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Sexually dimorphic subcortical brain volumes in emerging psychosis

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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

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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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