Full-length paper

Pituitary volume increase during emerging psychosis

Jeannine Büschlen[a], Gregor E. Berger[b], Stefan J. Borgwardt[a], Jacqueline Aston[a], Ute Gschwandtner[a], Marlon O. Pflueger[a], Pascal Kuster[c], Ernst Wilhem Radü[c], Rolf-Dieter Stieglitz[a], Anita Riecher-Rössler[a]

[a] University Psychiatric Outpatient Department, Psychiatric University Clinics Basel, c/o University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland

[b] Department of Adolescent Psychiatry, Integrated Psychiatry Winterthur – Zürcher Unterland, Klinik Schlosstal, Wieshofstrasse 102, P.O. Box 144, CH-8408 Winterthur, Switzerland

[c] Department of Radiology, University Hospital Basel, Basel, Petersgraben 4, CH-4031 Basel, Switzerland

Authors' e-mail addresses:
Jeannine.Bueschlen@stud.unibas.ch
bergerg@mac.com
stefan.borgwardt@upkbs.ch
Jacqueline.aston@upkbs.ch
ute.gschwandtner@upkbs.ch
marlon.pflueger@upkbs.ch
kusterp@uhbs.ch
RadueE@uhbs.ch
rolf-dieter.stieglitz@upkbs.ch

Corresponding author

Prof. Dr. med. Anita Riecher-Rössler
Head of the
Psychiatric University Outpatient Department
Psychiatric University Clinics Basel
c/o University Hospital Basel
Petersgraben 4
CH-4031 Basel
Phone: +41 61 265 5114
Fax: +41 61 265 4599
Anita.Riecher@upkbs.ch

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 x 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 with emerging psychotic disorders, and suggest that this is due to a stress-associated activation of the pituitary gland.

Keywords: pituitary; schizophrenia; prodrome; magnetic resonance imaging (MRI); hypothalamic-pituitary-adrenal axis (HPA-axis); prolactin

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. (2005; 2004) 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-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 adrenocorticotropic 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., 1998; 1994). 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 above; for review see Smieskova et al. (2009)), 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). 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 mm^3 and 913 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., 2007; 2006). 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; 2007b; 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 ≥4 on the hallucination item, or ≥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.

Insert TABLE 1 approx. here.

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.

2.5. Exclusion criteria

Exclusion criteria were: age below 18 years, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis treated with major tranquilizers for more than 3 weeks (lifetime), psychosis due to organic brain disease or substance dependency, or psychotic symptoms within a clearly diagnosed depression or borderline personality disorder. The latter differs to the Melbourne ultra-high risk ascertainment strategy that does not exclude subjects with a major depression with psychotic features, or borderline personality disorder with psychotic symptoms. We decided to exclude these subjects if the primary diagnosis of major depression or borderline personality disorder was present prior to the ARMS to focus on a narrower at-risk sample for schizophrenia.

When it was not suitable to perform an MRI (e.g. pacemaker, metal in the body), subjects were excluded from the imaging part of the FePsy study.

2.6. Clinical follow-up and transition to psychosis

All subjects were offered supportive counseling and clinical management. During the first year of follow-up, ARMS individuals were assessed monthly. During the second and third year, all individuals were assessed 3-monthly and thereafter once a year until the end of May 2007 or until transition to frank psychosis. Transition to psychosis was monitored using the BPRS transition criteria according to Yung et al. (1998). Applying these transition criteria, 16 of the 36 ARMS individuals made the transition to psychosis (ARMS-T) and 20 did not (ARMS-NT). The diagnosis was determined by a diagnostic interview

using ICD-10 research criteria at the time of transition, corroborated by a subsequent assessment at least one year post transition using OPCRIT (Operational Criteria OPCRIT checklist for psychotic and affective illness) (McGuffin et al., 1991).

2.7. Structural MRI

2.7.1. Image acquisition

All participants were scanned using a Siemens (Erlangen, Germany) Magnetom Vision 1.5 T scanner at the University Hospital Basel. Head movement was minimized by foam padding and velcro straps across the forehead and chin. A three-dimensional volumetric spoiled gradient recalled echo sequence generated 176 contiguous, 1-mm thick sagittal slices. Imaging parameters were: time-to-echo, 4 msec; time-to-repetition, 9.7 msec; flip angle, 12; matrix size, 200 x 256; field of view, 25.6 x 25.6 cm matrix; voxel dimensions, 1.28 x 1 x 1 mm.

