Neuropsychological and Brain Structural Alterations in Emerging Psychosis

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Laura Egloff

aus Basel, Basel-Stadt, Schweiz

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BASEL

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auf Antrag von

Professor Dr. Roselind Lieb
Professor Dr. Stefan Borgwardt

Basel, den _____

_____
Prof. Dr. Alexander Grob
Dekan

UNI
BASEL

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A big thank you goes to all my colleagues at work, who always supported me morally, especially during lunch and coffee breaks.

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Preface

The work described in this thesis was conducted from October 2014 until January 2018 under the guidance of Prof. Dr. med. Stefan Borgwardt at the Department of Psychiatry, University of Basel Psychiatric Hospital (UPK), Switzerland. The thesis was academically supervised by Prof. Dr. Roselind Lieb.

Part of this thesis has already been published in or submitted to peer reviewed journals. These manuscripts are included in the respective paragraphs. References in these sections are independent from the remainder of this PhD thesis.

The respective papers were written within the framework of the prospective FePsy (*F*rüh*e*rkennung von *Psy*chosen; early detection of psychosis) study.
The neuropsychological data were assessed at the Psychiatric Outpatient Department of the University Hospital Basel from March 2000 until September 2013 and in the Center for Early Detection and Gender Research at the University of Basel Psychiatric Hospital (UPK) Basel, Switzerland, from September 2013 until November 2015.
The structural MRI data were assessed in the radiology of the University Hospital Basel. Only data assessed on a 3 Tesla Siemens Verio Magnetic Resonance Imaging scanner between July 2008 and May 2016 were used for the analyses.

The included studies were approved by the Ethics Committee northwest/central Switzerland (EKNZ) and all procedures contributing to this thesis fully comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

The FePsy project and the included studies were supported by Grants of the Swiss National Science Foundation (Nos. 3200 – 057 216.99, 3200 – 0572 216.99, PBBSB-106 936, and 3232BO-119 382) and the Nora van Meeuwen-Haefliger Stiftung, Basel (CH).

Declaration by Candidate

I herewith declare that I have autonomously accomplished the PhD thesis entitled "Neuropsychological and Brain Structural Alterations in Emerging Psychosis" and that the work presented in it are my own. The three research articles have been published or submitted to peer-reviewed journals and were written in collaboration with the listed co-authors. All citations are indicated and cited accordingly and only the mentioned sources were used. For this cumulative thesis, the following articles are included and attached in appendices A, B, and C.

Article 1

Egloff, L., Studerus, E., Zimmermann, R., Heitz, U., Menghini-Müller, S., Ittig, S., Beck, K., Andreou, C., Borgwardt, S., Riecher-Rössler, A. (2018). Evaluating verbal learning and memory in patients with an at-risk mental state or first episode psychosis using structural equation modelling. *PLoS ONE*. doi: 10.1371/journal.pone.0196936

Article 2

Egloff, L., Lenz, C., Studerus, E., Heitz, U., Harrisberger, F., Smieskova, R., Schmidt, A., Leanza, L., Andreou, C., Borgwardt, S., Riecher-Rössler, A. (2018) No associations between medial temporal lobe volumes and verbal learning/memory in emerging psychosis. Manuscript submitted to *European Journal of Neuroscience.* Draft of September 28th, 2017.

Article 3

Egloff, L., Lenz, C., Studerus, E., Harrisberger, F., Smieskova, R., Schmidt, A., Huber, C., Simon, A., Lang, U.E., Riecher-Rössler, A., Borgwardt, S. (2018). Sexually dimorphic subcortical brain volumes in emerging psychosis. *Schizophrenia Research*. doi: 10.1016/j.schres.2018.03.034

In the following framework these articles are described cohesively. A detailed description of the methods, results and discussion including all references may be found in the original publications.

Date: _____

Signature: _____

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
CHR	clinical high-risk state
CPE	chlorpromazine equivalent
CSF	cerebrospinal fluid
CVLT	California Verbal Learning Test
EEG	electroencephalography
FEP	first episode psychosis
FePsy	Basel Projekt zur ***F***rüh***e***rkennung von ***Psy***chosen
FSL	FMRIB software library
GM	gray matter
GRD	genetic risk and deterioration syndrome
HC	healthy controls
LME	linear mixed effects model
MIMIC	multiple indicator multiple causes model
MNI	Montreal Neurological Institute
MPRAGE	magnetisation prepared rapid gradient echo sequence
MRI	magnetic resonance imaging
PACE	Personal Assessment and Crisis Evaluation
SEM	structural equation modelling
UHR	ultra-high risk
UPS	unspecified prodromal symptoms
VLM	verbal learning and memory
WM	white matter

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Abstract

Despite the growing interest in personally tailored interventions in medicine and health care, it is not possible to reach sufficient accuracy in the prediction of psychosis to date. Many factors are associated with transition to psychosis, such as neuropsychological impairments and structural alterations of the brain that have been shown to predate the onset of frank psychosis. However, the different disease trajectories male and female patients' experience may contribute to the mixed picture representing emerging psychosis. The prospective FePsy (Früherkennung von Psychosen) study was a project aiming to improve the early detection and intervention of psychosis through multilevel assessment. The in the following described articles are based on data assessed within the FePsy study.

In the first article, structural equation modelling and latent growth curve modelling were used to evaluate verbal learning and memory (VLM) performance between at-risk mental state (ARMS) and first episode psychosis (FEP) patients and healthy controls (HC). In line with our hypothesis, results indicated a worse performance of FEP compared to ARMS and HC and a performance of ARMS intermediate to those two groups. Since these differences were more pronounced in the slope than in the intercept of the learning curve, our results indicated that the verbal learning rate tends to be more impaired than attentional processes in both ARMS and FEP patients. In the second article we investigated whether VLM performance is associated with subcortical brain volumes. A significant negative association between amygdala and pallidum volume and attention span was found in ARMS and FEP patients combined, which however did not withstand correction for multiple testing. Although VLM is among the most impaired cognitive domains in emerging psychosis, the deficits in this domain seem not to necessarily stem from alterations in subcortical structures. In the third article, we investigated whether subcortical brain volumes are dependent on sex. Men presented with larger total brain volume and smaller caudate and hippocampus volumes than women independent of diagnostic group. These analyses confirmed previously described patterns of sexual dimorphism in total brain and caudate volume that are equally present in ARMS and FEP patients as well as HC. The only structure affected by reversed sexual dimorphism was the hippocampus (i.e. women showing higher volumes than men).

In conclusion, neuropsychological impairments in terms of VLM and subcortical brain structural alterations are present in emerging psychosis. However, subcortical volumes do not seem to be affected by altered sexual dimorphism and may thus not contribute to an effective prediction modelling of transition to psychosis.

1. General Introduction

1.1 Schizophrenia

Schizophrenia is a potentially debilitating disorder which affects the general population worldwide with a median lifetime prevalence of 0.40-0.48% (McGrath, Saha, Chant, & Welham, 2008; Simeone, Ward, Rotella, Collins, & Windisch, 2015). Schizophrenia typically emerges in adolescence or early adulthood (Häfner, Riecher-Rössler, Maurer, Fätkenheuer, & Löffler, 1992; Riecher-Rössler et al., 2007) and has early neurodevelopmental origins. These later manifest through disrupted neuromaturational processes (Walker & Bollini, 2002). Neurobiological stress (Walker & Diforio, 1997), perinatal complications affecting brain development (Walder, Faraone, Glatt, Tsuang, & Seidman, 2014), genetic liability (Lichtenstein et al., 2009; Wray & Gottesman, 2012), dopaminergic dysregulation, disturbed glutamatergic neurotransmission, increased proinflammatory status of the brain (Kahn & Sommer, 2015), as well as the so-called Polygenic Schizophrenia-related Risk Score (referring to the polygenic predisposition for schizophrenia in a clinical sample (Harrisberger et al., 2016; Lencz et al., 2014)) may contribute to brain changes before the onset of psychosis.

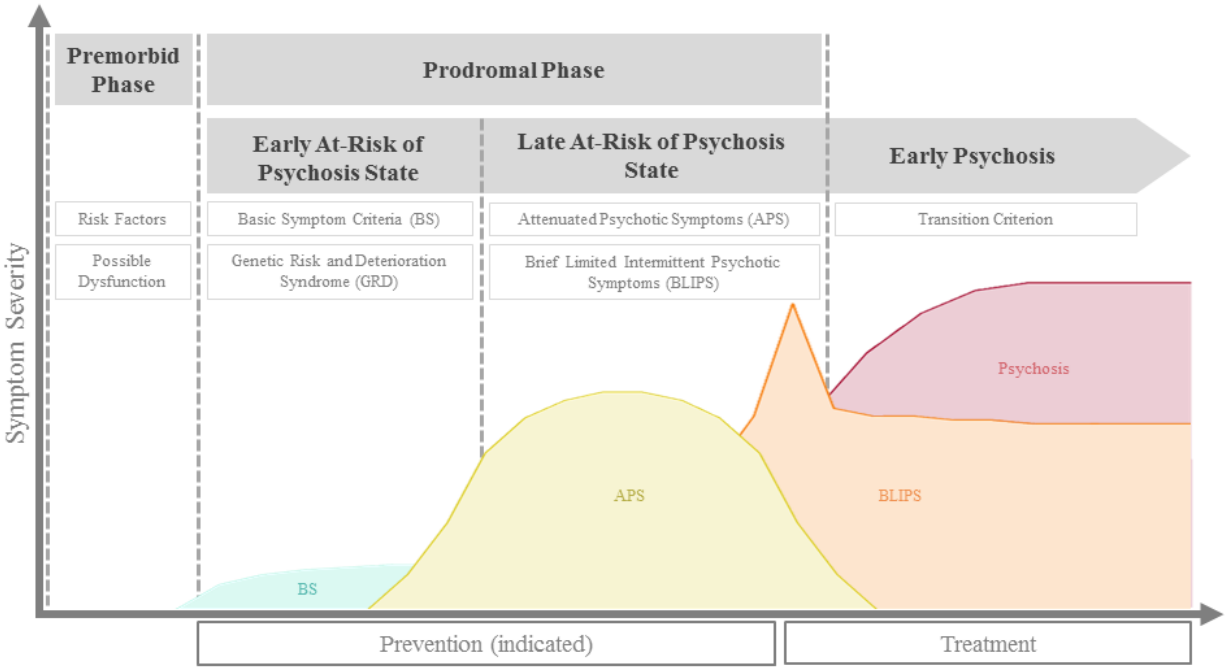
1.2 Emerging psychosis

To prevent a poor outcome in patients with a so-called at-risk mental state (ARMS) for psychosis, it is paramount to identify these patients as early as possible. Since early detection of psychosis based on clinical signs and symptoms (Yung et al., 1998; Yung, Phillips, Yuen, & McGorry, 2004) have proven to be a promising approach (Kim et al., 2011), many early detection centres worldwide have been established during the past 20 years. For the identification of the ARMS for psychosis, also often referred to as clinical high risk (CHR) or ultra-high risk (UHR), patients have to fulfil one or more of the following operationalised criteria: Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), Genetic Risk and Deterioration syndrome (GRD) and/or Unspecified Prodromal Symptoms (UPS) (see Figure 1; a detailed description of these criteria and their assessment can be found in Fusar-Poli et al. (2013)). For ease of interpretation and in accordance with the herein referenced original studies, the term ARMS will be used throughout this thesis.

ARMS patients experience an increased risk for developing psychosis, with a transition rate of about 32% within 3 years after initial presentation (Fusar-Poli, Bonoldi, et al., 2012; Fusar-Poli et al., 2013). Although many factors have been associated with the risk of transition to psychosis (e.g. impaired cognitive functioning (Bora et al., 2014; Fusar-Poli, Deste, et al., 2012) or brain

structural alterations (Fusar-Poli, McGuire, & Borgwardt, 2012)) it is still not possible to reach sufficient accuracy in the prediction of psychosis.

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 (adapted from Fusar-Poli et al. (2013); Schultze-Lutter et al. (2015))*



2. Theoretical Background

2.1 Neuropsychological impairments in emerging psychosis

Neuropsychological impairments are a robust marker in patients with schizophrenia (Bora, Yücel, & Pantelis, 2010). They predate the onset of psychosis and have been shown to be present in first episode psychosis (FEP) patients as well as in ARMS patients (Bora et al., 2014; Fusar-Poli, Deste, et al., 2012; Hauser et al., 2017; Smieskova et al., 2013; Thermenos et al., 2013).

Verbal learning and memory (VLM) are among the most impaired cognitive functions in these patients and are therefore potentially useful as discriminatory variables in the early detection of psychotic disorders (Cannon, 2015; Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Fusar-Poli, Deste, et al., 2012). Previous studies on VLM showed that FEP patients on average perform worse than ARMS and healthy controls (HC) and ARMS perform intermediate to FEP and HC (Juuhl-Langseth et al., 2015). Furthermore, ARMS patients who later transition

to psychosis (ARMS-T) were shown to have poorer functioning in verbal memory compared to ARMS without later transition to psychosis (ARMS-NT) (Hauser et al., 2017).

2.2 Neuroimaging in emerging psychosis

Not only neurocognitive impairments but also brain structural alterations are already evident in ARMS patients before the first psychotic symptoms emerge (Dazzan et al., 2015). These include gray (GM) and white matter (WM) volume reductions of prefrontal (Cannon, 2015; Smieskova et al., 2013), temporal (Fusar-Poli, Smieskova, Serafini, Politi, & Borgwardt, 2014; Smieskova et al., 2013), and cingulate cortices (Fusar-Poli, McGuire, et al., 2012; Fusar-Poli et al., 2014; Radua et al., 2012; Smieskova et al., 2013), the thalamus, putamen, right superior frontal gyrus (Cooper, Barker, Radua, Fusar-Poli, & Lawrie, 2014), parahippocampal gyrus and hippocampus (Fusar-Poli, McGuire, et al., 2012; Thermenos et al., 2013), insula (Radua et al., 2012), and caudate (Smieskova et al., 2013).

However, only a limited number of studies investigated the associations of brain structural alterations and VLM so far (Hartberg et al., 2011; Hurlemann et al., 2008; Juuhl-Langseth et al., 2015; Lappin et al., 2014). One study reported caudate volume to be larger in early onset schizophrenia spectrum disorders compared to healthy controls (HC) and to be negatively associated with verbal learning in these patients (Juuhl-Langseth et al., 2015). Another study reported bilaterally enlarged putamen volumes to be associated with poorer verbal learning in schizophrenia patients (Hartberg et al., 2011) whereas one study found reduced hippocampal volumes to correlate with poorer VLM performance in ARMS patients suspected to be in the late prodromal state (Hurlemann et al., 2008). Conversely, another study reported longitudinal bilateral hippocampus volume increases to be associated with better delayed verbal recall in a subset of FEP patients (Lappin et al., 2014). The basal ganglia, which consist of the nucleus caudatus (hereafter referred to as caudate) and the nucleus lentiformis (formed by the putamen and the pallidum) have also been shown to play substantial role in working memory (Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015; Nyberg & Eriksson, 2016) and thus in all processes involving learning.

Nevertheless, results remain largely inconclusive and a direct comparison of VLM and its associations with subcortical brain volumes in ARMS and FEP patients has not yet been conducted.

2.3 Sexual dimorphism in schizophrenia, emerging psychosis, and healthy subjects

Structural MRI studies in healthy subjects showed that men have larger total brain (Cosgrove, Mazure, & Staley, 2007) and intracranial volume (Tan, Ma, Vira, Marwha, & Eliot, 2016) than women across all ages (Giedd, Raznahan, Mills, & Lenroot, 2012). Brain structures affected by sex are white matter volumes of the corpus callosum (Ardekani, Figarsky, & Sidtis, 2013; Sacher, Neumann, Okon-Singer, Gotowiec, & Villringer, 2013) and cingulate cortex (Sacher et al., 2013), as well as GM volumes of the caudate, amygdala, hippocampus, and cerebellum (Giedd et al., 2012; Wang, Shen, Tang, Zang, & Hu, 2012). Sex-dependent variances in resting state connectivity have been found in the corpus callosum, anterior cingulate cortex, insula, orbitofrontal cortex and periaqueductal gray (Sacher et al., 2013). Men show enhanced activity in the right hemisphere (Sacher et al., 2013) with a higher structural within hemisphere connectivity (Ingalhalikar et al., 2014), whereas women show enhanced activity in the left hemisphere (Sacher et al., 2013), and predominant between hemispheric connectivity (Ingalhalikar et al., 2014). The male brain tends to be more asymmetrically organized than the female brain across both hemispheres (Hiscock, Perachio, & Inch, 2001; McGlone, 1980; Voyer, 1996). This may be due to sexually dimorphic patterns of white matter, whose myelinated fibers connect with GM throughout the brain (Fornito, Zalesky, & Breakspear, 2015; Ingalhalikar et al., 2014). These structural and functional differences in healthy men and women are also referred to as sexual dimorphism, a term which we will further employ in this study.

Disrupted patterns of structural sexual dimorphism in schizophrenia have been found for volumes of amygdala (Gur et al., 2004; Gur, Turetsky, et al., 2000; Takayanagi et al., 2011), hippocampus (Irle et al., 2011), hypothalamus (Goldstein et al., 2007), as well as orbitofrontal (Gur, Cowell, et al., 2000), anterior cingulate (Goldstein, Seidman, O'Brien, & et al., 2002; Takahashi et al., 2002), and insular cortex (Duggal, Muddasani, & Keshavan, 2005). Furthermore, implications for a disrupted sexual dimorphism have been found for asymmetry of GM volume in the inferior parietal lobe (IPL) (i.e. male patients had right-greater-than-left-IPL compared to male HC whereas no differences in asymmetry or volume were observed for female patients compared to female HC) (Frederikse et al., 2000), in the white matter geometry of the torque (i.e. female brains were more asymmetric than males whereas in HC male brains tend to be more asymmetric than female brains) (Savadjiev et al., 2013), in the gyrification index (Vogeley et al., 2000), and in the cortical folding of the right superior frontal cortex (Narr et al., 2004).

While sex differences in schizophrenia and healthy controls have been well studied (for review see Abel, Drake, and Goldstein (2010); Bao and Swaab (2011); Falkenburg and Tracy (2014); Giedd et al. (2012); Sacher et al. (2013)), research on sex differences in ARMS patients is scarce. Most studies used gender or sex as control variable, therefore controlling for the potential influence of sex (Barajas, Ochoa, Obiols, & Lalucat-Jo, 2015), but only few studies incorporated sex as main focus in their high risk or first episode psychosis research. However, as structural and functional alterations may underlie psychopathological symptomatology, it is crucial to further explore the possible alterations with a specific regard to sex-specific differences.

Especially in the field of neuroanatomical studies, sexual dimorphism in brain structure and function of ARMS patients has largely been neglected, even though evidence for disrupted sexual dimorphism in schizophrenia is given (Falkenburg & Tracy, 2014; Riecher-Rössler, Pflüger, & Borgwardt, 2010; Walder, Yaffe, & Ehrlich, 2015) and only little is known about the exact time when sexual dimorphism starts getting disrupted in emerging psychosis.

2.4 Early detection of psychosis - the *FePsy* study

All data used for the original publications of this thesis have been retrieved from the prospective early detection and intervention in psychosis (*FePsy*; *F*rüh**e**rkennung von *Psy*chosen) study Basel (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009), which has been conducted in the Psychiatric Outpatient Department at the University Hospital Basel and in the Center for Early Detection and Gender Research at the University of Basel Psychiatric Hospital (UPK) Basel, Switzerland, between March 2000 and September 2017.

Patients potentially at risk for psychosis, who were referred to the *FePsy* study, were subsequently screened using the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008) and the Brief Psychiatric Rating Scale Expanded Version (BPRS-E) (Lukoff, Nuechterlein, & Ventura, 1986; Velligan et al., 2005; Ventura, Green, Shaner, & Liberman, 1993). If inclusion criteria for the FePsy study were met (see Table 1) and the patients provided written informed consent, an extensive multidomain examination was conducted. This included a systematic assessment of psychopathological symptoms, neuropsychological assessment, structural magnetic resonance imaging (MRI), resting state electroencephalography (EEG), and an analysis of several blood parameters.

All ARMS patients were followed-up with at regular intervals (monthly during the first year after initial presentation, quarterly during the second and third year, and annually thereafter) to distinguish those ARMS patients with later transition to psychosis (ARMS-T) from the ones who did not transition (ARMS-NT).

Table 1. *Inclusion criteria for at-risk mental state or first episode psychosis patients in the FePsy project*

At-Risk Mental State (ARMS)	**A) "Attenuated" psychotic symptoms (APS)** Psychotic symptoms below transition cut off (BPRS scales: hallucinations 2–3, unusual thought content 3–4, suspiciousness 3–4) at least several times per week, in total persisting for>1 week) OR **Brief Limited Intermittent Psychotic Symptoms (BLIPS)** psychotic symptoms over transition cut-off (BPRS scales: hallucinations ≥4, unusual thought content ≥5, suspiciousness ≥5, conceptual disorganisation ≥5) but each symptom <1 week before resolving spontaneously **B) Genetic risk category** first or second degree relative with psychotic disorder and at least two further risk factors according to screening instrument (BSIP) **C) Unspecific risk category** minimal amount and combination of certain risk factors according to screening instrument (BSIP) Precondition for all categories: criteria of transition to psychosis not fulfilled.
First Episode Psychosis (FEP)	• 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 (incidents 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 three to five instances of incoherent phrases). • Symptoms at least several times a week. • Change in mental state lasting >1 week.

