



## Pituitary volume increase during emerging psychosis

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### ARTICLE INFO

#### Article history:

Received 16 June 2010

Received in revised form 7 September 2010

Accepted 23 September 2010

Available online 11 November 2010

#### Keywords:

Pituitary

Schizophrenia

Prodrome

Magnetic resonance imaging (MRI)

Hypothalamic-pituitary-adrenal axis (HPA-axis)

Prolactin

### ABSTRACT

**Background:** Morphologic abnormalities of the pituitary gland volume (PV) have been reported in schizophrenia, but at what point in time they occur remains unclear. This study determines PV across different stages of emerging psychotic disorders compared to healthy controls.

**Methods:** We compared PV of 36 individuals with an at-risk mental state (ARMS) for psychosis, 23 patients with a first episode psychosis (FEP) and 20 healthy controls (HC). Transition to psychosis was monitored using the BPRS transition criteria according to Yung et al. (Yung, A.R. et al., 1998. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br. J. Psychiatry Suppl.* 172 (33), 14–20). Applying these transition criteria, 16 of the 36 ARMS individuals made the transition to psychosis (ARMS-T) and 20 did not (ARMS-NT). We traced PV manually on 1 mm slices of magnetic resonance images in three dimensions (coronal, sagittal and axial) blind to group status. We used univariate analysis of covariance (ANCOVA) with PV as dependent variable, group and sex as between-subject factors and whole brain volume as covariate.

**Results:** PV increased from HC to ARMS-NT to ARMS-T/FEP. ANCOVA revealed a significant effect of group ( $F_{3,78} = 3.0$ ;  $p = .036$ ) and a sex  $\times$  group interaction ( $F_{3,78} = 6.5$ ;  $p = .001$ ). Over all groups, women had considerably larger PV than men ( $F_{1,78} = 9.8$ ;  $p = .003$ ).

**Conclusions:** Our findings provide further evidence that PV is increased in emerging psychotic disorders, and suggest that this is due to a stress-associated activation of the pituitary gland.

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## 1. Introduction

Magnetic resonance imaging (MRI) studies of the pituitary gland volume (PV) indicate that the pituitary is a dynamic

organ which seems to change its volume in response to different influencing factors, such as age or stress. It is larger in females than in males and increases for example in puberty, pregnancy or with the administration of exogenous estrogens (for review, see [Pariante, 2008](#)).

Also in psychotic disorders PV seems to be increased. As recent research has shown, the pituitary seems already to be increased during the prodromal phase of psychosis ([Garner et al., 2005](#)). [Pariante et al. \(2004, 2005\)](#) also found increased PV in neuroleptic-free patients with a first episode psychosis (FEP compared to healthy controls (HC)). Following this enlargement, however, the pituitary seems to become smaller in established, treated schizophrenia ([Pariante et al., 2004](#)). [Upadhyaya et al. \(2007\)](#) found decreased PV in antipsychotic-

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naïve schizophrenia patients after an average duration of psychosis of two years. They and also [Tournikioti et al. \(2007\)](#) found an inverse relationship between duration of illness and PV.

The pituitary gland produces different hormones which have been described to be abnormal in schizophrenic psychoses. Thus, it secretes adrenocorticotrophic hormone (ACTH), which regulates the hypothalamic-pituitary-adrenal (HPA) axis, and HPA abnormalities have been described in psychoses (for review, see [Pariante \(2008\)](#)). Furthermore, it secretes the follicle stimulating hormone (FSH) and luteinizing hormone (LH) that regulate the hypothalamic-pituitary-gonadal (HPG) axis, which has been found to be suppressed in patients with schizophrenia ([Riecher-Rössler et al., 1994, 1998](#)). It also produces prolactin which has been shown to be increased in many patients with schizophrenic psychoses, even in neuroleptic-free FEP patients ([Kahn et al., 2008](#)) and in at-risk mental state (ARMS) individuals ([Rechsteiner et al., 2007; Aston et al., 2010](#)). Thus, it could well be that schizophrenic psychoses are associated with an abnormal volume of the pituitary as a consequence of a dysfunction in these hormonal systems.

