see also

publication 3). In accordance with the second publication, we decided to discuss findings that were significant at an uncorrected level to account for potential false negative results.

Generally, the agreements between self-rating and observer-rating were rather low. Two significant correlations (out of seven) between self- and observer-rating covering the same symptom dimension (one with positive and one with negative symptoms) have been found. This finding stands in contrast to earlier studies which pointed out that negative symptoms are more difficult to report accurately than positive symptoms (Hamera et al., 1996; Preston & Harrison, 2003). Furthermore, also the lack of association between scales measuring affective symptoms is in contrast to previous studies (Biancosino et al., 2007; Hartmann et al., 2013).

With regard to the moderating influence of disease stage, we could not confirm that the agreement between self- and observer-rating is higher in AMRS than in FEP patients. When taking sex as influencing factor into account it has been found that women showed a higher association between BPRS and SSP positive symptoms than men, suggesting that women more accurately report their positive psychotic symptoms. This finding has to be interpreted with caution because there was no influence of sex in the two other comparisons regarding positive symptoms (i.e. BPRS vs. FCQ positive symptoms and BPRS vs. PS positive symptoms) and it is in contrast to the finding of Lincoln et al. (2010). Furthermore, findings of earlier studies demonstrating that women report their affective symptoms more accurately than men (Jolly et al., 1994; Shain et al., 1990) are not supported by our study. However, it should be noted that these earlier studies are difficult to compare as they were based on mixed patient samples.

5 Conclusion and Perspectives

Taken together, the results of my first publication provide further evidence for frequent hyperprolactinemia in emerging psychosis and highlight 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 between sexes. The question whether elevated prolactin levels are specific for emerging psychosis or rather associated with emerging illness (e.g. depression etc.) in general could not be ruled out. Hence, for future studies, recruitment of control groups (e.g. depressive controls but also healthy controls) should be planned. Furthermore, future studies should also assess individual perceived stress levels using, for example, the perceived stress scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). Myin-Germeys et al. (2004) showed already earlier that women are more characterized by increased stress sensitivity compared with men. The hypothesis of increased stress sensitivity suggests that not the stress level itself is responsible for developing symptoms but rather the way subjects react to it (Myin-Germeys

et al., 2004). Thus, it would be very interesting to investigate if prolactin levels may be an indicator for the increased stress sensitivity in women (correlation between PSS and prolactin), which would help to further clarify the role of prolactin in emerging psychosis.

The results of the second study suggest that sex differences in cognitive functioning in ARMS and FEP patients are not different from those seen in HC. Specifically, the female advantage in verbal learning and memory, which has frequently been found in HC seems to be equally present in ARMS and FEP patients. Nevertheless, the effects were small probably also because our neuropsychological tasks were originally selected to assess the risk for psychosis and not specifically to detect sex differences. Our test battery did not include some of the most sensitive tasks to detect sex differences such as visuo-spatial or mental rotation tasks. Beside this, future studies should also consider menstrual status in women as neuropsychological performance of women has been shown to fluctuate with their monthly cycle (Farage, Osborn, & MacLean, 2008; Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Gunturkun, 2000; Hoff et al., 2001; Kimura & Hampson, 1994)

Altogether, the third study reveals that the agreements between self-rating and observer-rating of psychopathology were rather low and generally not higher in women than in men. This implies that self-rating-scales cannot be a substitute for the more time-consuming observer-rating scales and vice versa neither in men nor in women.

Overall, the current dissertation reveals few sex differences in the second and third publication. The sex differences in cognitive functioning (publication 2) resemble those of the general population and were not different between HC and patients (ARMS+FEP). On the other hand, the sex difference regarding prolactin (more frequent hyperprolactinemia in women and higher prolactin levels in women as compared to men) seems to be more pronounced and represents a good point to continue and deepen research concerning sex dependent stress reactivity in emerging psychosis and the underlying biological parameters. Furthermore, our results imply that hyperprolactinemia is not only caused by antipsychotics but prolactin levels can be affected independent of any medication. Therefore, prolactin should be measured already before any antipsychotic treatment to exclude a pre-existing hyperprolactinemia, which would need thorough investigation.

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6 Curriculum Vitae

Curriculum Vitae

Person

Name	Ittig (ledig: Buholzer)
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Geburtsdatum	9.10.1982
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Ausbildung

Aug. 2016- aktuell	Anstellung als Assistenzpsychologin. Durchführen diagnostischer Abklärungen in der Früherkennungssprechstunde (FEPSY)
Okt. 2012 – aktuell	Doktorandin an den UPK im FEPSY-Projekt (Früherkennung von Psychosen) am Zentrum für gender research und Früherkennung, Prof. Dr. med. Anita Riecher-Rössler
Jan. 2010 – Juni 2010	Praktikum an der Universität Basel, Abteilung Molecular Neuroscience (Betreuung: Dr. Angela Heck)
Feb. 2008 – Dez. 2009	Master in Psychologie (Masterprogramm Kognitions- und Neurowissenschaften). Masterarbeit in der Abteilung Molecular Neuroscience bei Prof. Dr. Andreas Papassotiropoulos (The catechol-*O*-methyltransferase (*COMT*) *val*^{158}*met* polymorphism is associated with hippocampal activity during retrieval of neutral pictures: An fMRI study)
Sept. 2004 – Juni 2006	Licence de Psychologie (Bachelor) an der Université Louis Pasteur in Strasbourg (F)
Sept. 2003 – Juni 2004	Propädeutikum Grundstudium Psychologie an der Universität Bern
Juni 2003	Matura mit Schwerpunkt Psychologie, Philosophie und Pädagogik (PPP), Gymnasium St. Klemens, Ebikon (LU)

Sprachen

Deutsch	Muttersprache
Französisch	gute mündliche und schriftliche Kenntnisse
Englisch	gute mündliche und schriftliche Kenntnisse

Informatik

Programme	Microsoft Office
	Erfahrungen mit R
	Erfahrungen mit MATLAB und SPM (statistical parametric mapping)
	End Note
	Reference Manager
	Sigma Plot
	E-Prime
	SPSS
Kurse	SPM-Kurs (Freiburg Brain Imaging Lab), Auswertung eines fMRT-Beispieldatensatzes in der Einzelprobanden- und Gruppenauswertung mit SPM 8

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