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Increased Pituitary Volume in Antipsychotic-Free and Antipsychotic-Treated Patients of the Æsop First-Onset Psychosis Study

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Subjects at their first psychotic episode show an enlarged volume of the pituitary gland, but whether this is due to hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, or to stimulation of the prolactin-secreting cells by antipsychotic treatment, is unclear. We measured pituitary volume, using 1.5-mm, coronal, 1.5 T, high-resolution MRI images, in 78 patients at the first psychotic episode and 78 age- and gender-matched healthy controls. In all, 18 patients were antipsychotic-free (12 of these were antipsychotic-naïve), 26 were receiving atypical antipsychotics, and 33 were receiving typical antipsychotics. As hypothesized, patients had a larger pituitary volume than controls (+22%, $p<0.001$). When divided by antipsychotic treatment, and compared to controls, the pituitary volume was 15% larger in antipsychotic-free patients ($p=0.028$), 17% larger in patients receiving atypicals ($p=0.01$), and 30% larger in patients receiving typicals ($p<0.001$). Patients receiving typicals not only had the largest pituitary volume compared to controls but also showed a trend for a larger pituitary volume compared to the other patients grouped together (+11%, $p=0.08$). When divided by diagnosis, and compared to controls, the pituitary volume was 24% larger in patients with schizophrenia/schizophreniform disorder ($n=40$, $p<0.001$), 19% larger in depressed patients ($n=13$, $p=0.022$), 16% larger in bipolar patients ($n=16$, $p=0.037$), and 12% larger in those with other psychoses ($n=9$, $p=0.2$). In conclusion, the first-episode of a psychotic disorder is associated with a larger pituitary independently of the presence of antipsychotic treatment, and this could be due to activation of the HPA axis. Typical antipsychotics exert an additional enlarging effect on pituitary volume, likely to be related to activation of prolactin-secreting cells. This activation of the hormonal stress response could participate to the important metabolic abnormalities observed in patients with psychosis.
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INTRODUCTION

We have previously shown that subjects at their first episode of psychoses show an enlarged volume of the pituitary gland, but it is still unclear whether this is due to activation of the hormonal stress response during the psychotic experience, or to stimulation of the prolactin-secreting cells by antipsychotic treatment (Cotter and Pariante, 2002; Pariante *et al*, 2004). Both old (Sachar *et al*, 1970) and recent studies (Ryan *et al*, 2003, 2004a, b) have demonstrated hyperactivity of the main hormonal stress system, the hypothalamic–pituitary–adrenal (HPA) axis, in subjects experiencing their first psychotic episode. In turn, HPA axis hyperactivity—in major depression—has been linked to an increased volume of the pituitary gland (Axelson *et al*, 1992; Krishnan *et al*, 1991; MacMaster and Kusumakar, 2004). The pituitary gland regulates HPA axis activity by secreting the adrenocorticotropic hormone (ACTH), and its increased volume has been interpreted as reflecting an increase in the size and number of corticotrope cells producing ACTH (Axelson *et al*, 1992; Krishnan *et al*, 1991; Pariante *et al*, 2004). Indeed, in patients with major depression, the volume of the pituitary correlates with the

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circulating cortisol levels (Axelson *et al*, 1992; Krishnan *et al*, 1991).

Recently, we have described an increased volume of the pituitary gland, measured by magnetic resonance imaging (MRI), in 24 subjects with a first-episode of psychosis recruited in Melbourne, Australia (Pariante *et al*, 2004). This work supports the hypothesis that these patients have activation of the HPA axis. However, the interpretation of these findings is complicated by the fact that all patients were receiving antipsychotic medication at the time of scanning, and antipsychotics increase prolactin levels in humans and induce proliferation of prolactin-secreting cells in animals (Halbreich and Kahn, 2003; Perez *et al*, 1986; Saiardi *et al*, 1997). Furthermore, the small sample size did not allow us to evaluate any possible differences associated with specific diagnoses within psychoses. To clarify these issues, we have investigated the pituitary volume, using high-resolution MRI, in a different sample of 78 subjects at their first psychotic episode, recruited in London as part of the UK ÆSOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study (Dazzan *et al*, 2004; Dazzan *et al*, 2005). This is an epidemiologically based sample of patients at the first psychotic episode, which includes both antipsychotic-treated and antipsychotic-free subjects, and both affective and nonaffective psychoses. We hypothesized that the pituitary volume would be enlarged in both drug-free and antipsychotic-treated subjects, and across diagnoses.