Note. Criteria A) and B) correspond to those of Yung et al. (1998). Criterium C) additionally permits the inclusion of individuals at lower risk, i.e. of patients without pre-psychotic symptoms or genetic risk who only exhibit a combination of certain unspecific risk factors and indicators such as prodromal symptoms or marked social decline (unspecific risk group).
Patients with first-episode psychosis (FEP) are those who at intake already fulfil the criteria for transition to psychosis as defined by Yung et al. (1998).

The HC were gathered from the same geographical area as the patient groups and recruited via commercial school, hospital staff, and online advertisement. They were only included in the study if they had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical assessment.

The *FePsy* project and the analyses conducted for this thesis were approved by the Ethics Committee northwest/central Switzerland (EKNZ) and all procedures contributing to this thesis fully comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.5 Aims

The aims of this thesis were to investigate whether 1) patients with an ARMS or FEP show marked impairments in the neurocognitive domains of verbal learning and memory, 2) if such neurocognitive impairments are associated with subcortical brain volumetric alterations, and 3) if female and male ARMS and FEP patients show patterns of altered sexual dimorphism in these subcortical brain volumes.

2.6 Hypotheses

Article 1: Based on the existing literature, the sequence of performance on the California Verbal Learning Test latent factors *Attention Span*, *Learning Efficiency*, *Delayed Memory*, and *Inaccurate Memory* was expected to be the following: HC>ARMS>FEP and HC>ARMS-NT>ARMS-T>FEP, respectively. Additionally, a growth curve analysis was conducted to disentangle initial recall and learning rate still expecting the same sequence of performance (HC>ARMS>FEP and HC>ARMS-NT>ARMS-T>FEP).

Article 2: It was hypothesized that verbal learning and memory performance are positively correlated with subcortical brain structural volumes (i.e. amygdala, accumbens, caudate, hippocampus, pallidum, putamen, and thalamus) in ARMS and FEP patients.

Article 3: Based on the existing literature on sexual dimorphism in HC and Schizophrenia, it was hypothesized that I) normal sexual dimorphism will be found in HC; II) sexual dimorphism as found in HC is no longer present in FEP patients; III) ARMS patients show patterns of diminished sexual dimorphism, but not to the same extent as in FEP patients.

To examine these hypotheses, the following three original studies have been conducted and the manuscripts are currently in press (Article 1 and Article 3) or submitted (Article 2) in international peer-reviewed journals.

Article 1

Egloff, L., Studerus, E., Zimmermann, R., Heitz, U., Menghini-Müller, S., Ittig, S., Beck, K., Andreou, C., Borgwardt, S., Riecher-Rössler, A. (2018). Evaluating verbal learning and memory in patients with an at-risk mental state or first episode psychosis using structural equation modelling. *PLoS ONE*. doi: 10.1371/journal.pone.0196936

Article 2

Egloff, L., Lenz, C., Studerus, E., Heitz, U., Harrisberger, F., Smieskova, R., Schmidt, A., Leanza, L., Andreou, C., Borgwardt, S., Riecher-Rössler, A. (2018) No associations between medial temporal lobe volumes and verbal learning/memory in emerging psychosis. Manuscript submitted to *European Journal of Neuroscience.* Draft of September 28th, 2017.

Article 3

Egloff, L., Lenz, C., Studerus, E., Harrisberger, F., Smieskova, R., Schmidt, A., Huber, C., Simon, A., Lang, U.E., Riecher-Rössler, A., Borgwardt, S. (2018). Sexually dimorphic subcortical brain volumes in emerging psychosis. *Schizophrenia Research*. doi: 10.1016/j.schres.2018.03.034

3. Methods

3.1 Setting and recruitment

All data analysed in the three articles of this thesis were collected within the specialised FePsy (Früherkennung von Psychosen) clinic at the University of Basel Psychiatric Hospital (UPK) Basel, Switzerland. Patients were excluded if they fulfilled one of the following criteria: age <18 years, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis (treated with antipsychotics for >3 weeks (lifetime) and/or a total chlorpromazine equivalent dose of 2500mg), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder. HC were only included if they had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse, and no family history of any psychiatric disorder.

3.2 Psychopathological assessment

Positive psychotic symptoms (i.e. hallucinations, suspiciousness, unusual thought content and conceptual disorganisation) were assessed with the Brief Psychiatric Rating Scale Expanded Version (BPRS-E) (Lukoff et al., 1986; Velligan et al., 2005; Ventura et al., 1993).

3.3 Neurocognitive assessment

In Article 1 & 2 data from the California Verbal Learning Test (CVLT) were used for measures of VLM. The CVLT is a widely used neurocognitive task which allows for a brief assessment of verbal learning strategies and processes. The test consists of two word lists each containing 16 words. List A is orally presented over five immediate-recall trials. An interference list (List B) is then presented for one immediate recall trial, followed by short- and long-delay free- and cued-recall and recognition test of List A. During the long-delay interval (approximately 20 min), nonverbal testing is administered to the subjects (Delis, Kramer, Kaplan, & Ober, 1987).

3.4 Neuroimaging

Structural images were acquired using a 3 Tesla magnetic resonance imaging (MRI) scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 12-channel phased-array radio frequency head coil at the University Hospital Basel between July 2008 and May 2016.
A 3D T1-weighted magnetisation prepared rapid gradient echo (MPRAGE) sequence was used with the following parameters: inversion time = 1000 ms, flip angle = 8°, TR = 2 s, TE = 3.37 ms, bandwidth = 200 Hz/pixel, FOV = 256 × 256 mm^2, acquisition matrix = 256 × 256 × 176,

resulting in 176 contiguous sagittal slices with 1 × 1 × 1 mm^3 whole-brain isotropic spatial resolution.

All image processing steps were conducted according to the "ENIGMA1 - GWAS Meta Analysis of Hippocampal, Intracranial and Total Brain Volume" guidelines (http://enigma.ini.usc.edu/) using the FMRIB software library (FSL) 5.0 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) running on Ubuntu version 16.04. Volumetric segmentation of subcortical structures was estimated on the whole-brain T1-weighted data sets by applying the FMRIB's Integrated Registration and Segmentation Tool (FSL-FIRST) (Patenaude, Smith, Kennedy, & Jenkinson, 2011). To extract the different brain tissue volumes for normalisation purposes, all images were skull stripped using FSL-BET (Smith, 2002), aligned to the Montreal Neurological Institute (MNI) 152 FSL standard brain using FSL-FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) and segmented into WM, GM and cerebrospinal fluid (CSF) using FSL-FAST (Zhang, Brady, & Smith, 2001). The resulting brain tissue volumes could then be calculated according to the results from the FSL-FAST partial volume maps and the total brain volume was extracted according to the sum of WM, GM and CSF.

All data sets were then checked for overall quality, coverage of whole brain, contrast between WM and GM and presence of noise, artefacts, correct skull stripping and cropping, correct alignment to the reference brain (MNI 152 sample), and correct alignment of the subcortical volumes. Finally, all volumes were plotted for each subject individually to detect outliers. In case of successful fulfilment of the quality assessment steps the volumetric data were included for statistical analyses.

3.5 Statistical analyses

All statistical analyses were conducted using the R environment for statistical computing (R Core Team, 2016) and Mplus Version 7 (Muthén & Muthén, 1998-2015). Sample characteristics were compared between groups using the appropriate statistical tests (see Articles 1-3 for detailed description).

In Article 1, learning over the first 5 trials of the CVLT was investigated using latent growth curve analysis which allows disentangling initial recall (i.e. the intercept), which is strongly determined by attentional processes, from the rate of learning (i.e. the slope of the growth curve).

In Article 1 and 2, a four-factorial model containing the latent factors *Attention Span*, *Learning Efficiency*, *Delayed Memory*, and *Inaccurate Memory* (Donders, 2008) was extended by

regressing the four latent factors on group and sex to test CVLT performance differences between HC, ARMS, and FEP patients directly within the structural equation modelling framework. To account for missing data in the outcome measures, multiple imputations were performed using the Multivariate Imputation by Chained Equations software (Buuren & Groothuis-Oudshoorn, 2011).

Additionally, in Article 2, a potential association between VLM and subcortical volumes was analysed by again extending the measurement model of Donders (2008) by regressing the four latent factors on group, subcortical volume and the interaction between group x subcortical volume. Linear regression models were fitted for each subcortical volume, including the subcortical volume as dependent variable and group, age and sex as independent variables to evaluate whether there are any between group differences.

In Article 3 multiple linear regression models were applied to analyse group and sex differences in total brain, GM and WM volume. Each linear regression model included the brain structural volume as dependent variable, group, sex, and age as independent variables, and an interaction term between group and sex. Linear mixed effects models (LME) were applied to analyse the subcortical volumes and to take the bilateral measurement into account. For each subcortical structure an LME model was fitted including the volume as dependent variable and sex, group, hemisphere, and age as independent variables. Additionally, the LME models included all possible interaction terms between sex, group, and hemisphere and a per subject randomly varying intercept.

To account for multiple testing, corrected *p*-values were calculated using the false discovery rate throughout all analyses (Benjamini & Hochberg, 1995).

4. Summary of the Results

1) In the first study, we found ARMS and FEP patients to show impaired performances in *Attention Span*, *Learning Efficiency*, and *Delayed Memory* compared to healthy controls. FEP patients were additionally impaired in *Inaccurate Memory*. When investigating the ARMS subgroups, results showed that ARMS-NT but not ARMS-T performed significantly worse than HC on *Learning Efficiency*. Analysis of the growth curve revealed that ARMS patients were only impaired in the learning rate, whereas FEP patients showed impaired performances in initial recall and learning rate. No significant differences could be found in the growth curve analysis for ARMS-NT and ARMS-T.

2) When we extended the analyses of our first study to investigate potential associations of these significantly different between group performances in VLM with subcortical brain volumes (i.e. accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), uncorrected analyses revealed a significant negative association of amygdala volume with *Attention Span* and a significant positive association of pallidum volume with *Attention Span*. Furthermore, significant positive interaction effects were found for hippocampus volume × group and thalamus volume × group on *Attention Span*, hippocampus volume × group on *Inaccurate Memory* whereas a significant negative interaction effect was found for putamen volume × group on *Learning Efficiency* and *Delayed Memory*. However, after applying correction for multiple comparisons we could no longer demonstrate any significant associations. Nevertheless, we found significant group differences regarding the subcortical volumes with increased volumes of hippocampus, pallidum, putamen, and thalamus in FEP compared to ARMS patients, which persisted correction for multiple comparisons.

3) Driven by the non-significant finding from our second study arose the question whether potentially significant between group differences could have been masked by altered sexual dimorphism in the subcortical brain volumes of our samples. Results showed that men had significantly larger total brain volume and smaller caudate and hippocampus volumes than women independent of diagnostic group (ARMS, FEP, or HC). A significant interaction effect was found for group × hemisphere due to significantly larger left than right thalamus volumes in HC and significantly larger left than right thalamus volumes in ARMS patients. Analysis of the ARMS subgroups did not reveal a significant main effect of sex or significant interaction between sex and group. Further, age was significantly positively associated with GM and WM volumes.

5. Discussion

5.1 Aim of this thesis

The aim of this thesis was threefold: first, I wanted to investigate the verbal learning and memory (VLM) performance in ARMS and FEP patients compared to HC. Second, I sought to examine whether the observed pattern of VLM performance differences between ARMS, FEP, and HC were associated with subcortical brain volumes, i.e. accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. Third, I wanted to explore if we can find patterns of sexual dimorphism in these subcortical volumes and whether these adhere to normal patterns or if they are disrupted or even reversed in emerging psychosis.

5.2 General discussion

In Article 1 (Egloff, Studerus, et al., 2018), the findings of impaired VLM performances in *Attention Span*, *Learning Efficiency*, and *Delayed Memory* following the expected sequence of performance (HC>ARMS>FEP) confirmed our hypothesis for three out of the four latent CVLT factors. Furthermore, this expected sequence of performance was also confirmed within the growth curve analysis for learning rate. These findings are well in line with the present literature indicating impairments of attentional processing (de Paula, Hallak, Maia-de-Oliveira, Bressan, & Machado-de-Sousa, 2015; Valli, Tognin, Fusar-Poli, & Mechelli, 2012) and learning rate (Fusar-Poli, Deste, et al., 2012; Lencz et al., 2006; Studerus, Papmeyer, & Riecher-Rössler, 2016) in ARMS and FEP patients, reporting medium effect sizes for verbal learning (d = -.68) and verbal memory (d = -.50) in ARMS patients (Bora et al., 2014). Our results support the body of literature, which suggests that the trajectory of psychotic illness could be improved by integrating information on specific cognitive deficit patterns such as the verbal declarative memory (Giuliano et al., 2012).

Contrasting our hypothesis, we found ARMS-NT but not ARMS-T patients to perform significantly worse than HC regarding the latent factor *Learning Efficiency*. This could be due to the rather small sample sizes ($N_{ARMS\text{-}NT}$ = 48, $N_{ARMS\text{-}T}$ = 25) or reflect a feature of the at-risk mental state, which is not further associated with the onset of the illness. Congruently, a meta-analysis suggested that ARMS-NT and ARMS-T may not be differentiated solely based on verbal memory deficits (De Herdt et al., 2013). In contrast, other studies (Fusar-Poli, Deste, et al., 2012; Koutsouleris et al., 2012) reported that integrating information on VLM into the prediction of transition to psychosis has proven to efficiently distinguish between those patients who later transitioned to psychosis and those who did not.

In Article 2 (Egloff et al., 2018 submitted) we could not demonstrate any significant associations between subcortical volumes and VLM after correcting for multiple comparisons, even though VLM are among the most impaired cognitive domains in both ARMS and FEP patients. These findings contrast with the relatively small body of literature conducted in schizophrenia, FEP, or ARMS patients in the late prodromal stage, all of which reported significant associations of subcortical volumes with verbal learning, working memory, set shifting, or verbal recall (Hartberg et al., 2011; Hurlemann et al., 2008; Juuhl-Langseth et al., 2015; Knöchel et al., 2016; Lappin et al., 2014). However, all these studies either compared their patient samples with (matched) HC or with a sample of bipolar spectrum disorder patients, but not with a sample of patients at clinical high risk for psychosis. Moreover, none of the samples investigated in these studies were antipsychotic-naïve and only three of these studies (Hartberg et al., 2011; Hurlemann et al., 2008; Knöchel et al., 2016) also applied correction for multiple comparisons to their analyses.

The second main finding in Article 2 was that FEP patients presented with significantly larger hippocampus, pallidum, putamen, and thalamus volumes than ARMS patients in both uncorrected and corrected analyses. These findings are partially in agreement with two large-scale studies reporting enlarged pallidum volumes (Okada et al., 2016; van Erp et al., 2016) and enlarged putamen volumes (Okada et al., 2016) in schizophrenia patients. Contrasting, both studies found decreased hippocampus volumes in schizophrenia patients compared to HC. However, in both studies the investigated samples were neither FEP only nor antipsychotic-naïve, hence rendering these results difficult to interpret.

Regarding the ARMS as a high risk state in which up to 32% of patients transition to frank psychosis within 3 years after initial presentation (Fusar-Poli, Bonoldi, et al., 2012), our finding of enlarged volumes in FEP patients may be the result of an established risk marker in the ARMS before the onset of frank psychosis. Accordingly, Borgwardt et al. (2007) found ARMS-T patients to present with relatively higher GM volumes of the thalamus, parahippocampal gyri, and the parietal and posterior temporal cortex.

In Article 3 (Egloff, Lenz, et al., 2018), where we investigated sexual dimorphism of subcortical GM brain volumes, we found normal sexual dimorphism of total brain volume and bilateral caudate volume independent of diagnostic group. The only subcortical volume presenting with a reversed sexual dimorphism was the hippocampus. However, this finding was again stable across all three groups.

Larger total brain volume in men is a result widely expected and reported in the literature. In line with our finding, a recent meta-analysis also reported men to have larger brain volumes

than women (Ruigrok et al., 2014). Thus, total brain volume does not seem to be affected by a changed pattern of sexual dimorphism in emerging psychosis.

Our observed finding of larger bilateral caudate volumes in women compared to men is also in line with a review (Giedd et al., 2012) reporting proportionally larger caudate volumes in women across different ages and methodologies applied. As with total brain volume, caudate volume does not seem to be affected by altered sexual dimorphism in our sample of emerging psychosis. Nevertheless, a review reported the caudate to be associated with prodromal symptoms in patients at clinical high risk for psychosis in longitudinal studies (Smieskova et al., 2013). The cross-sectional nature of our study may have prevented the emergence of such an association. Moreover, the different conceptualisations of a clinical high risk (for overview see Fusar-Poli et al. (2013)) for psychosis may have led to distinct inclusion criteria thus rendering direct comparisons between studies difficult.

The larger bilateral hippocampus volumes in women compared to men in our study contradict the meta-analysis of Ruigrok et al. (2014), which reported men to have larger hippocampi. Overall, our result may be explained by the increased amount of oestrogen receptors in the hippocampus (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Sholl & Kim, 1989), which may be responsible for the reported larger hippocampus volumes in female children and adolescents (Giedd et al., 1997; Neufang et al., 2008). Furthermore, as one of the stress response regions, the hippocampus is regulated by the coordinated action of hypothalamic–pituitary–gonadal and hypothalamic–pituitary–adrenal axis (Goldstein et al., 2015). Therefore, the observed pattern of sexual dimorphism across HC and emerging psychosis might be due to higher perceived stress levels in men, leading to a neuro-hormonal deficit in the male hippocampus (Goldstein et al., 2015) and hence to decreased volumes. In line with this, early stressful life events (i.e. childhood maltreatment) have been reported to later manifest through enhanced stress sensitivity (Gorka, Hanson, Radtke, & Hariri, 2014; Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011), hypo- or hypercortisolaemia (Wieck 2014), and to be associated with reduced hippocampus volumes (Frodl & O'Keane, 2013) in healthy men, but not women (Samplin, Ikuta, Malhotra, Szeszko, & DeRosse, 2013).

Our finding of ARMS patients presenting with larger left than right thalamus is a rather controversial one, which was not altered when the subgroups ARMS-T and ARMS-NT were investigated. Even though HC and ARMS showed similar patterns of larger left than right thalamus, the difference between left and right hemisphere was significantly larger in ARMS than in HC. While the thalamus has been reported to most often present with a HC patient difference (Crow, Chance, Priddle, Radua, & James, 2013), the findings on the volumetric

changes themselves are highly inconsistent with some studies reporting decreases in the right (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008) or left thalamus (Ellison-Wright & Bullmore, 2010), whereas others reported bilateral volumetric loss (Bora et al., 2011; Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Glahn et al., 2008; Yu et al., 2010). Thus, our finding remains controversial and to be resolved by future studies incorporating equal group sizes, concise inclusion criteria, and balanced sex ratios.

Finally, our finding of older subjects to present with higher GM and WM volumes than younger subjects may be indicative of developmental trajectories of GM and WM volumes towards their estimated peak points (Giedd et al., 2012).

5.3 Strengths and limitations

The following limitations should be considered:

First, in all three articles sample sizes differed across groups. Particularly, when differentiating between ARMS-T and ARMS-NT moderate group sizes emerged. Hence, the small and distinct group sizes may have precluded the detection of small effects between these two groups. Furthermore, the probability of a type II error is considerably larger for comparisons of ARMS-T and ARMS-NT than for comparisons between ARMS, FEP and HC groups.

Second, to be identified as non-transitioned patients had to be in the follow-up for at least three years without transitioning to psychosis. Although research has shown that most ARMS-T patients make the transition to psychosis within the first 12 months of clinical presentation, a small percentage of patients transitions to frank psychosis within the next 24 months of follow-up. This cut-off contributed substantially to the small sample size of the ARMS-NT group. Yet, by setting this cut-off we were able to strongly decrease the risk of incorrectly classifying patients with a later transition to psychosis as non-transitioned cases.

Third, we applied statistical correction for multiple comparisons to preclude false-positive findings, which, however, may have caused type II errors. Even though we had maximized statistical power by using structural equation modelling, it might be that differences in subcortical volumes in relation to VLM performance between ARMS and FEP patients are too subtle to reach significance with our modest sample size.

Fourth, the cross-sectional nature of the studies must be taken into consideration. It may be that subtle differences, which only evolve over time could not be detected by our analyses. Thus, future analyses should focus on longitudinal data to assess such gradually emerging changes.

Fifth, we investigated the association of VLM with subcortical volumes using structural MRI. However, a multimodal approach including structural and functional MRI and/or EEG could have provided further useful insights. Multimodal approaches are required in future studies

investigating neurocognitive and brain structural and functional alterations predating the onset of psychosis. Furthermore, future studies should focus on analyses of longitudinal data of ARMS patients, who transition to psychosis and correlate the development of subcortical volumes with neurocognitive performance.

Sixth, in the sex-related analyses only about a third of the patients in our patient sample were female whereas in the HC sample only about a third of subjects were male. This unequal sex distribution may have prevented significant between-group sex differences. Moreover, when investigating ARMS-T and ARMS-NT the sex distribution got even more unbalanced due to the unique characteristics of these subgroups. Thus, the results of these analyses should be interpreted cautiously.

Seventh, some patients did take anxiolytic or antidepressant medication at the time of neurocognitive or MRI assessment. Even though we statistically controlled for the influence of all medications in Article 1 and use of anxiolytics and antidepressants did not differ significantly between ARMS and FEP patients in Article 2 & 3, we may not preclude a potential influence on brain structural volumes. In this respect, a recently submitted manuscript by our group reported significant positive associations of antidepressant dosage with putamen, pallidum, and several surface areas in a combined sub-sample of antidepressant treated ARMS and FEP patients (Bykowsky et al., 2018 submitted).