We therefore examined PV changes in emerging psychosis and assessed the timing of the changes in an MRI study. We compared PV between HC, FEP patients, and ARMS individuals. We further compared PV between ARMS who made a transition to psychosis (ARMS-T) and ARMS individuals who did not (ARMS-NT). Based on previous neuroimaging studies of subjects with ARMS (see previously mentioned data; for review see [Smieskova et al., 2010](#)), we expected PV to increase with the emergence of psychosis ( $HC < ARMS-NT < ARMS-T < FEP$ ). To our knowledge this is the first study comparing these four groups.

## 2. Materials and methods

### 2.1. Study design

This imaging study was embedded in a naturalistic, prospective study on the prediction of transition to psychosis in individuals with ARMS, the Basel Early Detection of Psychosis (FePsy) study. A more detailed description of the overall study design can be found elsewhere ([Riecher-Rössler et al., 2007, 2009a](#)). The Ethics Committee of Basel, Switzerland (EKBB), approved all aspects of the study and written informed consent was obtained from each participant.

### 2.2. Participants

Recruitment started in February 2000. Subjects were recruited over a four-year period from a service area covering 200,000 inhabitants in and around Basel, Switzerland. The last follow-up assessment was in May 2007. Eighty-two subjects agreed to participate in the imaging arm of the FePsy study. Two HC with very large PV ( $904 \text{ mm}^3$  and  $913 \text{ mm}^3$ , more than three times out of standard deviation) were excluded to avoid the leverage effect of outliers in regression analyses and one of the ARMS-NT subjects had to be excluded due to an indefinable pituitary structure on MRI (prior to unblinding the group status). Therefore, a total of 79

participants (36 ARMS, 23 FEP and 20 HC) were included in the statistical analysis. The exclusion of three subjects from statistical analysis explains the slight differences in sample size to a recently published study comparing hippocampal volumes in the same sample ([Buehlmann et al., 2009](#)).

### 2.3. Screening procedure

For screening purposes, we used the Basel Screening Instrument for Psychosis (BSIP) ([Riecher-Rössler et al., 2008](#)), a 46-item instrument based on variables which have shown to be risk factors for psychosis ([Riecher-Rössler et al., 2006, 2007](#)). These include DSM-III-R-‘prodromal’ symptoms, social decline, drug abuse, previous psychiatric disorders or genetic liability for psychosis, as well as the assessment of the severity of possible (pre-)psychotic phenomena (“attenuated” psychotic symptoms). Experienced psychiatrists and psychologists who underwent regular training conducted all assessments.

### 2.4. Inclusion criteria

#### 2.4.1. ARMS group

The ARMS group was defined using the BSIP ([Riecher-Rössler et al., 2008](#)) in conjunction with the Personal Assessment And Crisis Evaluation (PACE) criteria ([Phillips et al., 2002a; Yung et al., 1998](#)) previously employed in similar MRI studies ([Borgwardt et al., 2007a,b, 2008; Garner et al., 2005; Pantelis et al., 2003; Phillips et al., 2002b; Velakoulis et al., 2006](#)). Inclusion thus required one or more of the following: a) “attenuated” psychotic symptoms, b) Brief Limited Intermittent Psychotic Symptoms (BLIPS), or c) a first or second degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as a marked decline in social or occupational functioning. Symptom severity was rated on the Brief Psychotic Rating Scale (BPRS), extended version ([Lukoff et al., 1986](#)). Inclusion because of “attenuated” psychotic symptoms required BPRS scores of 2 or 3 on the hallucination item, 3 or 4 on the unusual thought content and/or suspiciousness items for at least several times a week and persisting for more than 1 week. Inclusion because of BLIPS required BPRS scores of  $\geq 4$  on the hallucination item, or  $\geq 5$  on the unusual thought content, suspiciousness or conceptual disorganization items, with each symptom lasting less than 1 week before resolving spontaneously.

#### 2.4.2. FEP group

The FEP group was defined applying the transition criteria according to [Yung et al. \(1998\)](#), see [Table 1](#). At least one of the symptoms must occur at least several times a week and persist more than one week.

#### 2.4.3. HC group

The HC group was recruited from the same geographical area by local advertisements. An experienced psychiatrist excluded the presence of a current or past psychiatric disorder, head trauma, neurological illness, serious medical or surgical illness, substance dependency (except for cannabis and nicotine) and family history of a major psychiatric disorder.

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