SUBJECTS AND METHODS

Subjects

We studied 156 subjects: 78 subjects at their first episode of psychosis and 78 age- and gender-matched healthy controls. Subjects were recruited in Southeast London as part of the ÆSOP study, which investigates, in three cities, the higher rates of schizophrenia in the African-Caribbean population in the UK (Dazzan *et al*, 2004; Dazzan *et al*, 2005). Ethical approval for the study was granted by the Ethical Committee of the Institute of Psychiatry, and the participants gave written informed consent, in accordance with the Declaration of Helsinki.

We approached subjects aged 16-65 years, who consecutively presented for the first time to the local psychiatric services of Southeast London for a functional psychotic illness (ICD10 F10-19, excluding coding F1*x*.0 for Acute intoxication; F20-29 and F30-39, psychotic codings) (World Health Organisation, 1992), over a 3-year period. Exclusion criteria were (a) a history of head trauma resulting in loss of consciousness for over 1 h; (b) the presence of a disease of the central nervous system; (c) moderate or severe learning disabilities as defined by ICD-10 (World Health Organisation, 1992); (d) poor fluency in English language; and (e) transient psychotic symptoms resulting from acute intoxication as defined by ICD-10 (World Health Organisation, 1992), following the administration of alcohol or other psychoactive substance. In total, 115 right-handed patients consented to have an MRI scan. A total of 10 patients terminated the scanning session before full image acquisition had been achieved and a further 15 scans were excluded from the analysis (13 due to subject motion, one because of congenital hydrocephalus, and one because of the presence of a subarachnoid cyst). Of the 90 subjects on which a valid MRI was available, 78 could be matched (for age and gender) to a sample of 78 healthy controls recruited from the same sociodemographic areas and who had consented to have an MRI scan.

Clinical Measures

We interviewed patients using the WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organisation, 1994). We made a diagnosis according to ICD-10 criteria (World Health Organisation, 1992) by consensus in meetings with senior clinicians (RM or JL) in which all clinical information was presented. We used both the patients' medical notes and the information obtained from the SCAN interviews to establish the date of onset, and duration of illness was operationalized as the time in weeks between the onset of psychotic symptoms and the MRI scan date. A total symptomatology score was obtained by summing the SCAN's individual symptom item scores, as previously done for the Present State Examination (PSE) (Wing *et al*, 1974; Wing and Sturt, 1978). This was an appropriate model to adopt as the SCAN incorporates the 10th edition of the PSE.

Pharmacological Treatment

From clinical notes, we completed a medication record for each patient. We calculated the total duration of antipsychotic exposure in days and the daily antipsychotic dose at the time of MRI scan, converted into chlorpromazine equivalents for typical antipsychotics. We also recorded information on treatment with antidepressants. Therapeutic interventions (type of medication and length of treatment) were decided by the responsible clinical team, based on clinical presentation, and were not influenced by participation to the study. For the purposes of the main study, we obtained one MRI scan as soon as possible after first presentation to the services, independently of length of antipsychotic treatment. Depending on their current treatment, subjects were divided into three groups: typical antipsychotics, atypical antipsychotics, and antipsychotic-free. The criteria for this division have been already published (Dazzan *et al*, 2005) and are based on existing literature on antipsychotic wash-out. We considered 'antipsychotic-free' those subjects who had not taken any antipsychotic in the 3 weeks prior to the MRI scan (Farde *et al*, 1986; Miller *et al*, 1997a; Miller *et al*, 1997b; Miller *et al*, 2001). We considered subjects as being on treatment with atypical antipsychotics if they had been taking one atypical antipsychotic only for at least 2 weeks prior to MRI, and had not taken more than one dose of a typical antipsychotic during this time. Similar criteria were used for the subjects on typicals; however, because typicals affect prolactin levels even when administered together with atypicals, patients who had received both typicals and atypicals during the 2 weeks preceding the scan ($n = 4$) were categorized as 'typicals'. Clearly, the allocation of subjects to each of these three groups was nonrandomized, but based on the medication prescribed by the clinician in charge at the time of MRI scan. Nevertheless, previous comparisons of brain structures morphology between these

three subgroups have highlighted qualitative differences in the effects of the different antipsychotic classes on the brain (Dazzan *et al*, 2005). One subject on which we had no medication history was excluded from this analysis.

