Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

ARTICLE INFO

Article history:
Received 19 September 2017
Received in revised form 27 January 2018
Accepted 18 March 2018
Available online xxxx

Keywords:
Psychosis
Schizophrenia
Prodromal
MRI
Sexual dimorphism

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).

https://doi.org/10.1016/j.schres.2018.03.034

(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

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

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

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

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

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

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.,

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

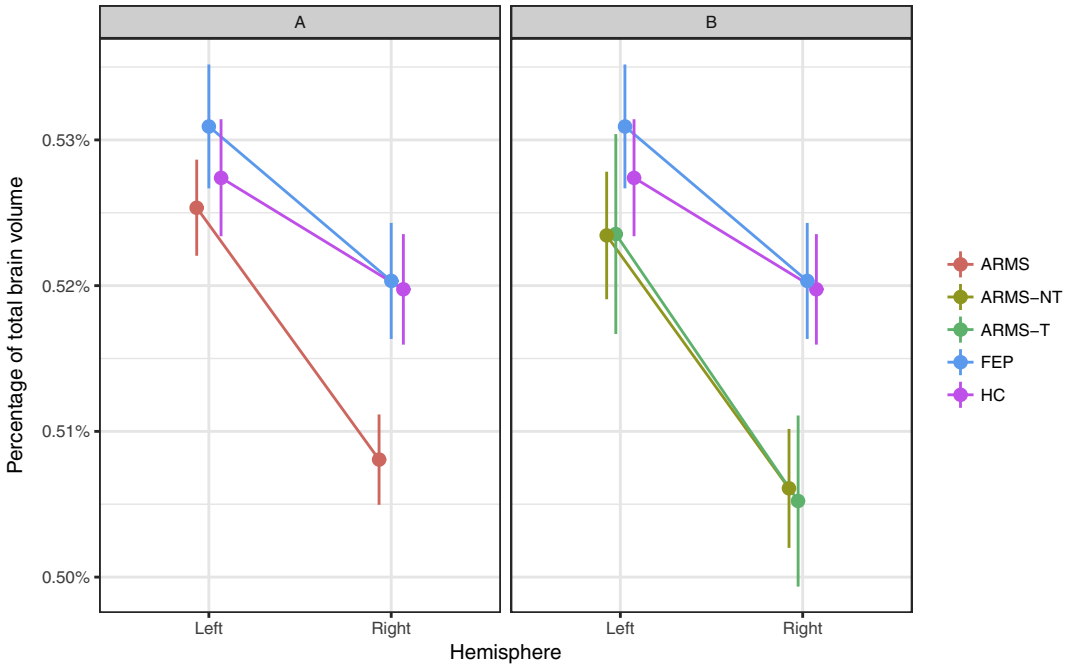

Fig. 1. Interaction effect of group × hemisphere for thalamus volume. *Note*. ARMS = at-risk mental state for psychosis patients; ARMS-NT = at-risk mental state for psychosis patients without later transition to psychosis; ARMS-T = at-risk mental state patients with later transition to psychosis; FEP = 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.

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

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.

Role of the funding source

This project was 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).

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.

Acknowledgements

We thank all patients who participated in the study as well as the referring specialists. We would also like to thank Tanja Haas for her support in MRI data acquisition.

References

Abel, K.M., Drake, R., Goldstein, J.M., 2010. Sex differences in schizophrenia. Int. Rev. Psychiatry 22 (5), 417–428.

Anacker, C., Scholz, J., O'Donnell, K.J., Allemang-Grand, R., Diorio, J., Bagot, R.C., Nestler, E.J., Hen, R., Lerch, J.P., Meaney, M.J., 2016. Neuroanatomic differences associated with stress susceptibility and resilience. Biol. Psychiatry 79 (10), 840–849.

Ardekani, B.A., Figarsky, K., Sidtis, J.J., 2013. Sexual dimorphism in the human corpus callosum: an MRI study using the OASIS brain database. Cereb. Cortex 23 (10), 2514–2520.

Barajas, A., Ochoa, S., Obiols, J.E., Lalucat-Jo, L., 2015. Gender differences in individuals at high-risk of psychosis: a comprehensive literature review. Sci. World J. 2015, 430735.