Eighth, different conceptualisations of the high-risk state for psychosis render the interpretation of results across studies somewhat difficult. The ARMS concept slightly differs from the general concept of clinical high risk (CHR) for psychosis, however the CHR concept (namely the ultra-high risk and basic symptom criteria) comprises the ARMS criteria (see Schultze-Lutter et al. (2015) for in detail description). Nevertheless, the different conceptualisations must be kept in mind when comparing our results to other studies.

A strength of Article 2 was that we analysed subcortical volumes in antipsychotic-naïve ARMS and FEP patients, whereas most existing studies focused on brain structural differences between ARMS patients and HC or FEP patients and HC, which were usually not free from antipsychotic medication. Also, in Article 3 we conducted the analyses in both whole sample and antipsychotic-naïve sample only, which did not alter the results. By investigating antipsychotic-naïve patients we could preclude the influence of any antipsychotic medication on the subcortical volumes in ARMS and FEP patients.

In Article 2 & 3 we used standardized protocols provided by the ENIGMA consortium to process and segment our structural MRI data thereby making our results comparable with those of other (future) studies.

Furthermore, in all three articles complex statistical analysis methods such as structural equation modelling (SEM), growth curve modelling, and linear mixed effects (LME) modelling were employed. The advantages of such models are that they allow for the individual modelling of individual properties of indicator variables, thus allowing for a more flexible representation of the underlying data.

Moreover, even though sample sizes seem not large at first glance, emphasis must be put on the difficulty to recruit ARMS and FEP patients for studies in general. Since suspiciousness, ideas of reference, and even paranoid ideas represent common features in these patients, the sample sizes in the three articles may be considered decent.

5.4 Conclusions

Overall, the present thesis provides new insights about neurocognitive impairments and their brain structural correlates in emerging psychosis. From the presented articles the following conclusions may be drawn:

Neurocognitive performances in terms of VLM follow an expected sequence, with FEP patients presenting with the most impaired performances compared to ARMS patients and HC and ARMS patients performing intermediate to these two groups. Since these impairments are more pronounced in the learning rate than in the initial recall, VLM impairments seem to be strongly driven by an impaired learning rate in both ARMS and FEP patients and not by attentional processes. However, even though VLM impairments are among the most often reported neurocognitive impairments, they do not seem to derive from subcortical volumetric alterations. Furthermore, subcortical brain volumes do not seem to be primarily affected by altered or even disrupted sexual dimorphism in emerging psychosis.

5.5 Perspectives

Adequate prediction of a potential transition to psychosis in terms of sufficient validity and clinical utility is still not possible to date. One of the factors contributing to this may be the different disease trajectories male and female patients experience. As psychotic disorders present with a broad cost to society (Gustavsson et al., 2011), it is vital to further explore and identify risk markers for transition to frank psychosis. Further longitudinal investigations are needed to clarify whether VLM may be a potential discriminatory variable in the early detection

of psychosis, and to establish reliable biomarkers of brain structural and functional correlates to psychosis. Pooling data for future analyses on sex differences is indicated to overcome the issue of small to moderate sample sizes as well as imbalanced gender ratios in clinical and control samples. This would further allow to incorporate multimodal data from genetic, neuroimaging, and treatment studies thus enabling a holistic approach to the investigation and prediction of possible causes of emerging psychoses. Furthermore, emphasis must be put in the harmonisation and consensus of the different conceptualisations of the high risk state for psychosis to allow direct comparability of results across studies.

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Appendix A: Article 1

Egloff, L., Studerus, E., Zimmermann, R., Heitz, U., Menghini-Müller, S., Ittig, S., Beck, K., Andreou, C., Borgwardt, S., Riecher-Rössler, A. (2018). Evaluating verbal learning and memory in patients with an at-risk mental state or first episode psychosis using structural equation modelling. *PLoS ONE*. doi: 10.1371/journal.pone.0196936

PLOS ONE

RESEARCH ARTICLE

Evaluating verbal learning and memory in patients with an at-risk mental state or first episode psychosis using structural equation modelling

Laura Egloff[1,2,3], Erich Studerus[3], Ronan Zimmermann[1], Ulrike Heitz[3], Stephanie Menghini-Müller[2,3], Sarah Ittig[3], Katharina Beck[2,3], Christina Andreou[3], Stefan Borgwardt[1], Anita Riecher-Rössler[3]*

1 Department of Psychiatry, University of Basel Psychiatric Hospital, Basel, Switzerland, **2** Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Basel, Switzerland, **3** Center for Gender Research and Early Detection, University of Basel Psychiatric Hospital, Basel, Switzerland

* anita.riecher@upkbs.ch

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Data Availability Statement: There are ethical restrictions on public data deposition because the study participants did not consent to public data sharing. Even the de-identified data set contains information on the age and transition status of the subjects. Since the study was conducted in a rather small city of Switzerland, it is likely that individual participants could still be identified. Interested researchers may request the data from this study by contacting the Center for Gender Research and Early Detection at info@fepsy.

Abstract

Background

Verbal learning and memory are impaired not only in patients with a first episode of psychosis (FEP) but also–to a lower extent–in those with an at-risk mental state for psychosis (ARMS). However, little is known about the specific nature of these impairments. Hence, we aimed to study learning and memory processes in ARMS and FEP patients by making use of structural equation modelling.

Methods

Verbal learning was assessed with the California Verbal Learning Test (CVLT) in 98 FEP patients, 126 ARMS patients and 68 healthy controls (HC) as part of the Basel early detection of psychosis (FePsy) study. The four-factorial CFA model of Donders was used to estimate test performance on latent variables of the CVLT and growth curve analysis was used to model the learning curve. The latter allows disentangling initial recall, which is strongly determined by attentional processes, from the learning rate.

Results

The CFA model revealed that ARMS and FEP patients were impaired in *Attention Span*, *Learning Efficiency and Delayed Memory* and that FEP patients were additionally impaired in *Inaccurate Memory*. Additionally, ARMS-NT, but not ARMS-T, performed significantly worse than HC on *Learning Efficiency*. The growth curve model indicated that FEP patients were impaired in both initial recall and learning rate and that ARMS patients were only impaired in the learning rate.

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

Since impairments were more pronounced in the learning rate than the initial recall, our results suggest that the lower scores in the CVLT reported in previous studies are more strongly driven by impairments in the rate of learning than by attentional processes.

Introduction

The identification of so-called at-risk mental state for psychosis (ARMS) patients based on clinical signs [1, 2] is a promising approach for the early detection of psychotic disorders [3–5]. Neurocognitive impairments are a robust marker and considered to be core features of psychotic disorders, especially as these impairments persist even after remission of psychotic symptomatology [6, 7]. Cognitive impairments have been shown to be present in first episode psychosis (FEP) [8] as well as in ARMS patients [9–11] and may be useful for the prediction of transition to frank psychosis [3, 12].

Verbal learning and memory are among the most impaired cognitive functions in these patients and are therefore potentially useful as discriminatory variables in the early detection of psychotic disorders [4, 8, 13–15]. Previous studies on verbal learning and memory showed that FEP patients on average perform worse than ARMS and healthy controls (HC) and ARMS perform intermediate to FEP and HC [16]. Furthermore, ARMS patients who later transition to psychosis (ARMS-T) were shown to have poorer functioning in verbal memory in compared to ARMS without later transition to psychosis (ARMS-NT) [10, 11]. However, even though abundant literature is available on verbal learning and memory in chronic and FEP patients, only few studies with prospective design investigating ARMS patients have been published on verbal learning and memory so far [4, 5, 13, 17–20]. To the best of our knowledge, none of these studies focused on verbal learning and memory in more detail or did compare performances of FEP, ARMS patients with later transition to psychosis (ARMS-T) and HC directly in their analyses. Only four studies [20–23] so far investigated a sample of ARMS and FEP patients as well as HC in their analyses. However, none of these studies applied structural equation modelling.

Hence, the objective of this study was to evaluate group differences between ARMS, FEP and HC, as well as between ARMS-T and ARMS-NT, in regard to their performance on the California Verbal Learning Test (CVLT) [24] using the four factor structure as proposed by Donders [25] in a structural equation model. Furthermore, we aimed to investigate the learning curve of ARMS and FEP patients using latent growth curve modelling [26]. An important advantage of this approach is that it allows disentangling initial recall, which is strongly determined by attentional processes, from the rate of learning (i.e. learning slope) [27].

Based on the existing literature, we expected the sequence of performance on the CVLT to be the following: HC>ARMS>FEP and HC>ARMS-NT>ARMS-T>FEP, respectively.

Materials and methods

Setting and recruitment

The CVLT data analysed in this study were collected within the prospective ***Früh*erkennung von *Psy*chosen** (FePsy; early detection of psychosis) study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere [3, 28]. Patients were recruited via the FePsy Clinic, University of Basel Psychiatric

Hospital Basel, Switzerland, which was set up specifically to identify, assess, and treat individuals in the early stages of psychosis. All patients were recruited between March 2000 and November 2015. They were followed-up in regular intervals in order to distinguish those who later transitioned to psychosis (ARMS-T) from those who did not (ARMS-NT). During the first year of the follow-up ARMS individuals were assessed monthly for transition to psychosis, during the second and third year 3-monthly, and subsequently annually. HC were recruited from a commercial school, hospital staff and through advertisements and were not included if they had a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of psychiatric disorder. The study was approved by the ethics committee of North-western and Central Switzerland (EKNZ). All participants provided written informed consent.

Screening procedure

The ARMS and FEP status was assessed using the Basel Screening Instrument for Psychosis (BSIP), which was developed by Riecher-Rössler, Aston [29]. The BSIP is based on the Personal Assessment and Crisis Evaluation (PACE) criteria by Yung, Philips [1] and has been shown to have a high predictive validity and a good inter reliability ($\kappa = 0.67$) [29]. Exclusion criteria were age younger than 18 years, insufficient knowledge of German, IQ <70, previous episode of psychosis (treated with antipsychotics for >3 weeks (lifetime) and a total amount of 2500mg chlorpromazine equivalent), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder. Patients were identified as ARMS-NT if they had a follow-up period of at least three years without developing frank psychosis. ARMS-T's time from first contact with the *FePsy* clinic until conversion to psychosis was 0.72 years in median (Mean = 1.18, SD = 1.32, Range = 0.03–4.64).

Neurocognitive assessment

The CVLT is a widely used neurocognitive task which allows for a brief assessment of verbal learning strategies and processes. The test consists of two word lists each containing 16 words. List A is orally presented over five immediate-recall trials. An interference list (List B) is then presented for one immediate recall trial, followed by short- and long-delay free- and cued-recall and recognition test of List A. During the long-delay interval (approximately 20 min), nonverbal testing is administered to the subjects [24]. In confirmatory factor analyses (CFA) on the CVLT conducted by Donders [25] within a large standardisation sample with three different age groups of healthy controls as well as in a sample of traumatic brain injury patients [30] it has been demonstrated that a four factor structure containing the factors *Attention Span*, *Learning Efficiency*, *Delayed Memory*, and *Inaccurate Memory* provided good fit to the data. The variables measuring these factors are shown in Fig 1.

Statistical analyses

All analyses were conducted using the R statistical environment, R version 3.2.3 [31] and Mplus Version 7 [32]. Sex was compared between groups with chi-square test. Age, years of education and BPRS total score were compared with independent t-test. Use of cannabis, antipsychotics, antidepressants, and anxiolytics were compared using Fisher's Exact test. Cannabis use was not further included in the analyses since a former study by our research group found that there were no significant differences in neurocognitive performance between current, former, and never users, and there were no significant interactions between cannabis use and patient group [33].

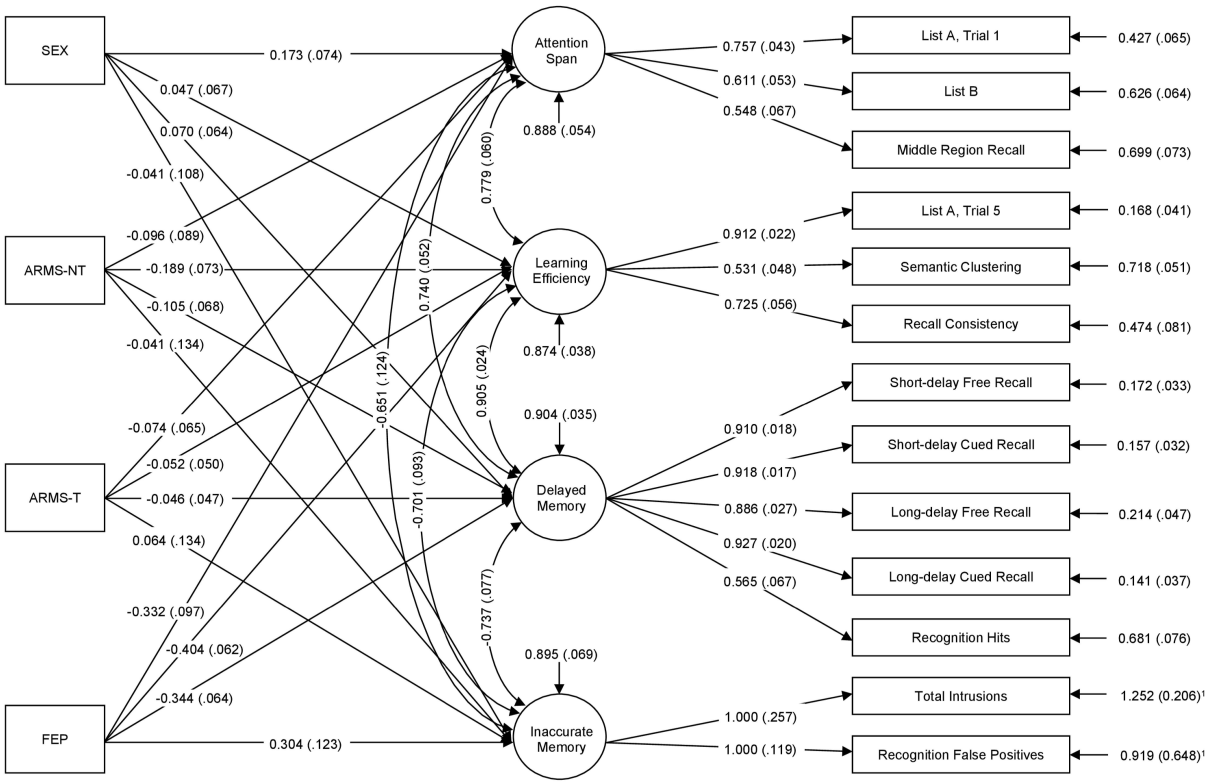

Fig 1. Visualisation of the confirmatory four factor analysis (CFA). The rectangles on the left represent the patient groups (at-risk mental state (ARMS) patients with (ARMS-T) and without later transition to psychosis (ARMS-NT) and first episode psychosis (FEP) patients). The circles in the middle represent the latent variables, which are measured by the indicator variables. The rectangles on the right represent the indicator variables, which consist out of observable data. Pathways are represented by arrows, showing the standardized XY estimates for each path. [1] Non standardized dispersion.

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Due to missing data in the outcome measures (see S1 Table), multiple imputations (MI) were performed using the Multivariate Imputation by Chained Equations software [34]. 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 (Enders 2010). Although the MAR or MCAR assumption is not directly testable [35], it was considered plausible in the present situation because the variables with the highest proportion of missing values, such as the long delay free and cued recall, 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. Furthermore, even if the data were missing not at random, the MI procedure most likely would have led to less biased results than the traditional complete case analysis [36]. To protect against a potential power falloff from a too small number of imputations [37], we generated 20 imputations of the missing values using the random forest imputation method [38]. The analyses of interest (see below) were then conducted in each completed data set, and parameter estimates were pooled according to Rubin's rules [39]. This method has previously been described by other members of this research group [33, 40].

In order to test CVLT performance differences between HC, ARMS-NT, ARMS-T and FEP patients directly within the structural equation modelling framework, we extended the measurement model of Donders [25] by regressing the four latent factors on group and sex. The variable group was represented in the model as three dummy coded contrast variables using the HC group as the reference group. This resulted in a so called multiple-indicator multiple-causes (MIMIC) model [41], which not only takes measurement error into account when testing group differences, but can also accommodate factorial non-invariance between group or so-called differential item functioning [41].

The following minimum standards have been specified a priori as desirable for the models: Comparative Fit Index (CFI) $\geq$0.95, Root Mean Squared Error of Approximation (RMSEA) $\leq$0.06, Tucker-Lewis Index (TLI) $\geq$0.95, Standardized Root Mean Square Residual (SRMR) $\leq$0.08 [42].

Second, learning over the first 5 trials of the CVLT was investigated using latent growth curve analysis which is a statistical technique used in the SEM framework to estimate growth trajectories. Several studies have successfully applied growth curve models on the CVLT or the closely related Rey Auditory Verbal Learning Task (RAVLT) [43–45]. An important advantage of this approach is that it allows disentangling initial recall, which is strongly determined by attentional processes, from the rate of learning (i.e., learning slope). Thus, we used the two latent parameters *initial recall* and *learning rate* as proposed by Jones, Rosenberg [45] to model the growth curve. Here, *initial recall* corresponds to the intercept and *learning rate* corresponds to the slope of the growth curve. Both parameters were estimated based on the number of recalled words over the first five trials of the CVLT (see Fig 2).

All analyses were first conducted with the three groups ARMS, FEP and HC. Thereafter, analyses were extended to the subgroups ARMS-T and ARMS-NT, compared to FEP and HC respectively. In a further step, we conducted secondary analyses for the MIMIC model proceeding exactly as described above but including the covariates that differed significantly between groups for completeness.

To account for multiple testing corrected p values were calculated using the false discovery rate [46].

Results

98 FEP patients, 126 ARMS and 68 HC fulfilled the inclusion criteria (see Table 1 for sociodemographic and clinical sample characteristics). Of the 126 ARMS patients, 25 had developed frank psychosis during the follow-up (ARMS-T), 48 had not developed psychosis after a follow up of at least 3 years (ARMS-NT), and 53 had not developed psychosis but were followed up for less than 3 years either because they were only recruited recently or because they dropped out during the first three years of the follow-up.

Confirmatory factor analysis (CFA)

The four factorial CFA model of Donders [25] narrowly missed acceptability of model fit in our data (χ^2 = 180.988, df = 59, $p < 0.001$, *AIC* = 10852.479, *CFI* = 0.921, RMSEA = 0.093, TLI = 0.895, SRMR = 0.045). In addition, an error warning indicated that the covariance matrix of latent variables was not positive definite.

We therefore made a small modification of the model of Donders by treating the indicators of the Inaccurate Recall factor (i.e. total intrusions and recognition false positives) as count variables and estimating their loadings on the Inaccurate Recall factor through zero-inflated negative binomial regressions. This not only solved the convergence problem, it also led to a more realistic data model as total intrusions and recognition false positives were now correctly

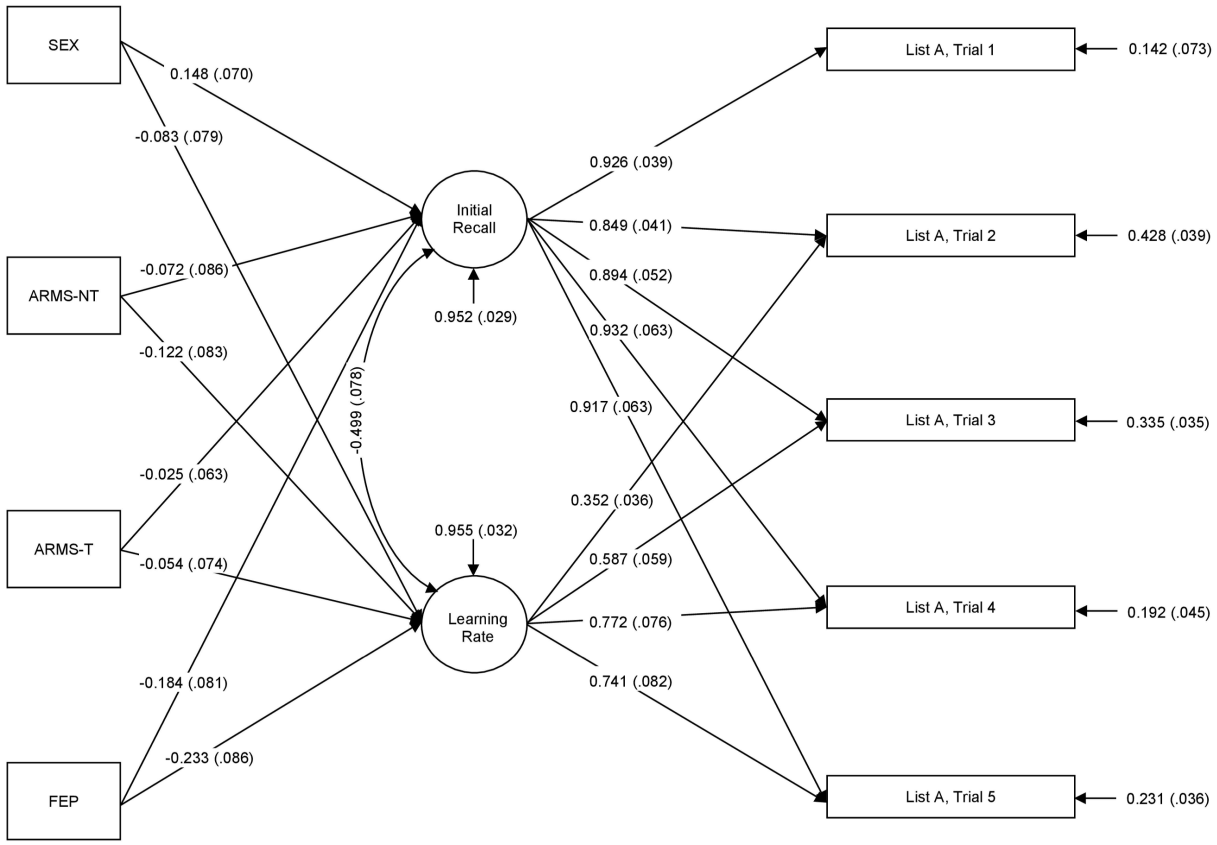

Fig 2. Visualisation of the growth curve analysis. The rectangles on the left represent the patient groups (at-risk mental state (ARMS) patients with (ARMS-T) and without later transition to psychosis (ARMS-NT) and first episode psychosis (FEP) patients). The circles in the middle represent the latent variables, which are measured by the indicator variables. The rectangles on the right represent the indicator variables, which consist out of observable data. Pathways are represented by arrows, showing the standardized XY estimates for each path.