Structural MRI Image Acquisition

Scans were acquired with a GE Signa 1.5-T system (GE Medical Systems, Milwaukee), at the Maudsley Hospital, London. The whole brain was scanned with a 3-D inversion recovery prepared fast spoiled GRASS (SPGR) T1-weighted data set. These T1-weighted images were obtained in the coronal plane with 1.5 mm contiguous sections. TR was 13.8 ms, TI was 450 ms, TE was 2.8 ms, and the flip angle was 20 degrees, with one data average and a $256 \times 256 \times 128$ pixel matrix. Acquisition time was 6 min and 27 sec.

Pituitary Measurement

Each pituitary was traced in all coronal slices where it could be visualized, using ANALYZE 7.5 (Mayo) with a method that has been used previously by us and others (MacMaster and Kusumakar, 2004; Pariante *et al*, 2004; Sassi *et al*, 2001). The pituitary stalk was excluded from the tracings, whereas we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect vasopressin concentrations). We traced around the usually well-defined borders of anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. Figure 1 shows these borders in a good-quality image from the original Australian sample in which we developed the measurement method (Pariante *et al*, 2004). Volume of the pituitary (in mm^3) was calculated by summing volumes for all relevant slices. All pituitaries were traced by two investigators (AD, FB), after training with another senior member of the team (PD). These investigators were blind to the clinical or sociodemographic characteristics of the subjects during the tracing process. The inter-raters reliabilities (between AD, FB, and PD) ranged 0.92–0.95; the intra-rater reliabilities ranged 0.95–0.97.

Statistical Analysis

Data are presented as individual values, mean $\pm$ standard deviation (SD), or adjusted means and standard error of mean (SEM), as detailed. All differences in pituitary volume between groups were examined conducting two-way analysis of variance tests, using group as between-subject factors and adjusting for gender, followed by pairwise comparisons of estimated means. Categorical variables were analyzed using the chi-square test. As there were no differences in whole-brain volume (WBV) between first-episode subjects and controls (ANOVA, $F = 0.05$; $df = 1, 155$; $p = 0.8$), the main analyses of pituitary volume did not include this variable as a covariate. However, we run a second set of confirmatory analyses using WBV as a covariate and found no difference in the results (data not shown). The relationships between pituitary volumes and clinical and sociodemographic continuous variables were examined using Pearson's *r*.

RESULTS

Characteristics of the Sample

The main demographics and clinical features of the first-episode subjects and controls are presented in Table 1. The first-episode subjects are presented as a whole group ($n = 78$) and after division according to

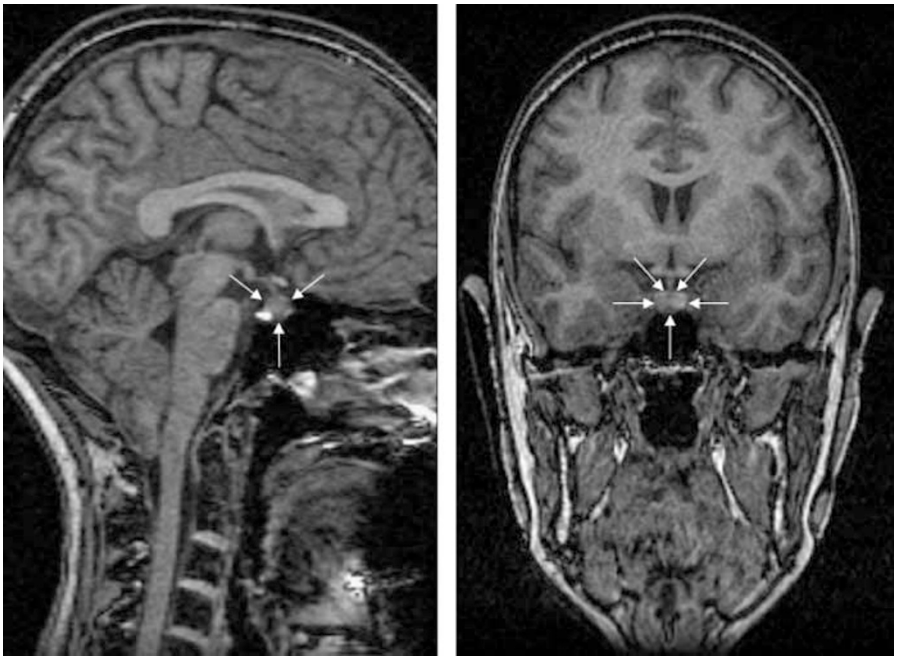

Figure 1 The pituitary gland in a sagittal (left) and coronal (right) MRI image. Coronal slices were used for the tracing of the pituitary, and the pituitary boundaries are indicated by the arrows. The pituitary stalk was not included in the tracings.