Bates, D., Maechler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 67 (1), 1–48.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate - a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B Stat Methodol. 57 (1), 289–300.

Bora, E., Pantelis, C., 2015. Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. Schizophr. Bull. 41 (5), 1095–1104.

Bora, E., Yücel, M., Pantelis, C., 2010. Cognitive impairment in schizophrenia and affective psychoses: implications for DSM-V criteria and beyond. Schizophr. Bull. 36 (1), 36–42.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S.J., Yucel, M., Velakoulis, D., Pantelis, C., 2011a. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr. Res. 127 (1–3), 46–57.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S.J., Yücel, M., Velakoulis, D., Pantelis, C., 2011b. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr. Res. 127 (1), 46–57.

Bora, E., Lin, A., Wood, S.J., Yung, A.R., McGorry, P.D., Pantelis, C., 2014. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatr. Scand. 130 (1), 1–15.

Cannon, T.D., 2015. How schizophrenia develops: cognitive and brain mechanisms underlying onset of psychosis. Trends Cogn. Sci. 19 (12), 744–756.

Carbon, M., Correll, C.U., 2014. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr. 19 (Suppl. 1), 38–52 (quiz 35–37, 53).

Cooper, D., Barker, V., Radua, J., Fusar-Poli, P., Lawrie, S.M., 2014. Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia. Psychiatry Res. 221 (1), 69–77.

Cosgrove, K.P., Mazure, C.M., Staley, J.K., 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol. Psychiatry 62 (8), 847–855.

Crawford, M.B., DeLisi, L.E., 2016. Issues related to sex differences in antipsychotic treatment. Curr. Opin. Psychiatry 29 (3), 211–217.

Crow, T.J., Chance, S.A., Priddle, T.H., Radua, J., James, A.C., 2013. Laterality interacts with sex across the schizophrenia/bipolarity continuum: an interpretation of meta-analyses of structural MRI. Psychiatry Res. 210 (3), 1232–1244.

Dazzan, P., Arango, C., Fleischacker, W., Galderisi, S., Glenthoj, B., Leucht, S., Meyer-Lindenberg, A., Kahn, R., Rujescu, D., Sommer, I., Winter, I., McGuire, P., 2015. Magnetic resonance imaging and the prediction of outcome in first-episode schizophrenia: a review of current evidence and directions for future research. Schizophr. Bull. 41 (3), 574–583.

Dennison, M., Whittle, S., Yucel, M., Vijayakumar, N., Kline, A., Simmons, J., Allen, N.B., 2013. Mapping subcortical brain maturation during adolescence: evidence of hemisphere- and sex-specific longitudinal changes. Dev. Sci. 16 (5), 772–791.

Duggal, H.S., Muddasani, S., Keshavan, M.S., 2005. Insular volumes in first-episode schizophrenia: gender effect. Schizophr. Res. 73 (1), 113–120.

Dukart, J., Smieskova, R., Harrisberger, F., Lenz, C., Schmidt, A., Walter, A., Huber, C., Riecher-Rössler, A., Simon, A., Lang, U.E., Fusar-Poli, P., Borgwardt, S., 2017. Age-related brain structural alterations as an intermediate phenotype of psychosis. J. Psychiatry Neurosci. 42 (5), 307–319.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr. Res. 117 (1), 1–12.

Ellison-Wright, I., Glahn, D.C., Laird, A.R., Thelen, S.M., Bullmore, E., 2008. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. Am. J. Psychiatr. 165 (8), 1015–1023.

Eranti, S.V., MacCabe, J.H., Bundy, H., Murray, R.M., 2013. Gender difference in age at onset of schizophrenia: a meta-analysis. Psychol. Med. 43 (1), 155–167.

Falkenburg, J., Tracy, D.K., 2014. Sex and schizophrenia: a review of gender differences. Psychosis 6 (1), 61–69.

Fornito, A., Yücel, M., Patti, J., Wood, S.J., Pantelis, C., 2009. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophr. Res. 108 (1), 104–113.