Original DICOM data were then converted to Analyze 7.5 format in axial direction coded to ensure blindness of the investigator and patients' confidentiality and finally imported into the image-analysis software AMIRA (Kappos et al., 2006).

2.7.2. Manual segmentation of pituitary gland volume

The pituitary glands (Figure 1) were manually traced in the interactive public domain software program AMIRA by the same trained and blinded

investigator (JB) using a method described by Sassi et al. (2001). The pituitary stalk was excluded, but the posterior pituitary was included. We traced around the borders of the pituitary in the same way as Pariante et al. (2004), Garner et al. (2009; 2005), MacMaster et al. (2007a), and Nicolo et al. (2010): the diaphragma sellae superiorly, the sphenoid sinus inferiorly, and the cavernosus sinus laterally. First, the pituitary was traced in all coronal slices where it could be visualized. In addition to the method of Sassi et al. (2001), the tracing was then corrected in sagittal and axial dimensions to be finally controlled on the coronal slices again. Partial volume effects were taken into account. The software calculates the traced ROI volume in mm^3 by summing the number of voxels of each traced slice. Intra-rater reliability in a subset of 10 scans measured twice within two weeks was .98. The whole brain volume was measured to correct for differences in head size as previously described (Borgwardt et al., 2007a; 2007b; Haller et al., 2009).

Insert FIGURE 1 approx. here

2.7.3. Image processing for whole brain volumes

The fully automated software SIENAX (structural image evaluation, using normalization, of atrophy in a single-time-point estimation) was used for estimation of whole brain volumes from a single image, normalized for skull size (Smith et al., 2007). This method has been described elsewhere in detail (http://www.fmrib.ox.ac.uk/fsl/siena/index.html).

Briefly, the software first strips non-brain tissue, and then uses the brain and

skull images to estimate the scaling between the subject's image and standard space. It then runs tissue segmentation to estimate the volume of brain tissue, and multiplies this by the estimated scaling factor, to reduce head-size-related variability between subjects (Smith et al., 2002).

2.8. Statistical analysis

We performed all analyses using the Statistical Package for the Social Sciences (SPSS) version 15. Clinical and demographic differences between groups were examined by one-way analysis of variance (ANOVA) or chi-square test (Monte Carlo exact significance). Differences in PV were compared using univariate analysis of covariance (ANCOVA) with PV as dependent variable, group (HC, ARMS-NT, ARMS-T, FEP) and sex as between-subject factors and whole brain volume as covariate.

The relationships between PV and demographic or clinical variables were examined with Pearson’s correlation coefficient r. Statistical significance was defined as $P < .05$ (two-tailed).

3. Results

3.1. Sample characteristics

The main demographic data and baseline clinical features of HC, ARMS-NT, ARMS-T and FEP are presented in Table 2. There were no significant differences between the groups in sex, age or whole brain volume. FEP

participants were scanned within 1-3 days of first contact. More than half of the FEP patients (14/23) were antipsychotic-naïve. The remaining nine participants were prescribed atypical antipsychotic medications (six of them for less than one month; three participants received risperidone, six olanzapine).

Thirty-two out of thirty-six ARMS individuals never received antipsychotic medication. Four participants had received low doses of atypical antipsychotic medication for behavioral control by the referring psychiatrist or general practitioner (three participants olanzapine, one risperidone) prior to study inclusion, all four for less than one month. Reanalyzing the data after excluding the nine FEP and four ARMS participants who were exposed to antipsychotic medication as outlined above did not change the overall results. Despite the markedly reduced sample size, the group x sex effect remained highly significant ($F_{3,57}$=4.750, p=.005), and the group effect became a trend ($F_{3,57}$=2.361, p=.081). All reported analyses therefore included the whole data set of 79 participants (independent of medication status). Furthermore, results did not change after adding age as covariate.

Insert TABLE 2 approx. here

3.2. Pituitary gland volumes (PV)

Correlational analyses of PV did not reveal a significant association between PV and whole brain volume (Pearson's ρ = -.059, p = .607) or age (Pearson's

ρ = -.024, p = .833) but did with sex (ANOVA: $F_{1,78}$ = 9.8; p = 0.003). As expected, over all groups women had significantly larger PV than men.

Regression analysis for sex-adjusted mean revealed PV increases from HC to ARMS-NT to ARMS-T/FEP (see Table 3). The ANCOVA model with PV as dependent variable, group and sex as factors, and whole brain volume as covariate was significant for group effect ($F_{3,78}$ = 3.0; p = .036). Additionally, there was a significant sex x group interaction (ANCOVA: $F_{3,78}$ = 6.5; p = .001). Female sex in the ARMS-T group mainly drove this effect (see Figure 2). These findings remained the same after adding age as covariate.