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modelled as non-negative integers with relatively large preponderances of zeros. Unfortunately, as this new model could only be estimated by numerical integration [47], traditional fit indices were not available for this modified model. However, the Akaike Information Criterion (AIC) indicated the modification led to an improved model fit (AIC_{OLD} = 10852.479, AIC_{NEW} = 10050.095).

Results from the MIMIC model showed significant worse performance of ARMS and FEP on *Attention Span*, *Learning Efficiency* and *Delayed Memory* compared to HC. Additionally, FEP showed significantly worse performance on *Inaccurate Memory* than HC (see Table 2).

When splitting up the ARMS group into ARMS-T and ARMS-NT only ARMS-NT showed a significant worse performance than HC on *Learning Efficiency* (p = 0.009). FEP still showed significant worse performance on all four factors compared to HC ($p_{Attention\ Span}$ = 0.001, $p_{Learning\ Efficiency} < 0.001$, $p_{Delayed\ Memory} < 0.001$, $p_{Inaccurate\ Memory}$ = 0.014) (see Table 2 and Fig 3). When comparing ARMS-T against ARMS-NT, no significant differences emerged on any of the four factors (see Table 2).

Table 1. Sociodemographic and clinical sample characteristics.

	N	HC	ARMS			FEP	Test Statistic HC vs. ARMS vs. FEP
		N = 68	*N* = 126			*N* = 98	
				ARMS-NT	ARMS-T		
				N = 48	*N* = 25		
Gender	292						$p = 0.226$[1]
Female		27 (40%)	36 (28.6%)	13 (27.1%)	10 (40%)	36 (36.7%)	
Male		41 (60%)	90 (71.4%)	35 (72.9%)	15 (60%)	62 (63.3%)	
Age	292	25.30 ± 6.04	25.6 ± 6.56	25.7 ± 7.32	26.85 ± 6.97	28.5 ± 8.16	$p = 0.003$[2]
Years of education	291	13.19 ± 2.84	11.8 ± 2.81	11.9 ± 3.29	11.40 ± 2.02	11.5 ± 2.92	$p = 0.001$[2]
Antipsychotics currently:	292	0 (0%)	9 (7.14%)	0 (0%)	3 (12%)	36 (36.7%)	$p < 0.001$[3]
Antidepressants currently:	292	0 (0%)	43 (34.1%)	20 (41.7%)	9 (36%)	18 (18.4%)	$p < 0.001$[3]
Anxiolytics currently:	292	0 (0%)	19 (15.1%)	5 (10.4%)	7 (28%)	19 (19.4%)	$p = 0.001$[3]
Cannabis use:	244	5 (8%)	24 (23.5%)	9 (28%)	4 (22%)	22 (26.5%)	$p = 0.023$[3]
BPRS total score	205		38.6 ± 9.13	37.3 ± 9.01	41.39 ± 8.82	50.8 ± 12.5	$p < 0.001$[2]

Note. N is the number of non-missing values. Values of continuous variables are stated as mean ± 1 standard deviation.

[1]Pearson's χ^2 test

[2]independent t-test

[3]Fisher's Exact test.

HC = healthy controls; ARMS = patients with an at-risk mental state for psychosis; ARMS-NT = patients with an at-risk mental state for psychosis without later transition to psychosis; ARMS-T = patients with an at-risk mental state for psychosis with later transition to psychosis; FEP = patients with a first episode of psychosis. Patients were identified as ARMS-NT if they had a follow-up period of at least three years without developing frank psychosis.

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Results from the secondary MIMIC model analyses showed no significant differences in the performances of ARMS, ARMS-NT, ARMS-T and FEP on any of the investigated latent variables compared to HC. The only covariates significantly influencing the latent factors were sex and years of education, indicating that women perform significantly better than men on *Attention Span* and those subjects with more years of education exhibiting superior performances on *Learning Efficiency* and *Delayed Memory*, independent of diagnostic group (see Tables 3–5). A stepwise integration of the covariates revealed that the performance differences between ARMS patients and HC were no longer significant when corrected for years of education and the performance differences between FEP patients and HC were no longer significant when corrected for use of antipsychotics.

Growth curve analysis

A comparison of three nested models with different shapes for the learning curve revealed that an approximately logarithmic growth curve ($\chi^2 = 51.361$, df = 15, $p < 0.001$, *AIC* = 6414.138, *CFI* = 0.960, RMSEA = 0.089, TLI = 0.939, SRMR = 0.061) and a freely estimated growth curve ($\chi^2 = 34.258$, df = 13, $p = 0.001$, *AIC* = 6399.236, *CFI* = 0.977, RMSEA = 0.074, TLI = 0.964, SRMR = 0.055) provided both good fit to the data. Hence, for ease of interpretation, the approximately logarithmic model was used for comparing *initial recall* and *learning* rate of ARMS and FEP patients. FEP showed significantly lower scores in *initial recall* ($p = 0.021$) and *learning rate* ($p = 0.010$) compared to ARMS and HC (see Fig 4). Additionally, a significantly worse performance of ARMS compared to HC was found regarding *learning rate* ($p = 0.050$). To further distinguish between ARMS-T and ARMS-NT a second growth curve analysis with these two subgroups was conducted. Results showed significant worse performances of FEP compared to HC in *initial recall* ($p = 0.024$) and *learning rate* ($p = 0.007$). No significant

Table 2. Results from the four factor multiple-indicator multiple-causes (MIMIC) model.

	FEP		ARMS		ARMS-NT		ARMS-T		SEX	
	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value
Comparison of FEP and ARMS vs. HC										
Attention Span	-0.33 (0.09)	<0.001***	-0.16 (0.08)	0.048*					0.25 (0.07)	<0.001***
Learning Efficiency	-0.39 (0.06)	<0.001***	-0.22 (0.06)	<0.001***					0.09 (0.06)	0.135
Delayed Memory	-0.32 (0.06)	<0.001***	-0.13 (0.06)	0.028*					0.11 (0.06)	0.041*
Inaccurate Memory	0.33 (0.12)	0.006**	0.02 (0.12)	0.870					-0.03 (0.10)	0.797
Comparison of FEP, ARMS-NT and ARMS-T vs. HC										
Attention Span	-0.33 (0.10)	0.001***			-0.10 (0.09)	0.284	-0.07 (0.07)	0.256	0.17 (0.07)	0.020*
Learning Efficiency	-0.40 (0.06)	<0.001***			-0.19 (0.07)	0.009**	-0.05 (0.05)	0.302	0.05 (0.07)	0.481
Delayed Memory	-0.34 (0.06)	<0.001***			-0.11 (0.07)	0.123	-0.05 (0.05)	0.332	0.07 (0.06)	0.274
Inaccurate Memory	0.30 (0.12)	0.014*			-0.04 (0.13)	0.762	0.06 (0.13)	0.634	-0.04 (0.11)	0.708
Comparison of ARMS-NT vs. ARMS-T										
Attention Span					0.00 (0.10)	0.971			0.17 (0.07)	0.021*
Learning Efficiency					-0.12 (0.09)	0.165			0.05 (0.07)	0.486
Delayed Memory					-0.04 (0.08)	0.581			0.07 (0.06)	0.279
Inaccurate Memory					-0.14 (0.19)	0.474			-0.04 (0.11)	0.731

Note. S.E. = Standard Error.

Level of significance for p-values

*$p \leq 0.05$

**$p \leq 0.01$

***$p \leq 0.001$.

ARMS = patients with an at-risk mental state for psychosis; ARMS-NT = patients with an at-risk mental state for psychosis without later transition to psychosis; ARMS-T = patients with an at-risk mental state for psychosis with later transition to psychosis; FEP = patients with a first episode of psychosis. Patients were identified as ARMS-NT if they had a follow-up period of at least three years without developing frank psychosis. To account for multiple testing corrected *p*-values were calculated using the false discovery rate.

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differences were found for ARMS-T and ARMS-NT compared to HC on these two factors (ARMS-T: $p_{Initial\ Recall} = 0.695$, $p_{Learning\ Rate} = 0.471$; ARMS-NT: $p_{Initial\ Recall} = 0.398$, $p_{Learning\ Rate} = 0.142$).

Also, when comparing ARMS-T against ARMS-NT no significant group differences emerged ($p_{Initial\ Recall} = 0.433$, $p_{Learning\ Rate} = 0.193$).

Discussion

This study examined learning curves in at-risk mental state (ARMS) patients, first episode psychosis (FEP) patients and healthy controls (HC) using structural equation modelling. We hypothesized that HC would perform best on all four factors of the CVLT, ARMS would perform intermediate to HC and FEP and that FEP would perform worst compared to HC and ARMS (i.e. HC>ARMS>FEP). This hypothesized sequence of performance was confirmed within the MIMIC model for the three out of four factors *Attention Span*, *Learning Efficiency* and *Delayed Memory* of the CVLT. Additionally, growth curve analysis verified this sequence of performance for the latent factor *Learning Rate*.

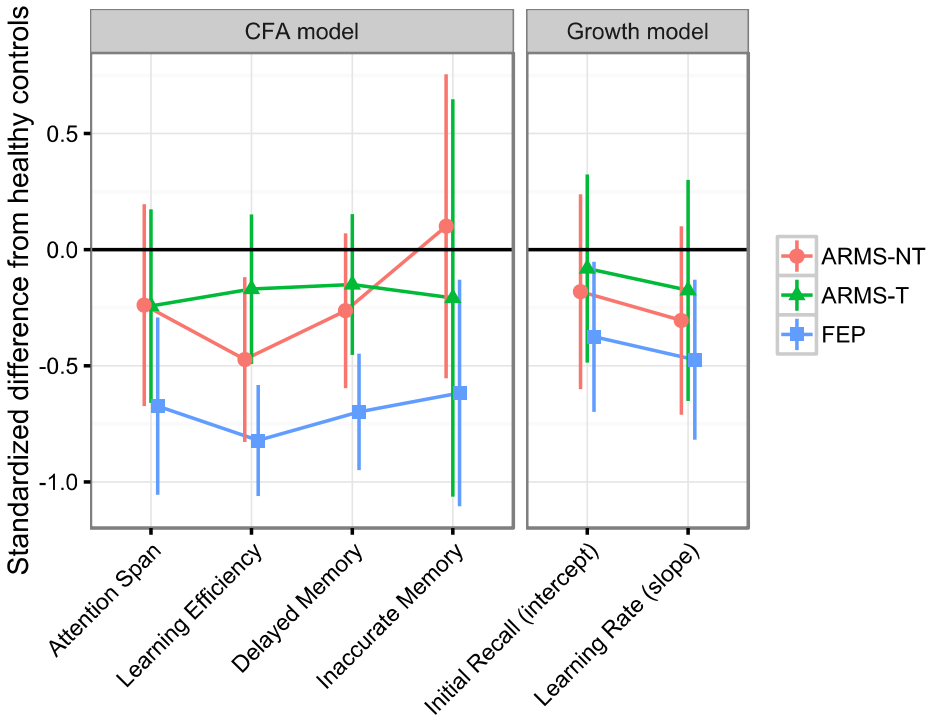

Fig 3. Performances of at-risk mental state (ARMS) patients with (ARMS-T) and without later transition to psychosis (ARMS-NT) and first episode psychosis (FEP) patients on the four factors of the California Verbal Learning Test (CVLT). The horizontal line at zero represents the performance of healthy controls. Differences are expressed in units of standardized mean differences. Differences are significant if the 95% confidence interval does not overlap with the horizontal line. The variable *Inaccurate Memory* was reversed such that high scores represent a good performance. Differences are adjusted for the influence of sex.

https://doi.org/10.1371/journal.pone.0196936.g003

When further differentiating the ARMS patient group into ARMS with later transition to psychosis (ARMS-T) and ARMS without later transition to psychosis (ARMS-NT), only ARMS-NT showed a significantly worse performance on the factor *Learning Efficiency* compared to HC. No further group differences between ARMS-T and ARMS-NT were found, neither within the MIMIC model nor in the growth curve analysis.

The herein found results show that impairments in verbal learning and memory in FEP patients are present in the domains of *Attention Span*, *Learning Efficiency*, *Delayed Memory* and *Inaccurate Memory*. Likewise, ARMS patients show similar impairments as FEP patients although less marked in the domains *Attention Span*, *Learning Efficiency* and *Delayed Memory*. Furthermore, it was shown that regarding the verbal learning curve only FEP patients demonstrated marked impairments in the initial recall (i.e. intercept of the slope), whereas in the learning rate both FEP and ARMS patients showed significant impairments compared to HC. Nevertheless, when representing the verbal learning curve graphically it became apparent from the development of the curve per group over the five trials of the CVLT, that the learning curve progresses similarly for each group (see Fig 4). More precisely, the development of the growth curve, given the increase of the slope, indicates that ARMS and FEP perform similarly to HC in regard to the Learning Rate, even though the increase of the curve is less steep than

Table 3. Results from the secondary four-factor multiple-indicator multiple-causes (MIMIC) model including covariates.

	FEP		ARMS		ARMS-NT		ARMS-T		SEX	
	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value
Comparison of FEP and ARMS vs. HC										
Attention Span	-0.206 (0.104)	0.188	-0.110 (0.092)	0.496					0.258 (0.066)	<0.001***
Learning Efficiency	-0.173 (0.083)	0.167	-0.153 (0.068)	0.162					0.082 (0.057)	0.378
Delayed Memory	-0.095 (0.088)	0.506	-0.014 (0.068)	0.857					0.113 (0.054)	0.167
Inaccurate Memory	0.148 (0.158)	0.524	-0.141 (0.135)	0.506					-0.025 (0.102)	0.857
Comparison of FEP, ARMS-NT and ARMS-T vs. HC										
Attention Span	-0.180 (0.112)	0.393			-0.049 (0.094)	0.797	0.008 (0.075)	0.965	0.180 (0.073)	0.187
Learning Efficiency	-0.162 (0.089)	0.393			-0.132 (0.073)	0.393	0.037 (0.058)	0.719	0.044 (0.063)	0.717
Delayed Memory	-0.132 (0.091)	0.403			-0.028 (0.073)	0.832	0.059 (0.059)	0.578	0.073 (0.062)	0.510
Inaccurate Memory	0.130 (0.168)	0.714			-0.153 (0.152)	0.578	-0.050 (0.143)	0.832	-0.037 (0.110)	0.832
Comparison of ARMS-NT vs. ARMS-T										
Attention Span					-0.061 (0.098)	0.712			0.180 (0.073)	0.149
Learning Efficiency					-0.182 (0.083)	0.186			0.045 (0.063)	0.698
Delayed Memory					-0.106 (0.079)	0.443			0.073 (0.062)	0.454
Inaccurate Memory					-0.082 (0.199)	0.827			-0.037 (0.111)	0.827

Note. S.E. = Standard Error.

Level of significance for p-values

*$p \leq 0.05$

**$p \leq 0.01$

***$p \leq 0.001$.

ARMS = patients with an at-risk mental state for psychosis; ARMS-NT = patients with an at-risk mental state for psychosis without later transition to psychosis; ARMS-T = patients with an at-risk mental state for psychosis with later transition to psychosis; FEP = patients with a first episode of psychosis. Patients were identified as ARMS-NT if they had a follow-up period of at least three years without developing frank psychosis. To account for multiple testing corrected *p*-values were calculated using the false discovery rate.

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the one of the HC. It has to be emphasized that, in contrast to most previous studies, this study does not rely solely on Trial 1, Trial 5 or the cumulative sum (i.e. sum of trials 1–5) of the CVLT but evaluates each of the five trials on its own, taking all available information into account.

The results from the confirmatory factor analysis (CFA) are in line with the present literature indicating impairments of attentional processing in ARMS and FEP, with ARMS performing intermediate to HC and FEP, and FEP performing worse than the other groups [16, 48].

Furthermore, the results correspond to the findings of the meta-analysis conducted by Bora, Lin [11] who reported medium effect sizes for deficits of ARMS patients in verbal memory (d = -.50) and in verbal learning (d = -.68). Giuliano, Li [49], who found similar effect sizes, suggested that it may be possible to improve the predicted trajectory of psychotic illnesses by integrating information about specific cognitive deficit patterns such as in the verbal declarative memory. Accordantly, Fusar-Poli, Deste [10] based on their meta-analysis suggest that ARMS patients are impaired in tests of verbal memory and later transition to psychosis is associated with poorer verbal memory. Congruently, Koutsouleris, Davatzikos [4] found that transition to psychosis was mainly predicted by executive and verbal learning impairments.

Table 4. Results from the secondary four-factor multiple-indicator multiple-causes (MIMIC) model including covariates.

		Years of Education		BPRS Total Score		Cannabis	
		Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value
Comparison of FEP and ARMS vs. HC							
	Attention Span	0.167 (0.061)	0.054	-0.059 (0.096)	0.640	0.046 (0.077)	0.640
	Learning Efficiency	0.199 (0.055)	<0.001***	-0.130 (0.083)	0.357	-0.062 (0.066)	0.524
	Delayed Memory	0.157 (0.051)	0.024*	-0.136 (0.079)	0.275	-0.017 (0.061)	0.857
	Inaccurate Memory	-0.136 (0.106)	0.450	0.116 (0.116)	0.517	0.089 (0.098)	0.524
Comparison of FEP, ARMS-NT and ARMS-T vs. HC							
	Attention Span	0.136 (0.068)	0.368	-0.130 (0.100)	0.485	0.038 (0.089)	0.832
	Learning Efficiency	0.215 (0.061)	<0.001***	-0.156 (0.096)	0.393	-0.098 (0.080)	0.498
	Delayed Memory	0.172 (0.055)	0.040*	-0.132 (0.090)	0.403	-0.023 (0.073)	0.832
	Inaccurate Memory	-0.089 (0.125)	0.717	0.202 (0.125)	0.393	0.038 (0.116)	0.832
Comparison of ARMS-NT vs. ARMS-T							
	Attention Span	0.136 (0.068)	0.240	-0.130 (0.100)	0.443	0.038 (0.089)	0.827
	Learning Efficiency	0.216 (0.061)	<0.001***	-0.155 (0.096)	0.384	-0.098 (0.080)	0.448
	Delayed Memory	0.173 (0.055)	0.032*	-0.132 (0.090)	0.387	-0.023 (0.073)	0.827
	Inaccurate Memory	-0.092 (0.126)	0.698	0.201 (0.125)	0.384	0.038 (0.116)	0.827

Note. S.E. = Standard Error.

Level of significance for p-values

*$p \leq 0.05$

**$p \leq 0.01$

***$p \leq 0.001$.

ARMS = patients with an at-risk mental state for psychosis; ARMS-NT = patients with an at-risk mental state for psychosis without later transition to psychosis; ARMS-T = patients with an at-risk mental state for psychosis with later transition to psychosis; FEP = patients with a first episode of psychosis. Patients were identified as ARMS-NT if they had a follow-up period of at least three years without developing frank psychosis. Cannabis refers to current use. To account for multiple testing corrected *p*-values were calculated using the false discovery rate.

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In contrast to our hypothesis, ARMS-NT, but not ARMS-T, performed significantly worse on the factor *Learning Efficiency* compared to HC. This rather counterintuitive result may on the one hand be due to the fact that the ARMS-T sample was too small to detect significant differences between groups ($N_{ARMS\text{-}T} = 25$, $N_{ARMS\text{-}NT} = 48$). On the other hand, a plausible explanation might be that impaired *Learning Efficiency* represents a feature/trait of the at-risk mental state but is not related to the onset of illness.

On all other factors no significant differences between ARMS-T and ARMS-NT emerged, therefore it may be speculated that only the overall performance in the domain of verbal memory may be predictive of a later transition to frank psychosis, but that single underlying factors of verbal learning and memory are not. This assumption would be in line with the results of Francey, Jackson [50] who showed that, despite the existence of sustained attention deficits in ARMS, there were no differences between subjects who converted to psychosis (ARMS-T) and those who did not (ARMS-NT). This led the authors to suggest that such deficits, although they may constitute a vulnerability factor, are insufficient for reliable predictions of the risk of conversion to psychosis. Also, a meta-analysis by De Herdt, Wampers [51] indicated that ARMS-T and ARMS-NT may not be differentiated based on verbal memory deficits. Furthermore, in their meta-analysis Bora, Lin [11] reported that effect sizes for between-group differences were modest with a Cohen's $d = 0.5$ at most for domains with the largest group

Table 5. Results from the secondary four-factor multiple-indicator multiple-causes (MIMIC) model including covariates.