Fox, J., Weisberg, S., 2011. An R Companion to Applied Regression, R Package Version 2.0-10. Sage, Thousand Oaks CA.

Frederikse, M., Lu, A., Aylward, E., Barta, P., Sharma, T., Pearlson, G., 2000. Sex differences in inferior parietal lobule volume in schizophrenia. Am. J. Psychiatr. 157 (3), 422–427.

Frodl, T., O'Keane, V., 2013. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol. Dis. 52, 24–37.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012a. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69 (3), 220–229.

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A.R., Howes, O., Stieglitz, R.D., Vita, A., McGuire, P., Borgwardt, S., 2012b. Cognitive functioning in prodromal psychosis: a meta-analysis. Arch. Gen. Psychiatry 69 (6), 562–571.

Fusar-Poli, P., McGuire, P., Borgwardt, S., 2012c. Mapping prodromal psychosis: a critical review of neuroimaging studies. Eur. Psychiatry 27 (3), 181–191.

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., McGorry, P., Klosterkötter, J., McGuire, P., Yung, A., 2013a. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiat. 70 (1), 107–120.

Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013b. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37 (8), 1680–1691.

Fusar-Poli, P., Smieskova, R., Serafini, G., Politi, P., Borgwardt, S., 2014. Neuroanatomical markers of genetic liability to psychosis and first episode psychosis: a voxelwise meta-analytical comparison. World J. Biol. Psychiatry 15 (3), 219–228.

Giedd, J.N., Castellanos, F.X., Rajapakse, J.C., Vaituzis, A.C., Rapoport, J.L., 1997. Sexual dimorphism of the developing human brain. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 21 (8), 1185–1201.

Giedd, J.N., Raznahan, A., Mills, K.L., Lenroot, R.K., 2012. Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. Biol. Sex Differ. 3 (1), 19.

Glahn, D.C., Laird, A.R., Ellison-Wright, I., Thelen, S.M., Robinson, J.L., Lancaster, J.L., Bullmore, E., Fox, P.T., 2008. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biol. Psychiatry 64 (9), 774–781.

Goldstein, J.M., Seidman, L.J., O'Brien, L.M., et al., 2002. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch. Gen. Psychiatry 59 (2), 154–164.

Goldstein, J.M., Seidman, L.J., Makris, N., Ahern, T., O'Brien, L.M., Caviness Jr., V.S., Kennedy, D.N., Faraone, S.V., Tsuang, M.T., 2007. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol. Psychiatry 61 (8), 935–945.

Goldstein, J.M., Lancaster, K., Longenecker, J.M., Abbs, B., Holsen, L.M., Cherkerzian, S., Whitfield-Gabrieli, S., Makris, N., Tsuang, M.T., Buka, S.L., Seidman, L.J., Klibanski, A., 2015. Sex differences, hormones, and fMRI stress response circuitry deficits in psychoses. Psychiatry Res. 232 (3), 226–236.

Gorka, A.X., Hanson, J.L., Radtke, S.R., Hariri, A.R., 2014. Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. Biol. Mood Anxiety Disord. 4, 12.

Gur, R.E., Cowell, P.E., Latshaw, A., et al., 2000a. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch. Gen. Psychiatry 57 (8), 761–768.

Gur, R.E., Turetsky, B.I., Cowell, P.E., et al., 2000b. Temporolimbic volume reductions in schizophrenia. Arch. Gen. Psychiatry 57 (8), 769–775.

Gur, R.E., Kohler, C., Turetsky, B.I., Siegel, S.J., Kanes, S.J., Bilker, W.B., Brennan, A.R., Gur, R. C., 2004. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. Biol. Psychiatry 55 (5), 512–517.

Häfner, H., Riecher, A., Maurer, K., Fätkenheuer, B., Löffler, W., An der Heiden, W., Munk-Jørgensen, P., Strömgren, E., 1991. Geschlechtsunterschiede bei schizophrenen Erkrankungen. Fortschr. Neurol. Psychiatr. 59 (09), 343–360.

Häfner, H., Riecher-Rössler, A., Maurer, K., Fätkenheuer, B., Löffler, W., 1992. First onset and early symptomatology of schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 242 (2), 109–118.