Insert TABLE 3 approx. here

Insert FIGURE 2 approx. here

4. Discussion

This ROI-based MRI study compared PV of individuals with ARMS according to transition status (ARMS-T, ARMS-NT) with FEP patients and HC. Pituitary volume increased from HC to ARMS-NT to ARMS-T/FEP (see Table 3). Our finding of a slightly larger PV in ARMS-T and FEP suggests that the gradual emergence of the first psychotic episode is associated with an activation of the pituitary function.

4.1. Are pituitary volume abnormalities associated with activation of stress hormones during emerging psychosis?

Our findings support previous work of Garner et al. (2005) and Pariante et al. (2008; 2004) suggesting that PV is increased already prior to the first psychotic episode in ARMS participants who will convert to psychosis and that PV enlargement is most pronounced with the first psychotic breakdown.

We further suggest that the increased pituitary volume in these patients might be due to over-activation of the stress response systems of the pituitary, associated with the development of psychosis. Thus, both ACTH and prolactin are so-called 'stress hormones', i.e. their secretion in the pituitary can be activated by psychological distress (for review, see (Pariante, 2008; Riecher-Rössler et al., 1998)).

4.1.1. ACTH as a stress hormone

Several lines of evidence point towards an altered HPA axis function in emerging psychotic disorders (Phillips et al., 2006). Increased levels of circulating cortisol and ACTH were found in drug-naïve first episode patients with schizophrenia (Ryan et al., 2004; Sachar, 1970). Furthermore, non-suppression of cortisol on the dexamethasone suppression test was found in some patients with schizophrenia, also in drug-naïve first episode cases (Coryell and Tsuang, 1992; Herz et al., 1985; Lammers et al., 1995; Tandon et al., 1991; Tandon et al., 1989). A small pilot study of patients with an at-risk mental state for psychosis also suggests that the HPA axis may already be dysfunctional prior to the first psychotic episode, particularly in ARMS subjects with depressive symptoms (Thompson et al., 2007). Regarding the time course of the volume changes, it was suggested that increased PV in ARMS-T and in FEP subjects may be the consequence of an acute (repetitive) HPA

axis activation, whereas in established schizophrenia repeated episodes of HPA axis hyperactivity may lead to suppression of the HPA axis and result in smaller PV (Berger et al., 2007; Pariante, 2008; Phillips et al., 2006). Recently Mondelli et al. (2008), based on their finding of enlarged PV even in unaffected relatives of patients with psychosis, have suggested that the enlargement could partly also be a preexisting abnormality due to a genetic susceptibility to overactivate the HPA axis.

4.1.2. Prolactin as stress hormone

Also prolactin secretion of the pituitary is activated by stress and could partly explain the pituitary volume abnormalities: PV increase might be due to activation of prolactin-producing lactotroph cells (MacMaster et al., 2007a; 2007b; Pariante et al., 2005; Riecher-Rössler et al., 1998).

Prolactin levels are increased by many antipsychotics (for review, see (Riecher-Rössler et al., 2009). And Mondelli et al. (2008) as well as MacMaster et al. (2007a) have shown that first-episode and chronic patients with schizophrenia who were receiving prolactin-elevating antipsychotics had an increased pituitary volume compared with controls. Thus, PV increase could theoretically also be associated with antipsychotic-induced hyperprolactinaemia. However, the robustness of our findings after excluding the four ARMS and the nine FEP subjects receiving antipsychotic medication at the time of scanning indicate that the PV effects can also be related to the illness itself and are not always a medication effect.

In this context it is interesting to note that prolactin in schizophrenia patients has shown to be increased also independent of antipsychotics (Rechsteiner et

al., 2007). And recently we have shown that prolactin is increased in many neuroleptic-free FEP patients (Kahn et al., 2008) and even in neuroleptic-naïve ARMS patients (Aston et al., 2010), although overall results remain discussed controversially (for review, see Pariante (2008)).

It is also unlikely, that PV differences in ARMS-T or FEP can be explained by antidepressant use, which is partly prescribed in this population, as long-term use of antidepressants hardly affects prolactin production (Molitch, 2005).

4.2. Is pituitary volume increase associated with increasing LH and FSH?

Also FSH and LH are produced in the pituitary. Theoretically it is also possible that the increase in PV is additionally due to an increased production of FSH and LH. This would be an indirect consequence of hyperprolactinaemia as the latter is known to suppress the HPG axis and the production of estrogens. Hypoestrogenism in a feedback-loop could then stimulate FSH and LH production.