Table 1 Characteristics of the Sample

	Controls	First-episode subjects			Group comparisons
Number	78	78			
Age (mean years ± SD)	28 ± 8	27 ± 7			ANOVA, F = 1.4; df = 1, 155; $p = 0.24$
Sex (M/F (% of males))	46/32 (59%)	46/32 (59%)			Chi-square = 0.0, df = 1, $p = 1.0$
Antipsychotic treatment		**Drug-free**	**Atypical**	**Typical**	
Number	78	18	26	33	
Age (mean years ± SD)	28 ± 8	27 ± 8	26 ± 8	27 ± 7	ANOVA, F = 0.5; df = 3, 152; $p = 0.69$
Gender (M/F (% of males))	46/32 (59%)	9/9 (50%)	16/10 (61%)	20/13 (61%)	Chi-square = 0.7, df = 3, $p = 0.87$
SCAN symptoms score		25 ± 16	35 ± 17	36 ± 20	ANOVA, F = 2.1; df = 2, 75; $p = 0.12$
Diagnosis of psychosis		**Schizofr.**	**Affective**	**Other**	
Number	78	40	29	9	
Age (mean years ± SD)	28 ± 8	25 ± 7	29 ± 8	25 ± 7	ANOVA, F = 0.9; df = 3, 153; $p = 0.43$
Sex (M/F (% of males))	46/32 (59%)	28/12 (70%)	12/17 (41%)	6/3 (78%)	Chi-square = 5.9, df = 3, $p = 0.12$
SCAN symptoms score		34 ± 21	35 ± 15	23 ± 14	ANOVA, F = 1.2; df = 2, 76; $p = 0.32$

antipsychotic treatment ($n = 77$; drug-free = 18, atypical = 26, typical = 33) or to diagnosis ($n = 78$; schizophrenia/schizophreniform disorder = 40, affective = 29, other psychoses = 9). As expected, there were no significant differences in age and gender between the controls and the first-episode subjects. When the first-episode group was further divided, there were no differences in age and gender based on antipsychotic treatment, while there was a nonsignificant tendency for more female subjects to be in the affective psychosis group ($p = 0.12$). Moreover, there was a trend for the extent of psychopathology according to the SCAN to be lower in drug-free subjects ($p = 0.09$ *vs* atypicals and $p = 0.06$ *vs* typicals).

Pituitary Volumes

There was a significant difference in pituitary volume between the first-episode and control subjects (ANOVA, F = 20.7; df = 1, 155; $p < 0.001$) (Figure 2). Specifically, pituitary volume in first-episode subjects was significantly larger (+22%) than in controls (estimated mean difference ± SEM: $+125 \pm 27\,mm^3$). Although the examination of the individual data showed an overlap between the groups, 63 of the 78 first-episode subjects (81%) had pituitary volumes that were larger than the median of the control subjects.

In the whole sample, female subjects had larger pituitaries than male subjects (uncorrected values: 671 ± 191 *vs* $607 \pm 170\,mm^3$; ANOVA, F = 5.4; df = 1, 155; $p = 0.021$), and pituitary volume was negatively correlated with age ($r = -0.25$, $p = 0.002$). There was no gender by group interaction in the differences in pituitary volume between first-episode and controls (ANOVA, F = 0.05; df = 1, 155; $p = 0.8$).

Effects of Antipsychotic Treatment

Of the 18 patients who were antipsychotic-free (for at least 3 weeks), 12 were antipsychotic-naïve, three had previously received an atypical, and three had previously received a typical (two for 2–3 days only, and one for 20 days). Of the 26 patients receiving atypicals, 19 were taking olanzapine, five, risperidone, one, sertindole, and one, amisulpride. Of the 33 patients receiving typicals, three were on depot, and the others were on oral medication.

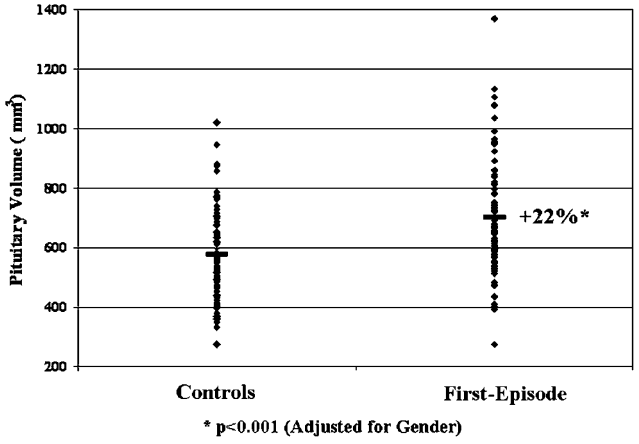

Figure 2 Individual measures of pituitary volumes in first-episode patients and healthy controls. The bars denote the estimated mean for each group after adjustment for gender. Patients' pituitary volume was 22% larger compared to controls' pituitary volume ($p < 0.001$).