Halekoh, U., Højsgaard, S., 2014. A kenward-roger approximation and parametric bootstrap methods for tests in linear mixed models–the R package pbkrtest. J. Stat. Softw. 59 (9), 1–32.

Harrisberger, F., Smieskova, R., Vogler, C., Egli, T., Schmidt, A., Lenz, C., Simon, A.E., Riecher-Rössler, A., Papassotiropoulos, A., Borgwardt, S., 2016. Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis. Transl. Psychiatry 6 (8), e868.

Hauser, M., Zhang, J.P., Sheridan, E.M., Burdick, K.E., Mogil, R., Kane, J.M., Auther, A., Carrion, R.E., Cornblatt, B.A., Correll, C.U., 2017. Neuropsychological test performance to enhance identification of subjects at clinical high risk for psychosis and to be most promising for predictive algorithms for conversion to psychosis: a meta-analysis. J. Clin. Psychiatry 78 (1), e28–e40.

Irle, E., Lange, C., Ruhleder, M., Exner, C., Siemerkus, J., Weniger, G., 2011. Hippocampal size in women but not men with schizophrenia relates to disorder duration. Psychiatry Res. Neuroimaging 192 (3), 133–139.

Ittig, S., Studerus, E., Papmeyer, M., Uttinger, M., Koranyi, S., Ramyead, A., Riecher-Rössler, A., 2015. Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects. Eur. Psychiatry 30 (2).

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5 (2), 143–156.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17 (2), 825–841.

Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., 2012. Fsl. NeuroImage 62 (2), 782–790.

Kahn, R.S., Sommer, I.E., 2015. The neurobiology and treatment of first-episode schizophrenia. Mol. Psychiatry 20 (1), 84–97.

Kenward, M.G., Roger, J.H., 1997. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 983–997.

Kim, H.S., Shin, N.Y., Jang, J.H., Kim, E., Shim, G., Park, H.Y., Hong, K.S., Kwon, J.S., 2011. Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra-high risk. Schizophr. Res. 130 (1–3), 170–175.

Lardinois, M., Lataster, T., Mengelers, R., Van Os, J., Myin-Germeys, I., 2011. Childhood trauma and increased stress sensitivity in psychosis. Acta Psychiatr. Scand. 123 (1), 28–35.

Lencz, T., Knowles, E., Davies, G., Guha, S., Liewald, D.C., Starr, J.M., Djurovic, S., Melle, I., Sundet, K., Christoforou, A., Reinvang, I., Mukherjee, S., DeRosse, P., Lundervold, A., Steen, V.M., John, M., Espeseth, T., Raikkonen, K., Widen, E., Palotie, A., Eriksson, J.G., Giegling, I., Konte, B., Ikeda, M., Roussos, P., Giakoumaki, S., Burdick, K.E., Payton, A., Ollier, W., Horan, M., Donohoe, G., Morris, D., Corvin, A., Gill, M., Pendleton, N., Iwata, N., Darvasi, A., Bitsios, P., Rujescu, D., Lahti, J., Hellard, S.L., Keller, M.C., Andreassen, O. A., Deary, I.J., Glahn, D.C., Malhotra, A.K., 2014. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). Mol. Psychiatry 19 (2), 168–174.

Lichtenstein, P., Yip, B.H., Bjork, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M., 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373 (9659), 234–239.

Lukoff, D., Nuechterlein, K., Ventura, J., 1986. Manual for the expanded brief psychiatric rating scale. Schizophr. Bull. 12, 594–602.

McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol. Rev. 30, 67–76.

Morse, J.K., Scheff, S.W., DeKosky, S.T., 1986. Gonadal steroids influence axon sprouting in the hippocampal dentate gyrus: a sexually dimorphic response. Exp. Neurol. 94 (3), 649–658.

Narr, K.L., Bilder, R.M., Kim, S., Thompson, P.M., Szeszko, P., Robinson, D., Luders, E., Toga, A.W., 2004. Abnormal gyral complexity in first-episode schizophrenia. Biol. Psychiatry 55 (8), 859–867.

Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G.R., Konrad, K., 2009. Sex differences and the impact of steroid hormones on the developing human brain. Cereb. Cortex 19 (2), 464–473.

Ochoa, S., Usall, J., Cobo, J., Labad, X., Kulkarni, J., 2012. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. Schizophrenia Research and Treatment. 2012.

Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M., 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. NeuroImage 56 (3), 907–922.

Paus, T., Nawaz-Khan, I., Leonard, G., Perron, M., Pike, G., Pitiot, A., Richer, L., Susman, E., Veillette, S., Pausova, Z., 2010. Sexual dimorphism in the adolescent brain: role of testosterone and androgen receptor in global and local volumes of grey and white matter. Horm. Behav. 57 (1), 63–75.

Perrin, J.S., Herve, P.Y., Leonard, G., Perron, M., Pike, G.B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2008. Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. J. Neurosci. 28 (38), 9519–9524.

R Core Team, 2016. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Riecher-Rössler, A., Häfner, H., 1993. Schizophrenia and oestrogens—is there an association? Eur. Arch. Psychiatry Clin. Neurosci. 242 (6), 323–328.

Riecher-Rössler, A., Kulkarni, J., 2010. Estrogens and gonadal function in schizophrenia and related psychoses. Biological Basis of Sex Differences in Psychopharmacology. Springer, pp. 155–171.

Riecher-Rössler, A., Studerus, E., 2017. Prediction of conversion to psychosis in individuals with an at-risk mental state: a brief update on recent developments. Curr. Opin. Psychiatry 30 (3), 209–219.

Riecher-Rössler, A., Gschwandtner, U., Aston, J., Borgwardt, S., Drewe, M., Fuhr, P., Pflueger, M., Radue, W., Schindler, C., Stieglitz, R.D., 2007. The Basel early-detection-of-psychosis (FEPSY)-study—design and preliminary results. Acta Psychiatr. Scand. 115 (2), 114–125.

Riecher-Rössler, A., Aston, J., Ventura, J., Merlo, M., Borgwardt, S., Gschwandtner, U., Stieglitz, R.-D., 2008. Das Basel Screening Instrument für Psychosen (BSIP): entwicklung, aufbau, reliabilität und validität. Fortschr. Neurol. Psychiatr. 76 (4).

Riecher-Rössler, A., Pflueger, M.O., Aston, J., Borgwardt, S.J., Brewer, W.J., Gschwandtner, U., Stieglitz, R.D., 2009. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. Biol. Psychiatry 66 (11), 1023–1030.

Riecher-Rössler, A., Pflüger, M., Borgwardt, S., 2010. Schizophrenia in women. In: Kohen, D. (Ed.), Oxford Textbook of Women and Mental Health. Oxford University, Oxford, pp. 102–114.

Ruigrok, A.N., Salimi-Khorshidi, G., Lai, M.C., Baron-Cohen, S., Lombardo, M.V., Tait, R.J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev. 39, 34–50.

Sacher, J., Neumann, J., Okon-Singer, H., Gotowiec, S., Villringer, A., 2013. Sexual dimorphism in the human brain: evidence from neuroimaging. Magn. Reson. Imaging 31 (3), 366–375.

Samplin, E., Ikuta, T., Malhotra, A.K., Szeszko, P.R., Derosse, P., 2013. Sex differences in resilience to childhood maltreatment: effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults. J. Psychiatr. Res. 47 (9), 1174–1179.

Savadjiev, P., Whitford, T.J., Hough, M.E., Clemm von Hohenberg, C., Bouix, S., Westin, C.F., Shenton, M.E., Crow, T.J., James, A.C., Kubicki, M., 2014. Sexually dimorphic white matter geometry abnormalities in adolescent onset schizophrenia. Cereb. Cortex 24 (5), 1389–1396.

Savadjiev, P., Seidman, L.J., Thermenos, H., Keshavan, M., Whitfield-Gabrieli, S., Crow, T.J., Kubicki, M., 2016. Sexual dimorphic abnormalities in white matter geometry common to schizophrenia and non-psychotic high-risk subjects: evidence for a neurodevelopmental risk marker? Hum. Brain Mapp. 37 (1), 254–261.