		Antipsychotics		Antidepressants		Anxiolytics	
		Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value
Comparison of FEP and ARMS vs. HC							
	Attention Span	-0.048 (0.073)	0.640	0.050 (0.072)	0.640	-0.101 (0.072)	0.393
	Learning Efficiency	-0.170 (0.077)	0.162	0.064 (0.058)	0.506	0.006 (0.067)	0.931
	Delayed Memory	-0.136 (0.076)	0.260	-0.040 (0.062)	0.640	-0.076 (0.067)	0.506
	Inaccurate Memory	-0.024 (0.111)	0.857	0.149 (0.101)	0.378	0.057 (0.096)	0.640
Comparison of FEP, ARMS-NT and ARMS-T vs. HC							
	Attention Span	0.002 (0.088)	0.983	-0.005 (0.082)	0.978	-0.167 (0.075)	0.260
	Learning Efficiency	-0.138 (0.090)	0.403	0.018 (0.066)	0.852	-0.059 (0.078)	0.714
	Delayed Memory	-0.083 (0.083)	0.578	-0.055 (0.069)	0.714	-0.126 (0.073)	0.393
	Inaccurate Memory	-0.081 (0.121)	0.719	0.173 (0.121)	0.403	0.127 (0.102)	0.498
Comparison of ARMS-NT vs. ARMS-T							
	Attention Span	0.002 (0.088)	0.984	-0.005 (0.082)	0.982	-0.167 (0.075)	0.186
	Learning Efficiency	-0.138 (0.090)	0.387	0.017 (0.066)	0.845	-0.060 (0.078)	0.698
	Delayed Memory	-0.083 (0.083)	0.562	-0.055 (0.069)	0.698	-0.126 (0.073)	0.375
	Inaccurate Memory	-0.081 (0.121)	0.698	0.176 (0.121)	0.387	0.128 (0.103)	0.448

Note. S.E. = Standard Error. ARMS = patients with an at-risk mental state for psychosis; ARMS-NT = patients with an at-risk mental state for psychosis without later transition to psychosis; ARMS-T = patients with an at-risk mental state for psychosis with later transition to psychosis; FEP = patients with a first episode of psychosis. Patients were identified as ARMS-NT if they had a follow-up period of at least three years without developing frank psychosis. Antipsychotics, Antidepressants, and Anxiolytics refer to current use. To account for multiple testing corrected *p*-values were calculated using the false discovery rate.

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differences (i.e. verbal fluency, verbal and visual memory, and working memory). Thus, the authors found a significant performance overlap of 67% between the groups, indicating that cognitive impairment has only a limited capacity to predict the outcome of high-risk patients.

However, when the analyses were repeated including all covariates significantly differing between groups, no significant group differences regarding performance on any of the latent variables could be observed anymore. A stepwise integration revealed that this was specifically due to the covariates years of education and antipsychotic medication. However, it could be argued that it is not sensible to correct for the influence of years of education here, because reduced years of education can be consequence of the psychotic disorder [52] and thus one would partial out variability of the illness itself. The same is true for antipsychotic medication, which was not present in HC, but in 7.1% of ARMS and 36.7% of FEP patients.

In line with our hypothesis, the results from the growth curve analysis indicated a worse performance of FEP compared to ARMS and HC and a performance of ARMS intermediate to those two groups. Since these differences were more pronounced in the slope (i.e. learning rate) than in the intercept (i.e. initial recall) of the learning curve, our results are in line with the existing body of literature indicating that the verbal learning rate tends to be more impaired than attentional processes in both ARMS and FEP patients [10, 11, 14].

Additionally, the results suggest that the worse performance in verbal learning and memory in FEP patients is due to both a lower initial recall and a lower learning rate pointing towards a possible underlying attentional problem in FEP. ARMS patients showed a similar pattern of impairment as FEP regarding learning rate. This finding is consistent with recently published reviews and meta-analyses indicating that already in the prodromal/at-risk mental state patients show marked impairments in verbal memory [10, 11, 48].

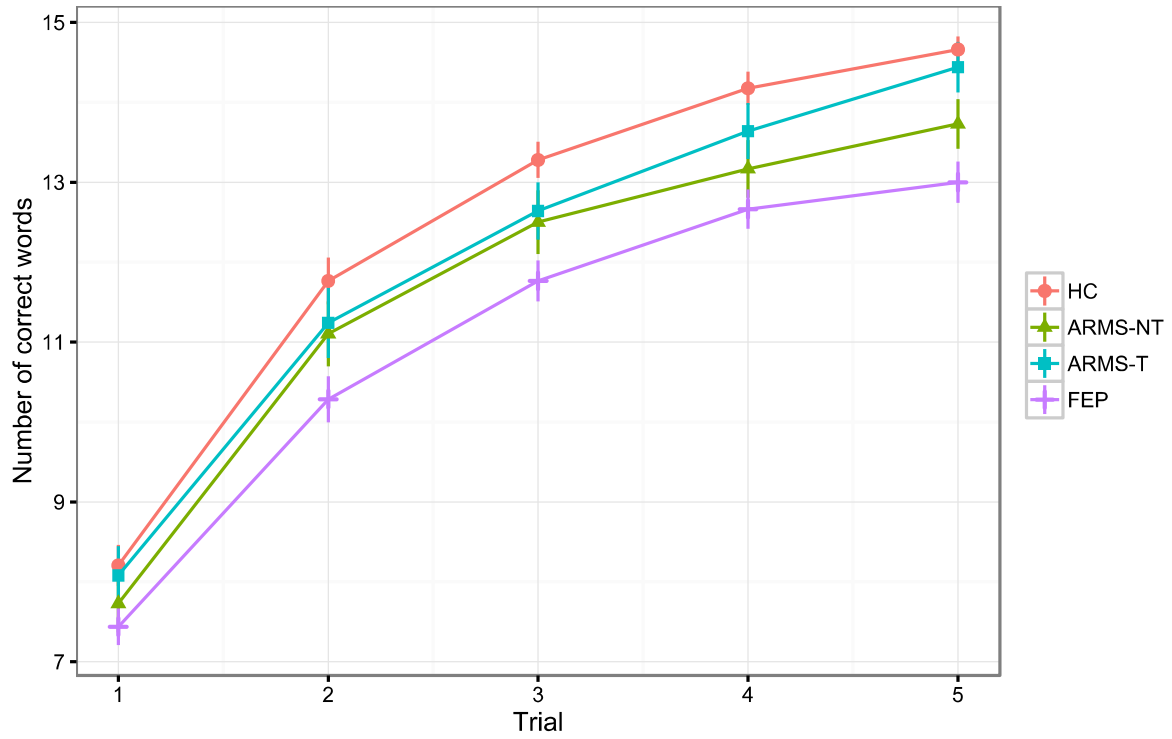

Fig 4. Growth curve. Verbal learning performances of at-risk mental state (ARMS) patients with (ARMS-T) and without later transition to psychosis (ARMS-NT) and first episode psychosis (FEP) patients. Lines per group correspond to the mean of total words remembered per trial.

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Limitations

The following limitations should be taken into account:

Firstly, sample sizes differed across groups. Particularly, when differentiating between ARMS-T and ARMS-NT moderate group sizes emerged. Literature suggests cognitive impairments in ARMS-T patients to be rather unspecific and generalized [12]. Hence, the small and distinct group sizes may have precluded the detection of small effects between these two groups. Furthermore, the probability of a type II error is considerably larger for comparisons of ARMS-T and ARMS-NT than for comparisons between ARMS, FEP and HC groups.

Secondly, to be identified as non-transitioned patients had to be in the follow-up for at least three years without transitioning to psychosis. Although research has shown that most ARMS-T patients make the transition to psychosis within the first 12 months of clinical presentation, a small percentage of patients transitions to frank psychosis within the next 24 months of follow-up (for meta-analysis, see [10]). This cut-off contributed substantially to the small sample size of the ARMS-NT group. Yet, by setting this cut-off we were able to strongly decrease the risk of misclassifying patients with a later transition to psychosis as non-transitioned cases.

Thirdly, the measurement model of Donders [25] used in our analyses was originally built based on the standardization sample data of the CVLT-II, whereas in this study we had

measured verbal learning and memory with the original CVLT. However, we could still fit the model of Donders with our CVLT data because all required indicator variables are also available in the original CVLT. The only difference is that Semantic Clustering is calculated slightly differently. However, since we calculated Semantic Clustering according to the CVLT-II instructions, we do not expect that the application of a CVLT-II model to our CVLT data has largely influenced the results.

Fourthly, since HC were not included if they had a current or former psychiatric disorder or neurological disease, we cannot rule out the possibility that our HC were healthier than a representative sample from the general population and that consequently differences between HC and patients were overestimated.

Conclusion

In conclusion, this is the first study to evaluate verbal learning and memory using structural equation modelling. In line with our hypothesis, results indicated a worse performance of FEP patients compared to ARMS patients and HC and a performance of ARMS patients intermediate to those two groups. Since these differences were more pronounced in the slope than in the intercept of the learning curve, our results indicate that the verbal learning rate tends to be more impaired than attentional processes in both ARMS and FEP patients. Further longitudinal investigations are needed to clarify whether verbal learning and memory may be a potential discriminatory variable in the early detection of psychosis.

Supporting information

S1 Table. Summary of missing values in each variable. *Note.* CVLT = California Verbal Learning Task. Missing Values resulted from changes in the study design over the years. (DOCX)

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Author Contributions

Conceptualization: Anita Riecher-Rössler.

Data curation: Laura Egloff, Erich Studerus.

Formal analysis: Laura Egloff, Erich Studerus.

Funding acquisition: Anita Riecher-Rössler.

Investigation: Laura Egloff, Ronan Zimmermann, Ulrike Heitz, Stephanie Menghini-Müller, Sarah Ittig, Katharina Beck, Christina Andreou, Stefan Borgwardt, Anita Riecher-Rössler.

Methodology: Laura Egloff, Erich Studerus, Anita Riecher-Rössler.

Project administration: Anita Riecher-Rössler.

Resources: Ronan Zimmermann, Ulrike Heitz, Stephanie Menghini-Müller, Sarah Ittig, Katharina Beck, Christina Andreou, Stefan Borgwardt, Anita Riecher-Rössler.

Software: Laura Egloff.

Supervision: Erich Studerus, Christina Andreou, Stefan Borgwardt, Anita Riecher-Rössler.

Validation: Anita Riecher-Rössler.

Visualization: Laura Egloff.

Writing – original draft: Laura Egloff.

Writing – review & editing: Erich Studerus, Ronan Zimmermann, Ulrike Heitz, Stephanie Menghini-Müller, Sarah Ittig, Katharina Beck, Christina Andreou, Stefan Borgwardt, Anita Riecher-Rössler.

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Appendix B: Article 2

Egloff, L., Lenz, C., Studerus, E., Heitz, U., Harrisberger, F., Smieskova, R., Schmidt, A., Leanza, L., Andreou, C., Borgwardt, S., Riecher-Rössler, A. (2018) No associations between medial temporal lobe volumes and verbal learning/memory in emerging psychosis. Manuscript submitted to *European Journal of Neuroscience.* Draft of September 28th, 2017.

No associations between medial temporal lobe volumes and verbal learning/memory in emerging psychosis

Laura Egloff,[1,2,3] Claudia Lenz,[4] Erich Studerus,[3] Ulrike Heitz,[3] Fabienne Harrisberger,[1] Renata Smieskova,[1] André Schmidt,[1] Letizia Leanza,[2,3] Christina Andreou,[1,3] Stefan Borgwardt,[1] Anita Riecher-Rössler[3]

[1] University of Basel Psychiatric Hospital, Department of Psychiatry, Basel, Switzerland

[2] University of Basel, Department of Psychology, Division of Clinical Psychology and Epidemiology

[3] University of Basel Psychiatric Hospital, Center for Gender Research and Early Detection, Basel, Switzerland

4 Institute of Forensic Medicine, University of Basel, Basel, Switzerland

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Corresponding Author:
Prof. A. Riecher-Rössler
Center for Gender Research and Early Detection
University of Basel Psychiatric Hospital
Wilhelm Klein-Strasse 27
CH-4002 Basel
Switzerland
Phone: +41 61 325 59 95
Fax: +41 61 325 81 60
E-Mail: anita.riecher@upkbs.ch

Abstract

Gray matter (GM) volume alterations have been repeatedly demonstrated in patients with first episode psychosis (FEP). Some of these neuroanatomical abnormalities are already evident in the at-risk mental state (ARMS) for psychosis. Not only GM alterations but also neurocognitive impairments predate the onset of frank psychosis with verbal learning and memory (VLM) being among the most impaired domains. Yet, their interconnection with alterations in GM volumes remains ambiguous. Thus, we evaluated associations of different subcortical GM volumes in the medial temporal lobe with VLM performance in antipsychotic-naïve ARMS and FEP patients.

Data from 59 ARMS and 31 FEP patients, collected within the prospective Früherkennung von Psychosen (FePsy) study, were analysed. Structural T1-weighted images were acquired using a 3 Tesla magnetic resonance imaging scanner. VLM was assessed using the California Verbal Learning Test (CVLT) and its factors Attention Span (AS), Learning Efficiency (LE), Delayed Memory (DM) and Inaccurate Memory (IM).

FEP patients showed significantly enlarged volumes of hippocampus, pallidum, putamen and thalamus compared to ARMS patients. A significant negative association between amygdala and pallidum volume and AS was found in ARMS and FEP patients combined, which however did not withstand correction for multiple testing.

Although we found significant between-group differences in subcortical volumes and VLM is among the most impaired cognitive domains in emerging psychosis, we could not demonstrate an association between low performance and subcortical GM volumes alterations in antipsychotic-naïve patients. Hence, deficits in this domain do not appear to stem from alterations in subcortical structures.

Introduction

Patients with a first episode psychosis (FEP) have repeatedly been shown to have brain structural alterations such as in whole brain volume (Fusar-Poli *et al.*, 2013), white matter (WM) and gray matter (GM) volume (Fusar-Poli *et al.*, 2013; Fusar-Poli *et al.*, 2014) including a large number of regions such as the anterior cingulate (Fusar-Poli *et al.*, 2012c; Fusar-Poli *et al.*, 2014), superior temporal gyrus (Fusar-Poli *et al.*, 2014), cerebellum (Fusar-Poli *et al.*, 2014), insula (Bora *et al.*, 2011; Fusar-Poli *et al.*, 2012d; Radua *et al.*, 2012) and hippocampus (Bora *et al.*, 2011).

Some of these neuroanatomical abnormalities are already evident in the so-called at-risk mental state (ARMS) for psychosis (Dazzan *et al.*, 2015), including GM volume reductions of prefrontal (Smieskova *et al.*, 2013; Cannon, 2015), temporal (Smieskova *et al.*, 2013; Fusar-Poli *et al.*, 2014) and cingulate cortices (Fusar-Poli *et al.*, 2012c; Smieskova *et al.*, 2013; Fusar-Poli *et al.*, 2014), parahippocampal gyrus and hippocampus (Fusar-Poli *et al.*, 2012c; Thermenos *et al.*, 2013), insula and caudate (Smieskova *et al.*, 2013).

Not only brain structural alterations but also neurocognitive impairments predate the onset of frank psychosis. Verbal learning and memory are among the most impaired cognitive domains in ARMS (Studerus *et al.*, 2016; Hauser *et al.*, 2017) as well as FEP patients (Fatouros-Bergman *et al.*, 2014) and may potentially be useful for the early detection and intervention of these disorders (Fusar-Poli *et al.*, 2012b). The basal ganglia, which consist of the nucleus caudatus (hereafter referred to as caudate) and the nucleus lentiformis (formed by the putamen and the pallidum) have been shown to play a substantial role in working memory (Eriksson *et al.*, 2015; Nyberg & Eriksson, 2016) and thus in all processes involving learning.

Only few studies have investigated the associations of verbal learning and memory with subcortical volumes in psychosis so far (Hurlemann *et al.*, 2008; Hartberg *et al.*, 2011; Lappin *et al.*, 2014; Juuhl-Langseth *et al.*, 2015). One study found that the caudate volume was larger in early onset schizophrenia (EOS) spectrum disorders than in healthy controls (HC) and negatively associated with verbal learning in EOS patients only (Juuhl-Langseth *et al.*, 2015). Another study reported that bilaterally larger putamen volumes correlated with poorer verbal learning in schizophrenia patients (Hartberg *et al.*, 2011). A third study (Hurlemann *et al.*, 2008) found reduced hippocampal volumes to be associated with poorer performance in verbal learning and memory in ARMS subjects suspected to be in the late prodromal state, which is characterized by the onset of attenuated positive or brief psychotic symptoms (Häfner *et al.*, 2004; Frommann *et al.*, 2011). Conversely, a recent study (Lappin *et al.*, 2014) reported

bilateral hippocampal increase over time to be associated with better delayed verbal recall in a subset of FEP patients.

Hence, although several different brain regions have been found to be associated with verbal learning and memory performance in ARMS, FEP and schizophrenia patients, results are largely inconclusive. Furthermore, a direct comparison of these associations between ARMS and FEP patients is lacking to date.

Thus, the aim of the present study was to evaluate associations between verbal learning and memory and subcortical brain structural alterations in antipsychotic-naïve ARMS and FEP patients using standardized segmentation protocols provided by the ENIGMA consortium (http://enigma.usc.edu/). We hypothesized that verbal learning and memory performance are positively correlated with subcortical brain structural volumes (i.e., amygdala, accumbens, caudate, hippocampus, pallidum, putamen, and thalamus) in ARMS and FEP patients.

Material and Methods

Setting and Recruitment

All data analysed in this study were collected within the prospective ***Früh**erkennung von **Psy**chosen* (FePsy; early detection of psychosis) 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). Patients were recruited via the ***FePsy*** Clinic, University of Basel Psychiatric Hospital Basel, Switzerland, which was set up specifically to identify, assess, and treat individuals in the early stages of psychosis. For this study, all patients were included that were recruited for the ***FePsy*** study between March 2000 and November 2015 along with a complete California Verbal Learning Test (CVLT) and 3 Tesla magnetic resonance imaging (MRI) data. The study was approved by the Ethics Committee northwest/central Switzerland (EKNZ) and all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent.

Screening Procedure

The ARMS and FEP status was assessed using the Basel Screening Instrument for Psychosis (BSIP), which was developed by Riecher-Rössler *et al.* (2008). The BSIP is based on the Personal Assessment and Crisis Evaluation (PACE) criteria by Yung *et al.* (1998) and has been shown to have a high predictive validity and a good inter reliability ($\kappa = 0.67$) (Riecher-Rössler

et al., 2008). Exclusion criteria were age <18 years, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis (treated with antipsychotics for >3 weeks (lifetime) and/or a total chlorpromazine equivalent dose of 2500mg), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder.

Psychopathological assessment

Positive psychotic symptoms (i.e., hallucinations, suspiciousness, unusual thought content and conceptual disorganisation) were assessed with the Brief Psychiatric Rating Scale Expanded Version (BPRS-E) (Lukoff *et al.*, 1986; Ventura *et al.*, 1993; Velligan *et al.*, 2005).

Neurocognitive Assessment

The CVLT is a widely used neurocognitive task for the assessment of verbal learning and memory (Elwood, 1995). It consists of two word lists each containing 16 words. List A is orally presented over five immediate-recall trials. An interference list (List B) is then presented for one immediate recall trial, followed by short- and long-delay free- and cued-recall and recognition test of List A. During the long-delay interval (approximately 20 min), nonverbal testing is administered to the subjects (Delis *et al.*, 1987; Delis *et al.*, 2005). In confirmatory factor analyses (CFA) of the CVLT using a large standardisation sample with three different age groups of healthy controls (Donders, 2008) as well as a sample of traumatic brain injury patients (DeJong & Donders, 2009) it has been demonstrated that a four factor structure consisting of the factors *Attention Span*, *Learning Efficiency*, *Delayed Memory*, and *Inaccurate Memory* provides a good fit to the data. Hence, we adopted this measurement model for the present study. The variables measuring these factors are shown in Supplementary Table 1.

Image Acquisition

Structural images were acquired using a 3 Tesla magnetic resonance imaging scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 12-channel phased-array radio frequency head coil at the University Hospital Basel. Participants were given earplugs and noise-cancellation headphones. Foam pads on each side of the headphones were used to minimize head motion during the scans. A 3D T1-weighted magnetisation prepared rapid gradient echo (MPRAGE) sequence was used with the following parameters: inversion time = 1’000 ms, flip angle = 8 degrees, TR = 2 s, TE = 3.37 ms, bandwidth = 200 Hz/pixel, FOV =

256x256 mm^2, acquisition matrix = 256x256x176, resulting in 176 contiguous sagittal slices with 1x1x1 mm^3 whole-brain isotropic spatial resolution.
All scans were screened for gross radiological abnormalities by resident neuroradiologists.

Image Processing

All image processing steps were conducted according to the ENIGMA guidelines (http://enigma.ini.usc.edu/) using the FMRIB software library (FSL) 5.0 (Jenkinson *et al.*, 2012) running on Ubuntu version 14.04. Volumetric segmentation of subcortical structures was estimated on the whole-brain T1-weighted data sets by applying the FMRIB's Integrated Registration and Segmentation Tool (FSL-FIRST) (Patenaude *et al.*, 2011). Furthermore, in order to extract the different brain tissue volumes for normalization purposes, all images were skull stripped using FSL-BET (Smith, 2002), aligned to the Montreal Neurological Institute (MNI) 152 FSL standard brain using FSL-FLIRT (Jenkinson & Smith, 2001; Jenkinson *et al.*, 2002) and segmented into white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) using FSL-FAST (Zhang *et al.*, 2001). The resulting brain tissue volumes could then be calculated according to the results from the FSL-FAST partial volume maps and the total brain volume was extracted according to the sum of WM, GM and CSF.

Image Quality Assessment

First, all data sets were checked for overall quality, coverage of whole brain, contrast between WM and GM and presence of noise and artifacts. Second, to check the whole brain volume all skull stripping files were controlled to ensure that the whole brain images were cropped correctly. In a further step, the alignment of each brain image was controlled with regard to the reference brain (MNI 152 sample). Third, all segmentation files were controlled for the alignment of the subcortical volumes. Fourth, all volumes were plotted for each subject individually to detect outliers. In case of successful fulfillment of the quality assessment steps the volumetric data were included for statistical analyses.
The following exclusion criteria were fulfilled and led to a removal of data sets before further analyses: motion artefacts (N = 1), shift of the interhemispheric fissure (N = 1), incorrect skull stripping (N = 1).