In this context it is interesting to note that a dysfunction of the hypothalamo-pituitary-gonadal (HPG) axis with hypoestrogenism has been described in women with schizophrenia long before the introduction of antipsychotics (for review, see (Riecher-Rössler and Häfner, 1993; Riecher-Rössler et al., 1998)).

Interestingly, mainly the female ARMS-T group drove the overall group difference (see Figure 2). It could be speculated that this is due to a hormonal dysbalance especially in women – either the women being more stress-

sensitive or stronger reacting with pituitary dysfunction. Also, in the above-mentioned study (Rechsteiner et al., 2007; Aston et al., 2010) mainly ARMS *women* showed hyperprolactinaemia independent of antipsychotics .

As expected from literature (for review see (MacMaster et al., 2007b; Pariante, 2008)), women in our study had a significantly larger PV than men. This gender difference has been described in healthy volunteers, but also in patients with psychosis or ARMS subjects (Garner et al., 2005; Pariante, 2008; Upadhyaya et al., 2007). MacMaster et al. (2007b; 2006a; 2006b) also showed sex differences of PV in pediatric obsessive-compulsive disorder and in major depressive disorder, suggesting that this is not specific for certain psychiatric disorders.

4.3. Limitations of our study and future perspectives

In contrast to Garner et al. (Garner et al., 2005) we did not find a statistically significant difference in PV between ARMS-T and ARMS-NT (although there was a numerical difference). These differences may not only be explained by limited statistical power due to small sample sizes but also by different ascertainment strategies. Thus, the FePsy-Clinic at the University Psychiatric Outpatient Department of the Psychiatric University Clinics Basel only includes subjects from 18 years onwards, whereas ORYGEN Youth Health includes subjects from 15 to 25 years of age (prior to 2002 up to 29 years of age). ORYGEN also includes subjects with a primary diagnosis of major depression or borderline personality disorder (BPD) presenting with psychotic-like or psychotic symptoms, whereas the FePsy study explicitly excludes such subjects.

Due to the modest sample size in the subgroup analysis we cannot exclude a statistical type II error and the possibility of missing small group differences. Furthermore, small differences in anatomic ROI definition and different MR acquisition parameters (e.g. different slice thickness) across studies may explain some of the discrepancies between studies.

Furthermore, PV and morphology seem to be influenced by many additional factors, such as the variability in neuroendocrine activity, e.g. during the hormonal cycle (Dinc et al., 1998) that we were unable to control for, and additional environmental factors (Kumar and Pariante, 2004; Phillips et al., 2006).

To finally address the question of the timing of PV changes across the stages of emerging psychotic disorders, further prospective longitudinal neuroimaging studies from ARMS onwards would be useful. Such studies should also include testing of pituitary function by measuring circulating cortisol, ACTH and prolactin levels, or the dexamethasone suppression test (DST) in combination with PV measurements to better understand the role of the pituitary in emerging psychotic disorders. Furthermore, the specificity of the findings for schizophrenic psychoses should be further investigated as hyperactivity of the pituitary function, i.e. HPA axis or prolactin secretion, and consecutive PV abnormalities can also occur in other conditions associated with psychological stress (e.g. Sassi et al. (2001), McMaster et al. (2006a), Jovev et al. (2008)).

5. Conclusions

In conclusion, our findings seem to indicate that volumetric alterations of the pituitary gland emerge during the prodromal and peri-onset phase of psychotic disorders and may reflect a hyperactivation of hormonal functions of the pituitary gland, particularly in women. Our findings especially encourage further investigation of the role of the HPA/HPG-axis as well as prolactin in emerging psychotic disorders as all of them have already been shown to be dysfunctional in psychosis. Of special interest are ACTH and prolactin as both are so-called 'stress hormones' and thus might well be involved in the pathogenesis of the disorder.

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Figure Legends

Figure 1. The pituitary gland in a sagittal (left), transversal (centre) and coronal (right) magnet resonance image

Traced pituitary is located between the white lines.

Figure 2. Pituitary gland volumes across groups

Boxplot with median, upper and lower quartiles and standard deviation separated for groups and sex. Men: HC n = 13, ARMS-NT n = 10, ARMS-T n = 11, FE n = 17. Women: HC n = 7, ARMS-NT n = 10, ARMS-T n = 5, FE n = 6