Schmidt, A., Crossley, N.A., Harrisberger, F., Smieskova, R., Lenz, C., Riecher-Rössler, A., Lang, U.E., McGuire, P., Fusar-Poli, P., Borgwardt, S., 2017. Structural Network Disorganization in Subjects at Clinical High Risk for Psychosis. Schizophr Bull. 43 (3), 583–591.

Sholl, S.A., Kim, K.L., 1989. Estrogen receptors in the rhesus monkey brain during fetal development. Brain Res. Dev. Brain Res. 50 (2), 189–196.

Simeone, J.C., Ward, A.J., Rotella, P., Collins, J., Windisch, R., 2015. An evaluation of variation in published estimates of schizophrenia prevalence from 1990–2013: a systematic literature review. BMC Psychiatry 15 (1), 193.

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034

Smieskova, R., Fusar-Poli, P., Aston, J., Simon, A., Bendfeldt, K., Lenz, C., Stieglitz, R.D., McGuire, P., Riecher-Rössler, A., Borgwardt, S.J., 2012a. Insular volume abnormalities associated with different transition probabilities to psychosis. Psychol. Med. 42 (8), 1613–1625.

Smieskova, R., Allen, P., Simon, A., Aston, J., Bendfeldt, K., Drewe, J., Gruber, K., Gschwandtner, U., Klarhoefer, M., Lenz, C., Scheffler, K., Stieglitz, R.D., Radue, E.W., McGuire, P., Riecher-Rössler, A., Borgwardt, S.J., 2012b. Different duration of at-risk mental state associated with neurofunctional abnormalities. A multimodal imaging study. Hum. Brain. Mapp. 33 (10), 2281–2294.

Smieskova, R., Marmy, J., Schmidt, A., Bendfeldt, K., Riecher-Rössler, A., Walter, M., Lang, U.E., Borgwardt, S., 2013. Do subjects at clinical high risk for psychosis differ from those with a genetic high risk?—a systematic review of structural and functional brain abnormalities. Curr. Med. Chem. 20 (3), 467–481.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155.

Studerus, E., Riecher-Rössler, A., Papmeyer, M., 2016. Neurocognition and motor functioning in the prediction of psychosis. In: Riecher-Rössler, A., McGorry, P. (Eds.), Early Detection and Intervention in Psychosis, 1 ed. Karger, Basel, pp. 116–132.

Studerus, E., Ramyead, A., Riecher-Rössler, A., 2017. Prediction of transition to psychosis in patients with a clinical high risk for psychosis: a systematic review of methodology and reporting. Psychol. Med. 47 (7), 1163–1178.

Takahashi, T., Kawasaki, Y., Kurokawa, K., Hagino, H., Nohara, S., Yamashita, I., Nakamura, K., Murata, M., Matsui, M., Suzuki, M., Seto, H., Kurachi, M., 2002. Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia: a volumetric magnetic resonance imaging study. Schizophr. Res. 55 (1–2), 69–81.

Takayanagi, Y., Takahashi, T., Orikabe, L., Mozue, Y., Kawasaki, Y., Nakamura, K., Sato, Y., Itokawa, M., Yamasue, H., Kasai, K., Kurachi, M., Okazaki, Y., Suzuki, M., 2011. Classification of first-episode schizophrenia patients and healthy subjects by automated MRI measures of regional brain volume and cortical thickness. PLoS One 6 (6), e21047.

Tan, A., Ma, W., Vira, A., Marwha, D., Eliot, L., 2016. The human hippocampus is not sexually-dimorphic: meta-analysis of structural MRI volumes. NeuroImage 124, 350–366.

Thorup, A., Petersen, L., Jeppesen, P., Ohlenschlaeger, J., Christensen, T., Krarup, G., Jorgensen, P., Nordentoft, M., 2007. Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. J. Nerv. Ment. Dis. 195 (5), 396–405.

Velligan, D., Prihoda, T., Dennehy, E., Biggs, M., Shores-Wilson, K., Crismon, M.L., Rush, A.J., Miller, A., Suppes, T., Trivedi, M., 2005. Brief psychiatric rating scale expanded version: how do new items affect factor structure? Psychiatry Res. 135 (3), 217–228.