There was a significant difference in pituitary volume between the three groups of patients and controls (ANOVA, F = 8.7; df = 3, 152; $p < 0.001$; see Figure 3). Specifically, compared to controls, the pituitary volume was 15% larger in antipsychotic-free patients ($+85 \pm 38\,mm^3$, $p = 0.028$), 17% larger in patients receiving atypicals ($+100 \pm 38\,mm^3$, $p = 0.01$), and 30% larger in patients receiving typicals ($+171 \pm 34\,mm^3$, $p < 0.001$). When the 12 neuroleptic-naïve patients were considered separately, their pituitary volume was also 17% larger than controls, but this difference only

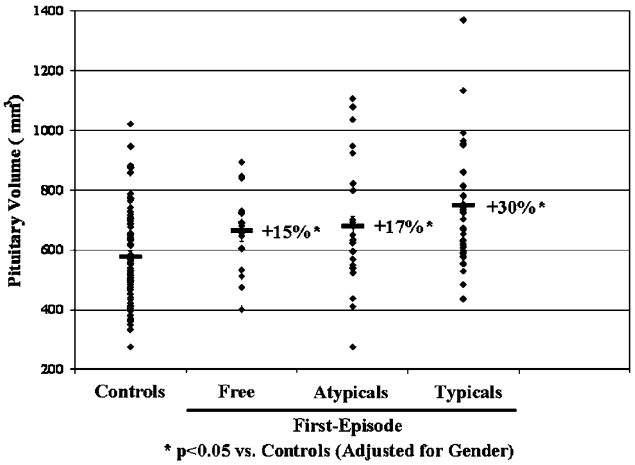

Figure 3 Individual measures of pituitary volumes in first-episode patients ($n=77$; one subject on which we had no medication history was excluded from this analysis) divided by antipsychotic treatment (free, $n=18$; atypicals, $n=26$; typicals, $n=33$). Bars denote the estimated mean for each group after adjustment for gender. Compared to controls, the pituitary volume was 15% larger in antipsychotic-free patients ($p=0.028$), 17% larger in patients receiving atypicals ($p=0.01$), and 30% larger in patients receiving typicals ($p<0.001$).

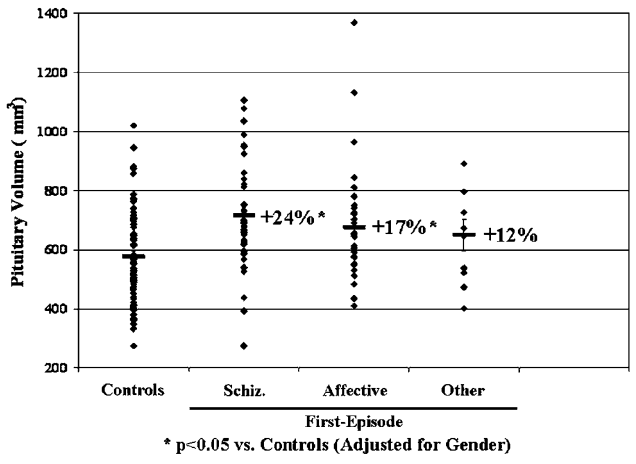

Figure 4 Individual measures of pituitary volumes in first-episode patients divided by diagnostic group (schizophrenia/schizophreniform (Schiz.), $n=40$; affective, $n=29$, other, $n=9$). Bars denote the estimated mean for each group after adjustment for gender. Compared to controls, the pituitary volume was 24% larger in patients with schizophrenia/schizophreniform disorder ($p<0.001$), 17% larger in those with affective psychosis ($p=0.006$), and 12% larger in those with other psychoses (not statistically significant, $p=0.2$).

reached trend statistical significance ($+97\pm51\,mm^3$, $p=0.08$). The patients receiving typicals not only had the largest pituitary volume compared to controls but also had a larger volume ($+11\%$) compared with all other patients taken together, although this difference also only reached trend statistical significance ($+74\pm42\,mm^3$, $p=0.08$). There was no effect of current antidepressant treatment on pituitary volume (ANOVA, $F=1.4$; $df=1, 74$; $p=0.7$). After adjusting for the class of antipsychotic treatment, there was no correlation between pituitary volume and either dose of antipsychotic at the time of the scan ($r=0.13$, $p=0.3$) or total days of antipsychotic treatment before the scan ($r=-0.11$, $p=0.3$).