Statistical Analyses

All analyses were conducted using the R environment for statistical computing, R version 3.2.5 (R Core Team, 2016) and Mplus Version 7 (Muthén & Muthén, 1998-2012). Sex and current

use of antidepressants or anxiolytics were compared between groups with Pearson's chi-square test. Age, years of education and BPRS total score were compared with Welch's two sample *t*-tests. Current use of cannabis was analysed using the proportional odds likelihood ratio test. For ease of interpretation of the brain structural volumes the following steps were applied: 1) the cube root was taken, 2) volumes were normalized to the individual whole brain volume by dividing them by the total brain volume, 3) volumes were centred and scaled (i.e., z-transformed).

In a first step, we evaluated whether there are any group differences in subcortical volumes by applying linear regression models. For each subcortical volume, a regression model was fitted including the subcortical volume as dependent variable and group, age and sex as independent variables.

In order to test CVLT performance differences as well as their correlations with brain structural alterations between ARMS and FEP patients directly within the structural equation modelling framework, we extended the measurement model of Donders (2008) by regressing the four latent factors on group, brain structural volume and the interaction between group x brain structural volume. The variable group was represented in the model as a dummy-coded contrast variable using the FEP group as the reference group. This resulted in a so-called multiple-indicator multiple-causes (MIMIC) model, which not only takes measurement error into account when testing group differences, but can also accommodate factorial non-invariance between groups or so-called differential item functioning (Brown, 2015).

Since the indicator variables *Total Intrusions* and *False Positives* are non-negative integer or count variables with relatively large preponderances of zeros, we estimated their loadings on the *Inaccurate Recall* factor through zero-inflated Poisson regressions.

To account for multiple testing corrected *p*-values were calculated separately for the correlational and interaction analyses using the false discovery rate (Benjamini & Hochberg, 1995).

Results

Descriptive Statistics

In total, 59 ARMS and 31 FEP patients fulfilled the inclusion criteria (see Table 1 for sociodemographic and clinical sample characteristics). Compared to the ARMS, FEP patients showed a significantly higher total score on the Brief Psychiatric Rating Scale (BPRS). Groups did not differ on any of the other investigated variables.

Group differences in subcortical gray matter volumes

Linear regression models revealed significant group differences regarding the subcortical volumes for hippocampus, pallidum, putamen, and thalamus, with FEP patients showing increased volumes in these regions compared to ARMS patients in both corrected and uncorrected analyses (see Table 2, Figure 1).

Associations between verbal learning and subcortical gray matter volumes

Without correction for multiple testing the factor *Attention Span* was significantly negatively associated with amygdala volume and significantly positively associated with pallidum volume. There also were significant positive interaction effects of hippocampus volume × group and thalamus volume × group on *Attention Span*, hippocampus volume × group on *Inaccurate Memory* and significant negative interaction effects of putamen volume × group on *Learning Efficiency* and *Delayed Memory* (see Table 3). However, after correction for multiple testing, these results were no longer significant.

All of the above mentioned results did not change when analyses were carried out with the subgroups of ARMS patients with (ARMS-T; n = 12) and without later transition (ARMS-NT; n = 22) to psychosis.

Discussion

To the best of our knowledge, this is the first study investigating the association between verbal learning and memory with subcortical gray matter volumes in ARMS and FEP patients.

Although we found that FEP patients had significantly larger hippocampus, pallidum, putamen and thalamus volumes than ARMS patients in both uncorrected and corrected analyses, we could not confirm that gray matter volumes in these regions were associated with verbal learning and memory performance, when corrected for multiple testing.

Our results regarding group differences in subcortical volume are in contrast to previous meta-analytical findings. While in the present study we found subcortical GM enlargements in antipsychotic-naïve FEP compared to ARMS patients, a previous meta-analysis (Fusar-Poli *et al.*, 2012d) could not demonstrate increased GM volumes in FEP compared to high risk (HR) for psychosis patients. In fact, these authors found significant GM decreases in the FEP group as compared with HR in the right superior temporal gyrus, right anterior cingulate, left cerebellum and in the left insula (Fusar-Poli *et al.*, 2012d). Similarly, a more recent meta-

analysis (Fusar-Poli *et al.*, 2014) comparing genetic high risk (GHR) for psychosis and FEP patients reported no increases in GM volumes.

However, the observed between-group differences in hippocampus, pallidum, putamen and thalamus volumes in antipsychotic-naïve FEP patients are in partial agreement with some more recent studies. Specifically, the largest cooperative data analysis to date conducted by the ENIGMA consortium, which was based on 2028 schizophrenia patients and 2540 HC, also found enlarged pallidum volumes in schizophrenia patients (van Erp *et al.*, 2016). Furthermore, a large-scale multisite study conducted in Japan (Okada *et al.*, 2016), comparing schizophrenia patients to HC, also reported enlarged putamen and pallidum volumes in schizophrenia patients. Yet, there are also discrepant results: within the ENIGMA analysis the authors (van Erp *et al.*, 2016) reported reduced hippocampal and thalamic volumes and within the Japanese study (Okada *et al.*, 2016) the authors found decreased bilateral hippocampus volumes in schizophrenia patients compared to HC. However, in both studies the investigated samples were neither only FEP nor antipsychotic-naïve and a potential influence of antipsychotic medication can therefore not be precluded.

With regard to the ARMS as a high risk state in which up to 36% of patients transition to frank psychosis within 3 years after initial presentation (Fusar-Poli *et al.*, 2012a), our finding of enlarged volumes in FEP patients may be the result of an established risk marker in the ARMS before the onset of frank psychosis. In line with this, Borgwardt *et al.* (2007) found the parahippocampal gyri, the parietal and posterior temporal cortex, and the thalamus to present with relatively higher GM volume in ARMS patients who later transitioned to frank psychosis (ARMS-T) compared to ARMS patients without later transition (ARMS-NT). Furthermore, in a subsequent study applying support vector machine analysis, Borgwardt *et al.* (2013) found that the subcortical structures discriminating best between ARMS-T and FEP patients were thalamus, pallidum, putamen and cerebellum. Therefore, it seems plausible that the regions found to be enlarged may be related to pathological processes associated with the subsequent onset of psychosis (Borgwardt *et al.*, 2007).

Although verbal learning and memory are among the most impaired cognitive domains in both ARMS and FEP patients, we could not demonstrate any significant association between subcortical volumes and verbal learning and memory. Schizophrenia is suspected to have early neurodevelopmental origins, which later manifest through disrupted neuromaturational processes (Walker & Bollini, 2002). Accordingly, a considerable amount of research has focused on the exploration of neuro-developmental trajectories of cortical brain volumes. However, only few studies have investigated the associations between subcortical brain

volumes and neurocognitive functioning, i.e. verbal learning and memory in particular, in patients with schizophrenia. Hence, to date and to the best of our knowledge there have been no studies comparing these associations directly in an antipsychotic-naïve sample of ARMS and FEP patients. While we could not demonstrate any significant associations of subcortical gray matter volumes with verbal learning and memory in ARMS and FEP patients that withstood statistical correction for multiple testing, Juuhl-Langseth *et al.* (2015), investigating verbal learning performance in 24 early onset schizophrenia (EOS) patients and 33 HC, found that an enlargement of the caudate was related to poorer verbal learning performance in patients with EOS. Another study (Hartberg *et al.*, 2011) reported significant relationships between larger bilateral putamen volumes and poorer performance on verbal learning, working memory and set-shifting in 117 schizophrenia patients. Furthermore, a previous study by Lappin *et al.* (2014) found bilateral hippocampal increases to be associated with superior verbal recall in FEP patients whereas Hurlemann *et al.* (2008) reported bilaterally reduced hippocampus volume to be associated with poorer delayed recall performance in ARMS patients in the late prodromal state. Moreover, Knöchel *et al.* (2016) reported higher bilateral thalamus volume in schizophrenia patients when compared to HC, which was associated with lower verbal learning performance in schizophrenia patients.

However, all of these studies compared their patient samples with (matched) HC or, in two cases (Hartberg *et al.*, 2011; Knöchel *et al.*, 2016), with a sample of bipolar spectrum disorder patients but not directly with a sample of patients at clinical high risk for psychosis. Additionally, only three studies (Hurlemann *et al.*, 2008; Hartberg *et al.*, 2011; Knöchel *et al.*, 2016) applied correction for multiple comparisons to their analyses. Not controlling for multiple comparisons might have led to increased Type I errors in the other studies.

Limitations and Strengths

The following limitations should be considered regarding this study.

First, we applied statistical correction for multiple comparisons to preclude false-positive findings. However, since this may have caused type II errors we also report unadjusted *p* values in our tables. Second, even though we had maximized statistical power by using structural equation modelling, it might be that differences in subcortical volumes in relation to verbal learning and memory performance between ARMS and FEP patients are too small to reach significance with our modest sample size. Furthermore, only data of 12 ARMS with transition, i.e. “true” patients at risk, were available. Third, the cross-sectional nature of this study has to

be taken into consideration. It may be that subtle differences that only evolve over time could not be detected by our analyses. Thus, future analyses should focus on longitudinal data to assess such gradually emerging changes.
Fourth, we investigated the association of verbal learning and memory with subcortical volumes using structural MRI. However, a multimodal approach including structural and functional MRI and/or EEG could have provided further useful insights. Multimodal approaches are required in future studies investigating neurocognitive and brain structural and functional alterations predating the onset of psychosis. Furthermore, future studies should focus on analyses of longitudinal data of ARMS patients, who transition to psychosis and correlate the development of subcortical volumes with neurocognitive performance.

A strength of this study was that we analysed subcortical volumes in antipsychotic-naïve ARMS and FEP patients, whereas most existing studies focused on brain structural differences between ARMS patients and healthy controls (HC) or HC and FEP patients, which were usually not antipsychotic free. We investigated antipsychotic-naïve patients and could therefore preclude the influence of any antipsychotic medication on the subcortical volumes in ARMS and FEP patients. Furthermore, we used standardized protocols provided by the ENIGMA consortium to process and segment our MRI data thereby making our results comparable with those of other studies.

Conclusion

Although we found statistically significant group differences between ARMS and FEP patients in subcortical volumes, we could not demonstrate any associations between verbal learning and memory and subcortical volumes after statistical correction for multiple testing. Thus, we conclude that impairments in verbal learning and memory do not stem from alterations in subcortical regions.

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These institutions had no further role in the study design; collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the paper for publication.

Competing Interests

None.

Author Contributions

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

Data Accessibility Statement

Owing to ethical concerns, supporting information cannot be made openly available. However, interested researchers may request the data from this study by contacting the Center for Gender Research and Early Detection at info@fepsy.

Abbreviations

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
AS	Attention Span
BPRS	Brief Psychiatric Rating Scale
BSIP	Basel Screening Instrument for Psychosis
CFA	Confirmatory Factors Analysis
CSF	Cerebrospinal Fluid
CVLT	California Verbal Learning Test
DM	Delayed Memory
EKNZ	Ethics Committee northwest/central Switzerland
EOS	Early Onset Schizophrenia
FEP	First Episode Psychosis
FePsy	***F***rüh***e***rkennung von ***Psy***chosen
FSL	FMRIB Software Library
GM	Gray Matter
HC	Healthy Controls
IM	Inaccurate Memory
MIMIC	Multiple-Indicator Multiple-Causes
MNI	Montreal Neurological Institute
MPRAGE	Magnetisation Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
PACE	Personal Assessment and Crisis Evaluation
VLM	Verbal Learning and Memory
WM	White Matter

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Tables

Table 1: Sociodemographic sample characteristics

	ARMS N=59	FEP N=31	*p*-value
Age	25.0 ± 6.01	27.3 ± 6.02	0.092 [1]
Gender:			0.506 [2]
Women	12 (20.3%)	9 (29.0%)	
Men	47 (79.7%)	22 (71.0%)	
Years of education	12.4 ± 2.63	12.0 ± 3.05	0.530 [1]
Antidepressants currently	18 (30.5%)	7 (22.6%)	0.582 [2]
Anxiolytics currently	8 (13.6%)	3 (9.68%)	0.742 [2]
Current cannabis use:			1.000 [3]
none	42 (75.0%)	23 (76.7%)	
rarely	3 (5.36%)	2 (6.67%)	
several times per month	1 (1.79%)	0 (0.00%)	
several times per week	7 (12.5%)	4 (13.3%)	
daily	3 (5.36%)	1 (3.33%)	
BPRS total score	37.9 ± 9.31	50.3 ± 11.4	<0.001*** [1]

Note. N is the number of non-missing values. Values of continuous variables are stated as mean ± 1 standard deviation. All other variables are given in total numbers and percentages in parentheses. [1] Welch Two Sample t-test; [2] Pearson's χ^2 test; [3] Proportional odds likelihood ratio test. BPRS = Brief Psychiatric Rating Scale. ARMS = patients with an at-risk mental state for psychosis; FEP = patients with a first episode of psychosis.

Table 2. Results from the linear regression model in the antipsychotic-naïve sample

	B	*SE B*	*t* value	*p*-value	*p*-value corrected
Accumbens	0.171	0.211	0.809	0.421	0.421
Amygdala	0.296	0.191	1.551	0.125	0.146
Caudate	0.304	0.184	1.655	0.102	0.143
Hippocampus	0.404	0.181	2.236	0.028*	0.049*
Pallidum	0.403	0.180	2.239	0.028*	0.049*
Putamen	0.430	0.180	2.395	0.019*	0.049*
Thalamus	0.413	0.176	2.346	0.021*	0.049*

Note. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. *p*-values were adjusted for multiple comparisons using the Benjamini Hochberg procedure.

Table 3. Results from the four factor multiple-indicator multiple-causes (MIMIC) model for the antipsychotic-naïve sample

	Attention Span		Learning Efficiency		Delayed Memory		Inaccurate Memory	
	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value	Estimate (S.E.)	*p*-value
Subcortical Structures								
Accumbens	0.102 (0.103)	0.322	0.029 (0.086)	0.741	0.084 (0.087)	0.339	-0.188 (0.147)	0.201
Amygdala	-0.294 (0.148)	0.047*	-0.109 (0.111)	0.327	-0.038 (0.113)	0.736	0.197 (0.119)	0.098
Caudate	0.099 (0.129)	0.441	0.006 (0.127)	0.965	0.047 (0.114)	0.680	0.149 (0.158)	0.344
Hippocampus	0.118 (0.134)	0.379	0.025 (0.096)	0.799	0.073 (0.100)	0.461	0.126 (0.109)	0.250
Pallidum	0.398 (0.130)	0.002**	0.100 (0.121)	0.408	0.178 (0.108)	0.101	0.058 (0.144)	0.690
Putamen	0.169 (0.119)	0.154	-0.103 (0.096)	0.281	0.071 (0.101)	0.486	0.115 (0.132)	0.386
Thalamus	0.070 (0.130)	0.588	-0.027 (0.100)	0.788	0.075 (0.108)	0.485	0.007 (0.114)	0.949
Interaction Effects (Group x Structure)								
Accumbens	0.308 (0.212)	0.147	0.033 (0.167)	0.845	0.052 (0.174)	0.766	-0.134 (0.267)	0.616
Amygdala	-0.112 (0.305)	0.713	-0.001 (0.220)	0.996	-0.058 (0.228)	0.799	0.008 (0.255)	0.975
Caudate	0.092 (0.257)	0.720	-0.088 (0.243)	0.717	-0.159 (0.227)	0.484	0.692 (0.388)	0.074
Hippocampus	0.747 (0.243)	0.002**	0.202 (0.202)	0.316	0.215 (0.192)	0.263	0.498 (0.212)	0.019*
Pallidum	0.192 (0.280)	0.492	-0.269 (0.231)	0.245	-0.213 (0.214)	0.320	0.420 (0.313)	0.181
Putamen	-0.105 (0.248)	0.673	-0.400 (0.188)	0.033*	-0.444 (0.184)	0.016*	0.358 (0.273)	0.190
Thalamus	0.546 (0.255)	0.032*	0.033 (0.210)	0.875	0.125 (0.212)	0.555	0.170 (0.233)	0.465

Note. S.E. = Standard Error. Level of significance for *p*-values: *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. ARMS = patients with an at-risk mental state for psychosis; FEP = patients with a first episode of psychosis. *p*-values are uncorrected for multiple testing.

Supplementary Table 1. CVLT variables contributing to the latent factor model

	Factors			
CVLT variables	Attention Span	Learning Efficiency	Delayed Memory	Inaccurate Recall
List A, Trial 1	*			
List B	*			
Middle Region Recall	*			
List A, Trial 5		*		
Semantic Clustering		*		
Recall Consistency		*		
Short-delay Free Recall			*	
Short-delay Cued Recall			*	
Long-delay Free Recall			*	
Long-delay Cued Recall			*	
Recognition Hits			*	
Total Intrusions				*
Recognition False Positives				*

Note. CVLT = California Verbal Learning Test

Figure Legend

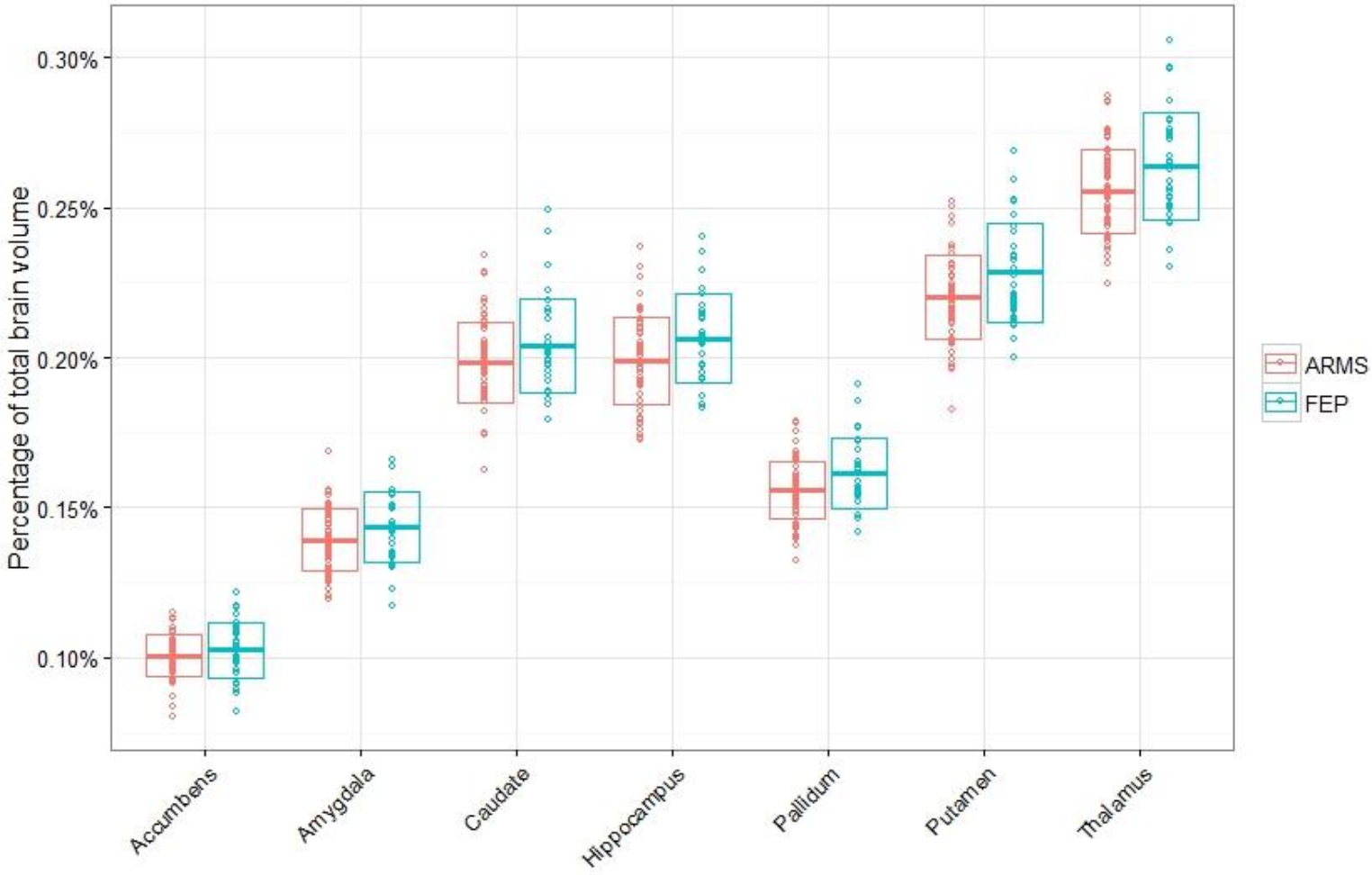

Figure 1. Visualisation of subcortical brain volumes per group. The crossbar indicates the mean of the group, the box indicates the range of ± 1 standard deviation. ARMS = patients with an at-risk mental state for psychosis; FEP = patients with a first episode of psychosis.