Ventura, J., Green, M.F., Shaner, A., Liberman, R.P., 1993. Training and quality assurance with the brief psychiatric rating scale: "the drift busters.". Int. J. Methods Psychiatr. Res.

Vogeley, K., Schneider-Axmann, T., Pfeiffer, U., Tepest, R., Bayer, T.A., Bogerts, B., Honer, W. G., Falkai, P., 2000. Disturbed gyrification of the prefrontal region in male schizophrenic patients: a morphometric postmortem study. Am. J. Psychiatr. 157 (1), 34–39.

Walder, D.J., Mittal, V., Trotman, H.D., McMillan, A.L., Walker, E.F., 2008. Neurocognition and conversion to psychosis in adolescents at high-risk. Schizophr. Res. 101 (1–3), 161–168.

Walder, D.J., Holtzman, C.W., Addington, J., Cadenhead, K., Tsuang, M., Cornblatt, B., Cannon, T.D., McGlashan, T.H., Woods, S.W., Perkins, D.O., Seidman, L.J., Heinssen, R., Walker, E.F., 2013. Sexual dimorphisms and prediction of conversion in the NAPLS psychosis prodrome. Schizophr. Res. 144 (1–3), 43–50.

Walder, D.J., Faraone, S.V., Glatt, S.J., Tsuang, M.T., Seidman, L.J., 2014. Genetic liability, prenatal health, stress and family environment: risk factors in the Harvard Adolescent Family High Risk for schizophrenia study. Schizophr. Res. 157 (1–3), 142–148.

Walder, D.J., Yaffe, B., Ehrlich, Y., 2015. Sexual dimorphisms in psychosis risk: a neurodevelopmental perspective. In: Shansky, R.M. (Ed.), Sex Differences in the Central Nervous System. Academic Press, p. 107.

Walker, E., Bollini, A.M., 2002. Pubertal neurodevelopment and the emergence of psychotic symptoms. Schizophr. Res. 54 (1–2), 17–23.

Walker, E.F., Diforio, D., 1997. Schizophrenia: a neural diathesis-stress model. Psychol. Rev. 104 (4), 667–685.

Walker, E.F., Walder, D.J., Lewine, R., Loewy, R., 2002. Sex Differences in the Origins and Premorbid Development of Schizophrenia.

Wang, L., Shen, H., Tang, F., Zang, Y., Hu, D., 2012. Combined structural and resting-state functional MRI analysis of sexual dimorphism in the young adult human brain: an MVPA approach. NeuroImage 61 (4), 931–940.

van der Werf, M., Hanssen, M., Kohler, S., Verkaaik, M., Verhey, F.R., Investigators, R., van Winkel, R., van Os, J., Allardyce, J., 2014. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. Psychol. Med. 44 (1), 9–16.

Wieck, A., Grassi-Oliveira, R., Hartmann do Prado, C., Teixeira, A.L., Bauer, M.E., 2014. Neuroimmunoendocrine interactions in post-traumatic stress disorder: focus on long-term implications of childhood maltreatment. Neuroimmunomodulation 21 (2–3), 145–151.

Wray, N.R., Gottesman, I.I., 2012. Using summary data from the Danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Front. Genet. 3, 118.

Yu, K., Cheung, C., Leung, M., Li, Q., Chua, S., McAlonan, G., 2010. Are bipolar disorder and schizophrenia neuroanatomically distinct? An anatomical likelihood meta-analysis. Front. Hum. Neurosci. 4.

Yung, A.R., Phillips, L.J., McGorry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., Patton, G. C., Jackson, H.J., 1998. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br. J. Psychiatry 172 (33), 14–20.

Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultrahigh-risk group: psychopathology and clinical features. Schizophr. Res. 67 (2–3), 131–142.

Zhang, Y., Brady, M., Smith, S., 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans. Med. Imaging 20 (1), 45–57.

Please cite this article as: Egloff, L., et al., Sexually dimorphic subcortical brain volumes in emerging psychosis, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.034