Effects of Diagnosis

A total of 40 patients had a diagnosis of schizophrenia/schizophreniform disorder, 29 had an affective psychosis (bipolar = 16, depression = 13), and nine had other psychoses. Again, there was a significant difference in pituitary volume between the three groups of patients and controls (ANOVA, $F=6.2$; $df=3, 152$; $p=0.001$; see Figure 4). Specifically, compared to controls, the pituitary volume was 24% larger in patients with schizophrenia/schizophreniform disorder ($+139\pm34\,mm^3$, $p<0.001$), 17% larger in those with affective psychosis ($+100\pm36\,mm^3$, $p=0.006$), and 12% larger in those with other psychoses (not statistically significant: $+72\pm56\,mm^3$, $p=0.2$). There was no difference between bipolar and depressive psychoses: compared to controls, the pituitary volume was 16% larger in bipolar patients ($+92\pm44\,mm^3$, $p=0.037$) and 19% larger in depressed patients ($+112\pm48\,mm^3$, $p=0.022$).

Interestingly, most patients with schizophrenia/schizophreniform disorder were on atypicals, while most patients with affective psychosis were on typicals. Specifically, 21 patients with schizophrenia/schizophreniform disorder (out of 39, 54%) were on atypicals, 13 (33%) were on typicals, and five (13%) were antipsychotic-free; in contrast, two patients with affective psychosis (7%) were on atypicals, 18 (62%) were on typicals, and nine (31%) were antipsychotic-free (chi square = 19.3, df = 4, $p=0.001$). There was no interaction between antipsychotic treatment and diagnoses on pituitary volume (ANOVA, $F=0.5$, $df=4, 73$; $p=0.7$), that is, patients on typicals had the largest pituitary volume across diagnoses (data not shown).

After adjusting for antipsychotic treatment and diagnosis, there was no correlation between pituitary volume and either duration of illness ($r=0.07$, $p=0.5$) or total symptom score ($r=-0.09$, $p=0.4$).

DISCUSSION

Our results indicate that the first-episode of a psychosis is associated with larger size of the pituitary gland, across diagnostic subgroups. This work confirms and extends our previous findings in a smaller Australian sample (Pariante *et al*, 2004). Furthermore, we now demonstrate that patients who are antipsychotic-free and patients on atypical antipsychotics have similar increases of pituitary volume (compared to matched controls), while patients on typical antipsychotics have an even larger pituitary volume. These results show that the enlarged pituitary is present independently of the effects of the antipsychotics, but also indicate that activation of prolactin-secreting cells by typicals may cause an additional enlargement of the pituitary.

We suggest that the increased pituitary volume is due to activation of the HPA axis. Animal and clinical studies have demonstrated that HPA axis activation by corticotropin-releasing hormone (CRH) or by stress leads to an increase in the number and size of corticotropes in the pituitary gland (Asa *et al*, 1992; Carey *et al*, 1984; Gertz *et al*, 1987; Westlund *et al*, 1985). This increase in the size and numbers of corticotropes can increase pituitary volume in humans as

shown on brain imaging (Kubota *et al*, 1992; Mineura *et al*, 1987). Moreover, patients with major depression, where HPA axis hyperactivity has been consistently demonstrated, also have increased pituitary volumes (Axelson *et al*, 1992; Krishnan *et al*, 1991; MacMaster and Kusumakar, 2004). Indeed, in depressed patients, the pituitary volume is positively correlated with post-dexamethasone cortisol levels, suggesting that the pituitary gland is larger in those patients who show less suppression of cortisol secretion by dexamethasone, and thus have a more hyperactive HPA axis (Axelson *et al*, 1992).