Appendix C: Article 3

Egloff, L., Lenz, C., Studerus, E., Harrisberger, F., Smieskova, R., Schmidt, A., Huber, C., Simon, A., Lang, U.E., Riecher-Rössler, A., Borgwardt, S. (2018). Sexually dimorphic subcortical brain volumes in emerging psychosis. *Schizophrenia Research*. doi: 10.1016/j.schres.2018.03.034

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Sexually dimorphic subcortical brain volumes in emerging psychosis

Laura Egloff [a,b], Claudia Lenz [c], Erich Studerus [a], Fabienne Harrisberger [a], Renata Smieskova [a], André Schmidt [a], Christian Huber [a], Andor Simon [d,e], Undine E. Lang [a], Anita Riecher-Rössler [a], Stefan Borgwardt [a,*]

[a] University of Basel Psychiatric Hospital, Department of Psychiatry, Basel, Switzerland
[b] University of Basel, Department of Psychology, Division of Clinical Psychology and Epidemiology, Basel, Switzerland
[c] University of Basel, Institute of Forensic Medicine, Basel, Switzerland
[d] University Hospital of Bern, University Hospital of Psychiatry, Bern, Switzerland
[e] Specialized Early Psychosis Outpatient Service for Adolescents and Young Adults, Department of Psychiatry, Bruderholz, Switzerland

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ABSTRACT

Background: In schizophrenic psychoses, the normal sexual dimorphism of the brain has been shown to be disrupted or even reversed. Little is known, however, at what time point in emerging psychosis this occurs. We have therefore examined, if these alterations are already present in the at-risk mental state (ARMS) for psychosis and in first episode psychosis (FEP) patients.
Methods: Data from 65 ARMS (48 (73.8%) male; age = 25.1 ± 6.32) and 50 FEP (37 (74%) male; age = 27 ± 6.56) patients were compared to those of 70 healthy controls (HC; 27 (38.6%) male; age = 26 ± 4.97). Structural T1-weighted images were acquired using a 3 Tesla magnetic resonance imaging (MRI) scanner. Linear mixed effects models were used to investigate whether subcortical brain volumes are dependent on sex.
Results: We found men to have larger total brain volumes ($p < 0.001$), and smaller bilateral caudate ($p = 0.008$) and hippocampus volume ($p < 0.001$) than women across all three groups. Older subjects had more GM and WM volume than younger subjects. No significant sex × group interaction was found.
Conclusions: In emerging psychosis there still seem to exist patterns of normal sexual dimorphism in total brain and caudate volume. The only structure affected by reversed sexual dimorphism was the hippocampus, with women showing larger volumes than men even in HC. Thus, we conclude that subcortical volumes may not be primarily affected by disrupted sexual dimorphism in emerging psychosis.

1. Introduction

Schizophrenic psychoses are potentially severe mental disorders, affecting approximately 0.48% of the population worldwide (Simeone et al., 2015) and typically emerging in late adolescence or early adulthood (Häfner et al., 1992; Riecher-Rössler et al., 2007). They are associated with structural changes in the brain (Bora et al., 2011a; Dukart et al., 2017; Schmidt et al., 2017), cognitive impairments (Bora and Pantelis, 2015; Bora et al., 2010) as well as positive (i.e., delusions, hallucinations (Häfner et al., 1992)) and negative (i.e., alogia, social withdrawal (Carbon and Correll, 2014)) symptoms. To prevent poor outcome in patients at risk for psychosis it is important to detect these patients as early as possible. The identification of so-called at-risk mental state (ARMS) patients based on clinical signs (Yung et al., 1998; Yung et al., 2004) is a promising approach (Kim et al., 2011; Riecher-Rössler et al., 2009; Riecher-Rössler and Studerus, 2017). ARMS patients experience an increased risk for developing psychosis, with a transition rate of about 32% within 3 years after initial presentation (Fusar-Poli et al., 2012a). Although many factors have been associated with the risk of transition to psychosis (i.e., impaired cognitive functioning (Bora et al., 2014; Fusar-Poli et al., 2012b; Hauser et al., 2017), brain structural alterations (Fusar-Poli et al., 2012c); for review see (Riecher-Rössler and Studerus (2017); Studerus et al. (2016)) it is still not possible to reach sufficient accuracy in the calculated prediction of psychosis. Apart from methodological problems (Studerus et al., 2017), one of the factors contributing to this may be the different disease trajectories male and female patients experience.

Sex differences in age of onset (Eranti et al., 2013; Häfner et al., 1991), clinical course (Walker et al., 2002) and functional impairment (Thorup et al., 2007) are well documented in schizophrenia. Men have a higher incidence (1.15-fold greater) than women (van der Werf et al., 2014) but there are no sex differences in prevalence (McGrath et al., 2008). Female onset is typically later, with a second peak post-menopause (Falkenburg and Tracy, 2014; Häfner et al., 1992). Some report men to show more negative but less depressive symptoms (Abel et al., 2010; Ochoa et al., 2012) and have a poorer prognosis than women

* Corresponding author at: Department of Psychiatry, University of Basel Psychiatric Hospital (UPK), Wilhelm Klein-Strasse 27, 4012 Basel, Switzerland.
E-mail address: Stefan.Borgwardt@upkbs.ch (S. Borgwardt).

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(Walder et al., 2013), whereas positive symptoms differ in content between sexes (Falkenburg and Tracy, 2014). Furthermore, women seem to have a better response to antipsychotics (Crawford and DeLisi, 2016; Riecher-Rössler and Häfner, 1993; Riecher-Rössler and Kulkarni, 2010).

A recent review on sex differences in ARMS reported male ARMS patients to present with more negative symptoms, worse social functioning and longer duration of untreated illness (Barajas et al., 2015). Furthermore, several studies reported neurocognitive impairments to differ between sexes, with female patients performing better especially on verbal tasks and male patients performing better on selective/working memory tasks (Ittig et al., 2015; Walder et al., 2008; Walder et al., 2015). Brain structural alterations are already evident in ARMS patients, before the first psychotic symptoms emerge (Dazzan et al., 2015) and include gray and white matter volume reductions of prefrontal (Cannon, 2015; Smieskova et al., 2013), temporal (Fusar-Poli et al., 2014; Smieskova et al., 2013) and cingulate cortices (Fusar-Poli et al., 2012c; Fusar-Poli et al., 2014; Smieskova et al., 2013), parahippocampal gyrus and hippocampus (Fusar-Poli et al., 2012c), and caudate (Smieskova et al., 2013). However, all of the aforementioned structural alterations in ARMS have not been investigated with a specific focus on sex differences. Sex, or in meta-analyses the gender ratio, was usually incorporated as covariate, thereby controlling for its potential influence. Nevertheless, one recent study (Savadjiev et al., 2016) found a reversal of the normal sexual dimorphism in white matter geometry of the corpus callosum in a sample of 35 subjects at familial high risk for psychosis compared to HC.

However, several methodological limitations (e.g., sampling bias, gender differences in help-seeking, diagnostic differences across studies regarding the at-risk state, or medication status (Crawford and DeLisi, 2016) make it difficult to generalise the results.

Results from structural studies showed that healthy men have larger white matter volumes than women (Paus et al., 2010), whereas women have a higher percentage of gray matter (Cosgrove et al., 2007) and present with a larger gray matter-white matter ratio than men (Sacher et al., 2013). Furthermore, males have larger total brain (Cosgrove et al., 2007) and intracranial volume (Tan et al., 2016) than females across all ages (Giedd et al., 2012). Brain structures affected by sex in healthy subjects are white matter volumes of the corpus callosum (Ardekani et al., 2013; Sacher et al., 2013) and cingulate cortex (Sacher et al., 2013), as well as gray matter volumes of the caudate nucleus and hippocampus (all structures lager in women than in men) and amygdala (Giedd et al., 2012) and cerebellum (Giedd et al., 2012; Wang et al., 2012) (both smaller in women than in men). These structural differences in healthy men and women are also referred to as sexual dimorphism, a term which we will further employ in this study.

Disrupted patterns of normal morphological sexual dimorphism in schizophrenia have been found for volumes of amygdala (Gur et al., 2004; Gur et al., 2000b; Takayanagi et al., 2011), hippocampus (Irle et al., 2011), hypothalamus (Goldstein et al., 2007), as well as orbitofrontal (Gur et al., 2000a), anterior cingulate (Goldstein et al., 2002; Takahashi et al., 2002), and insular cortex (Duggal et al., 2005). Furthermore, evidence for a disrupted sexual dimorphism has been found for asymmetry, which refers to neuroanatomical differences between the left and right hemisphere of the brain, of gray matter volume in the inferior parietal lobe (Frederikse et al., 2000), in the white matter geometry of the torque (i.e., female brains were more asymmetric than males whereas in HC male brains tend to be more asymmetric than female brains (Savadjiev et al., 2014)), in the gyrification index (Vogeley et al., 2000), and in the cortical folding of the right superior frontal cortex (Narr et al., 2004).

Especially in the field of neuroanatomical studies, sexual dimorphism in brain structure and particularly subcortical volumes of ARMS patients has largely been neglected, even though evidence for a disruption of normal sexual dimorphism in schizophrenia is given (Falkenburg and Tracy, 2014; Riecher-Rössler et al., 2010; Walder et al., 2015). Thus, the aim of the present study was to investigate the influence of sex on subcortical brain volumes (i.e., amygdala, accumbens, caudate, hippocampus, pallidum, putamen, and thalamus) in ARMS patients and compare those to FEP patients and HC. Based on the existing literature on sexual dimorphism in HC and Schizophrenia, we hypothesized that 1) normal sexual dimorphism will be found in HC; 2) sexual dimorphism as found in HC is no longer present in FEP patients; 3) ARMS patients show patterns of diminished sexual dimorphism, but not to the same extent as in FEP patients.

2. Materials and methods

2.1. Setting and recruitment

All data analysed in this study were collected by the specialized "Früherkennung von Psychosen" (FePsy) clinic at the University of Basel Psychiatric Hospital, Basel, Switzerland. A more detailed description of the overall study design can be found elsewhere (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009). Patients were recruited between July 2008 and May 2016 and included if they had complete 3 Tesla MRI data. The HC were gathered from the same geographical area as the patient groups and recruited via hospital staff and online advertisement. They were only included into the study if they had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical assessment (Smieskova et al., 2012a,b). The study was approved by the Ethics Committee northwest/central Switzerland (EKNZ). All participants provided written informed consent.

2.2. Screening procedure

The ARMS and FEP status was assessed using the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008) which is based on the Personal Assessment and Crisis Evaluation (PACE) criteria by Yung et al. (1998). Inclusion required one of the following: a) attenuated psychotic-like symptoms (APS), b) brief limited intermittent psychotic symptoms (BLIPS), c) a first or second degree relative with a psychotic disorder in combination with at least two further risk factors similar to the PACE criteria (Yung et al., 1998) or d) a minimal amount and combination of certain risk factors according to the BSIP (Riecher-Rössler et al., 2008) (see Table 1). All ARMS patients were followed-up at regular intervals (monthly during the first year after initial presentation, quarterly during the second and third year, and annually thereafter) to distinguish those ARMS patients with later transition to psychosis (ARMS-T) from those who did not transition (ARMS-NT). Exclusion criteria were age <18 years, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis (treated with antipsychotics for >3 weeks (lifetime) and/or a total lifetime chlorpromazine equivalent (CPE) dose of 2500 mg), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder.

2.3. Psychopathological assessment

Positive psychotic symptoms (i.e., hallucinations, suspiciousness, unusual thought content and conceptual disorganisation) were assessed with the Brief Psychiatric Rating Scale Expanded Version (BPRS-E) (Lukoff et al., 1986; Velligan et al., 2005; Ventura et al., 1993).

2.4. Image acquisition

Structural images were acquired using a 3 Tesla magnetic resonance imaging (MRI) scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 12-channel phased-array radio frequency

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Table 1
Inclusion criteria for at-risk mental state or first episode psychosis patients in the *FePsy* project.

At-risk mental state (ARMS)	**A) "Attenuated"psychotic symptoms (APS)** Psychotic symptoms below transition cut off (BPRS scales: hallucinations 2–3, unusual thought content 3–4, suspiciousness 3–4) at least several times per week, in total persisting for >1 week) OR **Brief limited intermittent psychotic symptoms (BLIPS)** Psychotic symptoms over transition cut-off (BPRS scales: hallucinations ≥4, unusual thought content ≥5, suspiciousness ≥5, conceptual disorganisation ≥5) but each symptom <1 week before resolving spontaneously **B) Genetic risk category** First or second degree relative with psychotic disorder and at least two further risk factors according to screening instrument (BSIP) **C) Unspecific risk category** Minimal amount and combination of certain risk factors according to screening instrument. (BSIP) Precondition for all categories: criteria of transition to psychosis not fulfilled.
First episode psychosis (FEP)	• 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 (incidents 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 three to five instances of incoherent phrases). • Symptoms at least several times a week. • Change in mental state lasting >1 week.

Note. Criteria A) and B) correspond to those of Yung et al. (1998). Criterium C) additionally permits the inclusion of individuals at lower risk, i.e., of patients without pre-psychotic symptoms or genetic risk who only exhibit a combination of certain unspecific risk factors and indicators such as prodromal symptoms or marked social decline (unspecific risk group). Patients with first-episode psychosis (FEP) are those who at intake already fulfil the criteria for transition to psychosis as defined by Yung et al. (1998).

head coil at the University Hospital Basel. Participants were given earplugs and noise-cancellation headphones. Foam pads on each side of the headphones were used to minimise head motion during the scans. A 3D T1-weighted magnetisation prepared rapid gradient echo (MPRAGE) sequence was used with the following parameters: inversion time = 1000 ms, flip angle = 8°, TR = 2 s, TE = 3.37 ms, bandwidth = 200 Hz/pixel, FOV = 256 × 256 mm^2, acquisition matrix = 256 × 256 × 176, resulting in 176 contiguous sagittal slices with 1 × 1 × 1 mm^3 whole-brain isotropic spatial resolution.

All scans were screened for gross radiological abnormalities by resident neuroradiologists.

2.5. Image processing

All image processing steps were conducted according to the "ENIGMA1 - GWAS Meta Analysis of Hippocampal, Intracranial and Total Brain Volume" guidelines (http://enigma.ini.usc.edu/) using the FMRIB software library (FSL) 5.0 (Jenkinson et al., 2012) running on Ubuntu version 16.04. Volumetric segmentation of subcortical structures was estimated on the whole-brain T1-weighted data sets by applying the FMRIB's Integrated Registration and Segmentation Tool (FSL-FIRST) (Patenaude et al., 2011). Furthermore, in order to extract the different brain tissue volumes for normalisation purposes, all images were skull stripped using FSL-BET (Smith, 2002), aligned to the Montreal Neurological Institute (MNI) 152 FSL standard brain using FSL-FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001) and segmented into white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) using FSL-FAST (Zhang et al., 2001). The resulting brain tissue volumes could then be calculated according to the results from the FSL-FAST partial volume maps and the total brain volume was extracted according to the sum of WM, GM and CSF.

2.6. Image quality assessment

First, all data sets were checked for overall quality, coverage of whole brain, contrast between WM and GM and presence of noise and artifacts. Second, to check the whole brain volume, all skull stripping files were controlled to ensure that the whole brain images were cropped correctly. In a further step, the alignment of each brain image was controlled with regard to the reference brain (MNI 152 sample). Third, all segmentation files were controlled for the alignment of the subcortical volumes. Fourth, all volumes were plotted for each subject individually to detect outliers. In case of successful fulfillment of the quality assessment steps the volumetric data were included for statistical analyses (see Table 2 for information on the volumes of each subcortical structure under investigation).

The following exclusion criteria were fulfilled and led to a removal of data sets before further analyses: motion artifacts (N = 6), shift of the interhemispheric fissure (N = 1), incorrect skull stripping (N = 1), and abnormal inclination of head (N = 1).

2.7. Statistical analyses

All analyses were conducted using the R environment for statistical computing, R version 3.4.0 (R Core Team, 2016). Sex, use of antipsychotics, antidepressants, and anxiolytics were compared between groups with Pearson's chi-square tests. Age and years of education were compared with ANOVA. Current use of cannabis was analysed using Fisher's Exact test and BPRS total score was compared with independent *t*-test. For ease of interpretation of the brain structural volumes the following steps were applied: 1) the cube root was taken, 2) volumes were normalised to the individual whole brain volume by dividing them by the total brain volume, 3) volumes were centred and scaled (i.e., z-transformed).

To analyse group and sex differences in total brain, GM and WM volume, we used multiple linear regression models. For each volume, a linear regression model was fitted that included the brain structural volume as dependent variable and group, sex, and age as independent variables. Additionally, the models included an interaction term between group and sex.

Since all subcortical structures were measured bilaterally we analysed them with linear mixed effects models (LME) using the lme4 package in R (Bates et al., 2015). For each subcortical structure an LME model was fitted including the volume as dependent variable and sex, group, hemisphere, and age as independent variables. Additionally, the models included all possible interaction terms between sex, group, and hemisphere and a per subject randomly varying intercept. Significance values of the LME models where estimated using the Kenward

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Table 2
Raw values of subcortical volumes by group and sex.

	ARMS		ARMS-NT		ARMS-T		FEP		HC	
	Women (n = 17)	Men (n = 48)	Women (n = 7)	Men (n = 30)	Women (n = 8)	Men (n = 10)	Women (n = 13)	Men (n = 37)	Women (n = 43)	Men (n = 27)
Accumbens										
Left	513.18	586.38	504	596.1	501.75	546.7	497.39	553.95	518.48	517.98
	(81.67)	(119.86)	(80.79)	(121.88)	(74.33)	(113.25)	(98.32)	(100.18)	(106.08)	(108.46)
Right	400.24	459.56	382	474.67	404.875	389.7	424.23	432	414.19	442.39
	(76.09)	(103.03)	(97.11)	(93.11)	(48.53)	(124.48)	(92.86)	(91.04)	(106.17)	(117.66)
Amygdala										
Left	1188.35	1293.67	1120.57	1273.2	1198.16	1363.5	1164.39	1281.62	1205.25	1280.95
	(209.48)	(231.19)	(137.78)	(219.42)	(256.95)	(271.62)	(229.40)	(225.31)	(218.74)	(394.43)
Right	1260.29	1396.94	1269.43	1392.63	1218.25	1400.6	1178.92	1318.22	1243.15	1391.24
	(276.51)	(265.98)	(244.35)	(291.86)	(340.29)	(267.91)	(208.20)	(237.86)	(244.98)	(299.70)
Caudate										
Left	3590.94	3880.50	3640	3923.63	3502.38	3765	3456.85	3745.16	3523.81	3637.52
	(393.14)	(317.55)	(497.79)	(310.65)	(346.38)	(342.01)	(455.74)	(431.35)	(440.08)	(550.33)
Right	3618.65	3946.08	3628.86	4004.27	3556.38	3739.3	3498.08	3757.32	3598.79	3617.25
	(418.98)	(352.21)	(538.75)	(294.77)	(365.62)	(494.63)	(412.95)	(424.60)	(477.66)	(651.94)
Hippocampus										
left	3592.35	3852.21	3568.86	3825.1	3527.25	3840.1	3538.85	3869.68	3686.30	3714.65
	(369.07)	(373.14)	(501.71)	(419.45)	(232.52)	(337.86)	(378.92)	(388.78)	(543.44)	(590.57)
right	3677.06	3889.71	3628	3950.03	3654.38	3843.9	3579.92	3975.51	3799.73	3855.21
	(393.13)	(499.49)	(455.94)	(505.87)	(390.04)	(293.67)	(430.97)	(398.38)	(433.10)	(415.49)
Pallidum										
Left	1655.53	1909.58	1653.29	1922.43	1688.38	1913.7	1693.85	1881.16	1704.04	1865.66
	(185.87)	(248.67)	(229.66)	(175.51)	(158.32)	(460.47)	(138.55)	(167.37)	(172.42)	(204.26)
Right	1689.06	1907.46	1669.72	1938	1712.25	1838.3	1713.15	1907.77	1709.99	1860.48
	(154.29)	(166.62)	(176.75)	(160.57)	(157.11)	(217.62)	(131.19)	(155.82)	(178.06)	(220.95)
Putamen										
Left	4756.47	5286.04	4793.14	5382.4	4772.38	5163.8	4692.54	5315.54	4759.85	5194.97
	(550.42)	(496.23)	(844.15)	(521.68)	(255.42)	(478.84)	(441.77)	(466.95)	(441.19)	(426.13)
Right	4924.77	5404.33	4966	5521.27	4883.75	5254.9	4852.77	5408.84	4796.01	5274.75
	(514.47)	(502.84)	(751.76)	(499.26)	(339.04)	(536.85)	(499.22)	(450.14)	(377.90)	(421.76)
Thalamus										
Left	7495.88	8526.98	7398.43	8641.07	7568.25	8335.3	7560.31	8389.73	7863.42	8318.18
	(473.75)	(636.27)	(512.03)	(692.71)	(464.85)	(580.43)	(517.50)	(687.11)	(744.65)	(696.20)
Right	7199.06	8268.38	7112	8366.47	7304	8047.1	7311.92	8258.95	7757.16	8185.48
	(464.68)	(623.79)	(440.73)	(674.73)	(457.84)	(546.61)	(495.16)	(648.33)	(709.19)	(709.26)

Note. Values are given in mean ± 1 standard deviation in parentheses. Volumes are presented as raw values in mm^3.

Roger modification of F-tests (Halekoh and Højsgaard, 2014; Kenward and Roger, 1997) for LME using the ANOVA function of the car package (Fox and Weisberg, 2011) in R with the option test.statistic = "F" and type III sums of squares (Supplementary File 1 shows the R code in detail).

In case of significant interaction effects, post-hoc analyses were conducted within each diagnostic group separately.

P-values were corrected for multiple testing across all tested brain structures using the false discovery rate (Benjamini and Hochberg, 1995).

3. Results

In total, 65 ARMS and 50 FEP patients fulfilled the inclusion criteria (see Table 3 for sociodemographic and clinical sample characteristics) and were compared to 70 HC. In the HC group there were significantly more women than in the ARMS and FEP groups. Compared to ARMS patients, FEP patients showed a significantly higher total score on the Brief Psychiatric Rating Scale (BPRS). While ARMS hardly had any intake of antipsychotic medication, some FEP patients had taken antipsychotics for a short time period (cumulative CPE dose < 2500 mg). Furthermore, both ARMS and FEP patients had significantly less years of education compared to HC.