Of course, our data in patients receiving typical antipsychotics indicate that the pituitary volume is also sensitive to activation of lactotrope cells. It is well known that blockade of the D2 dopamine receptors on lactotropes by typical antipsychotics induces proliferation of these cells in animals and increased prolactin levels in humans (Halbreich and Kahn, 2003; Perez *et al*, 1986; Saiardi *et al*, 1997). We now find that this phenomenon has a macroscopic brain correlate. Although prolactin secretion is also activated by stress, previous studies have found no evidence that this hormone is elevated in antipsychotic-free patients (Muck-Seler *et al*, 2004; Rao *et al*, 1994; Segal *et al*, 2004; Warner *et al*, 2001). In fact, one recent study found elevated cortisol levels but normal prolactin levels in the same antipsychotic-free patients with schizophrenia (Muck-Seler *et al*, 2004). This further supports the notion that the increased pituitary volume in our antipsychotic-free subjects (and in those receiving atypicals) is due to activation of the HPA axis. Indeed, a strength of this paper is that the antipsychotic-free subjects were either antipsychotic-naïve (67%) or had received antipsychotics only for a short period of time. Moreover, those who had received antipsychotics had stopped for at least 3 weeks before the MRI scan, and this interval is sufficient for prolactin levels to decrease in patients switched from a prolactin-increasing to a prolactin-spearing antipsychotic (Kinon *et al*, 2003). Therefore, we believe that there was no longer any effect of previous (typical) antipsychotics on pituitary volume in these antipsychotic-free subjects.

Clearly, the allocation of the subjects to the treatment groups was nonrandomized, and this could have influenced the results. For example, and perhaps unsurprisingly, antipsychotic-free subjects had lower symptoms severity compared to the treated groups, while symptoms score were similar in those on atypicals and those on typicals. However, pituitary volume was similar in antipsychotic-free patients and in those on atypicals, even if their symptoms scores were different; and pituitary volume was different in those on atypicals and those on typicals, even if their symptoms scores were similar. Taken together, these findings support the conclusion that subjects receiving typical antipsychotics have a larger pituitary volume because of the activation of lactotrope cells and not because of baseline clinical differences.

To our knowledge, this is the first study to compare a (putative) marker of HPA axis function in patients with a first-episode of schizophrenia, psychotic depression or psychotic mania. Previous studies have found raised cortisol and ACTH levels in patients with first-episode schizophrenia (Ryan *et al*, 2003, 2004a, b; Sachar *et al*, 1970), together with increased intra-abdominal fat (Ryan *et al*, 2004a) and impaired glucose tolerance (Ryan *et al*, 2003), thus suggesting that these endocrine abnormalities could have important metabolic consequences (Dinan, 2004). Studies of patients in the acute relapse phase of a psychotic disorder (with florid symptoms, newly hospitalized or unmedicated) have also found elevated cortisol levels that correlate with the severity of psychotic and arousal symptoms (Lammers *et al*, 1995; Tandon *et al*, 1991; Walder *et al*, 2000), nonsuppression of cortisol secretion by dexamethasone in the dexamethasone suppression test and in the dexamethasone/CRH test (Coryell and Tsuang, 1992; Herz *et al*, 1985; Lammers *et al*, 1995), and elevated levels of CRH in the cerebrospinal fluid (Banki *et al*, 1987). Finally, patients with bipolar disorder also show HPA axis hyperactivity (Kunzel *et al*, 2003; Linkowski *et al*, 1994; Watson *et al*, 2004). It is of note that a *smaller* pituitary volume has been described in psychiatric patients with long duration of illness and whose mental state is stable or less severely affected at the time of the MRI scan: for example, in euthymic and depressed bipolar patients, or in patients with chronic, treated schizophrenia (Pariante *et al*, 2004). As we and others have previously speculated, the explanations for the smaller pituitary volume have ranged from being the consequence of a chronic activation of the HPA axis to being a neurodevelopmental problem (Lum *et al*, 2002; Pariante *et al*, 2004; Sassi *et al*, 2001). A recent paper by Chen *et al* (2004), showing normal pituitary volume in children with bipolar disorder, supports the notion that is an acquired, rather than a neurodevelopmental, abnormality, and suggests that a long duration of illness (longer than the 3.9 years mean in this children's sample) is needed for the pituitary to decrease in size. In our previous study, which found a smaller pituitary volume in patients with chronic schizophrenia, the mean duration of illness was of 19 years (Pariante *et al*, 2004).

Interestingly, the HPA axis hyperactivity (and the increased pituitary volume) in depression has been interpreted as indicating a lack of negative inhibitory feedback by circulating glucocorticoid hormones on the HPA axis, especially at the level of the pituitary (glucocorticoid resistance) (Pariante *et al*, 2002; Pariante, 2003; Pariante and Miller, 2001; Raison and Miller, 2003). Indeed, increased size and number of corticotropes and increased volume of the pituitary are present also in subjects with a lack of negative inhibitory feedback by circulating glucocorticoid hormones because of Addison's disease (Mineura *et al*, 1987). In turn, glucocorticoid resistance is a common correlate of stress-induced HPA axis activation in animals and humans (Raison and Miller, 2003). Taken together with the aforementioned studies, our work suggests that glucocorticoid resistance may be present in the acute and severe phases of a psychosis. Stress-induced HPA axis activation in this sample could represent a *consequence* of the distress and arousal associated with the psychotic experience; or, alternatively, it could represent an increased activation of the stress response *preceding* the development of psychosis, for an increased susceptibility to daily life stress, an increased level of independent stressors, or both (Bebbington *et al*, 1993; Myin-Germeys *et al*, 2001). This cross-sectional study does not allow a clarification of this point; however, our recent data showing enlarged pituitary volume *preceding* the onset of psychosis, in a group of

subjects at ultra-high risk of developing psychosis, seem to support the latter model (Garner *et al*, 2005).

This work has been conducted in Southeast London, an urban region with a large proportion of migrants, deprived areas, and a high incidence of psychosis (Boydell *et al*, 2001; Boydell *et al*, 2003). Previous studies have identified environmental risk factors for schizophrenia, like urban place of birth (Pedersen and Mortensen, 2001) and neighborhood environment (van Os *et al*, 2000), which support the link between a stressful environment and the development of psychosis. Furthermore, cannabis abuse has been identified as a risk factor for schizophrenia (Arseneault *et al*, 2004), and activation of the hormonal stress response by cannabis could also participate to this phenomenon (D'Souza *et al*, 2004; D'Souza *et al*, 2005). Indeed, this sample may be at a higher risk of presenting all these environmental risk factors: for example, approximately 50% of these patients were currently using or abusing cannabis at the time of the study (unpublished data). Since the controls are from the same sociodemographic areas, the increased pituitary volume seems to be an effect of the psychosis and not simply of the 'stressful environment'. In fact, data from the 2000 British Crime Survey show that approximately 50% people aged 16–29 years in London have used cannabis at least once in their lifetime, and 31% of men and 22% of women in this age range have used cannabis in the previous year (London Health Observatory; www.lho.org.uk). Moreover, we have already described the increased pituitary volume in another sample of first-episode psychosis from a completely different sociodemographic context in Melbourne (Australia), thus indicating that this finding is independent of environmental risk factors (Pariante *et al*, 2004). Nevertheless, quantitative differences in pituitary volume—the 22% increase compared to controls in this sample *vs* the 10% increase in Melbourne—could be interpreted as showing a larger contribution of environmental risk factors to the development of psychosis in this sample.

Two lines of evidence further support our conclusions. First, the effects of age and gender on pituitary volumes in our sample are consistent with our and other previously published studies in young adults (Elster, 1993; Lurie *et al*, 1990; Pariante *et al*, 2004), thus confirming the reliability of our methods. Second, the most common causes of increased pituitary volume—administration of exogenous estrogens, hypothalamic tumour, pregnancy, and primary hypothyroidism (Elster, 1993)—are excluded in our subjects. A possible limitation of our study, common to all studies examining pituitary volume by imaging methods, is the difficulty in distinguishing between anterior and posterior pituitary volumes. However, the posterior pituitary, which releases vasopressin and oxytocin, comprises less than 20% of the total pituitary volume; moreover, there are no known conditions associated with posterior pituitary enlargement, except tumours. Therefore, we believe that the changes in volume we have described are due to changes in the volume of the anterior pituitary. We did not measure hormonal levels in this sample, nor did we control for menstrual cycle in female patients. Although an increased production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) during puberty and the menstrual cycle has been implicated in the enlarged pituitary volume in female subjects, these hormones seem to be reduced in female psychotic patients, independently from the effects of antipsychotics (Bergemann *et al*, 2005; Huber *et al*, 2001). Moreover, all statistical comparisons are adjusted for gender. Therefore, we would exclude that the differences in pituitary volume between groups are influenced by differences in the phase of menstrual cycle. However, our next studies on this topic will have to include hormone measurements and recording of the menstrual phase.

In conclusion, we have found that the first-episode of a psychotic disorder is associated with a larger pituitary, independently of antipsychotic treatment. These findings support the presence of an activation of the hormonal stress response during a first-episode of psychosis. Future studies should examine whether measurement of the pituitary volume (or of other indicators of the hormonal stress response) can increase our ability to predict the occurrence and the course of a first-episode of psychosis.

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