When comparing women against men across all groups, women showed significantly more years of education than men (see Table 3). On all other variables no significant sex differences were found.

Men had significantly larger total brain volume ($p < 0.001$) and smaller caudate ($p = 0.008$) and hippocampus ($p < 0.001$) volumes than women. There were no interactions between sex and hemisphere and sex and group, indicating that these sex differences were independent of hemisphere and diagnostic group (see Supplementary Table 1).

Brain volumes did not differ between diagnostic groups. However, there was a significant interaction between group × hemisphere for the dependent variable thalamus volume ($p = 0.016$). Analyses of simple main effects revealed that this was due to significantly larger left than right thalamus volumes in HC ($F(1, 69) = 5.3887$, $p = 0.023$) and significantly larger left than right thalamus volumes in ARMS patients ($F(1, 64) = 8.6831$, $p = 0.005$) (see Fig. 1.A). When further investigating the subgroups of ARMS with (ARMS-T; mean follow-up duration = 1.36 ± 1.45 years; min = 0.08 years) and without later transition to psychosis (ARMS-NT; mean follow-up duration = 3.94 ± 0.97 years; min = 2.13 years), there was no main effect of sex and no significant interaction between sex and group. However, both ARMS-NT ($F(1, 36) = 4.5109$, $p = 0.041$) and ARMS-T ($F(1, 17) = 4.5008$, $p = 0.049$) patients had significantly larger left and smaller right thalamus (see Fig. 1.B).

Age was significantly positively associated with GM and WM volumes (both $p < 0.001$).

All of the above reported results did not change when subjects with current antipsychotic medication were excluded. Results also remained stable for the main effects when analyses of subgroups ARMS-NT and ARMS-T were conducted (for whole and antipsychotic-naïve sample).

4. Discussion

We found normal sexual dimorphism of total brain and bilateral caudate volume across all groups. Reversed sexual dimorphism was found for bilateral hippocampus volume, again across all three groups. In

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Table 3
Sociodemographic sample characteristics.

	ARMS	FEP	HC	*p*-value[a]	ARMS-NT	ARMS-T	*p*-value[b]	Women	Men	*p*-Value
	N = 65	N = 50	N = 70		N = 37	N = 18		N = 73	N = 112	
Age	25.1 ± 6.32	27.0 ± 6.56	26.0 ± 4.97	0.238[c]	25.0 ± 6.65	25.8 ± 6.84	0.496[c]	25.8 ± 5.78	26.1 ± 6.05	0.662[c]
Sex:				<0.001***[d]			<0.001***[d]			
Women	17 (26.2%)	13 (26.0%)	43 (61.4%)		7 (18.9%)	8 (44.4%)				
Men	48 (73.8%)	37 (74.0%)	27 (38.6%)		30 (81.1%)	10 (55.6%)				
Years of education	12.5 ± 2.73	11.8 ± 2.88	15.5 ± 2.67	<0.001***[c]	13.0 ± 2.86	11.4 ± 2.15	<0.001***[c]	14.3 ± 2.95	12.9 ± 3.20	0.004**[c]
Antipsychotics currently	1 (1.75%)	14 (31.1%)		<0.001***[d]	0 (0.0%)	0 (0.0%)	<0.001***[d]	5 (18.5%)	10 (13.3%)	0.535[d]
Antidepressants currently	24 (42.1%)	11 (24.4%)		0.098[d]	15 (41.7%)	6 (50.0%)	0.127[d]	11 (40.7%)	24 (32.0%)	0.559[d]
Anxiolytics currently	7 (12.3%)	8 (17.8%)		0.619[d]	3 (8.33%)	2 (16.7%)	0.494[d]	6 (22.2%)	9 (12.0%)	0.215[d]
Cannabis use currently:				0.822[e]			0.389[e]			0.482[e]
None	42 (75.0%)	36 (76.6%)			27 (79.4%)	10 (71.4%)		23 (88.5%)	55 (71.4%)	
Rarely	5 (8.93%)	2 (4.26%)			3 (8.82%)	1 (7.14%)		0 (0.0%)	7 (9.09%)	
Several times per month	1 (1.79%)	0 (0.0%)			0 (0.0%)	1 (7.14%)		0 (0.0%)	1 (1.30%)	
Several times per week	5 (8.93%)	5 (10.6%)			3 (8.82%)	0 (0.0%)		2 (7.69%)	8 (10.4%)	
Daily	3 (5.36%)	4 (8.51%)			1 (2.94%)	2 (14.3%)		1 (3.85%)	6 (7.79%)	
BPRS total score	39.9 ± 9.74	52.6 ± 12.0		<0.001***[f]	39.0 ± 10.3	42.9 ± 9.56	<0.001***[f]	44.2 ± 11.2	45.9 ± 12.9	0.500[f]

Note. Values of continuous variables are stated as mean ± 1 standard deviation. ARMS = patients with an at-risk mental state for psychosis; FEP = patients with a first episode of psychosis; HC = healthy controls; ARMS-NT = patients with an at-risk mental state for psychosis without later transition to psychosis; ARMS-T = patients with an at-risk mental state for psychosis with later transition to psychosis.

[a] ARMS vs. FEP vs. HC.
[b] ARMS-NT vs. ARMS-T vs. FEP vs. HC.
[c] ANOVA.
[d] Pearson's χ^2 test.
[e] Fisher's Exact test.
[f] Independent *t*-test.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.

contrast to our hypothesis, we did not find evidence for disrupted sexual dimorphism in subcortical brain volumes in emerging psychosis. Moreover, our results indicate a significant effect of age, with higher GM and WM volumes in older compared to younger subjects. Unexpectedly, we did not find any group differences between HC and the patient groups.

Our finding of larger total brain volumes in men than in women is supported by a recent meta-analysis on sex differences in the healthy human brain (Ruigrok et al., 2014). The authors also reported men to have larger brain volumes than women. Thus, our results suggest that total brain volume remains sexually dimorphic even in emerging psychoses and may therefore not be useful to discriminate those subjects with subsequent transition to frank psychosis from those who won't transition to psychosis.

The observed main effect of sex regarding higher volumes of bilateral caudate in women compared to men are well in line with a review by Giedd et al. (2012) reporting proportionately larger caudate in women across different ages and different applied methodologies. Our results indicate that the caudate is well affected by sex but not by group, even though Smieskova et al. (2013) reported the caudate to be associated with prodromal symptoms in patients with a clinical high risk for psychosis. However, their review focused on longitudinal studies and we may not have found evidence for group differences due to the cross-sectional nature of this study. Another reason may be the differential conceptualizations of the at-risk state for psychosis leading to distinct study inclusion criteria regarding when the at-risk status is fulfilled and when not (i.e., in-/exclusion of unspecific symptoms; for overview see Fusar-Poli et al. (2013a)).

We found enlarged bilateral hippocampus volumes in women compared to men, which contradicts the meta-analysis of Ruigrok et al. (2014) reporting men to have larger GM volume in bilateral hippocampi. Our results even persisted, when the patient ($p < 0.002$) and the HC groups ($p < 0.005$) were investigated separately. However, Neufang et al. (2009) found in a sample of 46 males and 46 females aged 8–15 years that hippocampal size was larger in girls. Accordingly, Giedd et al. (1997) described in their study of 121 healthy children and adolescents hippocampal volume to increase for both sexes over time, but more in females than in males. This may probably be due to an increased amount of estrogen receptors in the hippocampus (Giedd et al., 1997; Sholl and Kim, 1989) as the hippocampus is, just as the caudate, a structure rich in sex steroid receptors (i.e., estrogen receptors) (Giedd et al., 2012; Morse et al., 1986). Some authors also reported that testosterone levels predicted hippocampal size in females, with larger hippocampus in younger females (Neufang et al., 2009).

Furthermore, the hippocampus is one of the stress response regions, which is regulated by the coordinated action of hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axis hormones (Goldstein et al., 2015). Hence, we may speculate that the observed pattern of sexual dimorphism across HC and emerging psychosis might be due to higher stress levels in men than in women, leading to a neuro-hormone deficit in the male hippocampus (Goldstein et al., 2015) and in consequence to a decreased volume. Conjunctly, early stressful life events such as childhood maltreatment may later manifest in enhanced stress sensitivity (Gorka et al., 2014; Lardinois et al., 2011) and hypo- or hypercortisolemia (Wieck et al., 2014) and have been reported to be associated with reduced hippocampus volume (Frodl and O'Keane, 2013) in healthy males, but not in females (Samplin et al., 2013).

Regarding the thalamus, we observed an interaction effect of group × hemisphere suggesting that ARMS patients have a significantly larger left and smaller right thalamus volume. When further investigating the ARMS group, and comparing those with (ARMS-T) and without (ARMS-NT) later transition to psychosis, results suggested that the significant between-group difference was due to both ARMS-NT and ARMS-T which had larger left and smaller right thalamus volumes. Even though ARMS-T and ARMS-NT patients showed a similar pattern of larger left than right thalamus volumes as HC, the difference between left and right hemisphere was significantly larger in ARMS than in HC. In a review of meta-analyses the authors found the thalamus to be the second most often reported structure to present with a patient (schizophrenia and bipolar disorder)-control difference (Crow et al., 2013). However, the findings on volumetric decreases in thalamus are somewhat inconsistent. Some studies reported higher volumetric decreases in the right thalamus (Ellison-Wright et al., 2008) or the left thalamus (Ellison-Wright and Bullmore, 2010), whereas others again reported bilateral volumetric loss (Bora et al., 2011b; Fornito et al., 2009; Glahn et al.,

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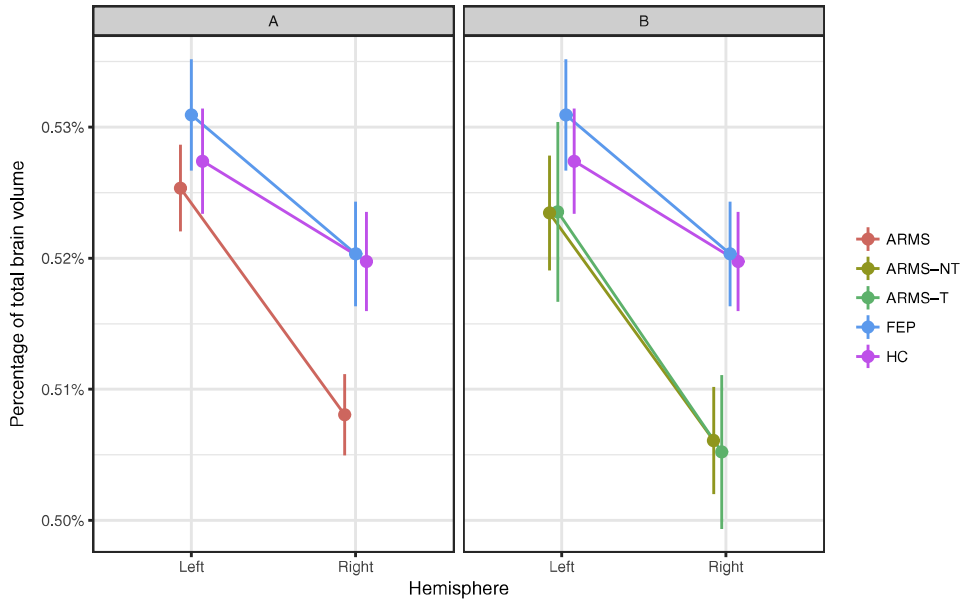

Fig. 1. Interaction effect of group × hemisphere for thalamus volume. *Note.* ARMS = at-risk mental state for psychosis patients; ARMS-NT = at-risk mental state for psychosis patients without later transition to psychosis; ARMS-T = at-risk mental state patients with later transition to psychosis; FEP = first episode psychosis patients; HC = healthy controls. Part A shows the comparison of ARMS, FEP and HC. Part B shows the post-hoc analyses of the interaction effect of group × hemisphere for thalamus volume using the subgroups ARMS-T and ARMS-NT.

2008; Yu et al., 2010). Another study on repeated MRI scans in 60 adolescent subjects reported heterogeneous maturation in the thalamus, with more pronounced thalamus volume decreases in the left hemisphere (Dennison et al., 2013). The authors also reported that this volumetric decrease was moderated by sex, with a significant effect for female subjects but not for males. Furthermore, a multimodal meta-analysis (Cooper et al., 2014) reported hypo-activation of the left thalamus in subjects at familial risk for psychosis and integrated this finding in the large body of findings on altered size, shape and structure of the thalamus in genetic and clinical high risk for psychosis patients as well as the reported hypo-activation in schizophrenia patients. Hence, we may speculate that the larger left thalamus found in our ARMS sample could be a compensatory reaction to adverse life events or perceived stress and in turn have prevented in some ARMS patients a probable transition to psychosis. In line with this hypothesis would be a recent study in mice, which reported higher thalamus volumes to be associated with lower social avoidance scores in resilient mice (Anacker et al., 2016). However, our finding remains controversial and may not ultimately be resolved based on the present data, especially due to the unequal group sizes and imbalanced sex ratio in our sample of ARMS-T and ARMS-NT patients.

The higher GM volumes in older participants may be an indicator for the stated inverse U shaped developmental trajectories in cortical GM volumes in longitudinal studies, which can reach peak sizes at different ages in different regions (Giedd et al., 2012). In contrast to the GM volume trajectories, WM volume increases mainly over the first four decades (Giedd et al., 2012). Thus, our results regarding GM and WM volumes in a relatively young sample may be indicative for developmental trajectories of the very same towards their estimated peak points. However, this finding needs further elucidation in longitudinal analyses to draw firm conclusions and may not be resolved solely based on the present data.

Interestingly, we could not observe any significant between-group or between-sex differences regarding amygdala, putamen and pallidum volumes. These subcortical structures have been described in the literature to be sexually dimorphic (Giedd et al., 2012; Ruigrok et al., 2014). Giedd et al. (2012) reported in their review putamen and pallidum volume to be larger in young adult men, whereas the amygdala has been reported to be proportionately larger in adult and adolescent men (Abel et al., 2010). Furthermore, WM volume has been described to increase more rapidly in men, supposedly due to enhanced testosterone levels (Perrin et al., 2008). However, the effect sizes derived from Ruigrok et al. (2014) and Giedd et al. (2012) differed (amygdala: $d' = 0.16_{right}/0.19_{left} - 0.79$; putamen: $d' = 0.12_{right}/0.11_{left} - 0.611$; pallidum: $d' = 0.19 - 0.625$). Hence, the lack of positive results regarding these subcortical volumes in our study may be due to the reasonable but not huge sample size and to the imbalanced sex ratio between groups.

Changes in GM volumes in FEP or schizophrenia patients might also be due to the effects of antipsychotic medication (Dazzan et al., 2015; Fusar-Poli et al., 2013b). A meta-analysis by our group (Fusar-Poli et al., 2013b) provided evidence for progressive brain changes in schizophrenia patients when compared to HC, with longitudinal decreases in GM volume in schizophrenia patients being associated with higher cumulative exposure to antipsychotic medication over time, while no effects were observed for duration of illness and severity of symptoms. However, as we only analysed cross-sectional data and our patient sample had not received a cumulative CPE dose higher than 2500 mg at the time of MRI acquisition, we may not draw any firm conclusions on the impact of antipsychotic medication in our sample. However, when we repeated our analyses with only antipsychotic-naïve patients, no different results emerged.

Schizophrenia has early neurodevelopmental origins, which later manifest through disrupted neuromaturational processes (Walker and Bollini, 2002). Neurobiological stress (Walker and Diforio, 1997) has to be taken into consideration as well as perinatal complications affecting brain development (Walder et al., 2014) and genetic liability (Lichtenstein et al., 2009; Wray and Gottesman, 2012). Additionally, dopaminergic dysregulation, disturbed glutamatergic neurotransmission and increased proinflammatory status of the brain (Kahn and Sommer, 2015) as well as the so-called Polygenic Schizophrenia-related Risk Score (PSRS; referring to the polygenic predisposition for schizophrenia in a clinical sample) (Harrisberger et al., 2016; Lencz et al., 2014) may contribute to brain changes before the onset of psychosis. Hence, these findings emphasize the need of taking evidence from genetic, neuroimaging and treatment studies into account when further investigating the possible causes of emerging psychoses.

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4.1. Limitations

The following limitations have to be taken into account. Firstly, only about a third of the patients in our patient sample were female whereas in the HC sample only about a third of subjects were male. This unequal sex distribution may have prevented significant between-group sex differences. Moreover, when investigating ARMS-T and ARMS-NT the sex distribution got even more unbalanced due to the unique characteristics of these subgroups. Thus, the results of these analyses should be interpreted with certain precaution. Pooling data for future analyses on sex differences are indicated to overcome the issue of imbalanced gender ratios in clinical and control samples.

Secondly, our results may not resolve the question of asymmetry since in our analyses we only corrected the subcortical volumes for individual total brain volume, but not for hemispherical (left/right) volume. Hence, we may not draw any conclusions regarding asymmetry.

A third point deserving attention is the cross-sectional nature of this study, which precluded the detection of subtle changes in subcortical volumes over time. Future studies warrant longitudinal data analysis to detect sex-specific and sex-dependent changes in subcortical brain volumes over time.

4.2. Conclusion

We found patterns of normal sexual dimorphism in total brain volume and caudate volume, which are in line with those reported in recent meta-analyses and reviews. The only structure affected by a reversed sexual dimorphism was the hippocampus. However, this finding was consistent across all three groups. We suggest that subcortical volumes are not afflicted by a disrupted or even reversed sexual dimorphism in emerging psychosis and may hence not be used for the prediction of transition to psychosis.

5. Ethical standards

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.03.034.

Conflict of interest

None.

Contributors

LE was responsible for the literature review, the conduct of statistical analyses, the interpretation of the same and the drafting of the manuscript. CL and ES assisted with the design of the analyses, the conduct and interpretation of the same. LE, FH and RS were responsible for the data collection. CL, ES, FH, RS, AS, CH, AS, UEL, ARR and SB critically revised the manuscript. ARR conceived and designed the study. All authors read and approved the final manuscript.

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Curriculum Vitae

Name:	**Laura Egloff**
Date of birth:	13th August 1988
Nationality:	Swiss
OrcID:	orcid.org/0000-0001-7809-7541

Education

Since 10.2014	**PhD Candidate** Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Switzerland
09.2012 – 06.2014	**Master of Science in Psychology** **Majoring in Cognitive Neuropsychology** Department of Psychology, Division of Personality Psychology and Developmental Psychology, University of Basel, Switzerland
09.2008 – 12.2011	**Bachelor of Science in Psychology** Department of Psychology, University of Basel, Switzerland
08.2002 – 06.2007	**General Qualification for University Entrance** Gymnasium Leonhard, Basel, Switzerland

Prizes, awards, fellowships

10.2017	Travel grant from the University of Basel to attend the II European Meeting on Women's Mental Health: Psychosis & Gender; 26-27 October 2017; Barcelona, Spain.
05.2017	Travel grant from the University of Basel to attend the 25th European Congress of Psychiatry EPA; 1-4 April 2017; Florence, Italy.
05.2016	Travel grant from the University of Basel to attend the 5th Biennial Schizophrenia International Research Society (SIRS) Conference; 2-6 April 2016; Florence, Italy.
01.-09.2015	Research and salary stipend from the research fund of the University of Basel Psychiatric Hospital (UPK); CHF 25'000.-

Personal skills

Languages	German	Mother tongue
	English	Cambridge Certificate of Proficiency – C2
	French; Italian	Good knowledge
	Swedish	Basic knowledge
Software	R; Microsoft Office; Open Office	Excellent knowledge
	Mplus; IBM SPSS Software; FSL	Very good knowledge
	Siemens *syngo*.via for MRI	Good knowledge
	Unix; Linux	Good knowledge
	Matlab; E-Prime	Basic Knowledge

Publications in peer-reviewed scientific journals

Egloff L, Studerus E, Zimmermann R, Heitz U, Menghini-Müller S, Ittig S, Beck K, Andreou C, Borgwardt S, Riecher-Rössler A. Evaluating verbal episodic memory deficits in at-risk mental state or first episode psychosis patients using structural equation modeling. PloS One. **2018**. https://doi.org/10.1371/journal.pone.0196936

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Egloff L. Sex differences in brain morphology in emerging psychosis. Oral presentation at the 2nd European Meeting on Women's Mental Health (WMH); 26-27 October **2017**; Barcelona, Spain.

Egloff L, Lenz C, Studerus E, Heitz U, Menghini-Müller S, Harrisberger F, Ittig S, Beck K, Leanza L, Andreou C, Riecher-Rössler A, Borgwardt S. Verbal learning and memory in at-risk mental state and first episode psychosis patients and their correlates to brain structural alterations. Oral presentation at the 25th European Congress of Psychiatry (EPA); 1-4 April **2017**; Florence, Italy. http://dx.doi.org/10.1016/j.eurpsy.2017.01.319

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Submitted but not yet accepted/published publications

Egloff L, Lenz C, Studerus E, Heitz U, Harrisberger F, Smieskova R, Schmidt A, Leanza L, Andreou C, Borgwardt S, Riecher-Rössler A. No associations between medial temporal lobe volumes and verbal learning/memory in emerging psychosis. European Journal of Neuroscience (submitted 05.2018)

Leanza L,† **Egloff L**,† Studerus E, Andreou C, Heitz U, Ittig S, Beck K, Riecher-Rössler A. The relationship between negative symptoms and cognitive functioning in patients with an at-risk mental state for psychosis. Psychiatry Research (submitted 02.2018; in revision)
†shared first authorship
